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Abstracts

Invited Lectures

Pathogenesis, including mitochondrial biology

IS-1

MOLECULAR PATHOLOGY OF MITOCHONDRIAL DISORDERS

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Mitochondria produce the bulk of cellular ATP through oxidative phosphorylation. Defects in the biogenesis or functionality of the OXPHOS (oxidative phosphorylation system) machinery cause severe human disorders that are primarily characterized by neuromuscular defects. However, the molecular dysfunctions, their physiological consequences, and tissue specificity are still ill defined. These gaps in our knowledge are due to the fact that mitochondrial DNA is not accessible to manipulation and that the biogenesis of the OXPHOS systems requires coordinated expression of both cellular genomes.
Here I will report on new technical approaches that allow us now to obtain insight into the mechanistic dysfunctions that eventually lead to mitochondrial OXPHOS defects. I will focus on how mitochondrial gene expression is regulated by the cellular environment to enable the biogenesis of physiological levels of the respiratory chain complexes. These approaches provide a basis to understand the molecular pathology of mitochondrial disorders.

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IS-2

ROLE OF MITOCHONDRIA IN SKELETAL MUSCLE DYSFUNCTION IN MYOSITIS

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Mitochondria are an integral part of muscle function and repair. Mitochondria meet the energy demands of the skeletal muscle by producing ATP and quickly distributing it across the muscle cell through a grid-like network. Recent studies have identified that active mitochondria are required to repair the sarcolemmal injury in healthy myofibers. Functional mitochondria facilitate plasma membrane repair independently of their role in ATP synthesis. Mitochondrial dysfunction is noted in myositis skeletal muscle. For example, mitochondrial membrane potential is significantly reduced in myoblasts from patients compared to healthy controls. We have identified that a mitochondria-localized activator of apoptosis–harakiri is up-regulated in myositis skeletal muscle cells. Muscle cells with higher HRK expression have reduced mitochondrial potential and poor ability to repair from injury compared to controls. We also found that subjecting healthy skeletal muscle cells to pro-inflammatory cytokines such as interferon beta reduces mitochondrial respiration. We propose that muscle weakness and degeneration in inflammatory myopathies are due to reduced mitochondrial respiration and poor repair of damaged myofibers, leading to leakage of damage-associated molecular patterns that activate TLR-mediated pro-inflammatory signaling. This sequence sets in motion a self-sustaining loop that exacerbates mitochondrial and myofiber damage, contributing to progressive worsening of the muscle pathology in myositis. Targeting mitochondria with exercise or other drugs that improve mitochondrial biogenesis would effectively treat inflammatory myopathies.

Genes and environment

IS-3

DEFINING CAUSAL GENES AT MHC IN SLE – IMPLICATIONS FOR MYOSITIS AND OTHER DISEASES THAT SHARE MHC RISK

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For many autoimmune diseases, including myositis and SLE, genome-wide association analyses reveal that the Major Histocompatibility Complex (MHC) is the site of the strongest association signals. Some of these associations have been known for fifty years, however the causal genes have been challenging to determine. The MHC associations in several autoimmune diseases have long been thought to arise from *HLA* alleles; consistently associated alleles are HLA-DRB1*03:01 and HLA-DRB1*15:01 (in Europeans) in many autoimmune diseases. The DRB1*03:01 allele resides on an extended MHC haplotype which encompasses the entire classical MHC region from HLA class I, through class III to HLA class II: from HLA-B8 to HLA-DQA1*05:01/DQB1*02:01 as well as complement C4 null genes in class III. The extensive linkage disequilibrium and structural variation in the MHC have made identifying the causal genes very challenging. The DRB1*03:01 allele (and by definition, the linked haplotype) has been associated with: SLE, Sjogren's, myositis, type I diabetes, Addison's disease, Graves' disease and myasthenia gravis.
In SLE, dense genotyping in large cohorts has hitherto suggested that multiple association signals were present, although the nature of driving alleles was disputed. Using NG sequencing data from access the MHC we have sought to analyse the associations accommodating class III structural variation involving the candidate genes coding complement C4A and C4B. To further improve the resolution of the association, we have employed a transancestral mapping approach in SLE: examining cohorts of European ancestry (from ImmunoChip) and data from the MHC region of an African American GWAS in SLE. The linkage disequilibrium is much less extensive in the African genome at the MHC compared with other common ancestries and this greatly facilitated resolution of the genetic associations. Comparing European and African data, we have shown that the association signals in SLE can be best explained by signals arising from:
1) copy number variation of the complement component 4 (*C4*) genes in the MHC locus and 2) by a shared region in the class II region on the HLA-DRB1*15:01 (in Europeans) and HLA-DRB1*15:03 (in Africans) that likely operates to elevated HLA class II gene expression. The *C4* locus, which has recently been found to increase risk for schizophrenia, generates a 7-fold variation in risk for lupus (95% CI: 5.88-8.61; $p<10^{-117}$ in total) and 16-fold variation in risk for Sjögren's syndrome (95% CI: 8.59-30.89; $p<10^{-23}$ in total), with *C4A* protecting more strongly than *C4B* in both illnesses. In schizophrenia elevated C4 copy number elevates disease risk, whereas in SLE and Sjögren's lower copy numbers of *C4* genes correlate with higher disease risk. In all three illnesses, *C4* alleles acted more strongly in men than in women: common combinations of *C4A* and *C4B* generated 14-fold variation in risk for lupus and 31-fold variation in risk for Sjögren's syndrome in men (versus 6-fold and 15-fold among women respectively) and affected schizophrenia risk about twice as strongly in men as in women. At a protein level, both C4 and its effector (C3) were present at greater levels in men than women in cerebrospinal fluid ($p<10^{-5}$ for both C4 and C3) and plasma among adults ages 20-50, corresponding to the ages of differential disease vulnerability.Sex differences in complement protein levels may help explain the larger effects of *C4* alleles in men, women's greater risk of SLE and Sjogren's, and men's greater vulnerability in schizophrenia. These results nominate the complement system as a source of sexual dimorphism in vulnerability to diverse illnesses.
It remains to be established which other diseases that are associated with this the DR3 haplotype are associated with inherited partial complement deficiency states.

Inclusion body myositis

IS-5

SELECTIVE T CELL DEPLETION FOR INCLUSION BODY MYOSITIS: WHY AND HOW

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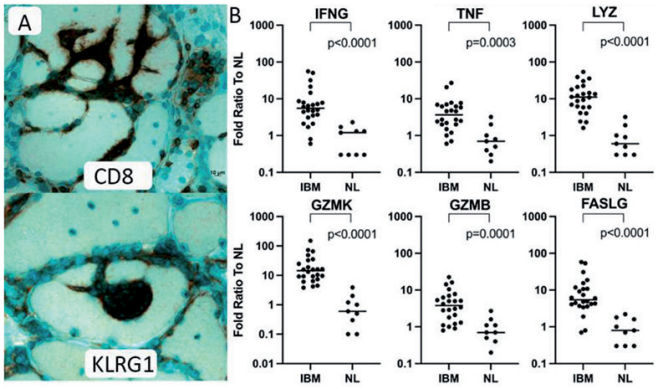
Inclusion body myositis (IBM) is a progressive autoimmune skeletal muscle disease. Whereas the earliest ideas just over 50 years ago regarding IBM pathogenesis were largely based on muscle microscopic pathological observations we can see with our eyes, technological advances, such as large-scale genomic methods, have enhanced our ability to "see" with much greater granularity the pathological processes occurring in IBM muscle.

Extending these increasingly rich and deep pathological observations to IBM pathogenesis causal inferences remains very challenging. Typically, the concepts of "autoimmunity" and of "degeneration" have been invoked. Autoimmunity is a reasonably well-defined term (tissue injury from molecules such as interferon-gamma, or cells, such as T cells, generally considered to be part of the immune system), but the term "degeneration" often conveys no specific pathophysiological information, creating a fundamental problem in its use. Microscopically observed pathological features, such as rimmed vacuoles (a reflection of myonuclear pathology), nuclear-to-sarcoplasmic mislocalization of heterogeneous ribonuclear proteins (hnRNPs including TDP-43), other sarcoplasmic protein aggregates such as p62, and mitochondrial abnormalities reflected by COX-deficiency are often called "degenerative pathology". This term has the misleading implication that these pathologies result from an obscure "degenerative disease" process when in fact their pathogenic implications are almost entirely unknown. The term, like the parallel fictional idea that perifascicular atrophy in dermatomyositis was a consequence of ischemia, likely evolved from the observation that these apparently sick myofibers often had no surrounding immune cells and must have some other mysterious process, called "degeneration" accounting for their presence. It might be better to replace the term "degenerative pathology" with "myonuclear and sarcoplasmic pathology" and to keep "mitochondrial pathology" separate.

Some of these pathologies are already known through *in vitro* studies to be downstream of autoimmunity, such as hnRNP and TDP-43 mislocalization (1-3) and COX-deficiency (4) resulting from exposure to cytokines. Although myofibers with "degenerative pathology" may not necessarily have microscopically visible immune cells nearby, these myofibers are literally bathed in extracellular fluid containing high levels of numerous cytokines and other harmful immune molecules that are invisible by microscopy but clearly visible by genomic technologies (Figure 1).



IS-5. Fig. 1. Visible and invisible IBM muscle autoimmune pathology. (A) Microscopically visible invasion of myofibers by $CD8^+$ T cells and further refined phenotyping of highly cytotoxic KLRG1+ T cells. (B) Microscopically invisible, but revealed by RNAseq profiling, T cell inflammatory mediators in IBM muscle from dataset GSE151757.

A potential approach to IBM therapy is the selective depletion of T cells. One well understood aspect of IBM pathology is the microscopically visible injury to myofibers by $CD8^+$ highly cytotoxic T (Tc) cells (Figure 1). Initial studies defining T cell pathology in the 1980s identified muscle infiltration and myofiber invasion by T cells as a whole and CD8 T cells in particular (5), leading to broad T cell depletion attempts with alemtuzumab and anti-thymocyte globulin. More recent finer understanding of the specific subtype of T cells invading IBM myofibers (6), including T effector memory (TEM) and terminally differentiated T effector cells (TEMRA), suggest that more targeted and selective approaches to T cell depletion might be more effective and less toxic.

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IS-6

INCLUSION BODY MYOSITIS IN 2022: FROM PHYSIOPATHOGENESIS TO CLINICAL TRIALS

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In 1995, ten years after the first dichotomic classification of polymyositis (PM) and dermatomyositis, inclusion body myositis (IBM) was distinguished from the PM from its clinical and pathological presentation (1). IBM is the most common acquired muscle disease in adults over age 50. This myositis is slowly progressive, it affects more men than women, in average it begins at the age of 60, patients use a walking aid after 5 years and are dependent on the wheelchair after 15 years (2). At the steady state of the disease, clinical and histological phenotypes are typical and form the diagnostic criteria which are clinically: finger flexor or quadriceps weakness, and pathologically: endomysial inflammation, and invasion of non-necrotic muscle fibres by lymphocytes or presence of rimmed vacuoles (3). Anti-cN1a auto-antibody seems relatively specific (4).

The presence of microscopic cellular inflammation (endomysial with the invasion of muscle fibres) is the hallmark of the inflammatory nature of IBM. However, the presence of rimmed vacuoles and other 'degenerative' features such as myonuclear degeneration, mitochondrial pathology and myofibrillar cytoplasmic protein aggregates has led to controversy regarding the pathogenesis of this disorder (5, 6). In essence, from an immunological point of view, my team, as well as others have clearly shown different subclasses of T lymphocytes (7, 8) or gene signature (9) from the other IIMs. It has been shown that IBM is driven by highly differentiated cytotoxic T cells: effector memory (TEM) and terminally differentiated (TEMRA) cells (5, 6). In a xenograft model by transplanting human IBM muscle into immunodeficient mice, myofibers in IBM xenografts showed invasion by human, oligoclonal $CD8^+$ T cells and exhibited MHC-I up-regulation, and all the 'degenerative' features (10). Reduction of human T cells within IBM xenografts by treating mice intraperitoneally with anti-CD3 suppressed MHC-I up-regulation. Rimmed vacuoles persisted, though these were never shown to disappear from the original transplanted biopsies and might simply be carried over myonuclear and sarcoplasmic aggregates. Primary or immortalized muscle cell lines obtained from muscle of IBM patients and cultivated without any inflammatory cells never presented in vitro any 'degenerative' features, which can be induced by the addition of some inflammatory cytokines (personal observation).

Regarding the recently published trials, bimagrumab an ActRIIB binding antibody that inhibits ligands including GDF11 and myostatin to induce skeletal muscle hypertrophy was trialed in a phase II/III on 251 participants but failed to achieve its primary (6MWD) and also many secondary endpoints (11). Arimoclomol (a chaperone protein which may reduce protein aggregates) also failed to meet its primary (IBMFRS) and secondary endpoints in a phase II/III trial on 150 patients (press release). Regarding the strategy against TEM/TEMRA cells, we did a monocentric phase II trial of rapamycin (sirolimus) against placebo on 44 patients (12). We found no evidence for efficacy of sirolimus based on maximal voluntary isometric knee extension strength (our primary endpoint) and other muscle strength measures. However, we believe there was enough evidence of benefit in certain secondary outcomes (6MWD, muscle fatty replacement by MRI, HAQ) to pursue a multicentre phase III trial to further assess the efficacy of sirolimus (12). This multicentric phase III testing sirolimus vs. placebo will start soon (ClinicalTrials.gov Identifier: NCT04789070). Finally, a Phase I Study of ABC008 (ClinicalTrials.gov Identifier: NCT0465903) a monoclonal antibody against KLRG1 (a marker of TEM/TEMRA cells) designed to deplete KLRG1+ T cells is ongoing, preparing a multicentric phase II/III.

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Antibodies and biomarkers

IS-7

RELIABILITY OF IMMUNOASSAYS FOR MYOSITIS AUTOANTIBODIES

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Myositis autoantibody testing has become a routine investigation for investigation of patients with myositis spectrum disease. Identification of a relevant autoantibody can provide additional diagnostic certainty and important prognostic information. Over 20 relevant autoantibodies have now been described and cohort studies have demonstrated that a myositis autoantibody can be identified in 60-70% of cases. Immunoprecipitation is the laboratory method used to detect novel myositis autoantibodies and is still widely considered the gold standard. Low through-put, expense and limited availability make immunoprecipitation highly impractical for autoantibody identification in the clinical setting. Several different commercial assays have now been developed to detect myositis relevant autoantibodies. Many have been developed with the practicalities of clinical practice in mind, offering rapid, affordable, and often multiplex testing. Despite this progress, the perfect system has yet to be realised. Commercial testing systems do not detect all known myositis relevant autoantibodies and concerns have been raised about the sensitivity and specificity of some assays, including to their ability detect some autoantibodies strongly associated with malignancy and ILD; important causes of mortality and morbidity.
The advantages and disadvantages of different myositis autoantibody testing systems will be discussed. Evidence for the reliability of different types of assays will be reviewed along with testing strategies that make the most of existing technology.

IS-8

AUTOANTIBODIES AND COMPLEMENT IN EXPERIMENTAL IMNM: FROM PATHOGENESIS TO THERAPY?

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Immune-mediated necrotizing myopathies (IMNM) represent a distinct group of inflammatory myopathies. IMNM are characterized by high creatine kinase levels, and necrosis of skeletal muscle fibers with deposition of C5b-9 membrane attack complex (MAC). Most IMNM patients have autoantibodies (aAbs) directed against signal recognition particle (SRP) or hydroxy-3-methylglutaryl-CoA reductase (HMGCR). In addition to their role as biomarkers, the relationship observed between aAb titers and disease severity has led to the suggestion that these aAbs could be pathogenic and therefore the central players in IMNM pathophysiology.
In vitro experiments show that anti- SRP and anti- HMGCR aAbs cause muscle fiber atrophy and impair the fusion of myoblasts, therefore limiting their regenerative capacity. Whereas they are normally intracellular proteins, SRP and HMGCR proteins can be found at the surface of myotubes exposed to purified patient-derived aAbs. Passive transfer of IgG from anti-SRP+ or anti-HMGCR+ IMNM patients to mice induce a muscle deficiency accompanied with IgG and complement deposition on muscle fibers and some level of muscle necrosis. Disease is less pronounced in complement-deficient mice and augmented in mice supplemented with human complement. Together, these results establish the pathogenic role of aAbs in IMNM mouse model.
The humanized murine model of IMNM was used to evaluate preclinically the efficacy of candidate therapies. Inhibition of complement activation showed a significant therapeutic effect in IMNM mouse model but the results of a recent therapeutical trial with a C5 inhibitor has concluded to lack of clinical efficacy (work funded by UCB pharma). Alternative approaches may include blockade of FcRn-mediated IgG recycling to lower the level of aAb. Experimental results in IMNM mice will be presented (work funded by argenx).

IS-9

NOVEL BIOMARKERS PREDICT WHETHER CANCER EMERGES IN ANTI-TIF1-Γ POSITIVE DM PATIENTS AT HIGH RISK FOR CANCER

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The temporal clustering of dermatomyositis (DM) diagnosis and cancer is strikingly associated with specific autoantibodies, most notably those recognizing transcriptional intermediary factor 1-gamma (TIF1-γ). Intriguingly, however, many patients with these antibodies never manifest a cancer. Since studies of anti-cancer immunity and response to checkpoint blockade suggest that diversity of the immune response correlates with successful cancer control, we investigated whether additional autoantibodies are found in anti-TIF1-γ-positive patients in whom cancer does not emerge. We used a proteomic approach to define 10 novel autoantibody specificities. Of these, the most frequently occurring was cell division cycle and apoptosis regulator protein 1 (CCAR1), which was significantly associated with a decrease in cancer emergence within 3 years of DM diagnosis. We found that cancers that emerged occurred later after DM onset, and were more likely to be localized. Additional novel autoantibodies defined in this study were similarly associated with decreased frequency of cancer diagnosis, especially when present in combination. Our results show that in those DM patients where the anti-TIF1-γ immune response has diversified, cancer is much less likely to emerge. These findings have important significance for cancer risk stratification in DM patients and for understanding natural immune regulation of cancer in humans.

Juvenile myositis/Juvenile to adult transition

IS-10

WHEN JM PATIENTS LOSE THEIR 'J': TRANSITION CHALLENGES IN MYOSITIS CARE

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Juvenile myositis (JM) has a prevalence of ~4 per 100,000 children. In some countries, JM patients may be cared for by adult providers; elsewhere, JM patients "graduate" from paediatric care and transfer care to the adult health system. Disruptions in care at the time of transfer can lead to increased morbidity and mortality. To improve transfer outcomes, it is crucial that preparation for transfer begin early, with healthcare teams helping young patients develop self-management skills, such as taking and refilling medications independently. In addition, families are better able to navigate the transfer of care when they are made aware of cultural differences that exist between the paediatric and adult care systems. In 2016, EULAR and PReS jointly published "recommendations for the transitional care of young people with juvenile-onset rheumatic diseases" (Foster *et al*), delineating 12 best practices, including direct communication between the paediatric and adult teams prior to and following transfer, along with a written medical transfer summary. Furthermore, it is important for adult providers to appreciate key differences in the presentation, prognosis, and management between JDM and adult-onset DM, including: poorer correlation between creatinine kinase (CK) and disease activity, the role of the childhood myositis assessment scale (CMAS) in the evaluation of JDM patients of any age, and increased risk for calcinosis and gastrointestinal involvement.

IS-11

PHYSICAL FITNESS IN LONG-TERM JDM

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Juvenile dermatomyositis (JDM) is a vasculopathy primarily affecting muscle tissue and skin. However, due to its systemic nature, it may also involve internal organs such as the heart and lungs. In early disease, inflammation is to a large extent responsible for the clinical picture; in long-term follow-up much of the active inflammation is replaced by disease damage and symptoms are often mild. In 2010, our study group investigated Norwegian JDM-patients after a disease duration of more than 15 years and found that many had recovered without much sequela. Still, a general complaint was that they felt as though they didn't reach their desired physical goals. Surprisingly, we found, in addition to reduced muscle strength, subclinically reduced lung function as well as cardiac function at rest compared to healthy controls. Thus, we wanted to further explore the role of muscle, cardiac and pulmonary function on physical fitness in these patients.
The American College of Sports Medicine has defined physical fitness as a combination of cardiorespiratory fitness, flexibility, muscle strength, muscle endurance, and body composition. Balance, reaction time, and coordination are also involved. We assessed submaximal (6-Minute Walk Test and Timed Up and Go, TUG) and maximal (Cardiorespiratory Exercise Testing, CPET) exercise testing, muscle strength (torque) and muscular endurance (work) as well as balance/basic mobility (TUG) in JDM-patients after approximately mean 20 years of disease duration and compared with healthy controls. We also measured accelerometer data for one week in patients and controls, performed magnetic resonance imaging (MRI) of thigh muscles in all patients, and a muscle biopsy of a subset of patients.
Our patients had lower cardiorespiratory fitness, muscle strength and muscle endurance compared to healthy controls; more pronounced in patients classified with active compared to inactive disease. In patients with inactive disease, reduced cardiorespiratory fitness was only visible at high intensities, and based on values obtained during cardiorespiratory exercise testing the reduction was likely due to deconditioning. In patients with active disease, on the other hand, cardiorespiratory fitness was reduced at both high and low intensity, and low lung volumes due to muscle weakness disabling proper expansion of the thorax seemed to play a role. Objective muscle weakness and muscle endurance were both lower in patients with active compared to inactive disease, however, when correcting for muscle cross sectional area measured on magnetic resonance imaging, only muscle endurance remained significantly lower. Biopsies of a subset of patients showed the possibility that structure and distribution of muscle fibers may play a role in muscle endurance differences between patients with active and inactive disease after long-term JDM.

IS-12

FATIGUE AND WELL-BEING OF CHILDREN WITH CHRONIC INFLAMMATORY DISEASE

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More than one in five children with a chronic disease, such as cystic fibrosis, an autoimmune disease, or children after the treatment of childhood cancer, reports severe fatigue. This is four times more than in children in the Dutch population. Fatigue seems to be a transdiagnostic symptom; it presents in a similar way across different diseases. Recent studies by our research group found that fatigue was more strongly related to a number of potentially modifiable factors such as physical fitness, depressive symptoms, social support and certain parental factors (such as parental burden), than to the diagnosis with which a child was diagnosed. Thus, fatigue is a prevalent and multidimensional problem across paediatric chronic diseases, with strong and overlapping correlations on the biological, psychological, and social domains explaining fatigue. This advocates an approach to fatigue in paediatric chronic disease using the biopsychosocial model. Through in-depth interviews, we explored children's and parents' perspectives on their disease with respect to the child's participation in daily life and the role of fatigue on this. From the child's perspective, participation was considered to be more than merely engaging in activities; rather, they viewed a sense of belonging, the ability to influence social interactions, and the ability to keep pace with peers as key elements of full participation. Parents focused primarily on ensuring their child's well-being rather than focusing on participation. Friction between parents and children was based on the degree of agreement about who takes the lead regarding the child's participation. Dialogue between parent and child about who makes the decisions regarding the child's participation is important.
To help the child take directorship over his/her fatigue and daily life participation, we investigated PROfeel; a combination of personalized assessment and feedback via an app. During six weeks, we assessed daily fatigue and associated symptoms via ecological momentary assessments in fatigued children aged 12-18 years old with a chronic disease. This led to a personalized report and tailored advice. PROfeel was feasible and useful, and children were enthusiastic about the tool.
In this session, Dr. Nijhof will talk about the cohort study on fatigue, daily life participation and quality of life she is conducting in children with chronic disease, focusing on children with chronic inflammatory disease.

COVID-19 and myositis

IS-13

EULAR COVID AND COVAX REGISTRIES' UPDATE: FOCUS ON MYOSITIS

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The EULAR COVID-19 registry, launched in March 2020, is an observational registry that captures physician-entered data on both adult and paediatric patients with a pre-existing rheumatic and musculoskeletal disease (RMD) and SARS-CoV-2 infection. Data are entered voluntarily directly into the European data entry portal. In addition, as some countries were already collecting COVID-19 data, either within existing registries or in new COVID-19 registries (France, Germany, Greece, Italy, Portugal, Sweden and Switzerland), they were invited to share their data with the EULAR COVID-19 registry. EULAR data are then merged with data from the Global Rheumatology Alliance (GRA) for analysis. The aim of the EULAR-GRA COVID-19 registry is to collect, analyze, generate and disseminate information about COVID-19 and rheumatology to patients, physicians and other relevant groups to improve the care of patients with rheumatic disease.
Later during the pandemic, patients with immune-mediated inflammatory diseases (including inflammatory RMDs) were excluded from SARS-CoV-2 vaccine clinical development programmes; therefore, questions regarding the safety, effectiveness and potential measures that may increase the safety and effectiveness of vaccination against SARS-CoV-2 were unanswered. Lack of data led to some contradictory advice from rheumatology organisations and healthcare professionals regarding some of these vaccination aspects. In order to contribute to more informed decisions by patients and healthcare professionals and more robust and homogeneous evidence-based recommendations from relevant organisations, EULAR decided to create a second registry to collect data and learn about vaccination outcomes in people with RMDs.
At the 4th Global Conference on Myositis (GCOM), myositis-specific data from these two registries will be presented.

Imaging in myositis

IS-14

MRI IN MYOSITIS

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Imaging methodology for IIM
The existence, extent and severity of chronic degenerative changes are evaluated with T1-weighted sequences. The inflammatory changes are detected as hyperintensities in images generated with fat suppressed T2-weighted sequences. Whole-body can help in several instances by revealing fatty replacement patterns relatively specific in inclusion body myositis (sIBM) and necrotizing autoimmune myositis (NAM). No other technique can determine as precisely as MRI the muscles that, in part or in totality, are irreversibly destroyed by chronic inflammatory processes Even more than at the time of diagnosis, imaging has an important role to play in the monitoring of disease progression and in the evaluation of response to therapy of IIMs. For these applications, quantitative evaluation and generation of parametric maps are of paramount importance. The evaluation of muscle trophicity is another benefit of a quantitative imaging approach.

MRI diagnostic role and imaging patterns in IIM
Today, the diagnosis and classification of IIM largely relies on the detection of specific auto-antibodies. Together with the clinical examination, they most often suffice to reach a diagnosis without having to perform a biopsy. In this context, the role of MRI has to be carefully considered. Disease activity is well estimated by MRI because it visualizes muscle edema/inflammation with an excellent sensitivity. This may serve to guide the biopsy. Whole-body STIR T2w imaging not only identifies all the edematous/inflamed muscles but also malignancies, osteonecrosis and interstitial lung disease.
MRI reveals patterns of muscle oedema, atrophy and fatty replacement and fascial oedema in IIM. Frequent lower limb asymmetric and distal involvement including the legs characterizes sIBM. The MRI signs can be quite variable in dermatomyositis (DM), similar to the variety in clinical presentations. In NAM, one observes earlier and more severe lesions, fatty replacement and atrophy, than in other IIMs. Muscle destruction is more severe in the anti-SRP form than in the anti-HMGCR form. STIR T2w hyperintensities are also present in rhabdomyolysis, toxic myopathies, infectious myopathies, sarcoidosis, acute neurogenic disorders, limb-girdle muscular dystrophies, mainly dysferlinopathies and anoctaminopathies. The patterns of muscle fatty replacement may provide clues for the differential diagnosis. Steroid myopathy may complicate the imaging evaluation of IIM and be hard to distinguish from chronic inflammatory damages.

MRI imaging for the evaluation of treatment
For the longitudinal follow up of IIM, CK assays and muscle manual testing have shown their limits while biopsies are too invasive to be repeated frequently. Quantified functional and strength tests as well as EMG have a role. Imaging and in particular quantitative MRI offers the unique possibility to assess muscle response to treatment in situ and non-invasively.
Few studies have so far taken advantage of quantitative imaging to evaluate precisely the impact of treatment on inflamed muscles. Almost thirty years ago, a pioneer work demonstrated the normalization of muscle T2, but also T1 and energy metabolites measured by 31P spectroscopy in DM patients treated by steroids. While using non-optimized acquisition sequences, it was nevertheless possible in another study to demonstrate and measure the effect of steroids on water T2 in acute juvenile DM. Muscle water T2 provided an objective measure of the impact of rituximab on muscle oedema and inflammation in IIM patients. The effect of activin II receptor blockade with bimagrumab was evaluated on thigh muscle volume of sIBM patients. Again in sIBM patients, a one-year treatment with sirolimus was carefully evaluated versus placebo. While the primary outcome of quadriceps strength failed to show a significant improvement, the thigh fat fraction increase was significantly less than in the placebo group.
The IIM investigators are strongly encouraged to select quantitative imaging protocols in clinical research but also in their practice, as an objective biomarker in precision medicine.

IS-15

MUSCLE ULTRASOUND FOR MYOSITIS

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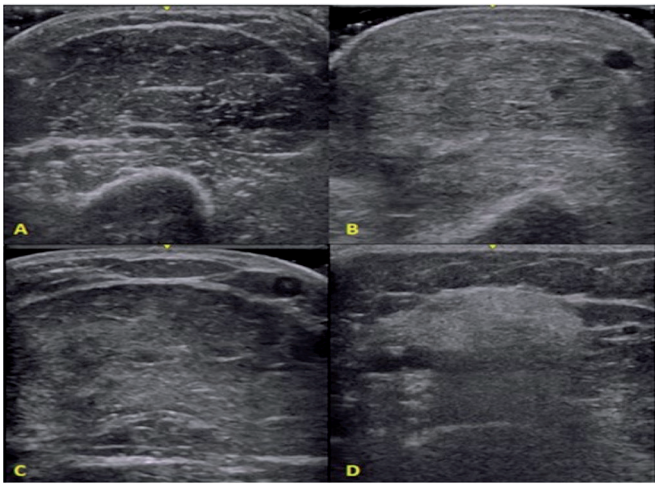
Ultrasound is a radiation free, inexpensive and easily accessible imaging tool that has high resolution for soft tissue. In the case of muscle, the ability to image in real time adds value for observing dynamic contractions and involuntary muscle activity.
Healthy muscle appears as a relatively anechoic (black) to hypoechoic (gray) structure, bounded by a hyperechoic (white) fascia and interspersed with hyperechoic perimysial septa. On cross section, the scattered perimysial septa give the muscle a "starry night" appearance. On longitudinal views of the muscle, the parallel orientation of muscle fibers come into view. When the muscle is healthy, no attenuation of ultrasound waves is seen, and deeper structures such as bone are well-visualized.
In pathologic muscle that slowly becomes replaced by fatty fibrous tissue, an increase in echointensity (EI) can be seen and is the most relevant parameter for myopathies. The degree of change in EI increases with advancing disease, and when severe, attenuation of ultrasound waves increases and there may be a reduction or loss of the underlying bone echo. In acute inflammation and muscle edema, the increase in EI is often mild, but there will be a disruption in architecture and loss of distinction between contractile muscle tissue and perimysial septa. The increase in EI of muscle can be gauged by a visual comparison with the overlying subcutaneous tissue which should be of similar EI. A semi-quantitative score is also available (Heckmatt score) which designates 1- normal, 2- increase in muscle echo while bone is still distinct, 3- marked increase in muscle echo and reduced bone echo, and 4- very strong muscle echo and complete loss of bone echo. Finally, a quantitative measurement of EI is also possible with the use of regions of interest within muscle and obtaining the level of grey within these regions (0-255). The use of quantitative measures allows comparisons over time, but requires that system presets are used, and normative values for the muscles in question have been established specific to the system.
In myositis, an increase in EI is also seen as an indicator of muscle involvement. In acute myositis (<1yr) with edema, these changes may be subtle as there can be an overall increase in EI but no attenuation or reduction in bone echo leading to what has been dubbed as "see-through" EI increase. Muscle size is usually normal and accompanied by a relatively low echogenicity. The abnormalities may also start as focal areas of increased EI that expand with disease advancement. Doppler has also been noted in acute myositis with higher vascularity scores in studies utilizing contrast-enhanced ultrasonography. In chronic myositis, higher EI and smaller muscles are noted and correspond to the presence of fat infiltration on biopsy.
The two main areas with the most data are in dermatomyositis and inclusion body myositis. In juvenile dermatomyositis, increases in EI have paralleled disease activity, with normalization after successful treatment. Muscle EI and not muscle size, could discriminate between high and low disease activity. Increased EI has also been seen in DM with normal muscle enzymes, suggesting it can be used to identify occult muscle disease. Fascial thickening with increased doppler signal indicating fasciitis has also been seen in DM.



IS-15. Fig.: Representative images of biceps muscles A) normal, B) dermatomyositis with an increased EI in both skin and subcutaneous tissue, C) IMNM with homogenously increased EI and loss of perimysial septations, D) IBM with severely atrophic and hyperechoic muscle with loss of underlying bone echo.

In IBM, muscle US has been very useful to detect muscle involvement given its ability to detect fatty fibrous change. Affected muscle presents with a marked increase in EI followed by a decrease in size with longer duration. The selective involvement of IBM for certain muscle groups like the quadriceps, flexor digitorum profundus and gastrocnemius is easily identified on ultrasound and can aid in diagnosis. In particular, the contrasting EI of an affected and unaffected muscle in a single image can be particularly helpful visually (flexor digitorum profundus versus flexor carpi ulnaris, gastrocnemius versus soleus).
Other than B-mode ultrasound imaging, newer techniques such as elastography are also promising for evaluating muscle stiffness as another parameter for quality. Using newer generation sheer wave elastography, lower muscle stiffness has been associated with more severe weakness in IBM as well as in active myositis compared with healthy controls. The use of machine learning algorithms to overcome the subjectivity in interpretation ascribed to ultrasound has also been tested with promising use for deep learning and deep convolutional neural networks.
Although gaining popularity for use in the inflammatory myopathies, the correct acquisition of images and interpretation of pathology requires experience, and standardization is still in its infancy. Its current role is clear in chronic myositis like IBM where changes are easily detected. This could provide an alternative and easily deployed imaging modality to assess muscle structure and quality in these diseases. However, in acute myositis and edema where changes are more subtle, further work is needed which includes comparison studies with MRI and clarification as to the role of doppler and elastography.

Skin in myositis

IS-16

THE NEUROIMMUNE BASIS OF CHRONIC ITCH

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The type 2 immune response has evolved to arm the mammalian host with the capacity to expel parasites and noxious environmental substances from barrier surfaces. One critical aspect of this defense mechanism is stimulating protective behavioral responses such as scratching. Increasingly, it is appreciated that a number of cytokines associated with type 2 immunity such as IL-4, IL-13, and IL-31 play critical roles in triggering itch via direct interactions with sensory neurons. However, the cellular mechanisms that activate such itch-sensory circuits remain unclear. Further, the key molecular events that initiate and regulate such highly conserved type 2 immune-neuronal interactions is a major field of inquiry in barrier immunology. Herein, we highlight how different type 2 immune cells critically promote various forms of itch. Collectively, these findings support an emerging paradigm in which itch is an evolutionarily conserved behavioral extension of the highly diverse type 2 immune response. The heterogeneity of these various neuroimmune axes are now helping us to understand the multitude of chronic pruritic disorders and paving the way for new therapies.

IS-17

OUTCOMES, BIOMARKERS, AND NOVEL TREATMENTS FOR THE SKIN IN DERMATOMYOSITIS.

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Defining the classification criteria for the skin in dermatomyositis with the EULAR/ACR criteria has greatly improved the ability to correctly many patients with clinically amyopathic dermatomyositis (CADM). There is an ongoing international collaborative effort to potentially further refine the skin variables, given that 25% of patients are not correctly classified with just 3 skin variables. Another issue relates to delayed diagnoses of CADM, sometimes for decades. Currently fewer than half of patients referred to our autoimmune disease clinic are correctly diagnosed as having dermatomyositis, with others frequently incorrectly labelled as having SLE or undifferentiated connective tissue disease. A correct diagnosis is key for appropriate inclusion in studies and for evaluating outcomes. Many studies have been performed to validate clinical outcome measures for the skin. More recent studies of the Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI) have determined that a 40% improvement in CDASI activity captures meaningful improvement from a patients perspective for those with moderate to severe skin disease (CDASI-activity ≥14). Data from the phase 2 lenabasum study show a good correlation between the change in CDASI and Skindex-Symptoms, Skindex-Emotion, Skindex-Functioning, Skindex-Itch, patient global assessment (PtGA) global disease activity, global skin activity, pain, and itch (p<0.001). Overall most PROMIS measures do not correlate with CDASI response, showing the importance of QoL measures that are developed to measure specifically skin. Studies utilizing tissue mass cytometry (CyTOF) of DM skin showed substantial monocyte-macrophage diversity, with the $CD14^+$ population correlating positively with cutaneous dermatomyositis disease area and severity index (CDASI) scores (p=0.031). The T cell compartment shows $CD4^+$ T, $CD8^+$ T, and $FOXP3^+$ T cells. Activated (CD69+) circulating memory T cells correlated positively with CDASI scores (p=0.0268). IFNβ protein was highly upregulated in the T cell, macrophage, dendritic cell, and endothelial cell populations of DM skin. Myeloid DCs (mDCs) expressed pPPARγ, pIRF3, IL4, and IL31 and their quantity correlated with itch as measured in the Skindex-29. Plasmacytoid DCs (pDCs) colocalized with IFNγ in addition to the known colocalization with IFNβ, although overall pDCs are much less prevalent in skin than are myeloid DCs. Further analysis of all patients in the phase 2 lenabasum biomarker data (n=22) identifies a trend to increased baseline IFNβ mRNA and protein associated with a response in CDASI, decreases in IL-31 protein area correlated with an improvement in CDASI (p=0.047) and trends for decreases in IFN-γ and IFN-β protein area correlating with an improvement in CDASI. The lenabasum phase 3 data suggests that the Total Improvement Score (TIS) is relatively insensitive to meaningful improvements in patients with predominantly skin activity, and studies wanting to evaluate skin will likely need a skin-directed measure or some modification of the current TIS that can capture meaningful but less than nearly complete improvement in skin activity. It is important to include CADM patients in studies since, although the EULAR/ACR criteria capture many of these patients, if they are not included in trials it may lead to exclusion of access of these patients to newly approved therapies, as is now happening for some CADM patients needing IVIG therapy. There are a number of novel therapies currently being developed, with targets that make sense given what is known about pivotal pathways in the skin in dermatomyositis. An anti-interferon-β antibody trial has completed recruitment and is ongoing. Other drugs that affect interferons, such as JAK inhibitors, are of interest and a ten-patient open label trial with tofacitinib suggested improvement in the skin. There are numerous other approaches being trialed, and careful clinical and biomarker changes, hopefully including those in the skin, will be very informative about drivers of inflammation in dermatomyositis skin.

Drug-induced myositis

IS-18

MYOSITIS TRIGGERED BY IMMUNE CHECKPOINT INHIBITORS

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Immune checkpoint inhibitors (ICI) improve overall survival in patients with metastatic disease. It is the most advanced oncology therapy in the last 20 years. Activation of T-cells depends on both the recognition of an antigen and co-signaling molecules (either co-stimulatory and co-inhibitory signals). ICI are monoclonal antibodies targeting co-inhibitory signaling pathways: either the PD1/PD-L1 or the CTLA4/CD80-CD86 pathways. ICI aims to restore anti-tumor cytotoxic $CD8^+$ T-cell activity by blocking co-inhibitory signals. However, this inhibition may induce a rupture of peripheral tolerance and the development of auto-immunity.
ICI induce frequently (50-80%) auto-immune toxicities that may involve any tissue. These can be life-threatening complications, eventually fatal in 0.3-1.26%. Myotoxicity is among the most life-threatening side effects of ICI revolution. ICI-myositis fatality rate range from 20% up to 50% in case of concomitant association with ICI-myocarditis. ICI-myositis is the most frequent immune toxicity in field of neurology, and the second most frequent rheumatic-immune related adverse event. It is important to know how to evoke this diagnosis early for a quick management for a better prognosis.
An important point is that this adverse effect occurs early after the first infusion (median <1 month). The second point is that the spectrum of clinical manifestations is broad, but in its typical form, the disease has a characteristic clinical presentation.
Patients may be asymptomatic and the diagnosis will be discussed on a systematic screening of skeletal and/or cardiac enzymes. In the typical form, the involvement is quite characteristic with a proximal motor weakness, but also axial deficit associated with oculomotor disorders and ptosis (15-20%). There is no extra-muscular signs. Only a minority of patients present others concomitant immune related adverse events. Myositis specific autoantibodies are usually absent, but some patients (15-20%) may have anti-anti-acetylcholine receptor antibodies. EMG may shows a myopathic pattern, but very rarely abnormal repetitive

nerve stimulation tests. The muscle biopsy is the gold standard for the diagnosis. Myopathological features combine muscle fibers necrosis with inflammatory infiltrates composed by both macrophages and T cells.
Once the diagnosis is made, it is important to look for signs of severity: bulbar, respiratory and myocardiac signs. These disorders are sometimes difficult to identify, especially for cardiac or respiratory involvement, but their diagnosis is crucial because it has immediate therapeutic implications. Blood gas measurements is important, as is ECG analysis. The elevation of cardiac enzymes may be non-specific in the context of myositis and cardiac MRI is frequently normal in the early stage of the disease so that endomyocardial biopsy should be systematically discussed.
From a therapeutic point of view, it is necessary to provide symptomatic care, including mechanical ventilation, heart stimulator and/or hemodynamic support if necessary. ICI must be stopped. Glucocorticoids are the first line therapy and must be proposed for symptomatic cases. Patients with signs of severity are frequently refractory to glucocorticoids, and additional immunosuppressive/modulator drugs are necessary especially in case of myocarditis. The ICI re-challenge is a collegial discussion which balance risk and benefit.

IS-19

MYOSITIS TRIGGERED BY STATINS

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Statins are a known risk factor for developing an autoimmune myopathy associated with proximal muscle weakness, elevated serum levels of muscle enzymes, a necrotizing muscle biopsy, and autoantibodies recognizing HMG-CoA reductase (HMGCR). Dr. Mammen will provide an update on the clinical presentation, genetic risk factors, pathophysiology, and management of patients with anti-HMGCR myopathy. This will include discussing a recent study demonstrating that anti-HMGCR myopathy can masquerade as a limb girdle muscular dystrophy in younger patients who do not have a statin exposure history. Dr. Mammen will also discuss several reports suggesting that Native Americans are at a dramatically increased risk for developing anti-HMGCR myopathy when exposed to statins. A case series showing that IVIG is an effective therapy for this form of immune-mediated necrotizing myopathy will be reviewed. In addition, Dr. Mammen will present data from animal studies suggesting that anti-HMGCR autoantibodies can cause muscle weakness and myofiber necrosis when transferred into mice and that this process is mediated by complement. The results of a clinical trial which failed to demonstrate a benefit of complement inhibition in patients with anti-HMGCR myopathy will be reviewed. Finally, Dr. Mammen will comment on future directions in trying to better understand and treat this form of autoimmune muscle disease.

Toward personalised treatment

IS-20

PERSONALIZED AND PRECISION MEDICINE IN MULTIPLE SCLEROSIS: SUBGROUP DISCOVERY AND CARE IMPROVEMENTS IN JOHNS HOPKINS INHEALTH

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Background. A precision medicine approach to multiple sclerosis (MS) provides the opportunity to identify subgroups of patients based on disease trajectories or outcomes and to use these insights to inform clinical decisions.
Objective. To describe the goals, design, and progress of the Johns Hopkins MS Precision Medicine Center of Excellence (PMCOE).
Methods. The MS PMCOE, part of Johns Hopkins inHealth, was launched in April 2017 with the initial goal of using data acquired as standard of care to define prognostic trajectories and new treatment targets and strategies. Additionally, we seek to generate tools to enable clinical-decision making and improve the value of care. With a team that includes 10 MS neurologists as well as experts in MS neuroimaging, neuropsychology, and neurorehabilitation, the expanded center delivers on the promise of precision medicine through five foci of integrated care and research:
1) technology-enabled tracking of neurologic functional performance and systematic clinical data capture at every clinic visit; 2) annual imaging of optic nerve damage using optical coherence tomography (OCT); 3) collection of blood at clinic visits for research to identify biomarkers of prognosis and treatment response; 4) standardization of brain magnetic resonance imaging (MRI) across (and beyond) the Johns Hopkins Health System, and 5) digital collection of data regarding modifiable exposures that may be relevant to the prognosis of MS.
Results. Since its inception, over 2,000 people with MS have participated in the PMCOE. We will highlight insights that have been generated in the context of the MS PMCOE and describe ongoing work leveraging these data.
Conclusions. The Johns Hopkins inHealth program provides an opportunity to make major advancements towards the goal of defining subgroups and using related insights to improve clinical care for people with MS.

IS-21

PRECISION MEDICINE IN RHEUMATOID ARTHRITIS

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Whilst precision medicine has become a relatively routine aspect of management for certain cancers, in rheumatoid arthritis (RA) treatment remains largely 'trial and error'. In this presentation I will provide examples of progress in the therapeutic targeting of RA whilst also highlighting aspects of the disease that have slowed advancement – which I have termed the 'Precision Gap'. In particular, I will discuss the importance of an excellent understanding of disease pathobiology, consideration of confounding factors when assessing the disease state and the need for robust and accurate outcome measures that reflect the disease pathobiology. Consideration must be given to all of these factors when designing precision medicine trials, and recent progress suggests that the Precision Gap between oncology and rheumatology is becoming narrower.

Repairing damage

IS-22

REPAIRING DAMAGE: FOCUS ON MUSCLE AND PHYSICAL FUNCTION

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The focus of this presentation is to consider repairing the damage in muscle fibres, strength, stamina as well as physical function and development. The focus will be in Juvenile Dermatomyositis (JDM) but many of the principals will be relevant for people of all ages with inflammatory myositis (IMM).
IMM causes damage and loss of muscle fibres, and this is impacted by abnormal changes in the cytokine profile, reduced neural activation, abnormal movement patterns, muscle imbalance and wasting due to lack of use. The symptoms of pain and fatigue are common in IMM but fear of movement and abnormal gait also contribute to damage and need to be considered when working to repair the affects if the inflammation.
In young people many gross motor skills, such as walking, are not developed and the IMM will interfere with the normal developmental milestones and these need to be re-established to avoid reduced global development. In other people the psychological impact as well as the physical loss may affect the ability for full repair and recovery in function.
Exercise is the main modality that can be used to repair these damages. Exercise will stimulate satellite cells in order to repair and replace muscle fibres. Exercise can reduce muscle inflammation, stabilise the cytokine profile and promote neural activation.
Exercise should be utilized in its complexity including stabilising, static, concentric and eccentric contractions. The use of specific muscle strengthening should be used before progressing to complex exercises involving several limbs or the whole body. Exercises must be progressed frequently using increasing repetitions and resistance to maximise recovery. Correct movement patterns in functional activities and gait need to be regained. Specific muscle stamina and global fitness need to be developed to reduce fatigue and the loss of physical function and muscle atrophy. The biopsychosocial model of management should be considered in order to repair the damage of pain, fatigue, loss of confidence, social isolation and lack of physical function and sport.

Oral Presentations

Pathogenesis, including mitochondrial biology

O-1

DISCOVERY OF ANTIGEN SPECIFIC CD4+ T CELLS IN ANTI-HMGCR-POSITIVE IMMUNE MEDIATED NECROTIZING MYOPATHY

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**contributed equally*

Background. Anti-3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGCR)-positive immune mediated necrotizing myopathy (anti-HMGCR+ IMNM) is a unique myopathy characterized by IgG autoantibodies against HMGCR and a strong association with specific HLA class II alleles (HLA-DRB1*11:01 in adults and HLA-DRB1*07:01 in children). Although these implicate HMGCR-specific CD4+ T cells in disease pathogenesis, no such cells have been identified thus far. In this study, we aimed to identify HMGCR-specific T cells in patients with anti-HMGCR+ IMNM and further delineate HMGCR epitopes using a natural antigen processing assay (NAPA).
Methods. Peripheral blood mononuclear cells (PBMCs) from 10 patients with anti-HMGCR+ IMNM and 10 patients with dermatomyositis (DM), as well as 5 healthy controls with HLA-DRB1*11:01, were screened for activation status in response to stimulation with HMGCR protein, based on CD154 upregulation. Subsequently, monocyte-derived dendritic cells (MoDCs) from 6 patients with anti-HMGCR+ IMNM were incubated with the HMGCR protein and presented peptides were identified using NAPA. Briefly, HLA-DR/peptide complexes were isolated by immunoprecipitation, and bound HMGCR peptides were sequenced by mass spectrometry. HMGCR peptides corresponding to the putative CD4+ T cell epitopes were synthesized and used to stimulate PBMCs from the above patients.
Results. Patients with anti-HMGCR+ IMNM had a significantly higher CD4+ T cell response to HMGCR protein when compared to patients with DM (median 0.06 vs 0.00, p=0.0059) (Figure 1a). In particular, IMNM patients with HLA-DRB1*11:01 allele demonstrated significantly higher responses to HMGCR than patients without this allele (median 0.09 vs 0.015, p=0.0190) (Figure 1b). There was a positive correlation between anti-HMGCR antibody titers and the frequency of HMGCR-specific CD4+ T cells (r2=0.5141, p=0.0453) (Figure 1c). Given the significant response to the HMGCR protein, we sought to identify specific HMGCR epitopes. A total of 7 different naturally processed HMGCR peptides were identified using NAPA. The number of distinct peptides presented per patient ranged from 1 to 5, with 5 epitopes being presented by at least two patients. All naturally presented HMGCR peptides elicited robust CD4+ T cell responses, with 9/10 anti-HMGCR+ IMNM patients responding to at least one peptide, compared to only 1/10 patients with DM (p=0.0003), and 1/5 healthy controls (p=0.006). The 9 responding anti-HMGCR+ IMNM patients responded to 1-6 peptides (median 3), and the T cell responses were significantly higher than those observed in patients with DM (p<0.0001) (Figure 1d).
Conclusion. Our findings represent the first report of antigen-specific CD4+ T cells in anti-HMGCR+ IMNM. HMGCR-specific CD4+ T cells had a Th2 phenotype and correlated with the levels of anti-HMGCR antibodies. Furthermore, leveraging NAPA, we were able to define a core set of HMGCR peptides naturally presented by MoDCs from patients with anti-HMGCR+ IMNM, defining precise immunologically relevant autoantigenic CD4+ T cell epitopes. Definition of these epitopes is key in understanding disease pathogenesis and will aid in the future development of antigen-specific research and therapeutic tools.
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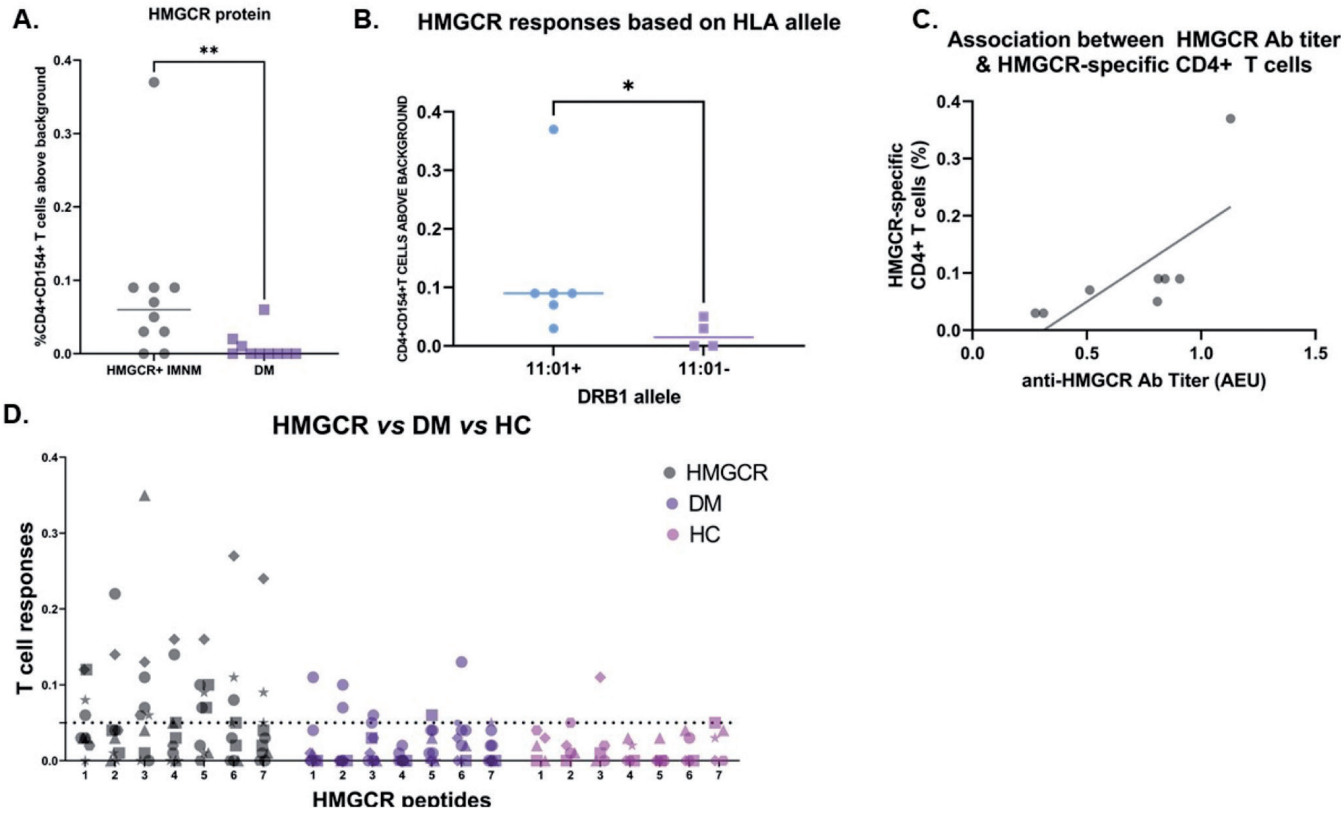

O-1. Fig. 1.

O-2

AN APPROACH COMBINING TRANSCRIPTOMIC AND TOPOGRAPHIC ANALYSIS REVEALS A POTENTIAL ROLE OF PROTEASOME AND AUTOPHAGY DEREGULATION IN THE PATHOPHYSIOLOGY OF DERMATOMYOSITIS

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Background. Dermatomyositis (DM) is a rare autoimmune muscle disease characterized by an atrophy and a type-I interferon signature in perifascicular fibers. We recently showed that muscle mitochondrial dysfunction is also a characteristic of this disease that participates to both decrease exercise capacity and maintenance of inflammation (1). Pathophysiological mechanisms underlying these characteristics are unknown. The objective of this study is to reveal the mechanisms underlying the modifications of perifascicular fibers during DM, taking advantage of a method combining transcriptomic and topographical information.
Methods. Fourteen patients with recent (<6 months) untreated myositis (DM: n=7, other myositis: n=7) who underwent a biopsy of the deltoid muscle for diagnostic purposes were included. Seven other patients with suspected but not confirmed neuromuscular pathology (normal creatine kinase level, electromyogram and deltoid biopsy) were also included (no myopathy: n=7). Under the control of optical microscopy, perifascicular fibers (about 400 fibers) and endofascicular fibers (about 400 fibers) were microdissected by laser. The transcriptome of endofascicular fibers and perifascicular fibers in all three groups of patients were then obtained by massive sequencing of total messenger RNA. The DAVID database (2) (http://david.abcc.ncifcrf.gov) were used to determine the deregulated molecular pathways in the perifascicular fibers during DM.
Results. 482 transcripts were differently expressed in perifascicular fibers of patients with DM compared to perifascicular fibers of the 2 other groups (348 overexpressed and 134 underexpressed). The most overexpressed transcripts were involved in the type I interferon response while the most underexpressed transcripts were involved in mitochondria and in proteasome functioning. The study of the transcripts differentially expressed in perifasicular versus endofascicular fibers revealed that there is a physiological perifascicular signature: in patients without myopathy, 83 genes were overexpressed and 54 were underexpressed in perifascicular fibers compared to endofascicular fibers. This physiological perifascicular signature was abolished in patient with myositis (DM and other myositis). In the group of patients with DM (but not other myositis), a specific perifascicular signature (18 genes overexpressed and 10 genes underexpressed in perifascicular fibers compared to endofascicular fibers) was identified. The most deregulated transcripts in DM perifascicular fibers were involved in autophagy/mitophagy, mitochondria and proteasome pathways.
Conclusion. In the physiological state, perifascicular fibers are characterized by a different transcriptomic profile from endofascicular fibers. During DM, this physiological perifascicular signature is abolished and replaced by a transcriptomic signature that reveal a potential role of proteasome and autophagy deregulation in the pathophysiology of DM.

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O-3

EFFECT OF TYPE I INTERFERON ON ENGINEERED HUMAN SKELETAL MUSCLE: A PROMISING MODEL FOR JUVENILE DERMATOMYOSITIS

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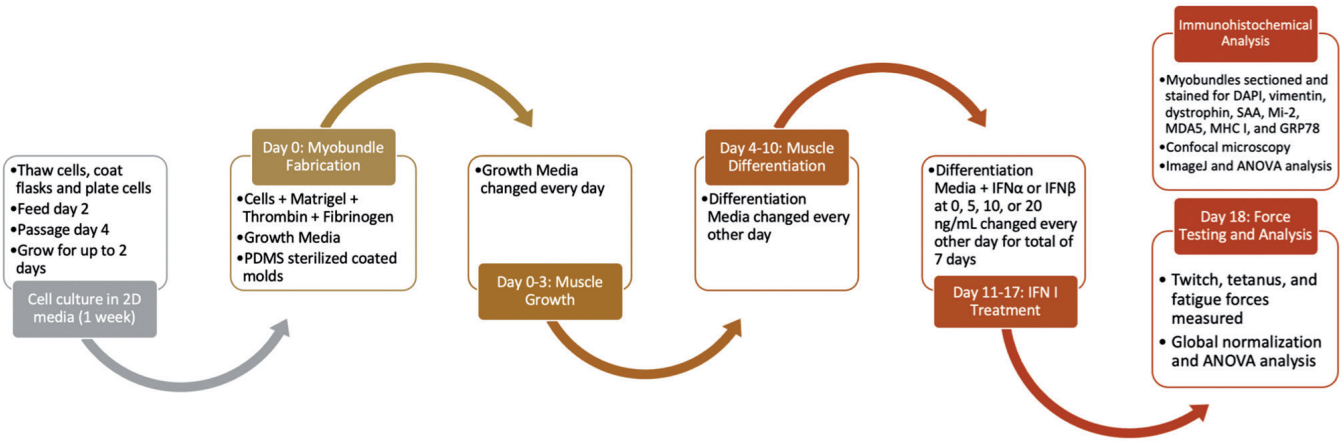
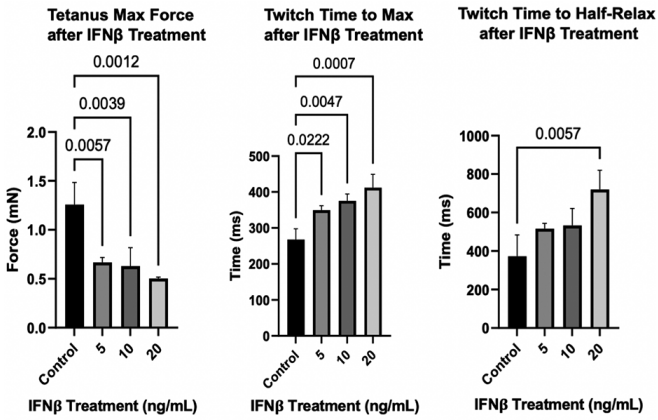
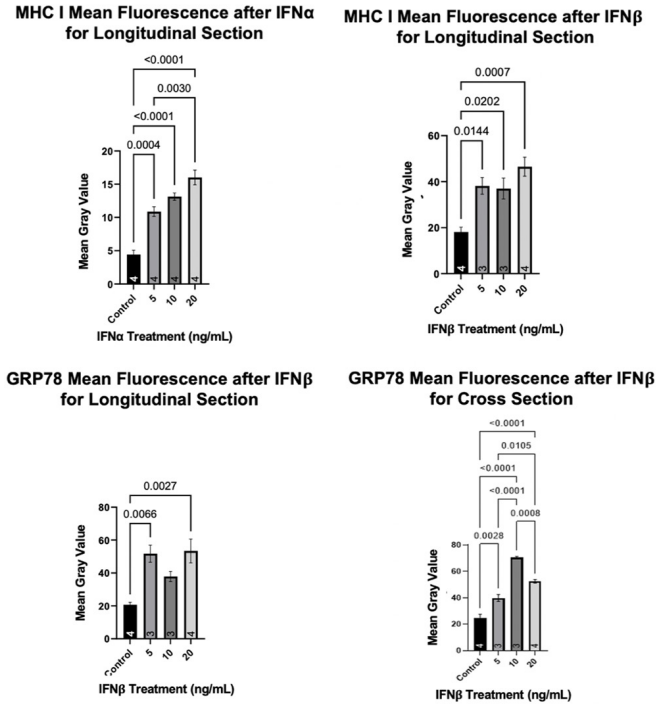
Background. Upregulation of Type I interferons (IFN I), such as IFNα and IFNβ, is a hallmark of Juvenile Dermatomyositis (JDM), but its role in pathogenesis is not clearly understood (1). Lack of adequate clinical trials, difficulty in obtaining routine JDM muscle biopsies, and absence of a disease model hinders understanding pathologic triggers and delays development of needed therapies. Aim: To define the effect of IFN I on healthy pediatric skeletal muscle using an in vitro three-dimensional engineered biomimetic construct ("myobundles"). Hypothesis: IFN I is associated with decreased contractile force and immunohistochemical features of JDM, including upregulation of major histocompatibility complex class I (MHC I), myositis-specific autoantigens Mi-2 and MDA5, and endoplasmic reticulum (ER) stress marker GRP78.
Methods. Myogenic cells isolated from 3 healthy pediatric donors were cultured and used to create donor-specific myobundles based on established protocols (2) and then exposed to 0 (control condition), 5, 10 or 20 ng/mL IFNα or IFNβ (Fig. A). After myobundle maturation, differentiation, and IFN I exposure for 7 days, contractile force and force kinetics were measured after twitch (1 Hz for 10 ms), tetanus (20 Hz for 1 s), and fatigue (20 Hz for 30 s) electrical stimulation. Force data for myobundles from 2 donors after IFNα exposure and 3 donors after IFNβ exposure was globally normalized and analyzed using one-way ANOVA with multiple post hoc comparisons. Immunohistochemical staining of myobundles from 1 donor was performed after IFN I treatment. Nuclei density, myofiber diameter, sarcomeric α-actinin (SAA) positive area per cross-sectional area, and mean fluorescence of vimentin, dystrophin, Mi-2, MDA5, MHC I, and GRP78 were determined with ImageJ analysis and compared across treatment groups using one-way ANOVA with multiple post hoc comparisons.
Results. Effect of IFN I on Contractile Force: IFNβ, but not IFNα, was associated with decreased tetanus contractile force and slower twitch force kinetics (Fig. B). Unexpectedly, percentage fatigue significantly decreased after any IFNα exposure (p=0.0031-0.0048). Those treated with IFNβ had decreased percentage fatigue, but not in a dose-dependent or statistically significant manner except after 5 ng/mL treatment (p=0.015). Immunohistochemical Analysis after



O-3. Fig. A. Experimental protocol for myobundle creation, maturation, treatment, force testing and immunohistochemical analysis.



O-3. Fig. B. Effect of IFNβ on tetanus contractile force and twitch kinetics of myobundles derived from three pediatric donors.



O-3. Fig. C. Immunohistochemical features of myobundles derived from one donor. Increase in MHC I mean fluorescence after IFNα (top left) and IFNβ (top right). Increase in GRP78 mean fluorescence after IFNβ treatment for longitudinal (bottom left) and crosss section (bottom right).

IFN I Exposure: IFNα and IFNβ were associated with significant increase in MHC I mean fluorescence (Fig. C, top panel). Myobundles treated with IFNβ also had increase in mean fluorescence of MDA5 in longitudinal sections at 5 ng/mL (p=0.0496) and GRP78 in both longitudinal and cross-sectional images (Fig. C, bottom panel). Nuclei density, myofiber diameter, SAA+ area, and mean fluorescence of dystrophin, vimentin, and Mi-2 were not affected by IFN I.

Conclusions. Data from this study supports that IFNβ, but not IFNα, is associated with decreased contractile tetanus force in this in vitro 3D engineered model using pediatric skeletal muscle. IFN I exposure correlates with myobundle upregulation of MHC I and evidence of ER stress. Myobundle expression of myositis-specific autoantigens Mi-2 and MDA5 has been variable after IFN I exposure. This 3D engineered tissue model is a promising platform to further elucidate JDM pathogenesis and develop novel therapeutics.

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Genes and environment

O-4

FAMILIAL ASSOCIATIONS OF AUTOIMMUNE DISEASES IN PATIENTS WITH IDIOPATHIC INFLAMMATORY MYOPATHIES - A SWEDISH POPULATION-BASED STUDY

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Background. Idiopathic inflammatory myopathies (IIM) are systemic rheumatic diseases (SRDs) affecting primarily proximal muscles and associated with manifestations in other organs. The pathogenesis of IIM is not completely clear, but involvement of both genetic and environmental factors has been suggested. Familial aggregation of one or two diseases is an indication of a genetic contribution to disease development and holds important information for guiding genetic studies. There is evidence showing that SRDs are likely to aggregate in families of patients with IIM and a study cross-analyzing genome-wide association study (GWAS) data of seropositive SRDs including IIM successfully discovered novel genetic loci associated with IIM. Familial clustering of other autoimmune diseases in patients with IIM has also been observed but findings are inconsistent, and some associations have not been tested in large population-based studies. In this study, we aimed to investigate the familial associations of IIM and a variety of autoimmune diseases including rheumatoid arthritis (RA), other SRDs comprising systemic lupus erythematosus (SLE), systemic sclerosis (SSc), Sjögren's syndrome and other systemic connective tissue diseases, multiple sclerosis (MS), inflammatory bowel diseases (IBD), type 1 diabetes mellitus (T1DM), autoimmune thyroid diseases (AITD), celiac disease (CeD) and myasthenia gravis (MG) in a Swedish population-based family study.

O-4. Table I. Adjusted odds ratios (aORs) of familial associations of autoimmune diseases in patients with IIM compared to individuals without IIM.

	Patients with IIM, n (%)	Individuals without IIM, n (%)	aOR[a] (95% CI)
Rheumatoid arthritis (RA)			
≥1 relative	104 (6.42)	432 (5.54)	1.14 (0.91-1.43)
≥2 relatives	6 (0.37)	27 (0.35)	1.10 (0.45-2.70)
Any first-degree relatives	110 (1.44)	462 (1.24)	1.14 (0.97-1.33)
Other systemic rheumatic diseases (SRDs)			
≥1 relative	98 (6.05)	341 (4.37)	1.40 (1.11-1.78)
≥2 relatives	6 (0.37)	12 (0.15)	2.40 (0.88-6.53)
Any first-degree relatives	104 (1.37)	354 (0.95)	1.34 (1.14-1.56)
Multiple sclerosis (MS)			
≥1 relative	23 (1.42)	105 (1.35)	1.12 (0.70-1.78)
Any first-degree relatives	24 (0.32)	106 (0.28)	1.19 (0.86-1.65)
Inflammatory bowel diseases (IBD)			
≥1 relative	98 (6.05)	404 (5.18)	1.23 (0.97-1.55)
≥2 relatives	6 (0.37)	29 (0.37)	1.10 (0.44-2.71)
Any first-degree relatives	104 (1.37)	435 (1.17)	1.20 (1.02-1.41)
Types 1 diabetes mellitus (T1DM)			
≥1 relative	23 (1.42)	109 (1.40)	1.01 (0.64-1.60)
Any first-degree relatives	24 (0.32)	113 (0.30)	1.10 (0.77-1.55)
Autoimmune thyroid diseases (AITD)			
≥1 relative	424 (26.17)	1877 (24.07)	1.12 (0.99-1.27)
≥2 relatives	72 (4.44)	327 (4.19)	1.08 (0.83-1.41)
Any first-degree relatives	509 (6.68)	2281 (6.11)	1.10 (1.02-1.19)
Celiac disease (CeD)			
≥1 relative	39 (2.41)	148 (1.90)	1.32 (0.92-1.90)
≥2 relatives	7 (0.43)	8 (0.10)	3.57 (1.28-9.92)
Any first-degree relatives	47 (0.62)	156 (0.42)	1.37 (1.08-1.74)
Myasthenia gravis (MG)			
≥1 relative	6 (0.37)	18 (0.23)	1.48 (0.57-3.80)
Any first-degree relatives	6 (0.08)	18 (0.05)	1.45 (0.77-2.74)

[a] In the analyses by number of affected first-degree relatives, controlled for sex and birth year of the patients with IIM and individuals without IIM, and additionally controlled for sex and birth year of the first-degree relatives when analyzing each relative pair as an independent unit.

Methods. We used a robust algorithm to identify patients with IIM in the National Patient Register, matched each patient with IIM with up to five individuals without IIM and identified the first-degree relatives of all study individuals via linkage to the Total Population Register and the Multi-Generation Register. We included 7,615 first-degree relatives in 1,620 patients with IIM and 37,309 relatives in 7,797 matched individuals without IIM. We defined each autoimmune disease in first-degree relatives by requiring at least one diagnostic code indicating that specific autoimmune disease. We modelled the familial association

between IIM and an autoimmune disease by the number of affected first-degree relatives and by treating each first-degree relative pair as an independent unit with logistic regression conditioning on matching clusters. We additionally adjusted for sex and birth year of the first-degree relatives and used a cluster robust sandwich estimator for standard errors in the second modelling method.

Results. As shown in Table I, patients with IIM had significantly higher odds of having ≥1 first-degree relative affected by other SRDs (adjusted odds ratio, aOR=1.40 95% CI 1.11-1.78) and a greater odds of having ≥2 first-degree relatives affected by CeD (aOR=3.57 95%CI 1.28-9.92) compared to the matched individual without IIM. In the analyses of any first-degree relative pairs, we observed familial associations for other SRDs (aOR=1.34 95% CI 1.14-1.56), IBD (aOR=1.20 95% CI 1.02-1.41), AITD (aOR=1.10 95% CI 1.02-1.19) and CeD (aOR=1.37 95% CI 1.08-1.74) while associations for RA (aOR=1.14 95% CI 0.97-1.33), MS (aOR=1.19 95% CI 0.86-1.65), TIDM (aOR=1.10 95% CI 0.77-1.55) and MG (aOR=1.45 95% CI 0.77-2.74) were not statistically significant.

Conclusion. The presented study showed familial associations of various autoimmune diseases in patients with IIM, suggesting potential shared genetic susceptibility between these autoimmune diseases and IIM. Given the similar strength of the familial associations between other SRDs and CeD, further investigation of cross-analyzing GWAS data of IIM and CeD may lead to identification of new genetic variants associated with IIM.

O-5

LOW GENE COPY NUMBERS OF COMPLEMENT C4 AND COMPLEMENT C4A DEFICIENCY ARE STRONG AND HIGHLY SIGNIFICANT GENETIC RISK FACTORS FOR IDIOPATHIC INFLAMMATORY MYOPATHY AND ITS MAJOR SUBGROUPS

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Background. Idiopathic inflammatory myopathies (IIM) are a group of autoimmune diseases with chronic muscle weakness and fatigue. It is characterized by inflammation, infiltrations of leukocytes into muscles and/or the skin, vasculopathy and necrosis with destruction of blood vessels and muscle fibers. Juvenile dermatomyositis (JDM), adult-onset dermatomyositis (DM), polymyositis (PM) and inclusion body myositis (IBM) are major categories of IIM. The etiology for IIM is largely unknown. Complement-mediated destructions of capillary endothelium has been documented in dermatomyositis.

Methods. Through collaborations with the Myositis Genetics Consortium and the UK Myositis Network, we studied complement C4A and C4B genotypic and phenotypic diversities in 1,650 Caucasian patients with IIM from the Great Britain, Sweden, Czech Republic, Belgium, and the US, plus 3,526 race- and geographically-matched healthy controls. Plasma protein levels for complement C4 and C3, HLA-DRB1 allelic polymorphisms, IIM disease subgroups, and the presence of myositis-specific and myositis associated autoantibodies were analyzed with reference to gene copy number variations (CNVs) of complement C4A, C4B, long genes (C4L) and short genes (C4S) to examine their roles in the genetic risks of myositis and its clinical phenotypes. CNVs for total C4 (C4T), C4A, C4B, C4L and C4S were determined by Southern blot analyses of TaqI, PshAI/PvuII and PmeI digested genomic DNA, and/or by TaqMan-based quantitative real-time PCR with five independent amplicons and verified as copy numbers of C4T= C4A+C4B= C4L+C4S. Protein concentrations of C4 were determined by single radial immunodiffusion.

Results. Low gene copy numbers of total C4 (C4T=2+3) and C4A deficiency (C4A=0+1) were present in close to half of the IIM patients. They were very strongly correlated with increased risk of IIM with odds ratios (OR), and 95% confidence intervals equal to 2.58 (2.28-2.91), p=5.0x10-53 for total C4; and 2.82 (2.48-3.21), p=7.0x10-57 for C4A deficiency. Similar findings were observed in all four major subgroups of IIM (JDM, DM, PM and IBM). Intriguingly, patients with IBM had the lowest mean copy numbers of total C4 (IBM: 3.40±0.79; CTL: 3.83±0.76; p=3.14x10-13), as well as prevalent deficiencies for both C4A (IBM: 40.7%, CTL: 21.0%; p=8.9x10-9) and C4B (IBM: 38.6%, CTL:30.4%, p=0.024). Contingency analyses revealed that among IIM patients with C4A deficiency, the presence of HLA-DR3 (or DRB1*03:01) became insignificant as a risk factor in IIM except for IBM. Among patients with IBM and C4A deficiency, 98.2% have HLA-DR3 with an OR of 11.02 (1.44-84.4), p=0.0012 (Table I). Intra-group analyses of IIM patients for C4 protein levels and IIM-related autoantibodies revealed that those with anti-Jo-1 or with anti-Pm/Scl had significantly lower C4 plasma concentrations than those without these autoantibodies (anti-Jo ±: 283.7±89.0 mg/L vs 324.7±408.9 mg/L, p=9.6x10-5; anti-Pm/Scl ±: 268.4±72.2 mg/L vs 321.5±108.1 mg/L, p=0.0005). Such phenomenon could be results of immune-complex mediated consumption of complement C4 protein, or lower C4 gene copy number leading to lower C4 protein biosynthesis, or both.

Conclusion. Low gene copy number of total C4 and complement C4A deficiency are important risk factors of IIM and its four subgroups. IBM patients had the lowest mean copy number of C4 genes. Patients with IBM and C4A deficiency almost uniformly had HLA-DRB1*03:01, with high effect size as a risk factor.

Acknowledgements. We are indebted to volunteers and patients with myositis who contributed precious samples for this study. This study is supported by NIH grants 1R21 AR070509 ,1R01 AR073311, and the CureJM Foundation.

O-5. Table I. Frequencies and contingency analyses of *HLA-DR3* and complement *C4A* deficiency in IIM and subgroups.

Group (N)		odds ratio	p
	C4A=0+1, %		
CTL (3499)	21.01		
IIM (1634)	42.87	2.82 (2.48-3.21)	3.54E-57
JDM (166)	40.40	2.54 (1.82-3.56)	1.43E-07
DM (564)	40.57	2.57 (2.13-3.10)	8.70E-22
PM (667)	45.63	3.15 (2.65-3.75)	2.15E-37
IBM (180)	40.68	2.57 (1.89-3.52)	8.94E-09
	HLA-DR3+, %		
CTL (625)	26.08		
IIM (871)	56.11	3.68 (2.94-4.60)	2.55E-32
JDM (121)	45.45	2.36 (1.56-3.79)	6.51E-05
DM (254)	47.64	2.57 (1.90-3.49)	1.08E-05
PM (358)	59.50	4.16 (3.15-5.48)	3.89E-25
IBM (114)	75.44	8.71 (5.48-13.82)	1.56E-23
C4A=0+1, Yes	HLA-DR3+, %		
CTL	83.05		
IIM	88.60	1.59 (0.89-2.81)	0.12
JDM	90.91	2.04 (0.66-6.35)	0.19
DM	81.98	0.93 (0.47-1.84)	0.83
PM	88.89	1.63 (0.82-3.24)	0.16
IBM	**98.18**	**11.02 (1.44-84.4)**	0.0012
C4A=0+1, No	HLA-DR3+, %		
CTL	12.82		
IIM	30.59	3.00 (2.16-4.15)	1.10E-11
JDM	15.87	1.28 (0.62-2.65)	0.51
DM	20.44	1.75 (1.07-2.85)	0.03
PM	35.23	3.70 (2.50-5.48)	9.49E-11
IBM	55.17	8.37 (4.69-14.94)	1.50E-12
DR3+, Yes	C4A=0+1, Yes, %		
CTL	60.12		
IIM	70.81	1.61 (1.11-2.33)	0.012
JDM	80.00	2.65 (1.24-5.68)	0.0078
DM	76.47	2.15 (1.27-3.65)	0.0035
PM	67.92	1.40 (0.91-2.15)	0.12
IBM	65.79	1.12 (0.65-1.92)	0.68
DR3+, No	C4A=0+1, Yes, %		
CTL	4.33		
IIM	12.09	3.04 (1.75-5.26)	3.89E-05
JDM	7.02	1.67 (0.55-5.06)	0.39
DM	15.50	4.05 (2.11-7.80)	4.47E-05
PM	12.59	3.18 (1.63-6.20)	0.0009
IBM	3.70	0.85 (0.11-6.58)	0.87

CTL, controls; DR3+, presence of DRB1*0301; C4A=0+1, homozygous and heterozygous deficiency of C4A.

Inclusion body myositis

O-6

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF ARIMOCLOMOL IN PATIENTS WITH INCLUSION BODY MYOSITIS

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Background. Inclusion body myositis (IBM) is the most common idiopathic inflammatory myopathy occurring in patients over the age of 45 years. Since immune suppression has not been effective, modulating the cytoprotective „heat shock response" (HSR) represents a candidate therapeutic approach targeting both inflammation and degeneration. In a pilot study, arimoclomol, an amplifier of the HSR, was safe and well tolerated with some trends suggesting efficacy at 8 months in subjects with IBM.
Methods. Our objective is to present the efficacy and safety/tolerability data from a phase 2/3 randomized controlled trial of arimoclomol in IBM (NCT02753530). In this international multicenter, double-blind, placebo-controlled trial, subjects were randomized (1:1) to receive either arimoclomol citrate 400 mg or matching placebo capsules three times a day (1,200 mg/day) for 20 months. The primary outcome measure was the change from baseline to Month 20 in the IBM Functional Rating Scale (IBMFRS) total score. Hierarchically ordered key secondary outcome measures included hand grip strength (strongest hand), Modified Time Up and Go, Manual Muscle Testing (24 muscles), 6-minute walk test distance, and the Short-Form 36 health survey. Other outcome measures included patient and clinician global impressions, and other measures of muscle strength and function. Drug safety and tolerability were evaluated.
Results. One hundred fifty-two IBM subjects fulfilling ENMC 2011 criteria were randomized with mean age 67.2 years (SD 8.1), mostly men (76%), mean disease duration 98 months (SD 58), and mean baseline IBMFRS of 27.4 (SD 4.6). The IBMFRS declined by a mean of 3.25 points with arimoclomol vs. 2.26 points with placebo over 20 months (p=0.11). Secondary efficacy outcome measures did not show any statistically significant treatment group differences. Most frequently reported AEs observed with higher incidence in arimoclomol group were gastrointestinal disorders (54.8% vs. 39.7%). Patients receiving arimoclomol were more likely to discontinue treatment due to AEs (17.8% vs. 5.1%). The relative frequency of serious AEs was comparable in the two treatment arms (arimoclomol 15.1% vs. placebo 23.1%). Elevated transaminases were reported in the first three months and were more frequently observed with arimoclomol than with placebo (15.4% vs. 6.4%).
Conclusions. This trial did not demonstrate a benefit of arimoclomol in IBM with respect to its primary and secondary efficacy endpoints.
Acknowledgements. We would like to acknowledge funding support from FDA-OOPD R01FD004809 and Orphazyme A/S.

O-7

ATYPICAL PRESENTATIONS OF INCLUSION BODY MYOSITIS: CLINICAL CHARACTERISTICS AND LONG-TERM OUTCOMES

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Background. Typically, IBM presents with progressive weakness involving finger flexion more than shoulder abduction, and/or knee extension equal to, or more than, hip flexion. However, IBM patients may have atypical onset or distribution of the weakness. Further, little is known about the frequency, clinical characteristics, and long-term outcomes of such patients, which we address in this study.
Methods. We retrospectively searched the Mayo Clinic electronic medical records to identify IBM patients with atypical disease onset, seen between January1st 2015 and December 31st of 2020. Patient were included if they fulfilled the 2011 European Neuromuscular Center criteria at a later stage in the disease course, or if they had all canonical histopathological features: auto-aggressive endomysial inflammation, rimmed vacuoles, and protein aggregates.
Results. We identified 50 patients with an atypical disease onset among 357 (14%) total IBM patients. The most common presentation was dysphagia (50%), followed by asymptomatic hyperCKemia (24%), foot drop (12%), proximal arm weakness (6%), axial weakness (4%), and facial diplegia (4%). The diagnosis was often delayed by an average of 9 years. Median age at diagnosis was 70.5 years (40-86). Patients presenting with dysphagia were more commonly females. Eight (16%) patients needed a walking aid. When tested, 32/37 (86.5%) patients had impaired swallowing; 41/49 (84%) had elevated creatine kinase levels, and 14/25 (56%) had elevated cytosolic nucleotidase-1A antibodies. Only 1 out of 26 patients who received immunotherapy had clinical improvement, mainly with their dysphagia. Upon follow up, most patients had generalization of their weakness as reflected by a progressive decline in their strength summated score (slope of -0.082/month), with marked variability of progression rate. Median follow-up duration was 42 months. 37 (74%) patients eventually satisfied the ENMC diagnostic criteria for IBM.
Discussion. A significant proportion of IBM patients may have an atypical presentation. Recognition of such heterogeneity improves early diagnosis, prevents unnecessary immunotherapy, and provides insight for future diagnostic criteria development and clinical trials.

O-8

DO VIRUS-SPECIFIC MEMORY T CELLS CONTRIBUTE TO INCLUSION BODY MYOSITIS?

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Background. Inclusion body myositis (IBM) is the most common inflammatory muscle diseases that primarily affects the elderly. It is characterised by autoimmune aggression and degeneration of skeletal muscles, which leads to severe disability over time. Although the aetiology of IBM is uncertain, numerous lines of evidence point to T cells playing a pathogenic key role. One of the major questions that remains unsolved regarding IBM muscle-invading T cells is the nature of the antigen that drives their autoreactivity. We hypothesised that the analysis of T cells' T cell receptor (TCR) repertoire will give insights into their specificity. We used high-throughput sequencing of TCRβ chains in T cells isolated from muscle biopsies and matched blood samples to compare T cell clonal profiles within the inflammation-affected muscle tissues and systemically.
Methods. Blood and muscle samples were collected on the same days for each of the four donors. Muscle-invading T cells were isolated as bulk while peripheral blood mononuclear cells were subjected to $CD4^+$ and $CD8^+$ T cell separation. The TCRβ sequencing was performed using the high-throughput Illumina Miseq platform. Downstream data analysis of TCRβ repertoires was performed using in-house VGAS tool, Immunarch R package and VDJtools. HLA haplotype of each donor was determined by high resolution typing of HLA class I and II alleles using Illumina Miseq platform in an American Society for Histocompatibility and Immunogenetics (ASHI)-accredited laboratory.
Results. Analysis of muscle-T cells for TCR repertoire overlap revealed shared clonotypes between patients. A unique TCRβ sequence was shared between patients 1, 3, and 4, while in patient 2, although this sequence was not found in the muscle, it ranked as a predominant clone in the blood. The patients 1 and 3 displayed nine sequences in common, as well as their top three TCRβ sequences. Furthermore, analysis of TCR repertoire usage in the corresponding blood samples showed common clonotypes between muscle and blood, but at higher frequency in muscles indicating that a preferential expansion occurred in this tissue. Moreover, querying the top five dominant TCRβ CDR3 sequences of muscle from each patient in a curated database of TCR identified multiple highly similar sequences with known specificity for antigens derived from virus and muscle proteins, especially in the $CD8^+$ T cell subset. In patient 1 and 3, the topmost clone showed a high level of similarity with a CDR3 specific for CMV-derived antigen as well as self-antigens derived from protein phosphatase 1F (PPM1F) and A-kinase anchor protein 9 (AKAP9). The HLA alleles reported to present these autoantigens matched with the HLA haplotype of patient 3. On the other hand, for patient 2, we identified a clone bearing high CDR3 similarity with known sequences documented to be associated with HIV-1 and EBV-derived antigens, and another CDR3 that exactly matched a sequence specific for a gluten-derived peptide. Interestingly, this patient carries HLA-DQ9 which is a reported risk factor for celiac disease.
Conclusions. Our findings identified public TCRs in IBM muscle, and the presence of expanded T cell clones harbouring TCR sequences with striking similarities between virus and muscle-derived antigens, suggesting that an underlying molecular mimicry mechanism may generate autoreactive T cells.

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Autoantibodies and biomarkers

O-9

ANTI-FHL1 AUTOANTIBODIES IN ADULT MYOSITIS PATIENTS: BASELINE AND LONGITUDINAL FOLLOW-UP ANALYSIS

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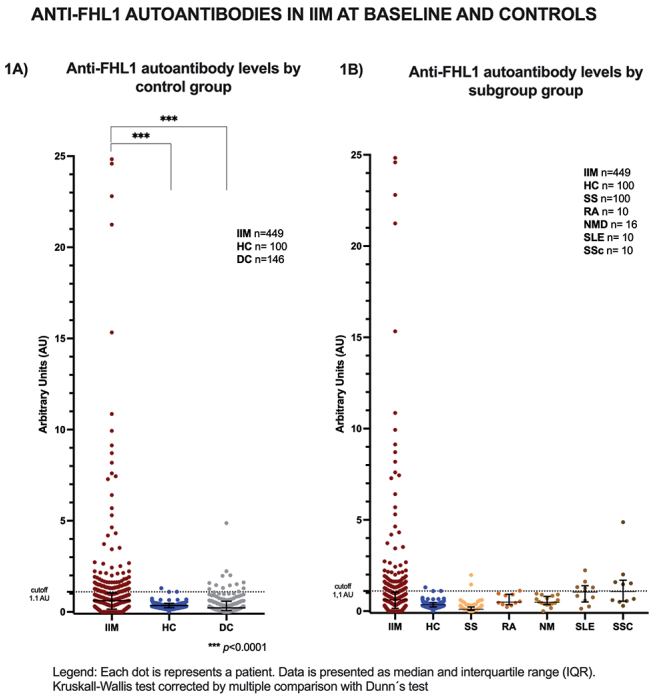
Objectives. Autoantibodies targeting a muscle-specific autoantigen, the Four-and-a-half-LIM-domain 1 (FHL1), have been identified in patients with idiopathic inflammatory myopathies (IIM). The aims of this study were to 1) to determine the prevalence and clinical associations of anti-FHL1 autoantibodies, in a Swedish cohort of IIM patients 2) to evaluate the presence anti-FHL1 autoantibodies in the course of the disease and if autoantibody levels vary over time.

Material and methods. Baseline sera from patients with IIM (n=449) from the Swedish myositis registry (SweMyoNet), autoimmune disease controls (DC, n=130), neuromuscular diseases (NM, n=16) and healthy controls (HC, n=100) were analyzed for anti-FHL1 autoantibodies by Enzyme-Linked ImmunoSorbent Assay (ELISA) according to the protocol we previously described (1). Additionally, we selected IIM FHL1+ and FHL1-patients from the baseline results for a longitudinal analysis, which had at least one sample available at time of diagnosis and one consecutive serum sample within an interval of 36 months.

Results. Autoantibodies to FHL1 were more frequent in patients with IIM (122/449, 27%) compared with DC (Autoimmune DC and NMD, 13/146, 9%, p<0.001) and HC (3/100,3%, p<0.001). Anti-FHL1 levels were higher in IIM [median (IQR)=0.62 (0.15-1.04)] in comparison with DC [0.22 (0.08-0.58)], HC [0.35 (0.23-0.47)] and NM [0.48 (0.36-0.80)] p<0.001 (Figure 1A). In the DC group, anti-FHL1+ autoantibodies were present in Sjögren's syndrome (2/100, 2%), rheumatoid arthritis (1/10, 0.1%), systemic lupus erythematosus (5/10, 50%), and systemic sclerosis (5/10, 50%) (Figure 1B). At baseline, anti-FHL1+ IIM patients were younger at time of diagnosis and serum sampling compared to the anti-FHL1- group (p=0.05 and p=0.03, respectively). The most common IIM subtypes among FHL1+ IIM patients were polymyositis (PM, 32/122, 26%), dermatomyositis (DM, 33/122, 27%), and inclusion body myositis (IBM, 18/122, 15%). No statistically significant differences in sex, ethnicity, HLA or myositis-specific (MSA) or -associated autoantibodies (MAA) were found when comparing anti-FHL1+ patients with their anti-FHL1- counterparts. In anti-FHL1+ patients, 47% were negative for other MSAs and 25% were negative for both MSA and MAA. The most frequent MAA was anti-Ro52 (24/113, 21%). Anti-FHL1+ patients had a higher ESR (p<0.03) at diagnosis and a higher trend towards less heliotrope rash (p<0.06) in comparison to the anti-FHL1- group. Longitudinal samples were available from 57 anti-FHL1+ IIM patients (median follow-up : n=5) and 30 anti-FHL1- patients (median follow-up samples 4). We subdivided the patients into 3 groups: anti-FHL1+ at baseline (n=33), FHL1- at baseline that "seroconverted" during follow-up (n=24), and anti-FHL1 "negative" group (n=30). Additionally, the anti FHL1+ at baseline was subdivided into 3 groups according to the anti-FHL1+ levels: "high-positive" (AU>5, n=6), "intermediate-positive" (AU 3-5, n=5), "low-positive" (AU 1-3, n= 22). Interestingly, 4/6 of the high-positive, 2/5 intermediate-positive and 14/22 low positive patients were negative in the first follow-up sample (median AU baseline-first follow-up: 2.48 vs 0.76, p<0.0001). Furthermore, 6/24 (25%%) of anti-FHL1- patients had seroconverted to anti-FHL1+ at the first follow-up.



O-9. Fig. 1.

Conclusion. We report a 25% prevalence of anti-FHL1 autoantibodies at baseline in a large cohort of patients with IIM, of these 25% were seronegative for MSA and/or MAA. Anti-FHL1 autoantibodies were also detected in other autoimmune diseases, but with a lower levels in comparison with the IIM patients but not in NM. Variation in serum levels of anti-FHL1 autoantibodies over time was frequently observed as well as seroconversion to anti-FHL1- in the first follow-up sample, indicating that the levels of this autoantibody varies with the disease course but this needs to defined by associations to clinical disease activity measures.

O-10

IDENTIFICATION OF CELL TYPES AND GENE EXPRESSION PROGRAMS ASSOCIATED WITH JUVENILE DERMATOMYOSITIS USING MULTIPLEXED SINGLE-CELL RNA SEQUENCING AND MATRIX FACTORIZATION

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Background. Juvenile Dermatomyositis (JDM) is a systemic autoimmune condition in which there are alterations in both the innate and adaptive immune responses and a strong type I interferon (IFN) signature. The immune cell types and cell-specific pathways that contribute to disease are not well understood. Increasing knowledge of immune dysregulation in JDM with detailed immunophenotyping at the cellular level could lead to identification of new therapeutic targets and insight into disease mechanisms.

Methods. Multiplexed single-cell RNA and protein sequencing was applied to 27 peripheral blood samples to simultaneously profile the gene expression and cell surface antibody signatures associated with JDM compared to healthy pediatric controls (HC). Demuxlet was used to remove doublets and assign cells to individuals. Data processing steps were performed using ScanPy and included quality control, dimensional reduction, clustering, and cell type annotation using canonical protein markers. To determine if JDM is associated with changes in immune cell composition, we performed two analyses: 1) cell type proportions were compared between treatment-naïve (TN)-JDM (n=9) and HC (n=5) using a Welch t-test, and 2) the correlation between cell proportion and disease activity, measured as the physician global visual analog score (VAS), was calculated using the Spearman correlation coefficient for all JDM samples (n=22) per cell type. Non-negative matrix factorization (NMF) was used to identify coordinated gene expression programs associated with cell type, disease state (JDM v HC), and disease activity for the following cell types: B, $CD4^+$ T, $CD8^+$ T, gdT, NK, and myeloid cells. We used gene set enrichment analysis (GSEA) to identify biological processes and pathways associated with identified ranked gene programs ad-

justing for multiple testing by controlling the false discovery rate (FDR) at <10%.
Results. We profiled 107,233 single cells and identified 21 distinct immune cell populations (Figure 1). Compared to HC, TN-JDM subjects displayed significant expansion of $CD4^+$ T regulatory cells (p=0.02) and a trend toward expansion of naïve B cells (p=0.08) and reduction of NK cells (p=0.09). The proportion of naïve B cells was positively correlated with disease activity (0.70, p<0.001), whereas the proportion of memory B cells (-0.43, p=0.045) and $CD4^+$ memory T cells (-0.71, p<0.001), was negatively correlated with disease activity. Using matrix factorization, we identified 29 gene programs associated with B cells, which included programs associated with cell subtype as well as programs associated with disease state and disease activity. A naïve B population expressing CD24 and CD38 was associated with TN-JDM and expressed a gene signature enriched in processes related to "B cell activation" (FDR=0.01) and "T cell activation" (FDR=0.047). This population also most strongly expressed the IFN gene program identified among B cells. Another gene program in the memory B cell compartment was associated with established JDM and enriched in processes "TNF-α signaling via NFκB" (FDR=0.01) and "inflammatory response" (FDR=0.06).
Conclusions. Alterations in immune cell composition within the B and CD4+ T cell compartments are associated with disease activity in JDM. Coordinated gene expression programs in the naïve and memory B cell compartments occur during different stages of JDM and may provide insight into the developing immune response over the disease course. NMF is a powerful method to differentiate coordinated gene programs associated with disease state and disease activity in JDM single-cell data. Future directions of this work include characterization of JDM-associated immunophenotypes at the transcriptomic and proteomic levels, NMF analysis of all immune cell types and subsequent network analysis to compare gene programs across populations, and prediction of cell-cell interactions using a novel network inference method.
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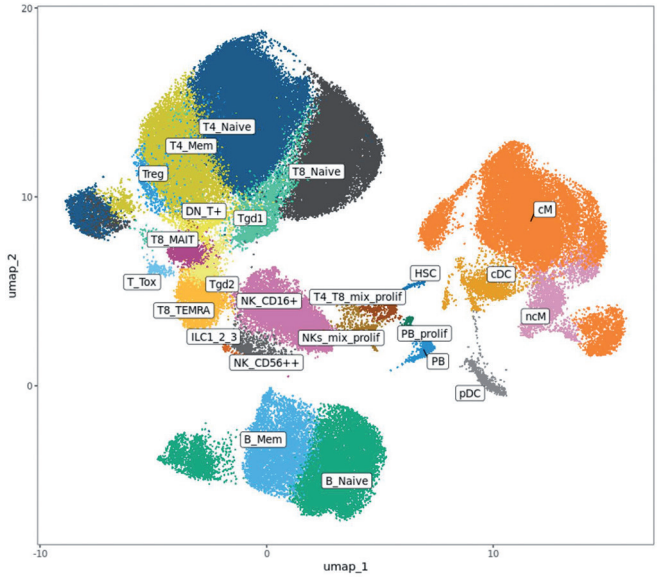

O-10. Fig. 1. Visualization of 21 clustered and annotated peripheral blood immune cell populations from 22 patients with JDM and 5 healthy controls using uniform manifold projection (UMAP).

Juvenile myositis/Juvenile to adult transition

O-11

MENTAL HEALTH SCREENING IN JUVENILE MYOSITIS: INTERIM ANALYSIS OF A PILOT STUDY

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Background. Qualitative studies in juvenile myositis (JM) suggest high rates of emotional distress but the prevalence of mental health comorbidities is not well described. This study assesses acceptability of mental health screening, rates of positive mental health screening results, and associations of mental health with outcomes and health behaviors in JM.
Methods. JM patients (5-21 yo) and their parents were eligible. Patient/parent-proxy mental health screeners included: Pediatric Symptom Checklist-17 (PSC-17), Patient Health Questionnaire-9 (PHQ9), and Screen for Child Anxiety Related Disorders (SCARED). Positive screening was defined as any total/domain score above established cutoffs. Patients/parents completed a 3-item mental health screening acceptability survey. Patient-Reported Outcomes Measurement Information System (PROMIS) pediatric/parent-proxy Depressive Symptoms, Anxiety, Psychological Stress Experiences, and Positive Affect measures assessed intensity of emotional distress. Clinical and health behavior measures included: 1) Physician/Patient/Parent-proxy Global Assessments of Disease Activity (PGA, patient/parent GA); 2) PROMIS Mobility/Upper Extremity Function; 3) medication adherence (Domains of Subjective Extent of Nonadherence [DOSE-NA]); 4) PROMIS Physical Activity; 5) Measures of Sun Protection Practices. Mann-Whitney U-test assessed positive vs negative screening group differences in PROMIS measures, outcomes, and health behaviors. Spearman's correlations for PROMIS emotional distress and outcomes/health behaviors were calculated.

O-11. Table I. Mental Health Measure* Descriptive Statistics.

	Patient Self-Report			Parent Proxy Report		
	n	median (IQR)	Positive screen, n (%)	n	median (IQR)	Positive screen, n (%)
PSC-17 Total	30	9 (4.8-13.3)	5 (16.7)	49	6 (3-11.5)	7 (14.3)
PSC-17 Internalizing	30	3 (1-6)	13 (43.3)	49	3 (1-4)	11 (22.4)
PSC-17 Externalizing	30	1.5 (0-4)	0 (0)	49	1 (0-3)	3 (6.1)
PSC-17 Attention	30	4 (1.8-5)	4 (13.3)	49	2 (0-4)	5 (10.2)
PHQ9	31	5 (2-7)	16 (51.6)	n/a	n/a	n/a
SCARED Total	48	24.5 (8.3-36)	24 (50)	49	10 (4-24)	12 (24.5)
SCARED Panic Disorder/Somatic	48	5 (1-10)	19 (39.6)	49	1 (0-5.5)	10 (20.4)
SCARED Generalized Anxiety	48	7 (2-11)	18 (37.5)	49	2 (0-6.5)	8 (16.3)
SCARED Separation Anxiety	48	3 (1-6)	20 (41.7)	49	1 (0-4.5)	12 (24.5)
SCARED Social Phobic Disorder	48	5 (2.3-8)	13 (27.1)	49	4 (0.5-5)	7 (14.3)
SCARED School Avoidance	48	1 (0-3)	13 (27.1)	49	1 (0-2)	11 (22.4)
PROMIS Measures:						
Depressive Symptoms	48	47.4 (39.5-58.1)	n/a	48	47.1 (38.4-55.8)	n/a
Anxiety	47	49.3 (35.7-57.9)	n/a	48	42.9 (33.7-54.8)	n/a
Psychological Stress Experiences	47	50.7 (45.2-60.9)	n/a	48	51.7 (41.5-62.3)	n/a
Positive Affect	46	48.3 (41.3-51.3)	n/a	48	48.6 (40.3-58.7)	n/a

*Patient self-report/parent report measures were respectively administered as follows: PSC-17 (12yo+ self; 5yo+ parent); PHQ9 (12yo+ self only); SCARED (8yo+ both self and parent report); PROMIS Depressive Symptoms, Anxiety, Psychological Stress Experiences, and Positive Affect computerized adaptive testing item banks (8yo+ self; 5yo+ parent).

Results. Data from 53 patient-parent dyads were analyzed. Most patients had dermatomyositis (n = 48, 91%), were female (n = 35, 66%), and were non-Hispanic white (n = 28, 53%), with a median 12 years old (interquartile range [IQR]: 10.5-16 years old). Disease activity was relatively low with PGA median = 1 (IQR 0-2.6), patient GA median = 0.5 (IQR 1-5), and parent GA median = 2 (IQR 1.6-4.9). PROMIS Mobility (patient self-report median [IQR] = 53.6 [46.4-57.9]; parent-proxy median [IQR] = 51.7 [40.2-60.2]) and PROMIS Upper Extremity

scores (patient median [IQR] = 57.3 [45.2-57.3]; parent median [IQR] = 55.7 [39.4-55.7]) were consistent with fair-to-good physical function for most participants. DOSE-NA scores (median [IQR] = 1 [1-2]) suggested adherence to prescribed regimens. PROMIS Physical Activity patient self-report (median [IQR] = 47.6 [42.9-53.8]) and parent-proxy report (median [IQR] = 44.9 [39.2-48.1]) were fair-to-good for most participants. Adherence to sun protection was variable based on patient self-report (median [IQR] = 10 [7-12]) and parent-proxy report (median [IQR] = 11 [9-13]) Sun Protection Total Scores. Most patients/parents respectively rated mental health screeners 'a little/not at all' difficult to complete (93.5%; 95.9%), agreed screening should continue (93.5%; 93.9%), and screening should be routine (87.1%; 95.9%). Almost three quarters of patients screened positive on at least one mental health screening measure (n=39; 74%) (Table I). 19.4% of patients who completed the PHQ-9 scored >10, consistent with at least moderate depression symptoms. Positive screening was associated with higher PROMIS Depressive Symptoms, Anxiety, and Psychological Stress scores by patient (all $p<0.001$) and parent-proxy report ($p=0.005$, 0.006, 0.029 respectively) and lower patient PROMIS Positive Affect score ($p=0.012$). Positive screening was not significantly associated with differences in outcomes/health behaviors. Small correlations in expected directions were noted for: patient PROMIS Depressive Symptoms and DOSE-NA (0.371) and PROMIS Physical Activity (0.364); patient PROMIS Psychological Stress and DOSE-NA (0.353); and PROMIS Positive Affect and Mobility (0.323 patient, 0.437 parent).

Conclusions. JM patients/parents find routine mental health screening acceptable and necessary. High rates of positive screening on mental health measures suggest substantial psychosocial burden, although statistical power in this interim analysis is limited to detect differences in outcomes. Enrolment in this study is ongoing, with analysis of the full cohort to follow.

O-12

ADIPOSE TISSUE DISTRIBUTION IS ASSOCIATED WITH CARDIAC DYSFUNCTION IN ADULT PATIENTS WITH JUVENILE-ONSET DERMATOMYOSITIS

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Background. The amount of visceral adipose tissue (VAT) is associated with cardiac dysfunction (1). Lipodystrophy, which is a well-known complication of juvenile dermatomyositis (JDM), probably occurs secondary to dysfunctional subcutaneous adipose tissue (2). Also, systolic cardiac dysfunction has been reported in young patients with congenital generalized lipodystrophy (3). We have previously described both lipodystrophy (4) and subclinical cardiac dysfunction in patients with long-term JDM (5). However, the association between cardiac dysfunction and VAT and lipodystrophy has not previously been studied in JDM. Here we aim to i) compare adipose tissue distribution in adult patients with juvenile-onset dermatomyositis, with matched controls, and ii) explore how adipose tissue distribution is associated with cardiac dysfunction in patients.

Methods. Thirty-nine JDM patients ≥18y (mean 31.7y, and 51% female) were examined mean 22.7y (SD 8.9y) after disease onset and compared with 39 age/sex-matched controls. In patients, lipodystrophy was assessed by validated tools in all participants. VAT was measured using dual-energy X-ray absorptiometry (DXA), and systolic and diastolic cardiac function by echocardiography. Occurrence of cardiac dysfunction was defined as: systolic function/long axis strain (LAS) ≤13.7% and/or diastolic dysfunction/early diastolic tissue velocity (e') ≤8.2 cm/s (both cut-offs were median – 2SD of control values). In patients, correlations between VAT and age, disease duration, and occurrence of cardiac dysfunction were determined by Spearman or Pearsons correlations when appropriate. Also, associations between the occurrence of cardiac dysfunction, adipose tissue distribution (VAT and lipodystrophy), sex, and disease duration were explored using logistic regression analyses (using "enter" for independent variables in the multivariate model).

Results. Patients exhibited a 2.4-fold higher VAT than the controls ($p\leq0.05$), and lipodystrophy was found in 10 (25.6%) patients. Cardiac dysfunction (systolic and/or diastolic) was found in n=9 (23.7%) patients, and in 3 (8.1%) controls ($p=0.07$). In patients, VAT levels were correlated with age (r=0.47 $p\leq0.05$), disease duration (r=0.44 $p\leq0.01$) and cardiac dysfunction (0.43 $p\leq0.01$). Further, lipodystrophy and male sex were independent determinants of the occurrence of cardiac dysfunction (Table I).

Conclusions. Adults with JDM showed more central adiposity and cardiac dysfunction than controls. Further, VAT was found to increase with disease duration, which was associated with the development of cardiac dysfunction. A novel finding was that lipodystrophy and male sex were independently associated with cardiac dysfunction in JDM patients.

O-12. Table I. Determinants of cardiac dysfunction in patients.

	Univariate analyses		Multivariate analysis	
	OR (95% CI)	p	OR (95% CI)	p
Lipodystrophy	12.5 (2.19, 71.36)	0.004	20.11 (1.61, 251.50)	**0.02**
Male sex	15.2 (1.66, 139.31)	0.16	21.50 (1.18, 393.08)	**0.04**
VAT	1.00 (1.000, 1.003)	0.28	1.00 (0.999, 1.003)	0.16
Disease duration	1.09 (0.99, 1.21)	0.10	0.99 (0.85, 1.16)	0.90

OR: odds ratio using univariate logistic regression. VAT: visceral adipose tissue.

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COVID-19 and myositis

O-13

COVID-19 OUTCOMES IN PATIENTS WITH DERMATOMYOSITIS: A REGISTRY-BASED COHORT ANALYSIS

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Background. Rheumatic diseases (RDs) like Dermatomyositis (DM) are previously known to be vulnerable to various infections due to its aggressive activity mandating high dose immunosuppressive therapy. The severity of COVID-19 in RDs is limited in literature due to the heterogeneous nature of the condition. Therefore, specific details on mortality are essential to navigate any precautions required in the treatment. This study aimed to determine outcomes of COVID-19 in DM as compared to controls, and identify the risk association of gender, race, interstitial lung disease, neoplasms, and use of immunosuppressants.

Methods. Retrospective data of individuals with DM and healthy controls (HCs), with COVID-19, between January and August 2020 was retrieved from the TriNetX database. A one-to-one matched COVID-19 positive control was selected using propensity score (PS) matching. We assessed COVID-19 outcomes such as mortality, hospitalisation, ICU admission, severe COVID-19, mechanical ventilation (MV), acute kidney injury (AKI), venous thromboembolism (VTE), ischemic stroke, acute respiratory distress syndrome (ARDS), renal replacement therapy (RRT) and sepsis. Subgroup analyses included gender, race, interstitial lung disease (ILD), cancer patients, disease-modifying rheumatic drugs (DMARDs) use, and glucocorticoids (GC) use.

Results. We identified 5,574 DM patients with COVID-19, and 5,574 HCs with COVID-19. DM patients with COVID-19 had a lower risk of mortality [RR 0.76], hospitalisation [RR 0.8], severe COVID-19 [RR 0.76], AKI [RR 0.83], and sepsis [RR 0.73] in comparison to HCs. Males and African Americans were more likely to develop AKI [RR 1.35, 1.65], while African Americans were at a higher risk of severe COVID-19 [RR 1.62] and VTE [RR 1.54]. DM patients with ILD were also at a higher risk of severe COVID-19 infection [RR 1.64], and VTE [RR 2.06]. DM patients receiving DMARDs and glucocorticoids had a higher risk of hospitalisation [RR 1.46, 2.12], and sepsis [RR 3.25] (Table I). Subgroup analysis of neoplasms amongst DM patients with COVID-19 had inadequate numbers for meaningful comparison.

Conclusions. DM patients are protected from certain poor clinical outcomes of COVID-19, including severe COVID-19, hospitalisation, and mortality, in comparison to healthy individuals. However, certain subgroups with DM have worse outcomes. Men, African Americans, and patients with interstitial lung disease, exhibited higher risk of severe COVID-19. DMARDs and glucocorticoid use were associated with frequent hospitalisations and severe sepsis.

Parameters	Unmatched Myositis with COVID-19	Unmatched General population with COVID-19				Matched Myositis with COVID-19	Matched General population with COVID-19			
Outcome	N = 5,578	N = 859,166	Risk Ratio	Risk Difference	p-value	N = 5,574	N =5,574	Risk Ratio	Risk Difference	p-value
Mortality	2% (112/5578)	1.8% (15527/859166)	1.11 (0.92,1.34)	0.2% (-0.17%,0.57%)	0.262	2% (112/5574)	2.6% (147/5574)	0.76 (0.6,0.97)	-0.63% (-1.19%,-0.07%)	0.028
Renal Replacement Therapy	0.3% (19/5485)	0.3% (2630/852378)	1.12 (0.72,1.76)	0.04% (-0.12%,0.19%)	0.615	0.3% (19/5482)	0.5% (26/5457)	0.73 (0.4,1.31)	-0.13% (-0.37%, 0.11%)	0.289
Mechanical Ventilation	1.9% (107/5578)	1.8% (15791/859166)	1.04 (0.86,1.26)	0.08% (-0.28%,0.44%)	0.656	1.9% (107/5574)	2.4% (136/5574)	0.79 (0.61,1.01)	-0.52% (-1.06%, 0.02%)	0.060
Hospitalization	16.8% (939/5578)	14.6% (125783/859166)	1.15 (1.08,1.22)	2.19% (1.21%,3.18%)	<0.001	16.8% (938/5574)	21.1% (1174/5574)	0.8 (0.74,0.86)	-4.23% (-5.69%,-2.78%)	0.000
Critical Care/ICU Admission	3.3% (186/5578)	2.4% (20268/859166)	1.41 (1.23,1.63)	0.98% (0.5%,1.45%)	<0.001	3.3% (186/5574)	3.8% (213/5574)	0.87 (0.72,1.06)	-0.48% (-1.17%, 0.21%)	0.169
ARDS	1.5% (82/5578)	1.1% (9866/859166)	1.28 (1.03,1.59)	0.32% (0.01%,0.64%)	0.025	1.5% (82/5574)	1.5% (85/5574)	0.96 (0.71,1.3)	-0.05% (-0.5%,0.4%)	0.815
Severe COVID (Mortality + Ventilation)	3.1% (174/5578)	2.8% (24329/859166)	1.1 (0.95,1.28)	0.29% (-0.17%,0.75%)	0.197	3.1% (174/5574)	4.1% (229/5574)	0.76 (0.63,0.92)	-0.99% (-1.68%,-0.29%)	0.005
Ischemic Stroke	1.3% (74/5578)	0.6% (5231/859166)	2.18 (1.73,2.74)	0.72% (0.42%,1.02%)	<0.001	1.3% (74/5574)	1.5% (85/5574)	0.87 (0.64,1.19)	-0.2% (-0.64%, 0.24%)	0.380
VTE	2.9% (163/5578)	1.5% (12779/859166)	1.96 (1.69,2.29)	1.43% (0.99%,1.88%)	<0.001	2.9% (163/5574)	2.7% (153/5574)	1.07 (0.86,1.32)	0.18% (-0.44%, 0.8%)	0.568
AKI	5.5% (308/5578)	3.9% (33170/859166)	1.43 (1.28,1.6)	1.66% (1.06%,2.26%)	<0.001	5.5% (308/5574)	6.7% (371/5574)	0.83 (0.72,0.96)	-1.13% (-2.02%,-0.24%)	0.013
Sepsis	3.7% (205/5578)	3.1% (26447/859166)	1.19 (1.04,1.37)	0.6% (0.1%,1.09%)	0.010	3.7% (205/5574)	5% (279/5574)	0.73 (0.62,0.88)	-1.33% (-2.08%,-0.57%)	0.001

ICU- Intensive care unit, AKI- Acute kidney injury, ARDS- Acute respiratory distress syndrome, VTE- Venous thromboembolism

O-13. Table I. Frequency and comparison of adverse outcomes related to COVID-19 infection between propensity-matched myositis cohort with COVID-19 as compared to control.

O-14

SARS-COV-2 ASSOCIATED MYOPATHY

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An association between SARS-CoV-2 infection and myopathy was suspected early in the pandemic: patients with severe COVID-19 showed increased levels of creatine kinase that could not be solely explained by cardiac affection. On the other hand, myalgia and muscle weakness are frequent symptoms in patients with mild or moderate COVID-19 – as with many other viral infections - and subsets of infected patients report persistent muscular weakness and fatigue even months after the initial infection. We performed a case-control autopsy comparing patients with severe COVID-19 to patients with other critical illnesses and assessed inflammation of skeletal muscle tissue by quantification of immune cell infiltrates, expression of major histocompatibility complex (MHC) class I and class II antigens on the sarcolemma. Relevant expression of MHC class I antigens on the sarcolemma was present in 23 of 42 specimens from patients with COVID-19 (55%) and upregulation of MHC class II antigens in 7 of 42 specimens from patients with COVID-19 (17%), but neither were found in any of the controls. In a subset of patients, MHC class I and MHC class II expression showed a clear perifascicular pattern. Signs of degenerating and necrotic fibers could also be found, however there was no statistically significant difference in the frequency of occurrence when compared to non-COVID-19 critically ill patients. We interpreted this as non-specific signs of muscular damage in critically ill patients. Numbers of macrophages, lymphocytes and natural killer cells were found to be increased in muscles from patients with COVID-19. Interestingly, no relevant expression of MxA on myofibers could be found by immunohistochemistry, but in some cases, expression of MxA was found on capillaries. Ultrastructural analysis of selected muscles with perifascicular MHC-expression did not show tubuloreticular inclusions. However, capillaries of the analyzed samples showed basement membrane alterations and signs of ongoing regenerative processes. In addition, we evaluated inflammation of cardiac muscles by quantification of immune cell infiltrates in the same patients, and found that skeletal muscles showed more inflammatory features than cardiac muscles. Moreover, inflammation was most pronounced in patients with COVID-19 with chronic courses. In some muscle specimens, SARS-CoV-2 RNA was detected by reverse transcription–polymerase chain reaction, but no evidence for a direct viral infection of myofibers was found by immunohistochemistry or electron microscopy. This suggests that SARS-CoV-2 may be associated with a postinfectious, immune-mediated myopathy.

O-15

HUMORAL RESPONSE TO 3RD DOSE SARS-COV-2 VACCINE IN PATIENTS WITH IDIOPATHIC INFLAMMATORY MYOPATHIES

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Background. Vaccine-induced SARS-CoV-2 antibody responses are reduced in patients taking lymphocyte-depleting therapies, which are commonly prescribed for patients with idiopathic inflammatory myopathies (IIM). While a third vaccine dose (D3) augments the SARS-CoV-2 anti-spike response in some patients, there is a paucity of data on the humoral response following D3 in patients with IIM. Furthermore, the durability of antibody response is unknown. In this study, we evaluated serial antibody response for three months following a 3rd dose SARS-CoV-2 vaccination in IIM patients.

Methods. Adults with a patient-reported diagnosis of idiopathic inflammatory myopathy who completed three-dose SARS-CoV-2 vaccination (two-dose BNT162b2 or mRNA-1273 followed by single mRNA or adenoviral vector dose) were recruited via social media campaign. Demographics and clinical characteristics were collected via patient report. Informed consent was provided electronically. Serial antibody responses were evaluated by the Roche Elecsys® anti-SARS-CoV-2 S enzyme immunoassay, which measures total antibody to the SARS-CoV-2 S-receptor binding domain (RBD) protein (range 0. 4-2500U/mL; positive >0.8U/mL). Poor antibody response was defined as anti-RBD titer <500U/mL based on predicted correlates of protective plasma neutralizing capacity. Those with prior COVID-19 infection were excluded. Associations were evaluated using Fisher's exact and Wilcoxon rank-sum tests as appropriate.

Results. We evaluated serial anti-RBD titers in 59 participants (Table I). Most (93%) were female with median (IQR) age of 51 (41-62) years. Mycophenolate mofetil was the most frequently prescribed medication (45.6%). Participants completed primary vaccination with two-dose BNT162b2(54%) or mRNA-1273(46%). Median pre-D3 anti-RBD titer (IQR) was 65.8U/mL (4.6,473) at 158 (136-183) days following primary vaccination. Dose 3 included BNT162b2(47%), mRNA-1273(47%) or Ad.26.COV2.S (6%). Most (89.9%) received homologous D3 vaccination. 39% of participants reported holding peri-D3 immunosuppression with mycophenolate mofetil being the most commonly held medication in the peri-D3 period. Repeat anti-RBD testing was performed at a median (IQR) 30 (28-32) days post-D3. A higher antibody titer was seen in 89.9% participants following D3 with median (IQR) titer of 2500 U/mL (92,2500). Thirty-seven percent remained <500U/mL following D3; a greater proportion of these participants reported use of rituximab and greater number of immunosuppressive therapies compared to those with anti-RBD ≥500U (72.7% versus 5.4%, $p<0.001$; 3 therapies versus 2 therapies, $p=0.03$). Furthermore, 13.5% (8/59) remained below the threshold of positivity following D3; 7/8 reported use of rituximab, 5/8 mycophenolate mofetil, or combination of these agents (4/8). There was not a significant difference in antibody titers among recipients of homologous/heterologous vaccination ($p=0.22$). Dose 3 was well tolerated with only 2 (3.4%) participants reporting disease flare requiring treatment within one month of vaccination; neither required intravenous therapy or hospital admission. Thirty-four (57.6%) participants underwent repeat anti-RBD testing three months following D3 with median (IQR) 2500U/mL (456,2500); 73.53% (25/34) remained above threshold of ≥500U/mL. Limitations of this study include small sample size and absence of healthy control group. Diagnosis was based on participant report and we did not routinely collect information on disease activity.

Conclusion. We observed an augmented humoral response in most IIM patients following 3rd dose SARS-CoV-2 vaccination; antibody response was durable at three months. Dose 3 was well tolerated. Over 1/3 participants failed to develop adequate response following D3, namely those on rituximab therapy and on higher number of immunosuppressive therapies. These patients should be prioritized for prophylactic therapies to enhance protection against COVID-19 infection.

O-15. Table I. Demographic and clinical characteristics of patients with IMM by post-D3 anti-SARS-CoV-2 RBD antibody response.

	≥500U/mL* (n=37)	<500U/mL* (n=22)	*p*-value†
Age, median (IQR)	52.2 (41.3, 62.0)	50.9 (40.7, 61.7)	0.93
Female sex, no. (%)	36 (97.3%)	19 (86.4%)	0.11
Non-white, no. (%)	3 (8.1%)	4 (18.2%)	0.25
Primary vaccine platform			
BNT162b2	20 (54.1%)	12 (54.5%)	1.00
mRNA-1273	17 (45.9%)	10 (45.5%)	
Withheld IS peri-D2	12 (32.4%)	6 (27.3%)	0.77
Days from D2 to pre-D3 Ab, median (IQR)	144.0 (89.0, 176.0)	136.0 (92.0, 181.0)	0.68
Days from D3 to post-D3 Ab, median (IQR)	30 (28, 32)	29 (28, 32)	0.57
Therapy included in regimen, no. (%)			
Azathioprine	9 (24.3%)	4 (18.2%)	0.75
Tacrolimus	1 (2.7%)	0 (0.0%)	0.44
Hydroxychloroquine	9 (24.3%)	4 (18.2%)	0.75
Mycophenolate§	13 (35.1%)	13 (59.1%)	0.07
Mycophenolate§ dose: median (IQR) (mg)	2000(1250-3000)	2000(2000-3000)	0.22
Methotrexate	9 (24.3%)	0 (0.0%)	0.02
Belimumab	0 (0.0%)	1 (4.5%)	0.37
Rituximab	2 (5.4%)	16 (72.7%)	<0.001
TNF inhibitor§	1 (2.7%)	1 (4.5%)	0.71
Glucocorticoid§	20 (54.1%)	10 (45.5%)	0.52
Immunomodulatory§	10 (27.0%)	9 (40.9%)	0.39
No. of therapies	2.0 (1.0, 2.0)	3.0 (2.0, 3.0)	0.03
Withheld D3 immunosuppression¶	15 (44.1%)	8 (44.4%)	>0.99
Flare requiring treatment post-D3	2 (5.4%)	0 (0.0%)	>0.99

*Range 0.4-2500U/ml; negative defined as anti-SARS-CoV-2 RBD antibody titer <0.8 U/mL.
† Comparisons were between <500 and ≥500U/mL groups. Categories with an overall n<10 were not analyzed, and all tests were two-sided with an $\alpha=0.05$
§ Mycophenolate includes mycophenolic acid and mycophenolate mofetil TNF inhibitors include adalimumab and etanercept. Corticosteroid includes prednisone and prednisone equivalents. Immunomodulatory includes intravenous immunoglobulin (IVIg) and subcutaneous Immunoglobulin (SCIg).
¶ Participants withheld the following medications: 3/13 azathioprine, 4/9 methotrexate, 6/18 rituximab, 8/26 mycophenolate, 2/2 TNF inhibitor.

Imaging in myositis

O-16

MUSCLE B MODE ULTRASOUND AND SHEAR-WAVE ELASTOGRAPHY IN IDIOPATHIC INFLAMMATORY MYOPATHIES: VALIDATION AGAINST MRI AND MUSCLE BIOPSY FINDINGS IN AN INCIDENT PATIENT COHORT (SWIM STUDY)

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Background. B mode ultrasound (US) and shear wave elastography (SWE) are easily accessible clinician lead imaging tools for idiopathic inflammatory myopathies (IIM) but require further validation against standard diagnostic procedures such as MRI and muscle biopsy. Our study aims to validate muscle B mode ultrasound (US) and shear wave elastography (SWE) in idiopathic inflammatory myopathies (IIM) against MRI and muscle biopsy findings.
Methods. In this prospective cross-sectional study, we compared US findings to MRI and muscle pathology in a group of 20 IIM patients seen in the clinic. US domains (echogenicity, fascial thickness, muscle bulk, shear wave speed and power doppler) in the deltoid and vastus lateralis were compared to MRI domains (muscle oedema, fatty infiltration, and atrophy) and muscle biopsy findings (inflammatory infiltrates, myonecrosis, atrophy and fibro-fatty infiltration) in the same muscle. A composite index score (1-4) was used as an arbitrary indicator of overall muscle pathology in biopsies.
Results. Increased echogenicity was significantly associated with the presence of fatty infiltration/atrophy on MRI (p=0.047) in the vastus lateralis and showed a non-significant association with muscle inflammation, myonecrosis, fibrosis, and fatty infiltration/atrophy (p>0.333). High echogenicity also had a non-significant association with a higher composite biopsy index score in the vastus lateralis (p=0.380). SWS and US measures of fascial thickness and muscle bulk showed poor discrimination in differentiating between pathologies on MRI or muscle biopsy. Power Doppler showed no statistical association with oedema on MRI or inflammation or fatty infiltration on biopsy. Overall, the US was very sensitive in detecting the presence of muscle pathology shown on MRI (67-100%) and showed reasonable specificity (75-100%). Increased echogenicity showed good sensitivity in detecting muscle pathology (83-100%) but lacked specificity in differentiating pathological muscle changes specific to IIM (0%).
Conclusion. Our findings show that muscle echogenicity has a high sensitivity but low specificity for detecting muscle pathologies specific to IIM. Traditional visual grading scores are not IIM-specific and require further refinement and validation. Future studies should focus on developing a feasible scoring system that is reliable and allows translation to clinical practice.
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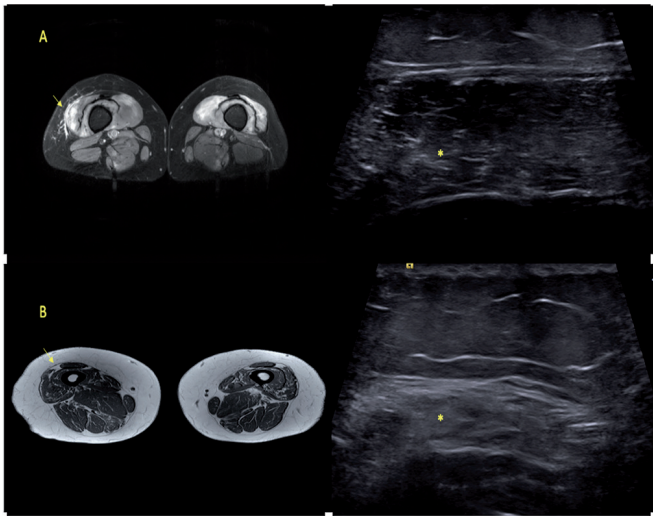

O-16. Fig. 1.
A: Increased uptake on T2 (fat suppression) sequence in the vastus lateralis (arrow) with corresponding mild, heterogeneous increase in echogenicity (*) on B mode ultrasound in a 26year-old with anti-NXP2 dermatomyositis.
B: Increased uptake on the T1 (not fat-suppressed) sequence in the vastus lateralis (arrow) with corresponding marked echogenicity in the vastus lateralis in a patient with inclusion body myositis (IBM).

O-17

USE OF 18-FDG PET-CT IN IDIOPATHIC INFLAMMATORY MYOPATHIES, A RETROSPECTIVE SERIES OF 93 EXAMINATIONS. A TOOL WITH UNCERTAIN PERFORMANCES

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Background. Idiopathic inflammatory myopathies (IIM) are divided into four main entities: immune mediated necrotizing myopathy (IMNM), dermatomyositis (DM), anti-synthetase syndrome (ASyS) and inclusion body myositis (IBM). 18-fluorodeoxyglucose positron emission tomography (18FDG PET-CT) is a common tool in the diagnosis, monitoring or search for neoplasia. Few studies have focused on its value in IIM.
Methods. In this descriptive monocentric retrospective study, all patients who underwent 18FDG- PET CT from 01/01/2014 to 01/07/2021 in internal medicine department and who were followed for any type of myositis were included. Patients were distributed in 4 diagnostic groups: IMNM, DM, IBM, and other inflammatory myositis (including ASyS, overlap myositis, infectious myositis, immune check point inhibitors induced myositis, granulomatous myositis, secondary to other inflammatory, toxic or undetermined diseases). History, assessment of activity by muscular MITAX score (scoring from A to E, activity defined for A and B ranks, inactivity for C to E), qualitative muscular metabolic uptake at PET CT and biological data such as Creatine Kinase (CK) levels at diagnosis and PET-CT were gathered.
Results. 93 PET CT were analysed corresponding to 73 patients. Diagnoses were 10 IMNM, 24 DM, 13 IBM, and 26 other inflammatory myositis (4 ASyS, 4 overlap myositis, 4 post-infectious, 4 secondary to immunotherapies, 2 granulomatous, 1 toxic on chronic ethylism, 5 of undetermined inflammatory cause, 2 secondary to other systemic inflammatory diseases). Mean age was 59±17 years, 47.95% of patients were men (n=35), 17.80% (n=13) had an history of neoplasia at the diagnosis of IIM and 12.33% (n=9) had active neoplasia. Majority of PET CT (79.57%; n= 74) were performed under corticosteroids. The median time between IIM diagnosis and PET-CT was 19 months [2-63.25]. The median CK level at myositis diagnosis was 1537 IU/L [450-4000] versus 162.5 IU/L [79-897] at PET-CT achievement. There was no significant difference in CK levels between muscularly metabolic or non-metabolic PET-CT scans (p=0.326). Half of PET-CT were performed in patients with active disease according to muscular MITAX score (53.76%; n=50). PET-CT had 71.43% sensitivity, 94.37% specificity and 91.78% negative predictive value (p<0.0001) to detect neoplasia, 4 patients were diagnosed with neoplasm within 3 years after first negative PET CT (2 breast adenocarcinomas, 1 laryngeal squamous cell carcinoma and 1 relapse of ovarian carcinoma), 2 of these patients had DM associated with anti-TIF1gamma antibodies. Qualitative PET-CT muscular hypermetabolism had a sensitivity of 64.29% and a specificity of 52.08% for the detection of an active disease referring to MITAX scoring (p=0.1402). Only the DM group showed superior performances with a sensitivity of 73.33%, a specificity of 92.86%, positive and negative predictive values respectively of 91.67% and 76.47% (p<0.0001) in this group. The restriction to PET-CT made under 20mg daily prednisone regimen (n=43) did not improve performance (sensitivity 57.14%, specificity 66.67%, p=0.215), PET CT made in the year following diagnosis did not show better performance (sensitivity 68.75%, specificity 50%, p=0.423).
Conclusion. In our study PET CT has shown good performances to rule out neoplasia in the IIM patients. However, the occurrence of neoplasia after an unsuspecting PET CT was still possible and should raise caution in case of strong clinical conviction and suggestive auto-immunity, especially for solid neoplasm. In addition, exception made of the DM group, PET CT muscular hypermetabolism appeared to be a poor indicator of IIM activity in this study.

Skin in myositis

O-18

LESIONAL AND NON-LESIONAL DERMATOMYOSITIS KERATINOCYTES SHARE IFN SIGNATURE WITH LUPUS BUT DISPLAY DISTINCT PATHWAY PHENOTYPES

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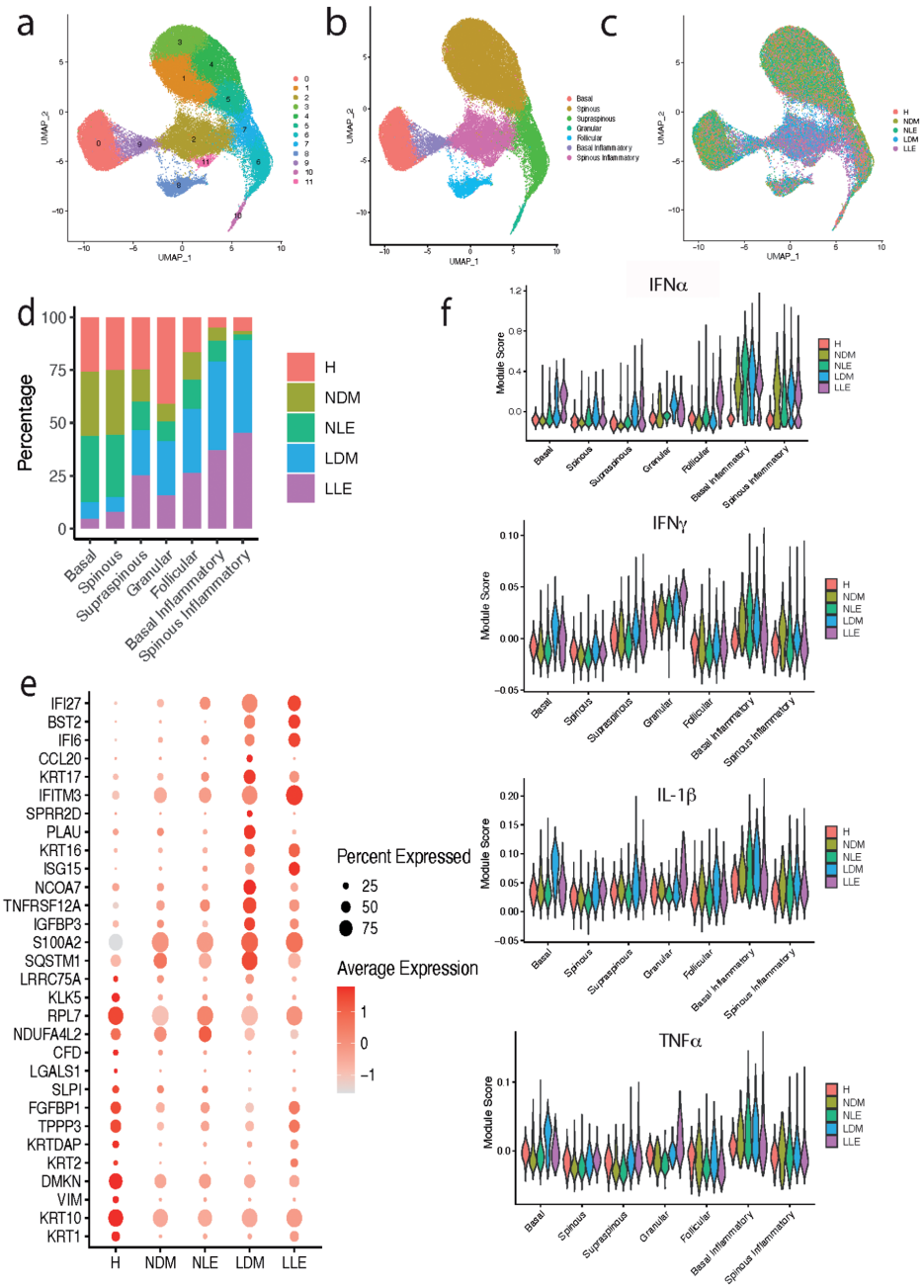
Background. Skin disease in dermatomyositis (DM) is relapsing and often refractory to treatment even when systemic disease is well controlled, reflecting a lack of understanding of the mechanisms driving skin inflammation. DM rashes are frequently challenging to differentiate clinically and histologically from cutaneous lupus erythematosus (CLE), leading to a delay in diagnosis and increased morbidity for patients. Prompt diagnosis is critical as DM and CLE have distinct systemic manifestations with prognostic significance. Delineation of the compositional and transcriptomic differences between DM and CLE will increase our understanding of their distinct immunopathogenic mechanisms in order to advance our therapeutic armamentarium and improve patient care.
Methods. We used single-cell RNA sequencing (scRNA-seq) to investigate cellular transcriptomes in lesional and sun-protected non-lesional skin samples from 8 patients with DM and 8 patients with CLE; all patients met ACR/EULAR criteria for DM and SLE, respectively. Data were analyzed in combination with skin biopsies taken from 8 sex-matched healthy control donors using Seurat. We then used Enrichr pathway analysis to predict cytokine pathways for the genes induced in lesional vs. non-lesional DM and to compare lesional DM vs. CLE.
Results. Clustering and annotation of keratinocytes (KCs) revealed 12 major clusters corresponding to 7 KC subsets (Fig. 1a,b), with prominent overlap in lesional KC populations of CLE (LLE) and DM skin (LDM) (Fig. 1c). In particular, KCs in lesional DM and LE skin exhibited an inflammatory signature most evident in basal and spinous layers (Fig. 1d). For a broader understanding of the transcriptomic differences, we performed differential expression analysis between non-lesional NDM), non-lesional lupus (NLE), lesional DM (LDM) and lesional LE (LLE) and identified type I IFN stimulated genes (*e.g.* IFI27, IFI6, ISG15) among the top upregulated genes in both LDM and LLE cells relative to



O-18. Fig. 1.

their non-lesional counterparts and healthy control (Fig. 1e), with NLE showing an increased IFN signature compared to NDM. Top canonical pathways enriched in lesional DM compared to non-lesional DM inflammatory KCs related to oxidative phosphorylation mitochondrial function, indicative of cellular stress (p=10-40), response to type I interferon (p=10-15), and interleukin 1 (IL-1) signaling (p=10-13). Top canonical pathways enriched in lesional DM vs CLE basal inflammatory KCs were VEGF2A (p=10-20) and IL-18 signaling (p=10-16). Corroborating this, cytokine module violin plots revealed that basal and spinous inflammatory subclusters from LLE and LDM consisted of KCs with high IFN-α and IL-1b module scores relative to control and non-inflammatory KC clusters, with less striking separation for IFNγ and TNF (Fig. 1f).
Conclusion. Collectively, our data outline the composition of DM epidermis compared to CLE at unprecedented resolution. We demonstrate a skewed transcriptional IFN-rich profile in both lesional LE and DM. Our pathway analysis suggests that VEGF2A and IL-18 signaling may underlie changes in DM skin and contribute to DM pathogenesis.

O-19

PHOTOSENSITIVITY IN THE SKIN OF PATIENTS WITH DERMATOMYOSITIS IS ASSOCIATED WITH TYPE I INTERFERON INDUCTION OF CXCL13-PRODUCING T PERIPHERAL HELPER CELLS

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Background. Dermatomyositis (DM) is a rare autoimmune disease that presents with chronic pruritic rash and photosensitivity and may be associated with debilitating muscle weakness. Previous studies identified a strong type I interferon (IFN-I) expression in both serum and lesional skin of patients with DM.
Methods. Suction blistering biopsies of treatment-naïve DM and healthy skin were analyzed using single-cell RNA sequencing (scRNA-seq) and spectral flow cytometry. Primary keratinocytes and T cells from DM patients and healthy controls were isolated and expanded to assess their response to UVB and IFN-I, in vitro. To confirm our findings, ELISA and immunohistochemistry (IHC) were performed on interstitial skin fluid and archived skin samples, respectively.
Results. scRNA-seq and flow cytometry identified a distinct population of CD4$^+$ T cells limited to lesional DM skin that highly expressed PD1 and CXCL13, in the absence of CXCR5. These cells exhibited a unique transcriptional and immunophenotypic profile characteristic of T peripheral helper (Tph) cells, a recently discovered subset of CD4$^+$ T cells originally described to promote B cell recruitment to inflamed synovium of patients with rheumatoid arthritis. ELISA on the interstitial skin fluid confirmed a high concentration of CXCL13 protein only in lesional DM skin (p<0.001), and IHC from DM skin highlighted strong CXCL13 staining on CD4$^+$ T cells infiltrating around blood vessels. Further analysis on scRNA-seq data indicated a strong IFN-I signature on Tph cells in DM skin, suggesting they are influenced by high expression of type I IFNs. Interestingly, expanded primary human keratinocytes (KCs) from lesional and non-lesional DM skin exhibited an enhanced IFN-I expression compared to healthy KCs in response to UVB, *in vitro*. Further, we found that CD4$^+$ T cells isolated from DM blood expressed a significantly higher level of CXCL13 compared to those from healthy when treated with IFN-Is, in vitro (p<0.01). Previous studies on Tph cells emphasized their role in driving autoimmunity via CXCL13/CXCR5-mediated recruitment of B cells to inflamed tissues. However, consistent with prior studies, we did not detect any B cells infiltrating DM skin using scRNA-seq, flow cytometry, or IHC. Instead, CXCR5 (CXCL13 cognate receptor) was detected on a distinct subset of cytotoxic CD8$^+$ T cells, suggesting a unique role for Tph cells in DM skin.
Conclusion. These findings propose a previously unknown role for the IFN-I/CXCL13 axis in DM pathogenesis and its potential contribution to photosensitivity where a pathologically enhanced UVB-induced IFN-I expression in DM KCs induces high CXCL13 secretion from Tph cells, which in turn promotes the recruitment of cytotoxic CXCR5$^+$ CD8$^+$ T cells to the inflamed skin.
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O-20

NON-INVASIVE TAPE STRIPPING IN JUVENILE DERMATOMYOSITIS HIGHLIGHTS INTERFERON SIGNATURE IN LESIONAL SKIN AND UPREGULATION OF METABOLIC SIGNALING PATHWAYS IN NON-LESIONAL SKIN

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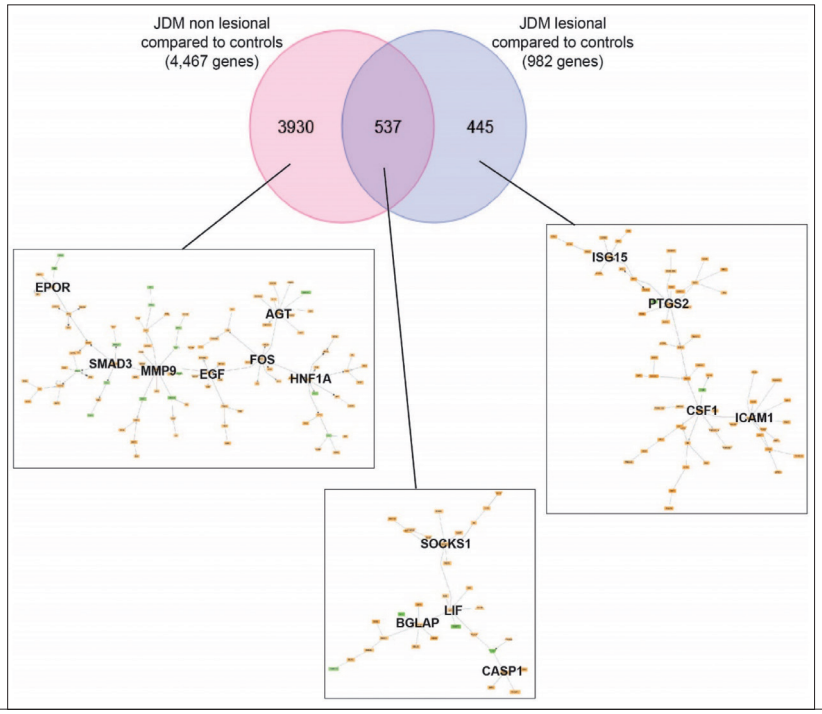
Background. Cutaneous inflammation often heralds disease in juvenile dermatomyositis (JDM); however, we do not fully understand mechanisms driving skin disease. Tape stripping is a non-invasive, epidermal sampling method that has been used in other inflammatory skin diseases to understand the connection of cutaneous transcriptomic signatures to disease activity and severity. The objectives of this study were to 1) define gene expression signatures in lesional and non-lesional JDM skin recovered with tape stripping, and 2) identify tape stripping signatures compared to previous microarray data from full-thickness JDM skin biopsies.
Methods. We utilized tape stripping to collect samples from lesional and non-lesional skin in a cohort of JDM (n=28 patients with ≥1 non-lesional sample; n=17 patients with ≥1 paired lesional sample) and healthy controls (CTL; n=20 patients, all with a one-time non-lesional sample). All JDM patients had a confirmed diagnosis by a pediatric rheumatologist or met 2017 EULAR/ACR classification criteria. At all visits, non-lesional skin from the upper thigh was obtained using 20 D-Squame adhesive discs, with additional sampling of lesional skin from Gottron's papules with active rash. mRNA was extracted from pooled tape strips using RNeasy Lysis (RLT) buffer and ultrasonication, followed by isolation using the QIAGEN RNeasy plus mini kit. RNA-seq libraries were generated using the SMARTer® Stranded Total RNA-Seq Kit v3 - Pico Input Mammalian, followed by Illumina sequencing through the University of Michigan Advanced Genomics Core. Limma-Voom was used to determine differentially expressed genes (DEGs; q-value ≤10%) between patient groups, after quality control and adjustments including the combination of all samples from unique subjects, batch correction using ComBat and controlling for sex. We then performed Ingenuity Pathway Analysis (IPA) to define regulated pathways and network analysis using Genomatix Pathway System (GePS) to characterize regulated genes.
Results. Upon comparison of JDM lesional to CTL skin, we identified 929 upregulated and 53 downregulated genes. IPA revealed interferon signaling as the top pathway (p-value<0.0001), with top 10 upregulated pathways including: role of pattern recognition receptors in recognition of bacteria and viruses (p-value=0.0014); Th1 and Th2 activation (p=0.0028); IL-13 signaling (p=0.0036); IL-17 signaling (p=0.0048); and TREM1 signaling (p=0.01). The top predicted upstream regulators expressed included IRF1 and SOCS1. JDM non-lesional skin demonstrated 4,138 upregulated and 330 downregulated genes compared to CTL. Pathway analysis demonstrated regulation of genes involved in nNOS signaling in skeletal muscle cells (p-value=0.002), neurovascular coupling signaling (p=0.003), phagosome formation (p=0.005) and calcium signaling (p=0.006), a striking difference compared to JDM lesional. Direct comparison of JDM lesional to non-lesional skin demonstrated only 10 DEGs, all downregulated in JDM lesional. Interestingly, two of these genes were LOR and FLG2, both related to epidermal barrier function and cornified envelope formation. There was overlap of 537 genes in JDM lesional and non-lesional skin compared to CTL (Figure 1), and a central node on GePS analysis of overlap genes was BGLAP, or osteocalcin, which encodes a bone matrix protein potentially involved in calcinosis. In comparing JDM lesional tape stripping RNAseq to microarray data from full thickness skin, we noted overlap with interferon-stimulated genes, including MX1, IRF1, IFI30, IFIT1, SAMD9, RSAD2, OASL, ISG15 and USP18 (all upregulated in both datasets).
Conclusion. Use of tape stripping to sample JDM lesional skin detects an interferon signature, likely originating from keratinocytes. JDM non-lesional skin also demonstrates many DEGs compared to CTL, notably with genes involved in vasodilation, angiogenesis, calcium signaling and metabolic dysregulation. Further analysis into association of expression signatures with disease activity, clinical phenotypes and response to therapy is ongoing.
Acknowledgements. Cure JM and Rheumatology Research Foundations.

O-20. Fig. 1.



Drug-induced myositis

O-21

THE TRANSCRIPTOMIC PROFILE OF MUSCLE BIOPSIES FROM PATIENTS WITH IMMUNE CHECKPOINT INHIBITOR-INDUCED MYOPATHY

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Background. Over the last decade, immune checkpoint inhibitors (ICI) have revolutionized the treatment of cancer. While these drugs may boost the immune response against tumor cells, they can also cause autoimmunity in certain patients. One of the potential immune-related adverse effects of these drugs is the development of immune-mediated myopathy. Given their relatively recent introduction, the pathogenesis of ICI-induced myopathy (ICI-myopathy) is still not completely understood.

Methods. An international effort between the National Institutes of Health (Bethesda, Maryland), the Mayo Clinic (Rochester, Minnesota), the Vall d'Hebron Hospital, and the Clinic Hospital (Barcelona, Spain), was conducted to study the transcriptional profiles of fresh frozen muscle biopsies from patients with ICI-myopathy. We performed RNA sequencing on 26 muscle samples from patients with ICI-myopathy and compared this with RNA sequencing data previously obtained from 33 normal muscle samples as well as 132 muscle samples from patients with different types of immune-mediated myopathies (16 inclusion body myositis, 54 immune-mediated necrotizing myopathy, 44 dermatomyositis, and 18 antisynthetase syndrome). 9 of 26 ICI-myopathy patients also developed myocarditis.

Results. Among ICI-myopathy patients, 85% were male, 14 different tumor types were represented, 80% had metastatic disease, and all were treated with anti-PD-1 or anti-PD-L1 therapies alone or in combination with an anti-CTLA-4 agents. A diagnosis of with ICI-myopathy was made between the first and fourth cycle of ICI therapy. Analysis of transcriptomic data revealed that ICI-myopathy muscle samples had marked overexpression of genes stimulated by interferon-gamma (IFNγ), similar to muscle samples from patients with dermatomyositis, antisynthetase syndrome, and inclusion body myositis. Genes upregulated by type I IFN were overexpressed, but to a lesser degree. We also found reduced expression of multiple mitochondrial genes compared with other types of myositis, including several mitochondrial-encoded transfer RNAs in ICI-myopathy muscle. Finally, we identified a number of pseudogenes that are specifically overexpressed in muscle samples from patients with ICI-myopathy. Of note, patients who developed myocarditis in addition to ICI-myopathy showed a trend towards having more robust activation of the IFNγ pathway. No differences were observed between patients receiving PD-1 versus PD-L1 inhibitors, or between those receiving monotherapy versus combination therapy with anti-CTLA-4 agents.

Conclusion. Muscle samples from patients with ICI-myopathy are characterized by activation of the IFNγ pathway and the repression of mitochondrial gene expression. Compared to patients with only ICI-myopathy, those with co-existing myocarditis appear to have increased activation of the IFNγ pathway; however, this will need to be investigated in a larger study that includes more patients with both ICI-myopathy and myocarditis.

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O-22

IMMUNE CHECKPOINT INHIBITOR-RELATED MYOTOXICITY: MUSCULOSKELETAL AND/OR NEUROMUSCULAR JUNCTION DISORDER?

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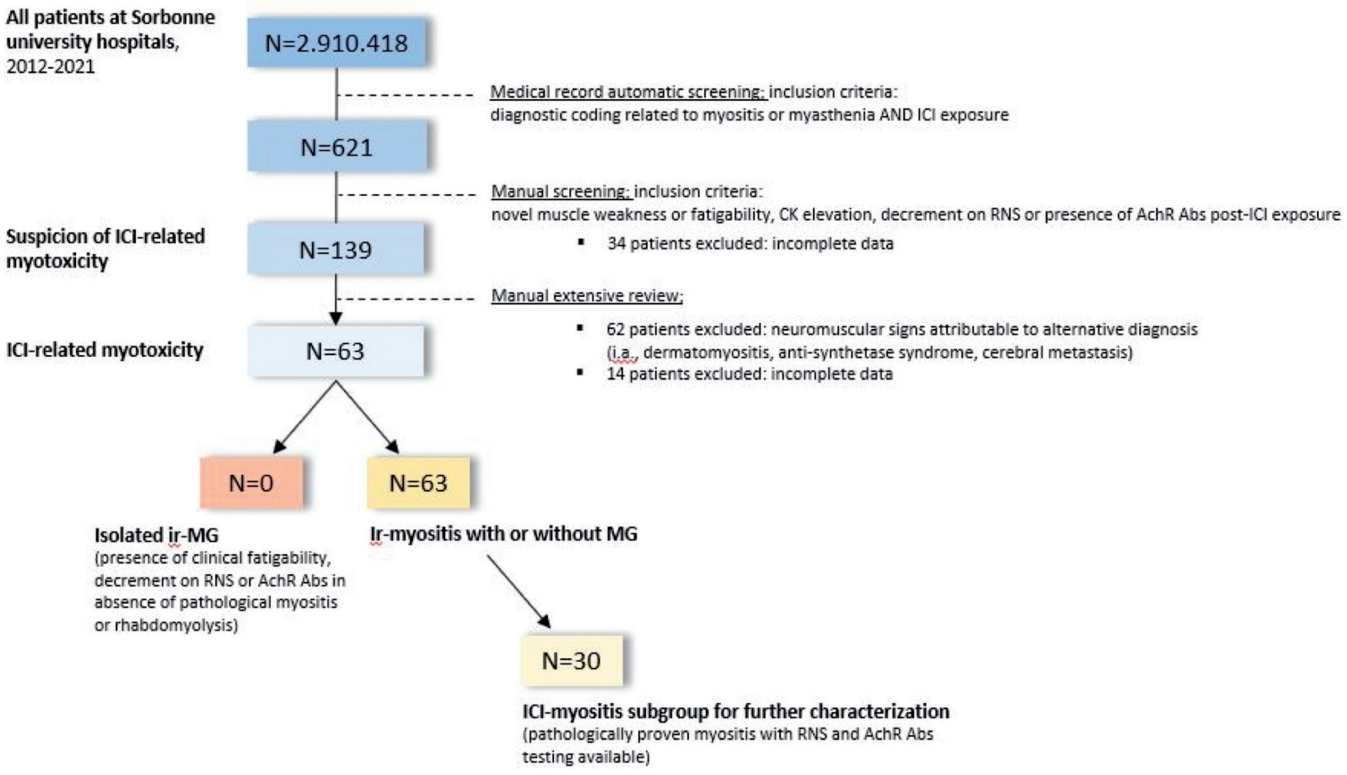
Introduction. Immune checkpoint inhibitor (ICI)-related adverse events (irAE) recently emerged as new diseases in the field of auto-immunity. Among them, ICI-related myotoxicity has the highest fatality rate and is the most frequent neurological irAE. Ir-myositis differs from its idiopathic counterpart by frequent oculobulbar and respiratory dysfunction. In addition, presence of acetylcholine receptor antibodies (AchR Abs) in a subset of patients may suggest neuromuscular junction disorder. Our study aimed to clarify whether ir-myositis and ir-myasthenia gravis (MG) represent distinct diseases or exist concurrently.

Methods. A monocentric, retrospective study was conducted at the university hospital trust (AP-HP) in Paris, between 2012 and 2021. Medical records were screened systematically by use of diagnostic coding related to 1) ICI exposure, and 2) signs of myositis or myasthenia. In subsequent manual review, we used the following inclusion criteria: novel oculomotor or other muscle weakness or fatigability, or CK elevation, after ICI exposure. We excluded patients with alternative diagnoses (i.a., dermatomyositis, anti-synthetase syndrome). Post-mortem histopathology of diaphragm and extraorbital muscles was examined in one and five patients, respectively.

Results. A total of 2.910.418 patients were screened. Finally, we retained 63 patients with definite or probable ir-myositis and/or MG. Fatigable or fluctuating weakness was never observed, with the exception of one patient with pre-existing MG. Decrement on repetitive nerve stimulation (RNS) was observed in two patients (5%; n=2/41). AchR Abs (>0.5nmol/L) were detected at diagnosis in 14 patients (22%; n=14/53). Among them, twelve had pathologically proven myositis and for the two remaining patients, CK level was higher than 8000 U/L. We examined serum obtained prior to ICI exposure for presence of antibodies and retrieved positive results in eight out of nine cases, and a borderline negative result (0.39nmol/L) in the remaining case. One additional patient exhibited no AchR Abs at diagnosis, however had a positive test result prior to ICI exposure. Titer of AchR Abs decreased after ICI treatment in half of cases (50%; n=4/8). Muscle biopsies revealed myositis (100%; n=55/55). We characterized 30 pathologically proven ir-myositis patients with available RNS and AchR Abs testing. Median age was 69 [IQR 61-80] years; 18 patients (60%) were male. Patients received anti-PD1 or anti-PDL1 monotherapy (80%; n=24/30) or combination therapy with anti-LAG-3 or anti-CTLA4 (20%; n=6/30). Time to symptom onset was 27 [19-40] days. Clinical manifestations included proximal and axial muscle weakness (90%; n=27/30) and myalgia (60%; n=18/30). CK level was 2963 [1478-6951] U/L. Patients frequently displayed diplopia and/or ptosis (60%; n=18/30) and dysphagia (47%; n=14/30). Respiratory failure requiring ventilatory assistance (invasive or non-invasive) occurred in over half of cases (57%; n=17/30). Electromyography (EMG) was myopathic in a majority of patients (60%; n=18/30). Decrement on RNS was observed in two patients (7%; n=2/30). Among them, one had pre-existing MG, and the other had atypical decrement with myogenic EMG. In total, nine patients (30%; n=9/30) exhibited AchR Abs at diagnosis. In all autopsy cases, diaphragm and extraocular muscles exhibited prominent, multifocally distributed $CD68^+$ and $CD8^+$ predominant inflammation, necrosis, MHC-I upregulation and C5b-9 deposition on non-necrotic fibers.

Conclusion. Study findings do not support existence of isolated ir-MG. In addition, although pattern of muscle weakness (*i.e.*, predilection for oculobulbar and respiratory musculature) in ir-myositis resembles that in MG, fatigable or fluctuating weakness is not observed and electromyographic analysis is not indicative of neuromuscular junction pathology. AchR Abs pre-exist in a quarter of patients and may be a biomarker of ir-myositis, however do not establish concurrent ir-MG. We propose that "MG-like" symptoms occur as a result of ir-myositis specific distribution of muscle inflammation. Indeed, necropsy revealed massive inflammation of both diaphragm and oculomotor muscles.



O-22. Fig. 1. Research methodology flowchart

Toward personalised treatment

O-23

RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL TO EVALUATE EFFICACY AND SAFETY OF SUBCUTANEOUS ABATACEPT IN ADULTS WITH ACTIVE IDIOPATHIC INFLAMMATORY MYOPATHY

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Background. Limited therapies are available for patients with idiopathic inflammatory myopathy (IIM), a heterogeneous group of chronic, systemic, autoimmune inflammatory diseases characterized by progressive muscle weakness and/or distinct skin rashes (1). Abatacept, a selective co-stimulation modulator, may be a useful treatment option (2). The objective of this study was to evaluate the efficacy, safety, and tolerability of abatacept + standard of care (SOC) in patients with IIM compared with SOC alone (placebo).
Methods. A 24-week, randomized, double-blind, placebo-controlled phase 3 trial of subcutaneous (SC) abatacept (125 mg weekly) + SOC (corticosteroids and immunosuppressants alone or combined; NCT02971683) in patients with active, treatment-refractory IIM (Manual Muscle Testing-8 [MMT-8] ≤135) was performed. The primary endpoint was the proportion of patients meeting the International Myositis Assessment and Clinical Studies definition of improvement (IMACS DOI) at week 24. Change from baseline in myositis Functional Index-2 (FI-2), Health Assessment Questionnaire disability index (HAQ-DI), Myositis Disease Activity Assessment Tool (MDAAT), and Myositis Response Criteria (MRC) were secondary endpoints with safety. Post hoc analyses by disease subtype were performed.

O-23. Table I. Primary and secondary (mean change from baseline at week 24 unless stated) endpoints.

Outcome	IIM	Abatacept	Placebo	Nominal *P* value (abatacept vs placebo) or adjusted mean difference from placebo (95% CI)
IMACS DOI,[a] n/N (%)	All	42/75 (56.0)	31/73 (42.5)	*P* = 0.083
	DM	22/40 (55.0)	21/42 (50.0)	*P* = 0.679
	Non-DM	20/35 (57.1)	10/31 (32.3)	*P* = 0.040
FI-2	All	4.1 (1.3)	1.2 (1.4)	2.9 (0 to 5.8)
	DM	2.3 (1.6)	0.3 (1.4)	1.9 (−2.3 to 6.2)
	Non-DM	3.2 (1.4)	−0.6 (1.5)	3.7 (−0.3 to 7.8)
HAQ-DI	All	−0.31 (0.07)	0.20 (0.07)	−0.12 (−0.28 to 0.04)
	DM	−0.31 (0.08)	−0.19 (0.07)	−0.11 (−0.32 to 0.10)
	Non-DM	−0.25 (0.09)	−0.07 (0.09)	−0.18 (−0.44 to 0.07)
MDAAT, Extramuscular Global Activity, (95% CI)[b]	All	−1.56 (−1.96 to −1.16)	−1.40 (−1.81 to −0.99)	−0.16 (−0.63 to 0.30)
	DM	−1.90 (−2.43 to −1.37)	−1.85 (−2.35 to 1.36)	−0.05 (−0.77 to 0.68)
	Non-DM	−1.09 (−1.46 to −0.72)	−0.85 (−1.27 to −0.43)	−0.24 (−0.80 to 0.32)
MMT-8	All	12.9 (1.9)	11.0 (2.0)	1.8 (−2.7 to 6.4)
	DM	14.4 (2.2)	14.0 (2.2)	0.4 (−5.7 to 6.4)
	Non-DM	12.1 (2.5)	7.8 (2.7)	4.3 (−3.0 to 11.7)
Physician Global Assessment[b]	All	−2.89 (0.30)	−2.69 (0.30)	−0.20 (−0.92 to 0.52)
	DM	−2.78 (0.29)	−2.43 (0.28)	−0.35 (−1.15 to 0.46)
	Non-DM	−2.35 (0.43)	−2.21 (0.48)	−0.14 (−1.43 to 1.15)
Patient Global Assessment[b]	All	−1.4 (0.31)	−0.98 (0.32)	−0.38 (−1.11 to 0.35)
	DM	−1.4 (0.33)	−1.4 (0.31)	−0.00 (−0.91 to 0.90)
	Non-DM	−1.2 (0.41)	−0.3 (0.44)	−0.93 (−2.14 to 0.29)
Adjusted mean MRC total improvement score	All	41.5	38.7	N/A
	DM	46.0	43.6	
	Non-DM	38.4	31.7	

Data are adjusted mean change from baseline score (standard error) unless stated.
[a]Defined as improvement of ≥ 20% in 3 IMACS core measures, worsening by ≥ 25% in ≤ 2 IMACS core measure scores, and a reduction of < 25% in MMT-8; [b]100 mm visual analog scale.
CI, confidence interval; N/A, not available.

Results. Overall, 148 patients were randomized (75 abatacept; 73 placebo); IIM subtypes were dermatomyositis (DM; 53.3% vs 57.5%), polymyositis (PM; 25.3% vs 34.2%), and autoimmune necrotizing myopathy (ANM; 21.3% vs 8.2%). Mean baseline MMT-8 and HAQ-DI scores were 112.7 and 1.5, respectively. Approximately 90% of patients completed week 24. Week 24 IMACS DOI rates were abatacept 56.0% vs placebo 42.5% (adjusted odds ratio, 1.8 [95% confidence interval, 0.9–3.5]; *p*=0.083). Pre-specified IMACS DOI analysis showed no differences for patients with DM but a notable benefit for those with non-DM subtypes, PM, and ANM (Table I). Secondary endpoints showed similar differences (Table I). The proportion of adverse events (AEs) (69.3% and 75.3%) and serious AEs (5.3% and 5.5%) were similar in the abatacept and placebo arms.
Conclusions. In this double-blind trial of SC abatacept vs placebo, abatacept failed to meet primary or secondary endpoints. Post hoc analyses suggest a treatment benefit in patients with PM and ANM (not DM) when treated with abatacept. Abatacept use was well tolerated.
Acknowledgements. This study was sponsored by Bristol Myers Squibb. Medical writing and editorial assistance were provided by Fiona Boswell, PhD, of Caudex and was funded by Bristol Myers Squibb. Study execution was provided by Sandra Overfield and Robin Scully.

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O-24

MUSCLE T CELL SIGNATURES AND CLONALLY EXPANDED CYTOTOXIC T CELLS ARE IDENTIFIED IN IDIOPATHIC INFLAMMATORY MYOPATHIES USING SINGLE-CELL SEQUENCING

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Background. Idiopathic inflammatory myopathies (IIM) are a group of rare autoimmune diseases characterized by skeletal muscle inflammation. The presence of immune infiltrates in the muscle is part of the IIM diagnosis but the characterization of T cell effector functions and clonality at the site of inflammation is still lacking. The main aim of this study is to investigate the transcriptome and clonality of single T cells from muscle biopsies in patients with myositis.
Methods. We performed single-cell sequencing on muscle-infiltrated T cells and paired circulating memory T cells from seven myositis patients, who are at an early stage of the disease. In two of these patients, we also analyzed T cells 9 months after treatment. We used smart-seq2 sequencing, reconstruct T cell receptor (TCR) sequences with the TraCeR software and did the biological interpretation of the transcriptome and TCRs with Seurat.
Results. We identified a muscle T-cell signature characterized by high gene expression of CXCR4, CREM and LMNA which have been associated with migration and activation of T cells. Pathway analysis also revealed high expression of tissue resident markers on muscle infiltrating T cells. Some of the T-cell subsets, like $CD4^+$ T cells, Granzyme K+$CD8^+$ T cells and Tregs were observed in multiple patients. On the other hand, the Hobit+$CD8^+$T cell subset was patient-specific. Hobit is a transcription factor associated with cytotoxicity as well as tissue resident memory T cells. TCR sequences showed clonally expanded cytotoxic $CD8^+$ and $CD4^+$ T cells and shared clones between muscle tissue and blood of each patient, but no shared clones between patients were recorded. Finally, we observed that same clones remained expanded after treatment, although both patients improved clinically.
Conclusions. Our study provides a detailed transcriptomic profile of muscle-infiltrated T cells in IIM patients which in the future could be used to design new therapeutic targets in myositis.

O-25

THE PRODERM STUDY: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE III TRIAL OF IVIG (OCTAGAM 10%) IN PATIENTS WITH ACTIVE DERMATOMYOSITIS

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Background. Intravenous immunoglobulin (IVIg) has been increasingly used for treatment of dermatomyositis (DM), but data from large randomized, controlled, trials was not available. The ProDERM study aimed to evaluate the efficacy and safety/tolerability of IVIg (Octagam 10%) in DM patients in a double-blind, randomized, placebo-controlled, international multi-center, phase III clinical trial.

Methods. In the double-blind, placebo-controlled First Period (16 weeks) adult patients with definite or probable DM (according to Bohan&Peter criteria) were randomized 1:1 to either high dose IVIg (2g/kg every 4 weeks) or placebo. Patients on placebo and patients without clinical worsening while on IVIg treatment entered the subsequent open label Extension Period (24 weeks) and received 2g/kg IVIg infusions every 4 weeks. Inclusion criteria included having active disease, muscle weakness and currently on or previous failure of DM treatment. Patients with clinical worsening (defined according to Oddis *et al*., 2013 - with slight adaptation) at 2 consecutive visits between week 8 and week 16 were switched to the alternate treatment arm. Primary endpoint was the proportion of responders in the IVIg vs. placebo arm at week 16. Response was defined per 2016 ACR/EULAR Myositis response criteria of at least minimal improvement [Total Improvement Score (TIS) ≥20 points)] and without clinical worsening at 2 consecutive visits up to week 16. Secondary endpoints included the proportion of responders by improvement category at Week 16 and Week 40 (end of Extension Period), time to minimal improvement, and mean change from baseline over time in TIS, individual core set measures and CDASI (Cutaneous Dermatomyositis Disease Area and Severity Index) total activity and damage score from baseline to end of First Period (Week 16).
Results. The study enrolled 95 adult DM patients (mean age: 53 years; 75% females; 92% Caucasian), with 47 and 48 randomized to IVIg and placebo, respectively. Baseline clinical characteristics (incl. medical history and prior DM medication) were balanced between the 2 arms. The study met the primary endpoint at week 16, with the proportion of responders being significantly higher in the IVIg group (37/47; 78.7%) as compared to the placebo group (21/48; 43.8%; p-value 0.0008). The mean (SD) TIS was also significantly higher in IVIg group [48.4 (24.4)] than in placebo arm [21.6 (20.2)] at week 16. Improvements were also significantly better for IVIg treated patients for all secondary endpoints including the subcomponents of TIS (MMT-8, MD global, extramuscular global, patient global, HAQ, except muscle enzyme). In addition, skin disease improved significantly with least square means for change from Baseline to Week 16 being -10.3 and -2.3 for IVIG versus placebo in CDASI total activity score and -0.7 versus -0.1 for total damage. After switching to IVIg in the Extension Period the placebo group attained similar response rates in all scores at Week 40 as did the IVIg treated patients at Week 16. A total of 664 infusion cycles were administered and 545 adverse events (AEs) were reported. Of these AEs, 282 in 62 (65%) subjects were assessed as being related to study drug. Most related AEs were mild (73.4%, 207), some moderate (23.4%, 66) or severe (3.2%, 9). Most were infusion reactions (92%, 260). Headache (42% of subjects), pyrexia (19%) and nausea (16%) were the most common AEs. More than 3/4th of patients (78.7%) did not need premedication before IVIg administration. Serious AEs were reported in 16 patients. In 7 patients these were assessed as related to IVIg including thromboembolic events (TEE) in 5 subjects. TEE events decreased significantly with decrease in maximum rate of infusion.
Conclusions. The ProDERM study demonstrated for the first time in a large international randomized, double-blind multicenter design the efficacy of IVIG (Octagam 10%) in improving different outcome scores in patients with DM. A good safety and tolerability of IVIg treatment in these patients was also demonstrated and the knowingly higher risk for TEE in DM patients could be counteracted by using a slow infusion rate.

Repairing damage

O-26

PERFORMANCE OF SIT-TO-STAND, TIMED UP-AND-GO AND SIX-MINUTE WALK TESTS IN THE HOME AND OFFICE SETTING

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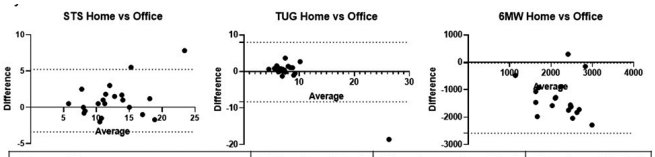
Introduction. Idiopathic inflammatory myopathies (IIM) are a group of autoimmune diseases that includes dermatomyositis (DM), polymyositis (PM), necrotizing myopathy (NM), and anti-synthetase syndrome (ASyS). The patients with IIM frequently experience limitations in their physical function related to disease activity or damage; therefore, accurate assessment of physical function is crucial in routine practice and clinical trials. Sit-to-stand (STS), timed-up-and-go (TUG), and six-minute walk distance (6MWD) tests are task-oriented functional tests, that can provide objective information about physical function. With an increasing number of virtual visits due to the pandemic, tools that can reliability assess physical function at home are necessary. In this study, we report test-retest reliability, construct validity and performance characteristics of these three functional measures in both the office and home environment.

Methods. Adult IIM patients seen at the University of Pittsburgh Myositis Center were prospectively enrolled. DM/PM patients had definite/probable IIM using the 2017 ACR/EULAR classification criteria. The patients had six myositis core set measures [manual muscle testing (MMT), extra-muscular global (EXGD), physician global (MDGD), and patient global disease activity (PtGD), creatine kinase (CK), HAQ-DI], as well as two physical function tests (PROMIS PF20 and SF36), three functional measures (STS, TUG, and 6MWD) and physical activity monitor (steps per min per day and peak 1-min cadence with Actigraph®). 6MWD measures the distance an individual is able to walk over 6 min on a flat surface. The TUG measures the time needed to stand up from a chair, walk 3 m, turn around, walk back to the chair and sit down. The STS measures the number of times a patient can repeatedly stand up from a chair and sit back down in 30 sec. STS and TUG were performed twice, 5-mins apart, and 6MW was performed single time at both home and office settings. Bland Altman plots compared the functional tests at home vs. office setting. Patients were categorized as having active or inactive disease by the treating physician. Spearman test assessed the correlation (Rho>0.50=strong; 0.30-0.49=moderate, <0.30=poor) between the functional tests and the other myositis outcome measures.
Results. Fifty patients [mean age 51.6 (SD 14.9), 60% female, 94% Caucasian, 6 PM, 9 NM, 24 DM, 11 ASyS) were studied. Of 50 patients, 24, 23, and 20 completed at-home STS, TUG, and 6MWD testing, respectively. The median time interval between office and home testing was 7 days for STS [IQR 4-17.7] and TUG [IQR 4-19], and 7.5 days [IQR 3.2-19] for 6MWD. Both STS and TUG had strong test-retest reliability in both the home (0.97 and 0.96, respectively) and office settings when performed two times five mins apart (ICC 0.98 and 0.97, respectively). STS, TUG, and 6MWD significantly discriminated between physician-defined active vs inactive disease supporting known-group validity. All three functional measures at baseline correlated strongly with the MMT (particularly in the lower extremity); moderately with disease activity (MDGD, PtGD, muscle disease activity), physical function measures (HAQ, PROMIS PF20, SF36 PF), and physical activity variables (peak 1-min cadence and step per min per day).and poorly with EXGD, pain, and fatigue. Both STS and TUG results were comparable between office and home setting with ICC 0.93 and 0.96, respectively, whereas the 6MWD results were less comparable with ICC of 0.54 (Figure). The 6MWD was significantly higher at the office compared to the home setting (median 2787 vs 1527).
Conclusion. Both STS and TUG have good test-retest reliability, construct and discriminant validity and perform similarly in the office setting compared to the home setting when self-performed by the patient. Thus, STS and TUG appear to be suitable metrics for remote self-assessment by patients. The 6MWD is a valuable tool providing information about physical activity/function when performed in the office, but has poor reliability when done at home by the patient.
Acknowledgements. The Myositis Association.



Outcome Measures	Sit-to-stand (Rho)	Timed up-and-go (Rho)	Six-min walk (Rho)
Manual Muscle Testing	0.53	-0.60	0.56
Physician global disease activity	-0.41	0.44	-0.54
Patient global disease activity	-0.43	0.45	-0.62
Extramuscular global disease activity	0.07	0.01	-0.17
Creatine kinase	-0.21	0.15	-0.42
HAQ-DI	-0.45	0.41	-0.54
PROMIS Physical Function	0.39	-0.37	0.56
SF36 Physical Functioning	0.41	-0.36	0.66
Peak 1-min cadence	0.43	-0.54	0.77
Steps per min per day	0.43	-0.49	0.69
Pain VAS	-0.12	0.03	-0.25
Fatigue VAS	-0.28	0.16	-0.35

O-26. Fig. 1. Functional measures (sit-to-stand (STS), timed-up-and go (TUG), and six minute walk (6MW)) when performed in the office *vs* home setting, and correlations of functional measures with other myositis measures.

O-27

SARCOPENIA IN MYOSITIS PATIENTS: A MARKER OF MUSCLE DAMAGE ASSOCIATED WITH MYOSITIS SEVERITY AND DISABILITY

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Background. Myositis are autoimmune diseases characterized by muscle inflammation and weakness. Even when disease activity has been resolved, myositis patients frequently present residual muscle weakness, decreased physical performance and disability. Sarcopenia is a progressive generalized skeletal muscle disorder characterized by low muscle strength and mass leading to disability, decreased quality of life and increased mortality. Sarcopenia has been reported in various autoimmune diseases, but it has never been studied in myositis. The aim of thes study was to investigate prevalence and significance of sarcopenia in myositis patients with low or no disease activity.

Methods. Adult myositis patients according to 2017 ACR/EULAR classification criteria, with disease duration greater than 12 months, creatine kinase serum level (CK) less than 500 U/l, stable medication for 6 months were enrolled. 30 healthy volunteers paired for age and sex were included as controls. At the enrolment, total (LM) and appendicular lean mass (ALM) were measured using dual-energy X-ray absorptiometry (DXA) and muscle grip strength using Jamar dynamometer. Sarcopenia was defined according to the European Working Group on Sarcopenia in Older People 2 consensus. Disease activity and damage were assessed according to International myositis assessment and Clinical Studies Group (IMACS). Muscle strength was measured by manual muscle test (MMT-8; MMT-12) and hand-held dynamometer, physical performance by 6-minute walking test (6mWT) and quality of life was assessed by Health Assessment Questionnaire (HAQ). Categorical data were expressed as percentages, normally distributed continuous variables as mean (± standard deviation), non-normally distributed continuous variables as median and interquartile range.

Results. 34 patients (22 females, 63.6%), average age 59.9 years (±14.1), were prospectively enrolled. They suffered from DM (n=5), necrotizing autoimmune myopathy (NAIM, n=10), anti-synthetase syndrome (ASS, n=11), scleromyositis (SM, n=8) since 4.9 years (3.0-8.6). 7 patients (20.6%) were sarcopenic (vs 0% in controls, p=0.03). At the enrolment, sarcopenic patients were globally weaker as highlighted by lower MMT-8 (134 (117.5-138) vs 142.5 (136-149), p=0.02) and MMT-12 (201 (176.3-209.5) vs 215.5 (207-218.3), p=0.01); they had a lower physical performance as demonstrated by distance covered at 6-minute walk test (196 meters ± 80.2 vs 484.5 ± 87, p<0.0001), and a poorer quality of life as suggested by HAQ score (2/3 (1.1-2.5) vs 0.6/3 (0.3-0.9), p=0.002). LM and ALM positively correlated with hand-held dynamometer measures, and 6mWT score (r=0.5, p<0.005 for LM; r=0.6, p<0.001 for ALM). Myositis subtype was differentially distributed between sarcopenic and non-sarcopenic patients (p=0.04): sarcopenic patients generally suffered from NAIM (57.1% vs. 22,2%) or DM (28.6% vs. 11.1%), none of them had AS (vs. 40.7%). Consistently, sarcopenic patients had higher maximum CK levels (5999 U/l (3153-6750) vs 1636 U/l (836-4528), p=0.1). Moreover, 50% of sarcopenic patients had myocarditis (vs 3.7%, p=0.002). By contrast, skin and/or joint and/or lung involvement were less frequent in sarcopenic patients (12.5% vs 87.5%, p=0.3), especially none of the patient had arthritis or inflammatory arthralgias during the follow-up (0% vs 48.2%, p=0.03). Cancer tended to be more frequent in sarcopenic patients (16.7% vs 3.7%, p=0.2). In a multivariate analysis, myositis subtypes and myocarditis were independently associated with sarcopenia (respectively p=0.04 and p=0.001). Sarcopenic patients required more frequently aggressive therapy as intravenous immunoglobulins (83.3% vs 33.3%, p=0.03), plasmapheresis (33.3% vs 3.7%, p=0.02) and/or janus kinase inhibitors (16.7% vs 0%, p=0.03). Both extent and severity of damage score according to the IMACS were significantly higher in sarcopenic patients, respectively 0.17 (0.14-0.25) vs 0.08 (0.03-0.11), p=0.0005; and 1.5 (1.1-2.2) vs 0.45 (0.27-0.82), p=0.0002.

Conclusions. Muscle mass measured by DXA is a biomarker of myositis damage. Sarcopenic myositis patients are a subgroup with important muscle damage and disability.

Workshop I: Juvenile dermatomyositis

JDM-1

OXIDISED MITOCHONDRIAL DNA: A NEW THERAPEUTIC TARGET IN JUVENILE DERMATOMYOSITIS (JDM)

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Background. Juvenile dermatomyositis (JDM) is a rare childhood autoimmune disease presenting with muscle weakness and skin rashes. Immunologically, JDM is characterised by a strong interferon (IFN) type I signature. The aim of this study was to identify 'druggable' dysregulated pathways up-stream of IFN type 1 to address the unmet need for novel targeted therapies in this devastating childhood condition.
Methods. CD14$^+$ monocytes were sorted by flow-cytometry from JDM patients [pre-n=10 on-n=12 treatment] and controls for RNA-sequencing. KEGG pathway analysis were used for differentially expressed genes (DEG) from RNA-seq data set. CD14$^+$ monocyte mitochondrial content was assessed by flow cytometry using MitoSox(MFI), JDM pre-treatment [n=5], on-treatment [n=6] and control [n=3]. Citrate synthase rate normalised to protein content in JDM [n=8] and control [n=10]. Mitochondrial superoxide quantification: total PBMC were stained with CD14 APC, Mitotracker green and MitoSox, JDM [n=6] and control [n=9]. Deconvolved images were used to calculate mitochondrial content, superoxide and overlap of superoxide with mitochondrial content. Levels of oxidised mitochondrial DNA(oxmtDNA) from monocyte were measured by western dot-blot, JDM [n=10] and CHC [n=11]. Plasma cell-free mtDNA (MT-CO3 copy number) was quantified for JDM pre-treatment [n=45] and CHC [n=16] using standard curve qPCR. Healthy-control PBMC samples [n=6] were cultured with IFN-alpha or oxmtDNA (+LL37) ± toll-like receptor 9 (TLR9) antagonist or n-acetyl cysteine(NAC) and IFN-stimulated gene (ISG) expression was measured by qPCR.
Results. We demonstrate that a dysregulation of mitochondrial-associated genes in CD14$^+$ monocytes in JDM, which correlates with an increase in ISG expression. Dysregulation in mitochondrial-associated genes in JDM CD14$^+$ monocytes was associated with altered mitochondrial biology including increased mitochondrial fragmentation, changes in cellular metabolism, and a reduction in expression of superoxide dismutase 1 (SOD1) leading to increased production of superoxide and oxidised mitochondrial oxmtDNA. *In vitro*, oxmtDNA induced up-regulation of ISGs, which could be blocked by addition of both TLR9 antagonist and the antioxidant N-actelycysteine (NAC).
Conclusions. These results demonstrate a novel pathway by which oxmtDNA production in CD14$^+$ monocytes stimulate ISGs and represent a therapeutically targetable mechanism in JDM and other IFN type 1-driven autoimmune diseases.
Acknowledgments. The Juvenile Dermatomyositis Research Group would like to thank all of the patients and their families who contributed to the Juvenile Dermatomyositis Cohort & Biomarker Study & Repository. We thank all local research coordinators and principal investigators who have made this research possible. We would like to thank the patients and volunteers who have contributed to the Centre for Adolescent Rheumatology Versus arthritis biobank, and to all the researchers who have made this possible. We thank CureJM, The Myositis Association, Versus Arthritis and the NIHR GOSH BRC for funding.

JDM-2

A PLASMA-INDUCED TRANSCRIPTOME SIGNATURE IN TREATMENT-RESISTANT JUVENILE AND ADULT MYOSITIS PATIENTS IS ASSOCIATED WITH ACTIVATED IFN, IL-6 AND INHIBITED IL-15 SIGNALING PATHWAYS, AS WELL AS REGULATORS OF NK AND CD4 T CELL DIFFERENTIATION

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Background. A novel approach to assess the immune response and upstream signaling pathways in disease states utilizes patient serum or plasma to induce gene expression in healthy, unrelated third-party PBMCs. Our objective in this study was to determine the plasma-induced transcriptome in treatment resistant juvenile and adult idiopathic inflammatory myositis patients.
Methods. Baseline plasma samples from 18 treatment-resistant adult and pediatric myositis subjects (4 dermatomyositis, 9 polymyositis, 5 juvenile dermatomyositis) who enrolled in the Rituximab in Myositis trial and 5 adult healthy controls were used for a plasma-induced transcription assay. Commercially cryopreserved PBMCs from a Caucasian HLA-A2 male donor (UPN119, Cellular Technology Ltd., Shaker Heights, OH) were co-cultured with subject plasma. cRNA was synthesized and amplified/labeled using the Affymetrix Express Kit, then fragmented and hybridized to the GeneChip Human Genome U133 plus 2.0 array in accordance with the manufacturer's protocol (Thermo Fisher, Waltham, MA). The statistical significance of differential gene expression was determined though Log2ratio, ANalysis Of VAriation (ANOVA), and false discovery rates (FDR). Pathway analysis was performed with Integrated Pathway Analysis (IPA).
Results. Relative to the healthy controls, there were 192 unique transcripts that met thresholds of |Log2ratio| >0.263) and FDR ≤0.2. The top Ingenuity canonical pathways in the myositis subjects included Sirtuin signaling, BEX2 signaling, and ATM signaling, which are correlated with cellular senescence, mitochondrial apoptosis, and DNA damage/ionizing radiation, respectively. Other prominent Ingenuity pathways included inhibition of ARE-mediated mRNA degradation pathway and the Human leukocyte antigen (HLA)-F adjacent transcript 10 (FAT10) signaling pathway, which are proteosome degradation pathways that are downstream of TNF and/or IFNγ signaling and are involved in the regulation of type I and II interferons. Upstream regulators that were predicted to be inhibited included STAT3, GLI1, EGFR, PRDM1, and IL15 whereas activated upstream regulators included STAT1, PTEN, GFI1, APP, and SIRT1. Common ontology Biological Process GO Annotations among inhibited upstream regulators included regulation of T cell differentiation, regulation of NK cell differentiation, and IL-15 mediated signaling pathway, whereas common GO Annotations among activated upstream regulators included regulation of IL-6, NF-kappaB, and response to and/or production of IFNγ.
Conclusion. Using a plasma-induced transcriptome assay, the top canonical signaling pathways in third party healthy donor PBMCs co-cultured with myositis plasma relative to healthy control plasma were associated with cell damage/survival and mediated by TNF, type I IFN, and type II IFN signaling. Our data indicate that dysregulation of IL-6 production as well as aberrant differentiation of Treg, Th17, and NK cell populations are associated with persistent disease activity in treatment resistant patients. The relative role of these factors in the underlying pathophysiology of myositis versus their impact leading to more severe disease in treatment resistant patients remains to be determined.

JDM-3

URINE PROTEOMICS BY MASS SPECTROMETRY IDENTIFIES PROTEINS INVOLVED IN KEY PATHOGENIC PATHWAYS IN PATIENTS WITH JUVENILE DERMATOMYOSITIS

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Background. Juvenile dermatomyositis (JDM) is a heterogenous autoimmune muscle disease that presents with weakness, fatigue, skin rashes, and in some cases, calcinosis. Previous biomarker studies for JDM disease course, activity, and assessment of treatment responses have primarily been performed on blood. Urine proteomics is an attractive approach for biomarker studies because urine is easy to collect and is less invasive, especially for children. Given the rarity of the disease and lack of outcome measures, urine biomarkers, if validated, can serve as surrogate markers of disease activity to monitor disease progression and response to therapy.
Methods. First morning void urine samples were collected from JDM patients (n=20) and healthy controls (n=21). Aliquots containing an equal amount of total protein from each sample were digested by trypsin and processed for multiplexing analysis using our standardized Tandem Mass Tag LC-MS/MS approach. Proteins were identified and quantified using a workflow designed in Proteome Discoverer 2.2 (Thermo Fisher Scientific). Significantly differentiated biomarker candidates were correlated with clinical measures of myositis disease activity and damage to determine relationships with protein expression.
Results. We identified a total of 2348 proteins in the urine of all JDM patient and control samples, with 1181 of these proteins detected in at least 7 samples per group. After data normalization and statistical analysis, 14 proteins were significantly increased, and 29 proteins were significantly decreased in the subset of urine samples of JDM patients compared to healthy controls. Many of the differentially altered urine proteins were associated with key pathogenic features of disease: 1) inflammatory and immune response proteins, such as galectin-3 binding protein (LGALS3BP), interleukin-1 receptor antagonist protein (IL1RA), and glycoprotein nonmetastatic melanoma protein B (GPNMB) were increased in JDM urine, 2) extracellular matrix proteins, including collagens (COL1A1, COL2A1, COL6A2, and COL12A1), procollagen C-endopeptidase enhancer 1 (PCOLCE), cartilage intermediate layer protein 2 (CILP2), basement membrane matricellular proteins (cartilage oligomeric matrix protein [COMP], tenascin-X [TENX]) and proteoglycans (aggrecan [ACAN] and lumican [LUM]) were decreased in JDM, and 3) bone mineralization proteins, including dentin matrix acidic phosphoprotein 1 (DMP1), matrix extracellular phosphoglycoprotein (MEPE), and osteocalcin (BGLAP) were decreased in JDM urine. Several of these proteins also correlated with clinical measures of disease activity or damage. For example, MMT8 scores were negatively correlated with CILP2 (r=-0.60, p=0.02) and ILIRA (r=-0.66, p=0.02) expression. We also found that CTSD (r=-0.54, p<0.05), COL1A2 (-0.54, p<0.05) and COL2A1 (r=-0.65, p=0.01) were negatively correlated with CMAS. CD84 expression was positively correlated with the CHAQ (r=0.50, p=0.03). IL1RA (r=0.80, p<0.01), CD84 (r=0.64, p=0.01), CTSD (r=0.55, p=0.03), COL1A1 (r=0.55, p=0.03), COL2A1 (r=0.53, p=0.04), and COL1A2 (r=0.54, p=0.04) were all positively correlated with MDI muscle damage. The MDI Total Severity score was positively correlated with COL2A1 (r=0.58, p=0.02). Finally, MD Global Damage scores positively correlated with PCOLCE (r=0.74, p=0.01).
Conclusions. We have optimized a urine proteomics workflow that allows for the identification of proteins associated with key biologic features of JDM. The main findings of this study include the confirmed presence of several proteins in the urine of JDM patients that, in previous studies, were found to be elevated in the blood. We also identified several novel proteins that require validation and determined that several of these proteins correlate with clinical measures of disease activity or damage. Overall, our results support using urine proteomics to characterize pathophysiological processes involved with this disease. Studies are underway to confirm and validate these proteins using independent samples and assays, and to determine if their expression changes in response to treatment.
Acknowledgements. CureJM; The Myositis Association.

JDM-4

PLASMA PROTEOMIC SIGNATURES IN JUVENILE DERMATOMYOSITIS DEFINE NOVEL DIFFERENTIALLY REGULATED PROTEINS IN TREATMENT NAÏVE PATIENTS AND ARE DISTINCT FROM CHILDHOOD-ONSET LUPUS

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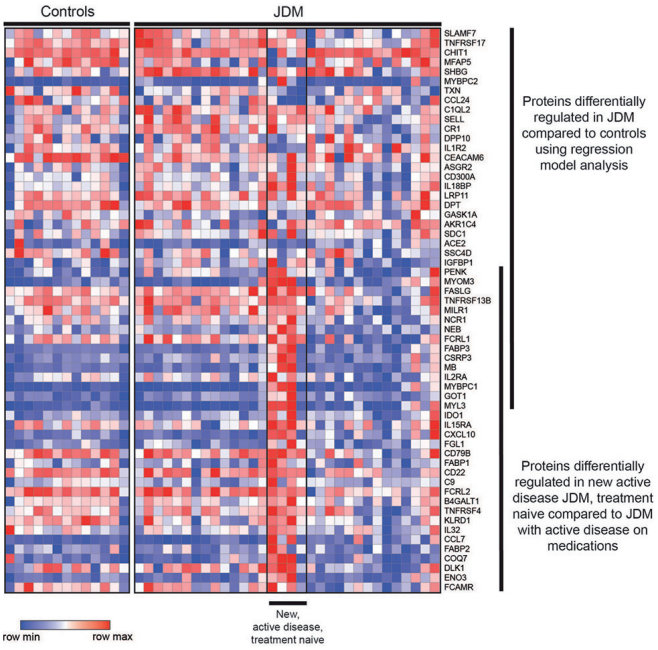
Background. Improving assessment of disease activity and prediction of disease severity are ongoing challenges in JDM clinical care. The use of a broad proteomics approach to define patient disease signatures has the potential to lend insight into targeted treatment. Our study used a multiplexed proteomics assay for simultaneous measurement of 1467 proteins in a well-phenotyped cohort of JDM, childhood-onset systemic lupus erythematosus (cSLE), and healthy control (CTL) patients. Our goals were to (1) identify differentially regulated proteins and pathways between JDM, CTL and cSLE and (2) determine the association of identified proteins with clinical disease activity in JDM.
Methods. We measured plasma levels of 1467 proteins using the multiplexed, Olink proximity extension assay panels (Inflammation I&II and Cardiometabolic I&II) in 32 JDM, 18 cSLE, and 13 CTL. JDM and cSLE all met either 2017 EULAR/ACR classification criteria for JDM or 2019 EULAR/ACR classification criteria for SLE, with exception of two lupus patients with isolated cutaneous disease. In JDM, we collected Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI) activity, Manual Muscle Testing (MMT-8), and Physician's Global Assessment of Disease Activity (PGA) scores. In our cohort, 18 (56.3%) JDM and 15 (83.3%) cSLE had clinically active disease. Four (12.5%) JDM and five (27.8%) cSLE had new-onset, treatment naïve disease. We identified proteins differentially regulated between groups using linear regression models adjusting for age, gender, disease activity, and whether on immunosuppression, with p-value<0.05 considered statistically significant. We also performed differential protein expression analysis with MultiExperiment viewer (MeV) software (false discovery rate (FDR)<0.10 considered statistically significant) and Ingenuity Pathway Analysis (IPA). We then correlated protein expression with CDASI, MMT8 and PGA scores using Pearson correlation (FDR<0.05 considered significant).
Results. Comparison of JDM to CTL identified 40 differentially regulated proteins by linear regression models, including SLAMF7, PENK, GOT1, MYOM3, FASLG, IL1R2, FCRL1, FABP3, and IL18BP (Figure 1). Top biological pathways dysregulated in JDM versus CTL included granulocyte adhesion and diapedesis (p-value=0.0003) and B cell activating factor signaling (p=0.0024). In treatment naïve JDM, 34 proteins were differentially expressed compared to active disease on treatment (Figure 1). Of these, the top upregulated proteins in treatment naïve JDM included MYOM3, CXCL10, and IDO1 (fold change (FC) of 30.5, 11.2, and 10.8) from inflammation panels and CSRP3, MYBPC1, FABP3 (FC 50.2, 40.7, 36.3) from cardiometabolic panels. GOT1 (FC 2.9) was also a notable protein. CCL7 demonstrated correlation with PGA (r=0.78), CDASI (r=0. 77), and MMT-8 (r=-0.70). Known biomarkers CXCL10 (r=0.84)



JDM-4. Fig. 1

and LGALS9 (r=0.71) also correlated with PGA. Additionally, GOT1 and IDO1 correlated with CDASI and PGA. When comparing JDM to cSLE, linear regression model and differential expression analyses identified 283 and 236 proteins respectively. Both strategies identified IL-6, TNF, IFNG, LAMP-3 and MERTK as upregulated in cSLE and MYOM3 and PENK as upregulated in JDM. Top biological pathways differentiating cSLE from JDM included crosstalk between dendritic and NK cells, Th1 and Th2 activation pathway, IL-17 signaling and STAT3 pathway.
Conclusions. We identified novel differentially expressed proteins in JDM, including IDO1, SLAMF7, and GOT1 and also confirmed known dysregulated proteins, including CXCL10 and LGALS9. Clinical disease activity measures were found to correlate with known interferon-stimulated proteins, such as CXCL10, CCL7, and LGALS9, as well as with novel metabolic proteins IDO1 and GOT1. Several of the top dysregulated proteins in treatment naïve JDM were related to muscle structure and require further comparison to traditional muscle enzyme biomarkers. JDM and cSLE had unique differentially expressed proteins, with cSLE having an overall higher inflammatory signature including upregulation of IL-6, TNF and IFNG.
Acknowledgements. Cure JM and Rheumatology Research Foundations.

JDM-5

SIGLEC-1 REFLECTS THE DYSREGULATED TYPE I IFN PATHWAY AND CAN PREDICT TREATMENT RESPONSE IN JDM

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Background. A dysregulated interferon (IFN) pathway is an important hallmark of JDM pathogenesis. Our aim was to determine the potential of Siglec-1, a macrophage/monocyte-restricted surface marker, as a novel IFN-stimulated biomarker in patients with JDM, and to study induction and inhibition of Siglec-1 in vitro.
Methods. PBMC samples were collected from 21 newly diagnosed JDM patients before start of treatment and, for 10 of these, also during follow-up. Fifteen healthy control subjects were included as well as 7 patients with Duchenne muscular dystrophy as non-autoimmune muscle disease controls. The expression levels of five type I IFN-stimulated genes, MX1, IFI44, IFI44L, LY6E and IFIT3, were measured by RT-qPCR to determine the IFN signature and calculate an IFN score. Surface protein expression of Siglec-1 was measured by flow cytometry in $CD14^+$ PBMCs from study subjects and in control PBMCs that were stimulated *in vitro* with Toll-like receptor (TLR) agonists or cytokines including type I or II IFNs, TNF-α, or IL-1β. Pre-incubation with various JAK-inhibitors (ruxolitinib, baricitinib, tofacitinib, filgotinib) at 1μM for 1 h was performed to study their effect on Siglec-1 expression.
Results. Siglec-1 and IFN score were increased in JDM patients compared with controls and correlated with clinical disease activity. Patients with high Siglec-1 expression at diagnosis had a higher risk of requiring treatment intensification within the first 3 months after diagnosis compared to those with low Siglec-1 expression (55% vs 0% of patients, p=0.01). Siglec-1 was superior to the IFN score in predicting treatment response (area under the curve 0.87 vs 0.53, p=0.01). *In vitro* studies showed that Siglec-1 was induced after 12 h by type I IFNs and certain TLR agonists, including TLR-7 (imiquimod), TLR-9 (Class A CPG ODNs), and, most potently, TLR-3 (poly I:C). Pre-incubation with ruxolitinib or baricitinib prevented induction of Siglec-1 by poly I:C, while pre-incubation with tofacitinib only partly reduced Siglec-1 induction, and filgotinib, a selective JAK-1 inhibitor, had no effect at all. Siglec-1 induction by IFNα could not be inhibited by any of the JAK-inhibitors.
Conclusions. Siglec-1 on circulating monocytes reflects the dysregulated type I IFN response in JDM and may serve as a novel biomarker for monitoring disease activity and predicting treatment response in JDM. Siglec-1 expression is induced *in vitro* by type I IFNs and TLR agonists, which can be inhibited to different extents by JAK inhibitors in the case of TLR stimulation but not IFNα. This suggests that JAK1 inhibition may not be sufficient to abrogate IFNα-induced activation. These findings may help develop a mechanism-based personalized treatment strategy and substantiate the use of novel drugs in children with JDM.

JDM-6

DEFINING CRITERIA FOR DISEASE ACTIVITY STATES IN JUVENILE DERMATOMYOSITIS BASED ON THE JUVENILE DERMATOMYOSITIS ACTIVITY INDEX

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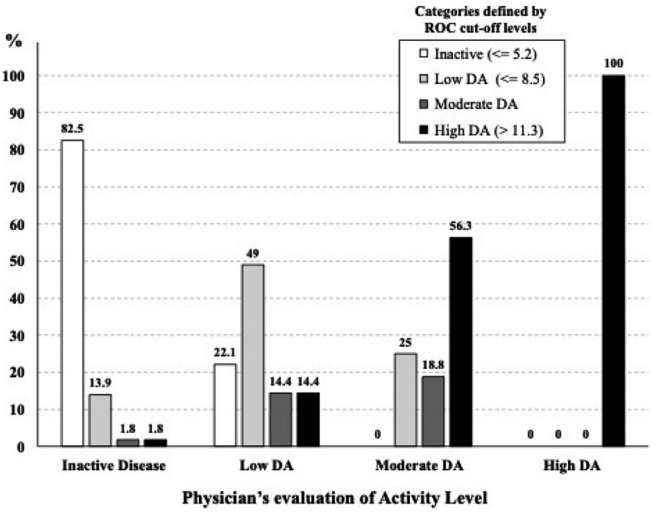
Background. The Juvenile DermatoMyositis Activity Index (JDMAI) is the first composite disease activity score validated for the measurement of muscle and skin involvement in juvenile dermatomyositis (JDM). Six preliminary versions (JDMAI1 to 6) have been proposed. Both JDMAI1 and JDMAI2 include the physician's global assessment of overall disease activity (PhGA) on a visual analog scale (VAS) (where 0 = no activity and 10 = maximum activity), the parent's global assessment of child's overall wellbeing (PaGA) on a VAS (where 0 = best and 10 = worst), and the hybrid MMT8/CMAS (hMC) expressed in deciles (0 = best to 10 = worst). To estimate the activity of skin disease, the JDMAI1 includes the skin activity VAS (where 0 = no activity and 10 = maximum activity), whereas the JDMAI2 includes the skin component of the Disease Activity Score (DAS) (score range 0 = no activity to 9 = maximum activity). The theoretical range is, therefore, 0 to 40 for the JDMAI1 and 0 to 39 for the JDMAI2. Cutoffs for the states of inactive disease (ID), low disease activity (LDA), moderate disease activity (MDA) and high disease activity (HDA) are necessary to interpret the JDMAI scores. The aim of the study was to develop and validate these cutoffs for JDMAI1 and JDMAI2.
Methods. The cutoffs definition cohort was composed of 129 patients included in the PRINTO JDM trial and evaluated at 6 months from baseline. Optimal cutoff values were determined against external criteria by calculating the 10th and 25th percentile (for ID), the 30th and 40th percentile (for LDA), and the 75th and 90th percentile (for HDA) of cumulative score distribution and through receiver operating characteristic curve analysis. External criteria included the modified PRINTO criteria for clinically inactive disease (for ID) and the PRINTO/ACR/EULAR level of improvement (for LDA and HDA). MDA cutoffs were defined as the score interval between LDA and HDA cutoffs. The choice of final cutoffs was based on clinical and statistical grounds. The validation cohort included 213 patients followed up in standard clinical care at 13 international paediatric rheumatology centres, and 275 patients enrolled in a study aimed to validate prospectively the provisional PRINTO/ACR/EULAR disease activity core set for the evaluation of response to therapy in JDM. Cutoff validation was conducted by assessing discriminative ability.
Results. The selected JDMAI1 cutoffs were 2.4 for ID, ≤6.6 for LDA, 6.7-11 for MDA, and >11 for HDA. The selected JDMAI2 cutoffs were ≤5.2 for ID, ≤8.5 for LDA, 8.6-11.3 for MDA, and >11.3 for HDA. In cross-validation analyses, the cutoffs showed strong ability to discriminate among disease activity states defined subjectively by physicians and parents, parents' satisfaction/dissatisfaction with illness outcome, levels of child's pain and fatigue, and presence/absence of functional impairment and disease damage.
Conclusions. Cutoff values for classifying various disease activity states in JDM using the JDMAI1 and JDMAI2 were developed. The cutoffs revealed good metrologic properties in both definition and validation samples, and are therefore suitable for application in clinical practice and research.



JDMAI-6. Fig. 1. Categories of disease activity defined according to ROC curve for JDMAI2 score and Physician's evaluation of Disease Activity Level (Routine sample n=213, all visits).

Workshop II: Physiotherapy and Occupational Therapy

IS-23

EXERCISE IS MEDICINE - POSITIVE EFFECTS ON PHYSICAL CAPACITY, QUALITY OF LIFE AND DISEASE ACTIVITY IN MYOSITIS

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Background. Despite a good effect of treatment on inflammation, many individuals develop sustained limitations in physical capacity and quality of life. The effects of this treatment in patients with inclusion body myositis (IBM) is uncertain, with a progression of muscle weakness. Further, many individuals with myositis experience pain and fatigue, including both muscle fatigue and a more general fatigue[3]. People with myositis also have a higher prevalence of cardiovascular risk factors, for ex. type 2 diabetes, and insulin resistance. Previously, people with myositis were refrained from exercise, due to a fear of increased muscle inflammation.
Exercise effects on physical capacity. During the last 20 years, around 40 publications evaluating different types of exercise interventions all support the safety of exercise in all myositis sub-types. A meta-analysis revealed a large positive effect of a combination of aerobic and resistance training on aerobic capacity and a moderate positive effect on muscle function in adults and children with myositis. However, studies on IBM were not included in this analysis. One study evaluating effects of combined aerobic capacity and resistance training reported significant positive effects on aerobic capacity in a small group with IBM. Further, studies support that 12-16 weeks of exercise can improve muscle strength, especially in muscles less affected by IBM. A recent study from Denmark on IBM reported that 12 weeks of blood-flow restricted submaximal resistance training resulted in a 6% increase in quadriceps muscle strength compared to an almost 10% reduction in strength in the non-exercising control group. There was a significant and clinically relevant difference between the groups over time in favor for the exercise group, which supports that exercise can preserve or slightly improve strength in a severely affected muscle group, such as the quadriceps, while no exercise leads to worsening.
Exercise effects on patient reported outcomes. Effects on patient-reported outcomes, which probably are the most important outcomes for patients, are less studied. However, many studies report that exercise improves quality of life and daily activity performance, and a few studies also show reduced fatigue levels by exercise, while there is very little evidence available on how exercise affects pain.
Effects on inflammation. Intensive exercise on 70% of maximal effort reduced disease activity and inflammation in adult, low inflammatory myositis compared to a non-exercising control group. The exercise group had significantly reduced clinical disease activity according to validated response criteria, genes regulating inflammation were downregulated and genes regulating muscle growth and development of capillaries were upregulated and mitochondrial enzyme activity improved compared to the control group, taken together supporting improved muscle health.
Exercise and physical activity to optimize health. In general population, physical activity and exercise prevent cardiovascular disease, osteoporosis, type 2 diabetes, and some forms of cancer. A combination of aerobic and resistance training can improve insulin resistance in established dermatomyositis, indicating that exercise can prevent cardiovascular disease also in myositis, but this needs further studies. It is important for everyone to be physically active in their daily life and to exercise regularly to improve to optimize health, including people with myositis.The many health benefits with physical activity and exercise could be important motivators for individuals with for example IBM who may not experience an effective response to exercise on muscle function.
How to get started and progress exercise. If you recently were diagnosed with myositis, if you experience a flare or have not exercise before, it is important to get started with exercise with support from a physiotherapist with knowledge of myositis. Start on a low-intensity level and increase slowly towards goal intensity, adapting exercise to physical capacity, fatigue, and pain levels. Long-term support can be important to progress exercise along with improvements or reduce intensity in a flare. It is important to evaluate objective and self-reported function before starting to be able to assess exercise effects over time.
A global collaboration including patient research partners and myositis experts and clinicians, the IMACS Rehabilitation and Exercise Scientific Interest Group are currently developing consensus, evidence-based exercise guidelines for all adult and juvenile myositis subtypes delineating content and quality of publications. Information to patients and health-care providers will be translated to many languages to spread the evidence supporting exercise for everyone living with myositis.

IS-24

TRAINING FOCUSED ON ACTIVITIES OF DAILY LIVING (ADL) IN IDIOPATHIC INFLAMMATORY MYOPATHIES

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Chronic inflammation of the muscles, subsequent muscle atrophy, and permanent muscle damage in patients with IIM are the cause of a decrease in muscle strength and endurance. Moreover, IIM also affect internal organs and manifest often with impaired lung and heart function. All of these involvements lead to a decrease in the quality of life of patients.
Due to limitations in pharmacological therapy, non-pharmacological interventions could help bring patients back into their everyday life and improve their quality of life.
The data on efficacy of non-pharmacological care in IIM are very limited due to the heterogeneity of the studied interventions and/or outcomes. None of them has yet focused mainly on ADL training (Activities of Daily Living).
Therefore, the presentation will present the results of our study together with the procedures and content of the exercise unit focused mainly on ADL training (86% composition of physical intervention), strengthening the deep muscular system (HSSP), stability training and intensive strengthening of proximal muscle groups.
Then there will be a practical demonstration of ADL training.

IS-25

OCCUPATIONAL THERAPY FOR PEOPLE WITH IDIOPATHIC INFLAMMATORY MYOPATHIES.

Hana Šmucrová[1*], Malin Regardt[2*]
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Equally contributed

Occupational therapy is an essential part of rehabilitation of people with idiopathic inflammatory myopathies. By the nature of these disorders, patients are limited in the performance of activities of daily living. In personal activities of daily living, they have difficulty with hygiene, dressing, and transfers (from lying to sitting, sitting to standing, or rising from squatting). This is associated with shortness of breath and increased general fatigue, which limits the performance of these activities. Walking (on flat ground and in rough terrain) is also difficult. Of the instrumental activities of daily living, shopping, transport (by public transport) and routine household cleaning are difficult. In the case of inclusion body myositis, reduced hand grip function is prominent.
Therefore, occupational therapy also includes not only training of self-sufficiency in ADL activities, but also training of grip function and hand muscle strength. In order for therapy to be successful, it is necessary to educate patients in energy conservation techniques. These are specific techniques, that allow patients to perform activities of daily living, work and leisure as efficiently as possible. They will learn to assess their potential for managing everyday activities and learn to plan ahead so that they have sufficient space to carry out these activities.
An introduction to occupational therapy for idiopathic inflammatory myopathies, specific techniques, and compensatory aids will be part of this workshop. There will also be space for patient questions. Demonstration of exercises for grip function and hand muscle strength will be then presented.

Poster Presentations

Genes and environment

P-1

ASSOCIATION WITH *HLA-DRB1* POSITION 37 DISTINGUISHES JUVENILE DERMATOMYOSITIS FROM ADULT-ONSET MYOSITIS

Claire T. Deakin[1,2,3], John Bowes[4,5], Lisa G. Rider[6], Frederick W. Miller[6], Lauren M. Pachman[7], Helga Sanner[8,9], Kelly Rouster-Stevens[10], Gulnara Mamyrova[11], Rodolfo Curiel[11], Brian M. Feldman[12], Adam M. Huber[13], Ann M. Reed[14], Heinrike Schmeling[15], Charlotte G. Cook[1], Lucy R. Marshall[1,2,3], Meredyth G. Ll. Wilkinson[1,2,3], Stephen Eyre[4,5], Soumya Raychaudhuri[*4,5,16,17], Lucy R. Wedderburn[*1,2,3] on behalf of the Juvenile Dermatomyositis Cohort and Biomarker Study, the Childhood Myositis Heterogeneity Study Group, and the Myositis Genetics Consortium (MYOGEN)

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Background. Juvenile dermatomyositis (JDM) is a rare, severe autoimmune disease and the most common idiopathic inflammatory myopathy (IIM) of children. JDM and adult-onset dermatomyositis (DM) have similar clinical, biological and serological features, although these features differ in prevalence between childhood-onset and adult-onset disease, suggesting age of disease onset may influence pathogenesis. Therefore, a JDM-focused genetic analysis was performed using the largest collection of JDM samples to date.
Methods. Caucasian JDM samples (n=952) obtained via international collaboration were genotyped using the Illumina HumanCoreExome chip. Additional non-assayed HLA loci and genome-wide SNPs were imputed.
Results. *HLA-DRB1*03:01* was confirmed as the classical HLA allele most strongly associated with JDM (OR 1.66; 95% CI 1.46, 1.89; p=1.4×10^{-14}), with an independent association at *HLA-C*02:02* (OR=1.74; 95% CI 1.42, 2.13, p=7.13×10^{-8}). Analyses of amino acid positions within *HLA-DRB1* indicated the strongest association was at position 37 (omnibus p=3.3×10^{-19}), with suggestive evidence this association was independent of position 74 (omnibus p=5.1×10^{-5}), the position most strongly associated with adult-onset DM. Conditional analyses also suggested the association at position 37 of *HLA-DRB1* was independent of some alleles of the Caucasian HLA 8.1 ancestral haplotype (AH8.1) such as *HLA-DQB1*02:01* (OR=1.62; 95% CI 1.36, 1.93; p=8.70×10^{-8}), but not *HLA-DRB1*03:01* (OR=1.49; 95% CR 1.24, 1.80; p=2.24×10^{-5}). No associations outside the HLA region were identified.
Conclusion. Our findings confirm previous associations with AH8.1 and *HLA-DRB1*03:01*, *HLA-C*02:02* and identify a novel association with amino acid position 37 within *HLA-DRB1* which may distinguish JDM from adult DM.
Acknowledgements. SR and LRW contributed equally to this manuscript. This work was funded by a TMA Fellowship and a Cure JM grant to CTD.

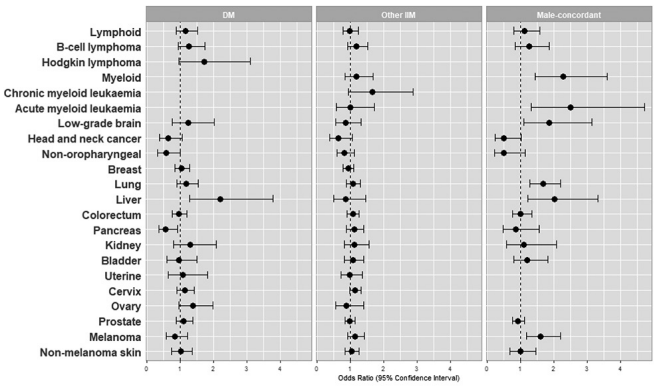
P-2

CLUSTERING OF CANCERS IN FAMILIES OF IDIOPATHIC INFLAMMATORY MYOPATHIES: ASSOCIATIONS VARY BY CLINICAL PHENOTYPE AND SEX

Weng Ian Che, Fredrik Baecklund, Karin Hellgren, Ralf Kuja-Halkola, Ingrid E. Lundberg, Helga Westerlind, Marie Holmqvist

Karolinska Institutet, Stockholm, Sweden

Background. Idiopathic inflammatory myopathies (IIM) are rare rheumatic inflammatory diseases characterized by muscle weakness and various extramuscular manifestations. Cancer is one of the complications associated IIM and associations with various types of cancer have been observed, particularly among patients with dermatomyositis (DM) or patients in male sex. The pathogenesis of cancer in IIM remains unclear. It has been suggested that IIM shares susceptibility with cancer, but it is unknown what are the contributing factors. There are a few family-based studies investigating familial clustering of hematological cancers in patients with IIM and none of them reported strong signals of association which might be hampered by small number of cancer cases. No previous study to date has analyzed clustering of solid cancers in families of patients with IIM. In this study, we aimed to explore the potential contribution of shared familial susceptibility to the development of cancer in IIM by investigating the familial clustering of cancer and IIM with nationwide register data in Sweden.
Methods. Via linkage to the Swedish health-, and population registers, we first identified patients with IIM with a robust algorithm. Each patient was matched with up to five individuals without IIM and then we linked all index individuals (patients with IIM and matched individuals) to their first-degree relatives. It resulted in 8,640 first-degree relative pairs of patients with IIM versus 41,127 relatives of the matched individuals without IIM. We ascertained lifetime cancer diagnosis in the first-degree relatives using data from the nationwide cancer and death registers. To estimate familial clustering of cancer and IIM, we used conditional logistic regressions where we compared the odds of cancer in the first-degree relatives of patients with IIM to that of first-degree relatives of individuals without IIM. We adjusted for sex and birth year of the index individuals and their first-degree relatives. We performed overall analyses and sub-group analyses by IIM subtypes and sex-concordance of the relative pairs. As exploratory analyses, we computed familial clustering for specific cancer types by IIM subtypes and by sex-concordance of relative pairs. We controlled for multiple testing with Benjamini and Hochberg (BH) false discovery rate procedure.
Results. We did not detect familial clustering of cancer overall in patients with IIM (adjusted odds ratio, aOR=1.04, 95% CI 0.99-1.09). However, in the subgroup analyses, we observed statistically significant clustering of cancer in male-concordant relative pairs of patients with DM compared to the male-concordant relative pairs of individuals without DM (aOR=1.39, 95% CI 1.15-1.68). Among female-concordant and sex-discordant relative pairs, no differences in familial clustering of cancer between the comparative groups were noted for DM, other IIM or juvenile IIM. In the exploratory analyses by IIM subtypes and by sex-concordance of relative pairs, only myeloid malignancy (aOR=2.27, 95% CI 1.43-3.60) and liver cancer (aOR=2.01, 95% CI 1.21-3.33) showed familial associations with IIM among male-concordant relative pairs after controlling for multiple testing (n=110) (Figure 1).
Conclusion. This is the first population-based family study comprehensively investigating familial clustering of cancer in patients with IIM. Our findings did not support shared familial susceptibility between cancer and IIM overall, but it might be of more importance in men with DM having male first-degree relatives affected by cancer given the observed familial clustering. The cancer types likely to share familial susceptibility with IIM were myeloid malignancy and liver cancer, and those factors might be relevant to male sex, but this needs to be investigated further.



P-2. Fig.1.

P-3

RNA-SEQUENCING OF THE COMPLEMENT GENES IN THE MUSCLE BIOPSIES OF AUTOIMMUNE MYOPATHIES

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Introduction. Complement deposition may play a pathogenic role in inflammatory myopathies (IM) but its local expression in IM muscle has not been described.
Objectives. To assess the local expression of complement and identify the cells producing these genes in different types of IM. Also, to determine whether the local expression of complement is correlated with disease activity.
Methods. We performed bulk RNA-sequencing on muscle biopsy specimens from 119 IM patients and 20 healthy comparators. We also performed single-cell and single-nuclei RNA-sequencing to identify which cells express complement genes.
Results. Complement genes C1-C3, C5, C7 were overexpressed in all the types of IM compared with normal muscle tissue (all q<0.013), with minimal differences among the IM subsets. Single-cell and single-nuclei studies showed that RNA of C1qA, C1qB, and C1qC were produced by macrophages whereas C1r, C1s, and C3 were produced by fibroblasts. C2 was produced by both macrophages and fibroblasts. C5 and C7 were expressed at lower levels and could not be identified by single-cell/nuclei RNA-seq. Also, we found a positive correlation of the expression of these genes with RNA markers of disease activity.
Conclusions. C1-C3, C5, C7 complement genes are overexpressed in all types of IM and were associated with the activity of the disease. There were minimal differences among IM subsets. Our results raise the possibility that the coordinated local expression of the initial components of the complement cascade in macrophages and fibroblasts primes the activation of the complement system in affected tissues.

P-4

CLINICAL, SEROLOGICAL AND GENETIC CHARACTERISTICS OF A HUNGARIAN MYOSITIS-SCLERODERMA OVERLAP COHORT

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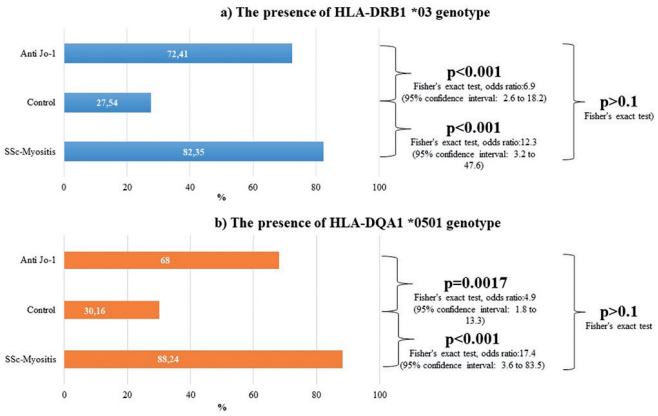
Background. Overlap myositis is a distinct subgroup of idiopathic inflammatory myositis (IIM) with various clinical phenotypes. The aim of this study was to determine the clinical, serological and genetic features of IIM - systemic sclerosis (SSc) overlap patients.
Methods. It was a retrospective study using clinical database of 39 patients, fulfilling both the criteria of SSc and IIM. DNA was genotyped using a commercial sequence-specific oligonucleotide kit.
Results. 56.4% of the patients had limited cutaneous, 43.6% had diffuse cutaneous SSc, whereas 7.7% of the patients had dermatomyositis and 92.3% polymyositis. The two diseases occurred simultaneously in 58.97%, while in 10.26% myositis and in 30.77% scleroderma were initially diagnosed. The frequencies of organ involvement were: interstitial lung disease 71.8%, dysphagia 66.7%, cardiac involvement 41%, pulmonary arterial hypertension (PAH) 30.8% and renal involvement 12.8% respectively. The presence of human leukocyte antigen (HLA)-DRB1*03 and DQA1*05:01 alleles were significantly higher in the overlap patients than in healthy controls (82,4% vs. 27.5%; $p<0.0001$ and 88.2% vs. 30.2; $p<0.0001$). Fever at diagnosis (41.7% vs. 7.4%, $p=0.0046$), cardiac involvement (83.3% vs. 22.2%, $p=0.0008$) subcutaneous calcinosis (41.7 vs. 11.1., $p=0.01146$) and claw hand deformity (25% vs. 11.1%, $p=0.00016$) were significantly associated with the presence of PAH. Major clinical and genetic results of the overlap patients showed similarities with anti-Jo-1 positive antisynthetase patients, however SSc-IIM overlap patients could be distinguished with higher erythrocyte sedimentation rate (ESR) level, more frequent presence of Raynaud's phenomenon ($p<0.0001$; OR: 20.00), dysphagia ($p<0.0001$, OR: 15.6; and infrequent livedo reticularis ($p<0.01$, OR: 0.11).
Conclusions. SSc-IIM overlap myositis is a unique group within IIM-s possessing characteristic clinical and genetic features.



P-4. Fig. 1.

P-5

GENE EXPRESSION PROFILES OF TREATMENT RESPONSE AND NON-RESPONSE IN CHILDREN WITH JUVENILE DERMATOMYOSITIS

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Background. Despite substantial improvements in juvenile dermatomyositis (JDM) treatment in recent decades, many children continue to have active disease years after diagnosis suggesting a substantial failure rate of first-line treatments. In the recent Pediatric Rheumatology International Trials Organization (PRINTO) clinical trial of prednisone, methotrexate, and cyclosporine even the most effective treatment arm, prednisone plus methotrexate, had a failure rate of approximately 25% in the first 6 months. To date, the early effects of standard treatment on the biology of newly diagnosed JDM are poorly understood, but are important for understanding the effects of current treatment and opportunities for future treatments to better address the existing unmet need for these children.
Methods. We used polyA selection RNA-sequencing to evaluate changes in JDM gene expression (GE) based on clinical response to treatment using the 2016 American College of Rheumatology/European League Against Rheumatism criteria (2016 Criteria) for minimal, moderate, and major clinical response in JDM. JDM subjects were dichotomized into treatment non-responders (NR) and responders (TR) if they had no to minimal response or moderate to major response to treatment based on the 2016 Criteria, respectively. Differential expression and pathway analysis using gene set enrichment analysis (GSEA) were used for the analyses. Three analyses were performed (A1-3) comparing differentially expressed genes (DEGs) and pathway analysis exploiting the timing of sample acquisition to perform these comparative analyses.
Results. 17 JDM subjects and 10 age-matched controls were included. A1 included all 17 JDM subjects and 10 controls to establish genes affected by JDM in our cohort. A2 compared DEGs at the baseline visit with clinical response on average 7 months later (outcome visit) in 12/17 JDM subjects (TRs n=7, NRs n=5). Average clinical response using the total improvement score from the 2016 criteria was 56/100, corresponding to moderate improvement. A3 evaluated 11/17 JDM subjects at 3 time points during the first 12 months of treatment (visit 1=day 0, visit 2=day 144, and visit 3=day 287, on average) regardless of treatment response. A1: At baseline, there were 1830 significant DEGs between children with JDM and health controls (HCs). A2: there were 10 DEGs between TRs and NRs. At the pathway level, TRs were enriched in diverse biological processes including inflammation (complement, TNF-α signaling, B-cell receptor signaling, and FCγR-mediated phagocytosis, platelet activation), energy metabolism (adipogenesis and glycolysis), and UV response. Non-responders were enriched in transcription factors and pathways involved in cell cycle regulation. At the outcome, TRs had incomplete normalization of DEGs as 21.3% of the genes associated with JDM continued to be differentially expressed compared to HCs at the outcome visit. TRs had pathway enrichment in myogenesis, protein production, and translation regulation while NRs were enriched in numerous inflammation-related pathways including interferon-α and -γ, TNF-α, IL-6-JAK-STAT, TGF-β, and complement. A3: DEGs

seen at visit 2 compared to baseline (n=876) tended not to persist at visit 3 (n=124) and 0 and 4 DEGs between JDM and HCs (JUP, CCL2, HES4, LY6E-DT) showed ongoing significant increases or decreases, respectively. With additional time on treatment (visit 3), inflammatory pathways were no longer enriched.
Conclusions. At diagnosis few genes distinguish TRs from NRs. TRs have higher expression of inflammatory pathways initially and have greater, but incomplete, resolution of their inflammation compared to NRs with standard JDM therapies at 6 months. Longitudinal analysis of TRs and NRs together showed ongoing enrichment in inflammatory pathways at visit two but not at visit three suggesting that suppression of several inflammatory pathways, including interferon-α and -γ, TNF-α, IL- 6-JAK-STAT, and TGF-β occurs somewhere between four and eight months with current standard therapy.

P-6

ANALYSIS OF MIRNA EXPRESSION PROFILES OF MYOSITIS SUBGROUPS IN MUSCLE BIOPSIES

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Background. MicroRNAs (miRNAs) are small non-coding RNAs that negatively regulate messenger RNA (mRNA) expression at the post-transcriptional level. They modulate many biological processes, and their expression has been reported to be dysregulated in several diseases. To date, our knowledge regarding the most relevant miRNAs in myositis and how these may play a role in the pathogenesis of the different myositis subgroups is still limited. This study was intended to define miRNAs that may play pathological roles in patients with dermatomyositis (DM), the antisynthetase syndrome (AS), immune-mediated necrotizing myopathy (IMNM), and inclusion body myositis (IBM). We propose that once identified, these miRNAs could be targeted to beneficial effect in patients with one or more of these myositis subgroups.
Methods. We included muscle biopsies from healthy controls and patients with DM, AS, IMNM, or IBM. Following RNA extraction from each muscle biopsy, miRNAs were detected using the nCounter miRNA expression assay. The miRNA profile of the myositis samples was analyzed for each myositis subgroup. Differentially expressed miRNAs were identified and their expression was correlated among them and with that of mRNA – detected and quantified by bulk RNA sequencing of the same samples – to have a more integral view of their role in the disease.
Results. miRNAs already known to play a role in the regulation of muscle biology were differentially expressed in myositis muscles in comparison to controls. While this result was expected, we found that they also correlated with other less well-characterized miRNAs. We propose that these additional miRNAs might play a role in myositis. Regarding the analysis of miRNAs in separate myositis subgroups, the most remarkable profile was that of DM, which revealed miRNAs specifically and significantly altered in this subgroup. The correlation of the miRNA and mRNA data suggests that these miRNAs are part of the interferon signaling pathway known to play a prominent role in DM.
Conclusion. The results of the present study highlight the contribution of miRNAs to pathways previously described as relevant in the pathogenesis of myositis (e.g., interferon signaling in DM). We propose that the specific miRNAs identified in this analysis could potentially be harnessed in the development of novel therapeutic approaches in the treatment of myositis.
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P-7

SPATIAL TRANSCRIPTOMIC ANALYSIS OF DERMATOMYOSITIS MUSCLE UNVEILS A UNIQUE SIGNATURE IN ATROPHIC PERIFASCICULAR MUSCLE FIBERS

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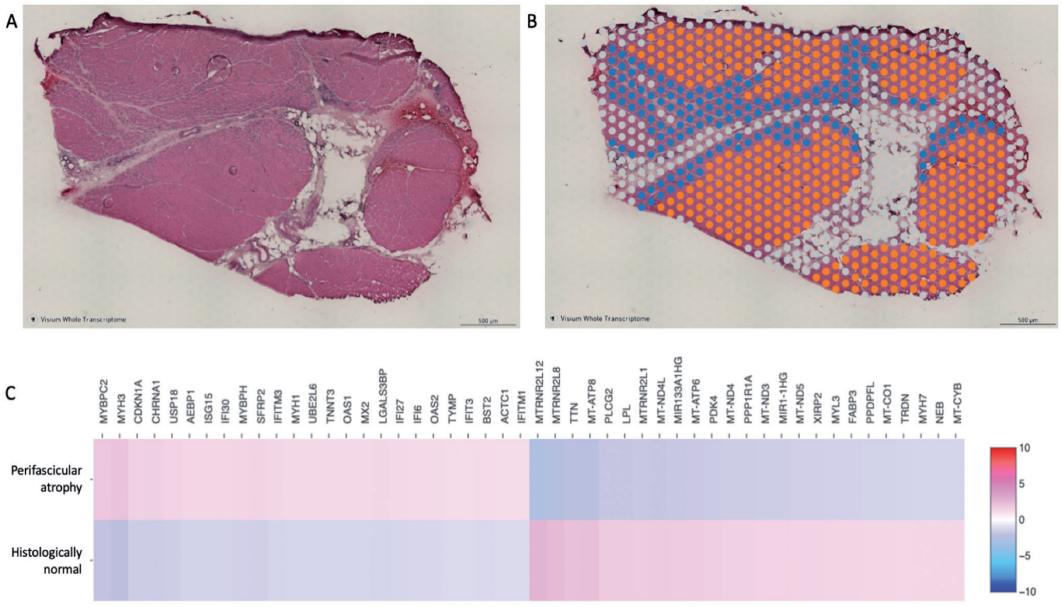
Background. Perifascicular atrophy (PA) is a morphologic feature of dermatomyositis (DM) and anti-synthetase syndrome (AS). In this work, we analyze the differential gene expression in muscle biopsies with PA.
Methods. For the bulk RNAseq analysis, we sequenced RNA obtained from 120 muscle biopsies from patients with inflammatory myopathies and 33 healthy donors. We then calculated the log Fold Change (logFC) of the genes in biopsies with PA compared to those without PA. For the spatial transcriptomic analysis, we evaluated a muscle biopsy with prominent PA. We then calculated the logFC of the differentially expressed genes in myofibers from PA compared to morphologically normal regions.
Results. Thirty-seven biopsies (30.8%) included regions with PA; 29 (78.3%) had DM, 6 (16.2%) AS and 2 (5.4%) immune mediated necrotizing myopathy.



P-7. Fig. 1. Differential gene expression in areas of PA. A muscle biopsy from a dermatomyositis patient (panel A) underwent spatial transcriptomic analysis using the 10X platform (panel B). Gene expression was compared between areas with (blue dots) and without (orange dots) PA. The heat map (C) shows those genes that were most up-regulated or down-regulated in atrophic perifascicular fibers.

Using the bulk RNAseq data, we found upregulation of genes related to the cytosolic RNA sensors pathway such as dhx58 (1.79, p=1.11x10-17), which enhances the activation of RIG-I and MDA5, was upregulated. Similarly, there was upregulation of the cytosolic DNA sensor zbp1 (4.14, p=1.11x10-17). As expected, upregulation of these nucleic acid sensors was accompanied by the upregulation of the type I interferon-stimulated genes (ISG) such as isg15 (5.09, p=1.11x10-20), ifi6 (4.36, p=7.02x10-12), isg20 (2.90, p=7.02x10-18), irf7 (2.23, p=2.76x10-17), ifi35 (2.19, p=1.59x10-20), ifi27 (2.66, p=7.02x10-18), parp10 (1.89, p=2.76x10-17), and helz2 (2.21, p=1.39x10-17). In contrast, genes involved in the metabolism of reactive oxygen species such as cat (-0.85, p=1.12x10-12), and aco1 (-0.93, p=1.94x10-11) were downregulated in muscle biopsies that included PA. Also, there was a decreased expression in the genes related to RNA translation like eif4b (-1.01, p=4.17x10-11), eif3l (-0.64, p=7.12x10-11), rps6ka3 (-1.01, p=1.25x10-9), and pabpc4 (-0.76, p=1.32x10-10); and structural proteins like ttn (-1.7, p=5.12x10-11), epdr1 (-0.88, p=2.20x10-10) and h2az2 (-0.60, p=3.27x10-10). Also, we observed a diminished expression of gene encoding the endothelial protein f8 (-1.09, p=5.43x10-10). Using spatial transcriptomics, we identified genes that were specifically upregulated in areas of PA (see Figure 1). This included structural proteins such as myh3 (2.08, p=6.98x10-8), mybpc2 (1.93, p=4.93x10-8), chrna1 (1.55, p=1.07x10-5); regulators of cell growth like cdkn1a (1.52, p=1.94x10-5) and sfrp2 (1.40, p=9.15x10-5); as well as enhancers of collagen synthesis such as aebp1 (1.34, p=0.0003). Likewise, we observed an increased expression of type I ISGs such as ifitm3 (1.26, p=0.0001), isg15 (1.34, p=5.22x10-5), usp18 (1.47, p=0.0001) and ifi27 (1.21, p=0.0001). In areas with PA the spatial transcriptomic analysis revealed decreased expression of ttn (-2.2, p=1.72x10-13) and xirp2 (-1.39, p=4.47x10-5), which binds to actin and prevents its depolymerization. Also, there was downregulation of genes encoding proteins related to cell signal transduction like ppp1r1a (-1.54, p=4.96x10-5) and plcg2 (-1.80, p=3.11x10-7) and to mitochondrial function like mt-atp8 (-2.23, p=4.27x10-9), mt-nd4l (-1.78, p=6.24x10-7), mt-atp6 (-1.73, p=3.03x10-8), pdk4 (-1.66, p=3.8x10-7), mt-nd4 (-1.53, p=1.4x10-6) and mt-nd3 (-1.50, p=2.51x10-6). Furthermore, we observed a decrement in the expression of lpl (-1.80, p=1.63x10-6), which is produced by endothelial cells.

Conclusion. Muscle fibers in regions of PA are characterized by a unique gene expression signature involving protein synthesis, mitochondrial function, and ISGs.

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P-8

A SQSTM1 POLYMORPHISM CONFERS RISK FOR SPORADIC INCLUSION BODY MYOSITIS DISEASE EXPRESSION

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Background. Inclusions of Sequestosome1 (SQSTM1/p62) within muscle fibers are a pathological hallmark of sporadic inclusion body myositis (sIBM) with p62 overexpression reported in patients. Mounting evidence suggests a role for p62 expression and/or variation in sIBM pathology, due to the presence of rare and potentially pathogenic missense variants (A117V, G194R, K238E, P392L). Consequently, we hypothesized that genetic modifiers of SQSTM1 may present a critical missing link for sIBM pathology and contribute to disease expression. Short structural variants (SSVs) are a class of genetic variation that can be difficult to characterized due to their highly repetitive and complex nature. Evidence that SSVs play an important role in complex diseases such as Alzheimer's Disease, Amyotrophic lateral sclerosis, Spinocerebellar Ataxia type 2, and Huntington's disease is now confirmed and further investigations of this type of genetic variation is necessary to uncover missing heritability in complex diseases. We and others have previously reported an SSV within SQSTM1 that is associated with altered expression of p62. The SSV rs60327661 is a CAAA insertion/deletion within intron 5 of SQSTM1, which also confers risk for familial Amyotrophic lateral sclerosis. Due to the role of the SSV in Amyotrophic lateral sclerosis and altered p62 expression, we hypothesized the SSV rs60327661 may have disease-modifying effects in a longitudinal cohort of sIBM patients.

Methods. DNA samples from 218 sIBM patients and 242 healthy controls were received from The Institute for Immunology and Infectious Diseases, Murdoch, Western Australia, and the NINDS Repository, Coriell Institute for Medical Research, New Jersey. Genomic DNA samples were systematically assessed through polymerase chain reaction, capillary separation, and Sanger sequencing for rs60327661 allele genotyping.

Results: In the present study, when controlling for self-declared ancestry, carriage of the D/D genotype is associated with sIBM disease expression (p<0.05). Both the case and control groups did not violate Hardy-Weinberg equilibrium (p=0.99, p=0.98; respectively. Intriguingly, patients who were CN1A seropositive were more likely carry the D allele (n=18) when compared to patients without a D allele (n=3; p<0.047). Patients classified as fast progressors (n=2) carried only the D/D genotype.

Conclusion. In this study, we present the first report of an association between the SQSTM1 insertion/deletion and sIBM disease expression. We provide evidence that the investigation of genetic variants outside of the HLA region is warranted, and that such investigations are likely to uncover critical information for sIBM. We present the SSV rs60327661 as a novel disease modifying variant for sIBM which is functionally linked to p62 by altering protein expression. Our data adds to growing evidence that examination of SSVs may uncover novel genetic risk markers, and consequently further understanding of the pathogenic mechanisms at play.

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P-9

GENETIC LOCI FOR POLYMYOSITIS/DERMATOMYOSITIS ARE ASSOCIATED WITH HEPATITIS B VIRUS INFECTION: A GENOME-WIDE ASSOCIATION STUDY IN HAN CHINESE

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Background. Polymyositis/dermatomyositis (PM/DM) are autoimmune diseases influenced by an interaction between genetic and environmental factors. We conducted a genome-wide association study (GWAS) for PM/DM in Han Chinese population, and found PM/DM was associated with two novel HLA-DP SNPs, which have been revealed as major genetic determinants of response to booster hepatitis B virus (HBV) vaccination.

Methods. A two-stage GWAS was performed. In the discovery stage, we genotyped 467,384 single nucleotide polymorphisms (SNPs) in 576 PM/DM (232 PM and 344 DM) and 1,455 healthy controls using the Affymetrix Axiom Genome-Wide CHB 1 Array Plate. In the replication stage, we validated 69 promising SNPs in 601 PM/DM (152 PM and 449 DM) and 1,941 healthy controls using the iPLEX MassARRAY platform (Sequenom). We also examined the prevalence of serological markers of HBV infection in 1,678 connective tissue diseases, and analyzed the association between serological markers of HBV infection and PM/DM genetic loci.

Results. Two HLA-DP SNPs were associated with PM/DM at genome-wide significance level (rs35953215, odds ratio [OR]=0.63, 95% confidence interval [CI], 0.54 – 0.74, p=1.17×10-8; rs7770370, OR=1.52, 95% CI=1.32–1.76, p=1.69×10-8). Meta-analysis of the discovery and the replication stages revealed a significant association of rs35953215 with PM/DM (OR=0.66, 95% CI=0.59–0.73, p=2.10×10-15) and with DM (OR=0.66, 95% CI=0.58–0.74, p=1.10×10-11). No HLA association with anti-Jo-1 autoantibodies and interstitial lung disease in PM/DM was found. In addition, PM/DM showed lower prevalence of anti-HBV surface antibody and higher prevalence of HBV surface antigen than systemic lupus erythematosus. Association of rs35953215 GG and rs7770370 AA genotypes with higher-titer vaccine response in PM, as well as association of rs35953215 AA genotype with prevalence of anti-HBV core antibody in DM, were found under additive models.

Conclusion. HLA-DP rs35953215 and rs7770370 were determined as genetic variants with GWAS-level significance conferring susceptibility to PM/DM in Han Chinese population, and these two loci were significantly associated with HBV infection. Our findings indicate that genetic loci associated with HBV infection overlap with loci for PM/DM, and provide new insight into the potential mechanism between PM/DM and HBV infection.

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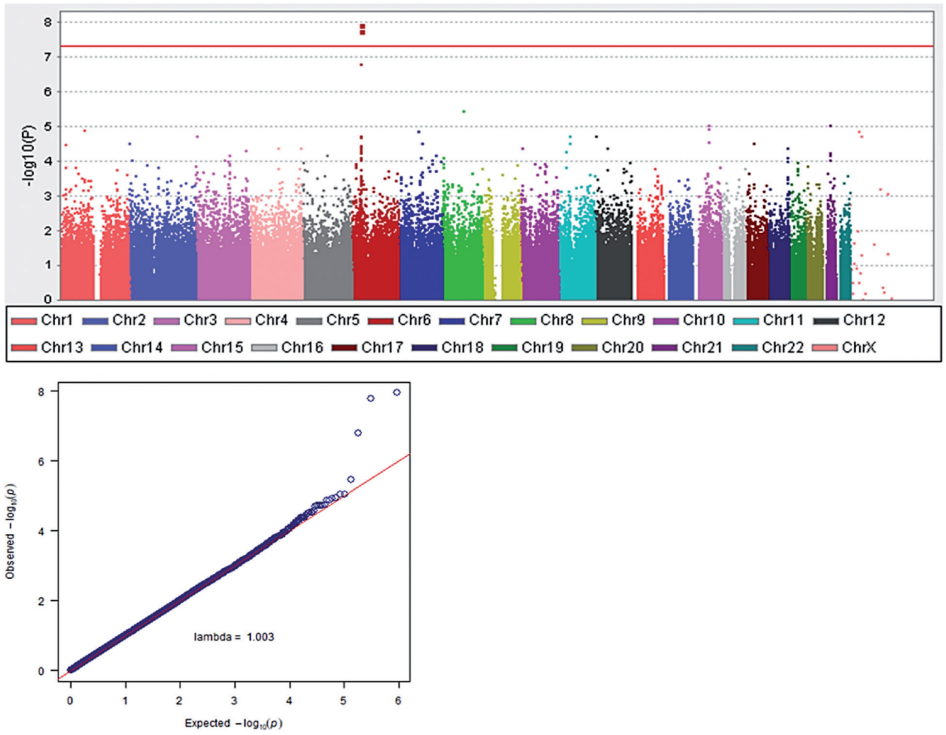

P-9. Fig. 1. Manhattan plots and quantile-quantile (Q-Q) plots of the genome-wide association analysis (GWAS). (A) Manhattan plots showing *p*-values for 467,384 successfully genotyped single-nucleotide polymorphisms (SNPs) in GWAS of 576 polymyositis/dermatomyositis and 1,455 controls. Genome-wide level of significance ($p<10\text{-}8$) was shown by the red line. Two significant SNPs (rs35953215 and rs7770370) was discovered. (B) Q-Q plots of 576 polymyositis/dermatomyositis and 1,455 controls ($\lambda = 1.003$). Chr = chromosome.

P-10

WHOLE EXOME SEQUENCING IDENTIFIES RARE PROTEIN-CODING VARIANTS IN DERMATOMYOSITIS

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Background. Dermatomyositis (DM) is an idiopathic inflammatory myopathy characterized by chronic skeletal muscle and skin inflammation. Despite the identification of multiple common genetic variants associated with DM, rare genetic variants have been less explored. This study aimed to investigate the rare variants in juvenile DM (JDM) and adult DM (ADM) of Han Chinese using whole exome sequencing (WES).
Methods. WES was conducted in a discovery set comprising 20 patients with JDM, 20 patients with ADM and 20 healthy controls of Han Chinese. WES data were generated for the cases and controls. Variants were annotated and filtered by quality, minor allele frequency, and deleteriousness on gene function. Candidate variants were identified in patients compared to healthy controls as well as controls from China National GeneBank. For validation, Multiplex polymerase chain reaction (PCR) was performed in an additional independent set of 34 JDM, 262 ADM and 241 healthy controls of Han Chinese.
Results. In discovery stage, nine rare variants with predicted protein-damaging effects in DM were identified in cases but not in controls, harboured in FCRL1, DMBT1, COL1A1, KIAA1033, DDX58, DYSF, IL31RA, JAK2 and WDFY4. These variants were subsequently subject to multiplex PCR. A novel variant in WDFY4 (chr10: 50154140 C>T) was validated to be associated with JDM. Another novel variant in DDX58 (chr 9: 32487565 T>C) was validated to be associated with ADM.
Conclusion. Our findings are helpful for providing new ideas for understanding the pathogenesis of DM by detecting and analyzing gene mutations at the whole-exome level. Rare putative protein-damaging genetic variants in WDFY4 and in DDX58 may be new susceptibility loci for DM, but their roles in the pathogenesis of DM are worthy of further study.
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Pathogenesis, including mitochondrial biology

P-11

NECROPTOSIS CONTRIBUTES TO MYOFIBER DEATH IN IDIOPATHIC INFLAMMATORY MYOPATHIES

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Background. Myofiber necrosis is a significant pathological characteristic of idiopathic inflammatory myopathies (IIMs) with the molecular mechanism largely unknown. Necroptosis is a recently identified form of regulated necrotic cell death, and its activation might have crucial biological consequences. The present study aimed to investigate the role of necroptosis in IIM muscle damage.
Methods. Western blot and immunohistochemistry analyses were performed to examine the expression of receptor-interacting protein 3 (RIP3) and mixed lineage kinase domain-like (MLKL) proteins in 26 IIM patients and 4 healthy controls, as well as necroptosis-related damage-associated molecular pattern molecules. TNF-α was used to stimulate cultured C2C12 myoblasts and the involvement of necroptosis in cell death of C2C12 cells was studied *in vitro*.
Results. The expression of RIP3 and MLKL proteins and their phosphorylated forms was significantly increased in the muscle of IIM patients compared to that in healthy controls. The expression levels of RIP3 and MLKL proteins are associated with clinical and pathological muscle severity in IIM patients. Significant colocalization of MLKL with HMGB1 in necrotizing myofibers was observed in IIM muscle biopsy. Stimulation of C2C12 myoblasts with TNF-α and a pan-caspase inhibitor, z-VAD, resulted in the overactivation of necroptosis and significantly increased necrotic cell death. Necroptosis inhibitor necrostatin-1s or knockdown of MLKL successfully prevented C2C12 cells from necroptosis-induced cell death.
Conclusions. These data demonstrate that overactivated necroptosis contributes to muscle damage in IIMs, and suggest that necroptosis inhibitors could represent a new therapeutic target for IIMs.
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P-12

UPREGULATION OF STRUCTURAL PROTEINS IN IMMUNE-MEDIATED NECROTIZING MYOPATHY IS INDEPENDENT OF UNDERLYING AUTOANTIBODIES

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Background. Immune-mediated necrotizing myopathies (IMNM) are part of the idiopathic inflammatory myopathies (IIM) and are defined by international consensus criteria based on clinical, morphological, and serological features. The main characteristics are proximal muscle weakness, highly increased serum CK levels and detection of the myositis-specific autoantibodies anti-SPR54 or -HMGCR in about 70% of the patients. Both autoantibodies target endoplasmic reticulum (ER) resident proteins and are involved in protein processing. In previous studies, we examined ER stress and activation of the unfolded protein response (UPR), since these signaling pathways were altered in the proteomic signature of patient-derived muscles. We could not detect significant differences between the two subgroups. However, additional pathways were also altered in the proteomic profile including cytoskeleton. Therefore, we choose this subcellular compartment for the current project to further elucidate the pathogenesis in IMNM patients and to delineate potential differences between subgroups.
Methods. Unbiased proteomic profiling was performed (n=3 SRP+ IMNM, n=3 HMGCR+ IMNM, n=5 non-diseased controls/NDC). Structural proteins were selected from altered signaling pathways to identify markers affecting cytoskeleton with an impact on membrane architecture in SRP54+ vs. HMGCR+ IMNM patients.
Results. We identified 283 proteins as significantly upregulated in IMNM patients (SRP+HMGCR) compared to NDC, of which 48 proteins (17%) are structural components such as myosin, actin, and associated proteins. When comparing the subgroups with NDC, we identified the same proteins as altered, with slightly different extents between SRP54+ vs. HMGCR+ patients. The top three proteins included myosin light chain 6B (11- and 14-fold), vimentin (4- and 5-fold) and ankyrin repeat domain-containing protein 2 (4.5 and 5-fold). In addition, one of the upregulated proteins may also allow differentiation between subgroups, since abundance of PDZ and LIM domain protein 1 (PDLI1), a cytoskeletal protein that may act as an adapter tethering other proteins to the cytoskeleton, was also increased by 2.16-fold in SRP54+ patients when compared to HMGCR+ patients.
Conclusion. Several proteins affecting structural components were altered in IMNM patients compared to NDC. This might be driven by inflammation, fibrosis and necrosis within the affected muscle tissue. Interestingly, besides the protein PDLI1, no major differences were found between the subgroups, showing that the changes in cytoskeleton proteins are antibody-independent.
Acknowledgements. This work was supported by a grant of the French Muscular Dystrophy Association (AFM-Téléthon; #23216) to WS and AR

P-13

EXPRESSION OF IMMUNE REGULATING PROTEINS IN SKELETAL MUSCLE OF ADULT IDIOPATHIC INFLAMMATORY MYOPATHIES (IIM) SUBTYPES

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Background. Idiopathic inflammatory myopathies (IIMs) are autoimmune diseases classified as polymyositis (PM), dermatomyositis (DM), immune-mediated necrotizing myopathy (IMNM), anti-synthetase syndrome (ASyS) and sporadic inclusion body myositis (sIBM). Adaptive and innate immune responses play a role in the pathogenesis of IIM and immunomodulatory treatment is the recommended therapy. The individual regulatory mechanisms in IIM subtypes might differ and a better understanding of the pathophysiology would improve the individual therapeutic approaches. With whole muscle section morphometry, we want to analyze the immune regulating proteins in certain subtypes of IIM.
Methods. Muscle biopsies from 24 adult patients with IIM (average age at biopsy 54.6 years; 65.2% female; DM n=5; IMNM n=5; ASyS n=7; sIBM n=7), neurogenic atrophy (NA; n=4) and controls (HC; n=6) were included in the study. All biopsies were re-evaluated according to the common classification. The degree of pathology severity was estimated using a semiquantitative pathology score (p-score from 0 to 10). Double immunofluorescence staining was performed with antibodies against MHC-1 (major histocompatibility complex 1), MHC-2, ICAM-1 (intercellular adhesion molecule 1) and VCAM-1 (vascular cell adhesion molecule 1) and with antibodies against spectrin or desmin. The sections were subsequently digitalized using a Zeiss Axio Scan.Z1 slide scanner. The coexpression was analyzed on entire sections using ImageJ software and quantified using the Manders' coefficient (M). Clinical and serological findings were estimated retrospectively and correlated with the results.
Results. MHC-1 expression was significantly upregulated on muscle fibers of patients with ASyS (M=0.559), DM (M=0.609), sIBM (M=0.557) and NA (M=0.208) compared to HC (M=0.009). For IMNM (M=0.079), the expression was significantly lower compared to ASyS and DM. Significant upregulations of MHC-2 were found for ASyS (M=0.263), DM (M=0.504), sIBM (M=0.336) and NA (M=0.416) compared to HC (M=0.036), as well as a significant upregulation for DM compared to IMNM (M=0.055). Only ASyS samples showed a significant upregulation of ICAM-1 compared to HC (M=0.060), whereas in general, the expression varied strongly (ASyS M=0.263±0.182; DM M=0.270±0.256; sIBM M=0.337±0.249; IMNM M=0.335±0.295) with no significant difference between the IIM subtypes. VCAM-1 expression showed no significant difference between the IIM subtypes. However, in comparison to HC (M=0.036), we found VCAM-1 significantly upregulated in ASyS (M=0.200), DM (M=0.377) and sIBM (M=0.371). Correlating our results with the p-score, a positive correlation (r=0.774) for ICAM-1 expression in sIBM was found.
Conclusion. We analyzed protein expression levels on muscle fibers in whole section analysis, which provides accurate data on larger sections. Different expression patterns of MHC-1/2, ICAM-1 and VCAM-1 were found in IIM subtypes with lower expressions in IMNM for MHC1/2 and VCAM-1. Interestingly, in sIBM ICAM-1 expression correlated with the pathology score. These insights might help to improve morphological diagnosis in IIM subtypes and identify individual immune response patterns, which may improve the accuracy of future diagnoses.

P-14

FOCAL MYOSITIS AND NEOPLASIA: A NON-FORTUITOUS ASSOCIATION. CASE SERIES AND LITERATURE REVIEW

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Introduction. Focal myositis (FM) is a rare inflammatory muscle disease, first individualized amongst idiopathic inflammatory myositis by Heffner *et al*. in 1977. FM presents as a painful mass restricted to one muscle. Magnetic resonance imaging shows T2 enhanced hypersignal within the muscle, and electromyography demonstrates the focal myogenic process. Histology identifies myopathic changes, interstitial fibrosis and inflammatory infiltrates. The disease is considered as benign, healing spontaneously or under corticosteroid treatment. The etiology of the disease remains unknown and the pathologic process is poorly understood. An association between FM and cancer was recently reported (1). In this study, we report and analyze the particular association of FM with neoplasia.
Methods. Confirmed cases of FM with a focal myositis simple score ≥2 (1) in the Lyon University Hospital's myopathological database between 2000 and 2019 were retrieved. Adult patients presenting a histologically proven neoplasia occurring within 3 years of the disease onset (before or after) were included (FM K+). We performed an additional literature review of FM and neoplasia association and included patients who met inclusion criteria. Patients' characteristics and outcome were collected through a standardized and anonymous form. A control group (FM K-) was made following the same inclusion/exclusion criteria but without associated neoplasia.
Results. Among 41 cases of FM, 8 patients (20%) presented an associated neoplasia. The literature review identified 6 additional cases. Median follow up duration was 1.25 (IQR [1-2,5]). The median age was 55 years (IQR [45-71]). Ten patients had solid cancers, all carcinomas; the remaining patients presented malignant hemopathies (n=4). FM preceded the neoplasia in 10/14 patients (71%), with a median delay of 6 months (IQR [2-8]). The course of FM and cancer was synchronous for 8 cases (71%). Noticeably, the FM site was close to the tumor location for 5 patients (Table I) and an intramuscular tumoral contingent was found retrospectively in two patients. Compared to FM K- population, FM K+ patients

were older (p=0.002) and more often females (p=0.02). FM locations outside of calves were more frequent in FM K+ patients (p=0.025). There were no differences in biological features or in imaging. Histologic analysis retrieved a more necrotic component in FM K+ muscle biopsies (p=0.03). More fibrosis and less C5B9 expression were found in FM K+ group. No difference was found regarding treatment or relapses, neither in follow up duration (p=0.682). Fifty-seven percent of the FM K+ patients and none of the FM K- patients were deceased after a median follow-up of 1.75 years (p<0.001).

Discussion. This work identified 14 patients who presented a chronological association between neoplasia and FM. The pathophysiology of this association remains uncertain, with two different hypotheses: a paraneoplastic phenomenon or a peri-neoplastic process. The immunohistochemical analyses of the muscle formally excluded the presence of tumor in 4 patients with hematological malignancies: this observation supports paraneoplastic process. However, the proximity between the tumor or its metastasis and the FM location for 5 cases, and the identification of a tumoral contingent into the muscle biopsy for two cases, are some strong arguments for a peri-neoplastic process for some patients. This is of interest, considering that muscle is not a usual site of metastasis.

Conclusion. Though limited to 14 patients, this work highlights the co-occurrence of neoplasia and FM, which goes against the usual consideration. Clinicians should be forewarned of this association, and perform systemic assessment following the diagnosis of focal FM, especially in cases of atypical anatomic location, general symptoms or marked necrosis on muscle biopsy.

Reference

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P-14. Table I. Patients' characteristics.

No.	Gender/ Age, years	FM site	Cancer type	Cancer stage	FM occurrence before neoplasia	Time between cancer and FM (months)	Tumor or metastasis location nearby FM	Synchronous evolution of cancer and FM	Llive status at last visit (follow-up, months)
1	F/54	LL	UCUP	IV	Yes	6	Yes	NA	D (3)
2	M/39	LL	HD	III	Yes	8	No	Yes	A (32)
3	F/75	CP	PTC	I	Yes	2	Yes	No	D (96)
4	M/78	LL	UC	IV	Yes	8	Yes	No	D (1)
5	M/56	UL	UC	I	Yes	2	No	Yes	A (24)
6	F/33	LL	ALL	-	No	1	Yes	No	D (10)
7	F/54	UL	PTC	I	No	24	No	No	A (24)
8	F/62	UL	RCC	IV	No	36	No	Yes	D (5)
Zenone, 2011	F/51	LL	UCUP	IV	Yes	9	No	Yes	D (7)
Naschitz, 1992	M/78	UL	HD	II	Yes	6	No	Yes	A (12)
Uppal, 2004	F/44	LL	SRCCS	IV	Yes	0	No	Yes	NA
Terrier, 2005	F/74	UL	CLL	-	Yes	0	No	Yes	A (12)
McLendon, 1989	F/63	Tongue	SCCT	IV	Yes	16	No	Yes	D (9)
McCluggage, 1996	F/26	MH	SCCC	I	No	24	Yes	No	A (84)

A: alive; ALL: Acute lymphocytic leukemia; CLL: Chronic lymphocytic leukemia; CP: cricopharyngeal; D: deceased; FM: focal myositi; HD: Hodgkin's disease lymphoma; LL: lower limb; MH:mylohyoid; NA: Not available; No.: number; PTC: papillary thyroid carcinoma; RCC: renal cell carcinoma; SCCC: squamous cell carcinoma of the cervix; SCCT: squamous cell carcinoma of the tongue; SRCCS: signet cell ring carcinoma of the stomach; UC: urothelial carcinoma; UCUP: undifferentiated carcinoma of unknown primary; UL: upper limb.

P-15

MUSCLE INFLAMMATION DISRUPTS MITODYNAMICS AND IMPAIRS MITOCHONDRIAL FUNCTION IN IBM

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Background. Inclusion body myositis (IBM) is an inflammatory myopathy in patients over fifty years of age, presenting with progressive muscle weakness and wasting. Histopathological findings include autoreactive inflammation, accumulation of misfolded proteins as well as mitochondrial impairment. Interplay between those mechanisms in the pathogenesis of IBM and, in particular, the role of mitochondria, have so far remained elusive. We hypothesized that chronic muscle inflammation drives mitochondrial damage, leading to disrupted energy production with consecutive muscle wasting and weakness.

Methods. RT-PCR was performed to assess expression of mitochondrial fusion and fission genes (MFN1/2, DNM1L, FIS1) from 14 IBM patients and 10 healthy donors. For serial section analysis, muscle tissue was obtained in diagnostic biopsies of four IBM patients and two non-myopathic controls and semiquantitative analysis as well as single fiber analysis for markers of inflammation, autophagy, degeneration and mitochondrial damage was performed. Human primary myotubes were studied in a well-established cell culture model of IBM and assessed regarding mitochondrial morphology and function. Mediators of mitochondrial fission and fusion were evaluated using RT-PCR, Western Blot and immunocytochemistry. Mitochondrial function was examined using spectrophotometry of COX-IV activity and seahorse metabolic cell assay.

Results. IBM muscle samples revealed increased expression levels of MHC-I, αB-crystallin, iNOS, 6E10 and p62 compared to controls. IBM muscle stained for signs of mitochondrial damage showed an increased number of fibers deficient of COX and an upregulation of TOM20 expression. Additionally, a significant co-upregulation of TOM20 and MHC-I (56.4% of TOM20 positive fibers stained positive for MHCI; p<0.0001) as well as a significant co-staining of TOM20 and αB-crystallin (83.3% of TOM20 positive stained positive for αB-crystallin; p<0.0001) was detected in IBM muscle. No significant changes in the expression of fusion and fission genes in IBM patients compared to controls were noted. Non-myopathic individuals displayed a positive correlation of age and gene expression of MFN1 (p=0.017), MFN2, DNM1L and FIS1. This correlation was absent in IBM. *In vitro*, exposure of muscle cells to the pro-inflammatory cytokines IFNγ and IL-1β promoted a significant shift of mitochondrial network morphology towards fragmentation. STED microscopy revealed, after 72 hours of cytokine exposure, a fragmentation rate of 37.9% compared to 16.8% in controls (p=0.011). Protein levels of the fission mediator DRP1 were increased in the cytokine exposed cells. After cytokine exposure for 72 hours, spectrophotometry revealed a significant reduction of COX-IV activity (p=0.013) and seahorse analysis showed a trend towards reduced ATP production compared to controls.

Conclusion. A dysregulation of genes controlling mitochondrial fusion and fission processes is evident in muscle biopsies of patients with IBM thus underlining a possibly impaired mitochondrial quality control in response to inflammatory cell stress. Our ex vivo data demonstrate that, in IBM muscle, inflammation and mitochondrial distress are interlinked pathomechanisms, whereas in vitro findings elucidated that inflammation can induce mitochondrial fragmentation and disrupt mitochondrial function. The data offer an explanation how myoinflammation contributes to mitochondrial damage resulting in impaired mitochondrial function and altered mitochondrial morphology. Studies on implications for mitophagy and accumulation of degenerative proteins are needed to further illuminate the consequences for IBM pathophysiology.

Acknowledgements. We thank Iris Iben for excellent technical support. We thank our patients and donors of muscle specimen for their voluntary participation. S.M. is supported by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) within the Clinician Scientist Program "Cell Dynamics in Disease and Therapy" at the University Medical Center Goettingen (project number 413501650).

P-16

AUTOIMMUNITY AGAINST MELANOMA DIFFERENTIATION-ASSOCIATED PROTEIN 5 INDUCES INTERSTITIAL LUNG DISEASE IN MICE WITH LUNG INJURY

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Background. Anti-melanoma differentiation-associated protein 5 (MDA5) antibody-positive dermatomyositis (DM) is characterized by amyopathic DM with interstitial lung disease (ILD). Patients with anti-MDA5 antibody-associated DM sometimes develop rapidly progressive-ILD and present high mortality rate in acute phase. Because MDA5, a member of the retinoic acid-inducible gene-I family, works as a cytosolic sensor recognizing viral double-strand RNA, it has been suspected that viral infection might trigger the development of anti-MDA5 antibody-positive DM. However, the pathogenesis of anti-MDA5 antibody-positive DM/ILD remains unclear.

Methods. C57BL/6-background wild-type mice were immunized by subcutaneously injection of emulsion, including complete Freund's adjuvant (CFA) and recombinant mouse MDA5 whole protein produced by baculovirus-insect cell protein expression system, 4 times once a week. Some of the MDA5-immunized mice were intranasally administrated with polyinosinic-polycytidylic acid [poly (I:C)] at the same time of the last immunization. Control mice were subcutane-

ously injected with emulsion of CFA without proteins. Inguinal lymph node T cells and plasma samples were collected from the mice 14 days after the 4th immunization, and used for a WST-I cell proliferation assay and an enzyme-linked immunosorbent assay, respectively. Lungs, femoral muscles, and joints of feet were histologically and immunohistochemically evaluated. The contents of hydroxyproline in the left lobes of the lungs were also measured.
Results. T cells from MDA5-immunized mice showed reactive proliferation in co-culture with MDA5 recombinant protein-pulsed bone marrow-derived dendric cells. Antibodies against mouse MDA5 protein were detected in the plasma of MDA5-immunized mice. Though neither rash nor histological change in the muscles and joints were observed, inflammatory foci with $CD4^+$ T cells and CD11b+ macrophages blowing the pleurae were significantly more frequently detected in the lungs of MDA5-immunized mice than control mice. Moreover, MDA5-immunized mice with an additional intranasal administration of poly (I:C) showed more intense inflammation in their lungs than control mice [lung inflammation score, median (interquartile range); 0.56 (0.54-0.60) and 0.41 (0.39-0.48), respectively; $p<0.05$ by Mann-Whitney's U test] at a day after the poly (I:C) administration. At 14 days after the poly (I:C) administration, 70% of MDA5-immunized mice developed inflammatory cell-rich and fibrotic lung disease, while no control mouse did ($p<0.01$ by Fisher's exact test). $CD4^+$ T cell-rich peri-bronchial inflammation was also observed in 80% of MDA5-immunized mice, but not in any control mice ($p<0.01$ by Fisher's exact test). MDA5-immunized mice also showed higher mortality rate (42.3%) within 14 days after the poly (I:C) administration than control mice (7.1%, $p<0.01$ by Kaplan-Meier survival analysis). The contents of hydroxyproline of the lungs in MDA5-immunized mice were also upregulated compared to those of control mice (mean ± standard error; 144.1±16.1 μg and 60.6±6.6 μg, respectively; $p<0.05$ by Turkey's multiple comparison test).
Conclusion. These results proved that autoimmunity against MDA5 exacerbates acute lung injury induced by activation of innate immunity, and prolongs the inflammation resulting in the development of fibrotic ILD. This is the first murine model of ILD in patients of anti-MDA5 antibody-positive DM, and would be useful to establish new treatment strategy of anti-MDA5 antibody-positive ILD.

P-17

DIFFERENT PHENOTYPE AND PROGNOSIS OF IMMUNE-MEDIATED NECROTIZING MYOPATHY

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Objective. To analyze the characteristics and prognosis of immune-mediated necrotizing myopathy (IMNM) base on serological classification and refine the spectrum of IMNM with distinguished features and prognosis.
Methods. A total of 138 IMNM patients, including 62 anti-SRP-positive, 32 anti-HMGCR-positive, and 44 seronegative patients, were enrolled in this study. The characteristics and prognosis of IMNM patients with different serological phenotype were analyzed. Unsupervised clustering analysis was used to identify new subgroups of IMNM patients.
Results. Muscle weakness (93.5%) and elevated creatine kinase (99.3%) were the most common clinical manifestations of patients with IMNM. Anti-HMGCR-positive patients were more likely to develop V sign than anti-SRP-positive and seronegative patients (18.8% vs. 3.2% and 6.8%, $p<0.05$). More seronegative patients were combined with other connective tissue diseases (31.8% vs. 9.1% and 3.1%, $p<0.01$). However, no difference was observed on the prognosis among different serological groups. Three clusters with distinguished features and prognosis were identified using clustering analysis. The first cluster(n=102) with severe weakness (52.9%) and more inflammation infiltration (CD4[95.1%]) had intermediate prognosis. The second cluster (n=27) characterized as severe weakness (40.7%) and less inflammation infiltration (CD4[29.6%]) with a poor prognosis. The third cluster(n=9) with mild weakness (66.7%) or without muscle weakness (89.9%) had a good prognosis.
Conclusion. IMNM is a heterogeneous disease. Serological phenotypes may not distinguish it well. Subgroups based on clustering analysis may make more knowledge on the subclassification and guide for treatment of IMNM.

P-18

IDENTIFICATION OF JO-1 SPECIFIC AUTOREACTIVE T CELLS IN IDIOPATHIC INFLAMMATORY MYOPATHIES

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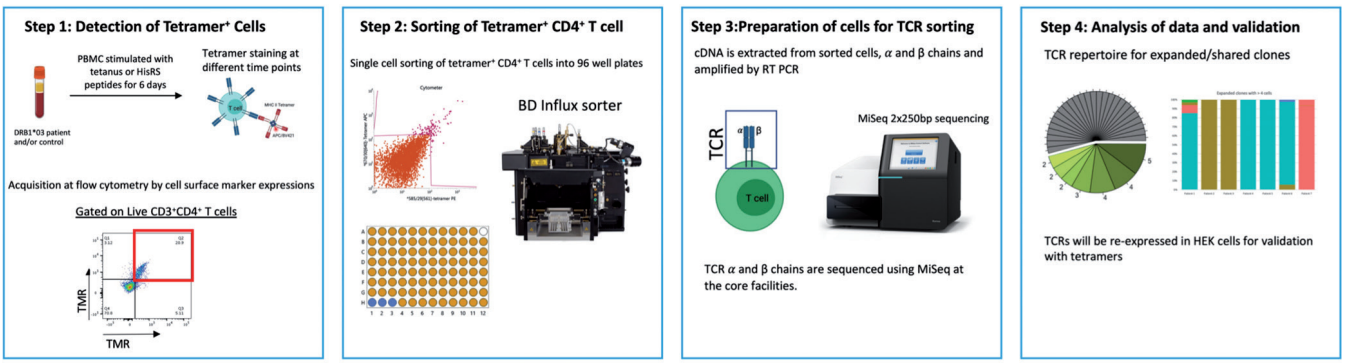
Background. One of the most common autoantibodies in myositis, with a prevalence of 25-35%, is anti-Jo-1, targeting the histidyl-transfer RNA synthetase (HisRS). The presence of T cells at the site of inflammation suggest their implication in the pathogenesis of myositis. We previously showed that upon stimulation of peripheral blood mononuclear cells (PBMC) and bronchoalveolar lavage fluid cells (BALF) with HisRS protein/peptides, $CD4^+$T cells were activated and produced inflammatory cytokines such as IFNγ. The presence of Jo-1 autoantibodies in patients along with a genetic association with the HLA-DRB1*03:01 alleles highly suggest the existence of autoantigens being recognized by autoreactive $CD4^+$T cells. However, the presence of antigen specific T cells in myositis has not been established yet. The main aim of this project is to detect and characterize $HisRS^+CD4^+$T cells using HLA Class II tetramers and single T cell receptor (TCR) sequencing.
Methods. HLA-DRB1*0301 tetramers, which allows the detection of rare antigen specific $CD4^+$T cells, were used to identify T cells that recognize HisRS in PBMC of Jo1+ IIM patients. For the preparation of tetramers, HLA-DRB1*03 monomers with selected HisRS peptides and tetanus peptides as positive controls were produced in-house in an E.coli system. The peptides of interest were covalently attached to the N-terminus of the HLA B-chain via a flexible peptide linker. Tetramers were then assembled using a commercial fluorescently labelled streptavidin. The efficacy of the peptide-HLA tetramers was validated by flow cytometry upon stimulation of PBMCs from HLA-matched healthy controls with tetanus peptide. T cell activation surface receptors upregulation (CD69, CD25, PD-1 etc) was investigated in conjunction with tetramer staining. The cytokine profile in the supernatants of the stimulated cultures was investigated. Finally, TCRa/b library preparation was performed and sequenced on a MiSeq instrument after single cell sorting $HisRS^+CD4^+$T cells from Jo1+ IIM patients (Figure 1).
Results. $Tetanus^+CD4^+$T cells were detected from healthy control PBMCs upon tetanus peptide stimulation by staining with dual fluorochromes tetramer staining. Next, we used this optimized protocol on PBMC from myositis patients (n=5) stimulated with HisRS peptide and could detect $HisRS^+CD4^+$T cells. In addition, there was a significant increase in IFNg levels in the supernatants of stimulated cultures where tetramer+ cells were detected. $HisRS^+CD4^+$T cells from patients (n=5) were single cell sorted and their TCRs alpha/beta chains genes were sequenced (n=3). Analysis of TCR sequencing revealed presence of expanded T cell clones in all patients (n=3).
Conclusions. We have for the first-time detected HisRS specific $CD4^+$T cells in PBMC of Jo1+ IIM patients. Furthermore, we detected expanded T cell clones in patients, which strongly implies the contribution of autoreactive T cells to the disease pathogenesis. We are now including more patients to confirm our findings



P-18. Fig. 1. Summary of experimental design.

and before/after treatment samples to assess the effect of conventional treatment on the frequency of autoreactive T cell clones.

P-19

AUTOANTIBODIES IN MYOSITIS PATIENTS DECREASE SARCOLEMMAL MEMBRANE REPAIR CAPACITY

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Background. Idiopathic inflammatory myopathies (IIM) are a group of disorders in which autoimmune responses produce a chronic state of inflammation resulting in degeneration of skeletal muscle structure and function2-4. These IIM include five major conditions: polymyositis, dermatomyositis, juvenile dermatomyositis, inclusion body myositis, and immune-mediated necrotizing myopathy. Both adaptive and innate immune responses are involved in the pathogenesis of IIM but the pathogenic mechanisms are not yet well defined. Previous studies with synaptotagmin VII null (SytVII-/-) mice displayed impaired sarcolemmal membrane repair capacity and developed mild myositis at two months in age, suggesting that antigen presentation of internal skeletal muscle proteins may play a role in initiating or exacerbating myositis. Our previous work generated a more robust model of inflammatory myositis by combining the SytVII-/- model with scurfy mice that have a regulatory T cell deficiency (FoxP3-/Y/SytVII-/-), further linking the progression of myositis with defects in sarcolemmal membrane repair. The sarcolemmal membrane repair response is a conserved response necessary to restore membrane integrity in myocytes as part of normal cellular physiology. Defects in membrane repair are linked to a variety of muscle diseases. Our previous work and that of others helped identify TRIM72/MG53 and dysferlin proteins as critical components of the membrane repair process. Our current studies address if antibodies against TRIM72/MG53 and dysferlin contribute to the progression of myositis.
Methods. Levels of antibodies against repair proteins were measured in FoxP3-/Y/SytVII-/-mouse model and dermatomyositis and polymyositis patient serum samples with custom enzyme-linked immunosorbent assay (ELISA). Membrane repair function was determined using mechanical glass bead wounding or multi-photon infrared laser microscopy was used to damage the cell membrane of muscle fibers. Confocal live cell imaging is used to record the entry of FM4-64 dye, which only fluoresces once it enters the cell. We also measured membrane integrity in vivo through the use of IgG immunostaining of muscle histology sections. A coblock ploymer known to increased sarcolemmal membrane integrity, poloxamer 188 (P188), was tested for potential therapeutic effects.
Results. Our results identified novel autoantibodies against membrane repair proteins in IIM patient serum. We also found that exogenous antibodies against TRIM72 or dysferlin can compromise membrane repair in isolated muscles. Adoptive transfer of lymph nodes from our FoxP3-/y/SytVII-/- mice into a Rag1-/- mouse background demonstrated that sarcolemmal repair is significantly compromised in distal skeletal muscle in the absence of inflammation suggesting that these antibodies are sufficient to compromise membrane repair. Additional studies show that IIM patient serum with a high titer of TRIM72 antibodies can also compromise membrane repair in healthy muscle ex vivo while P188, a membrane stabilizing agent, can ameliorate these defects.
Conclusion. Our results reveal that autoantibodies against membrane repair proteins that compromised sarcolemma repair could represent a novel disease mechanism in IIM. We find targeting membrane integrity minimizes these effects, indicating a new potential therapeutic approach.
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P-20

DESCRIPTION OF MACROPHAGES IN IDIOPATHIC INFLAMMATORY MYOPATHIES USING IN-SITU RNASEQ

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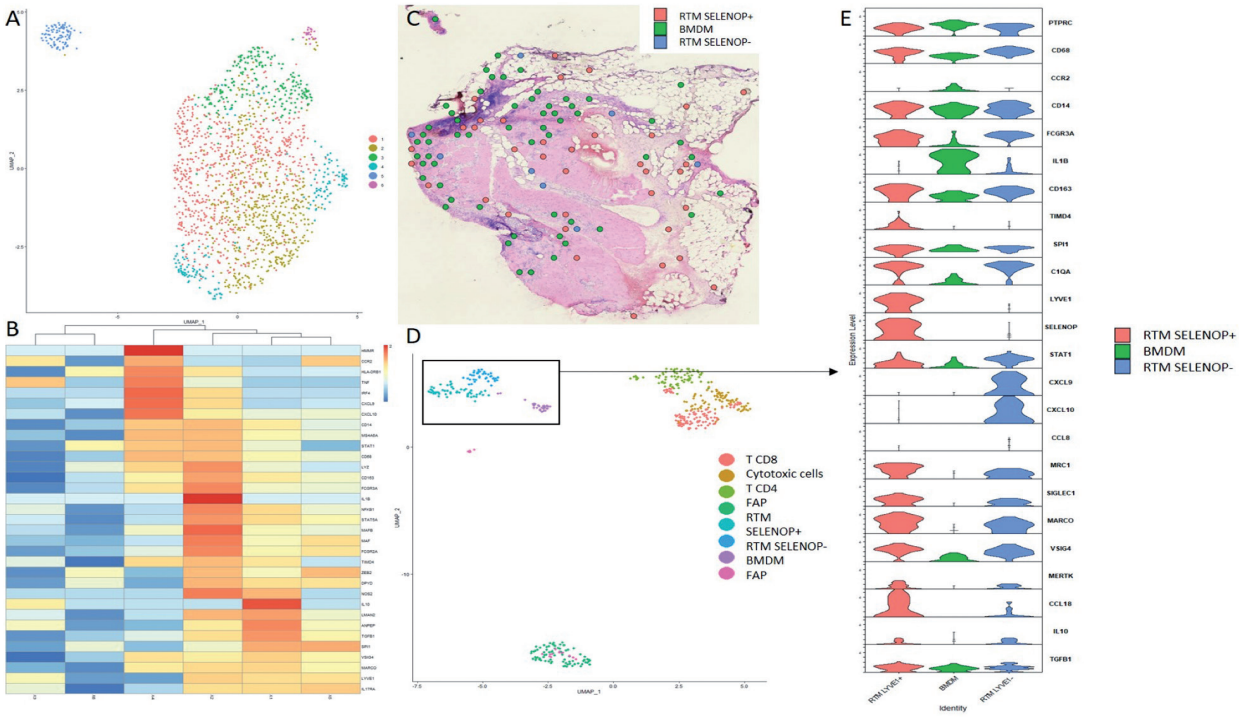
Background. Idiopathic inflammatory myopathies are a heterogenous group of pathologies characterized by autoimmunity mainly targeted at the skeletal muscle. Each subgroup of myositis shows specific clinical manifestations, au-



P-20. Fig. 1.
A. UMAP clustering from ICI-myositis-specific inflammatory subset isolated from comparison with healthy donors biopsy in spatial transcriptomics (Visium, 10x Genomics) (n=10 with HD=5 and ICI-myositis = 5) **B.** Heatmap of macrophage gene distribution across 6 spatial transcriptomics clusters (A) **C.** Spatial distribution and clustering from macrophage-expressing spots (CD68>1) in ICI-myositis biopsy **D.** Single-cell (Chromium, 10x Genomics) UMAP clustering from ICI-myositis inflammatory infiltrate (n=3) E. ViolinPlot representation of macrophage genes characterizing subpopulation from single-cell macrophage analysis in ICI-myositis.

toreactive antibodies, and pathological features. Subgroups include inclusion body myositis, dermatomyositis, anti-synthetase syndrome, immune-mediated necrotizing myopathies, and lastly immune checkpoint inhibitor-induced myositis (ICI-myositis). These disorders exhibit different levels and composition of inflammatory infiltrates in skeletal muscle, invariably including macrophages. Macrophages represent a heterogeneous and plastic population adapting its phenotype to the cytokine environment and are known to play a role in the muscle regeneration and differentiation process.
Objective. We wanted to further characterize macrophage population in myositis and describe their potential pathologic role.
Methods. Spatial transcriptomics (Visium, 10X Genomics) was performed, sequencing RNA information from pathological muscle biopsies sampled for each idiopathic inflammatory myopathy subgroup as well as healthy donor. Considering the high density of inflammatory infiltrate in ICI-myositis, single-cell RNAseq was performed on digested inflammatory cells from biopsies to further corroborate in situ results.
Results. We isolated different phenotypes corresponding to bone-marrow-derived macrophages ($CD14^+$ $CCR2^+$ $CD68^+$ $IRF4^+$), and resident macrophages ($CD68^+$ $CD163^+$ $MAFB^+$ $SPI1^+$ $MARCO^+$ $VSIG4^+$ $APOE^+$ $TIMD4^+$). Pro-inflammatory mediators TNF, CXCL9, CXCL10, NOS2 and IL1B were overexpressed in specific tissue domains. Conversely, IL10 and TGFB1 were found upregulated across other tissue domains. Resident macrophages were split into two subgroups defined by key genes as MRC1, CCL18, SELENOP using single-cell RNAseq in muscular inflammatory infiltrate.
Conclusion. One of the main advantages of in situ sequencing is the possibility to study macrophages in their tissue-specific state, avoiding the plasticity changes linked to other methods. This work showed several phenotypes of macrophage distributed across a same pathologically inflammatory tissue, resident subgroups and recently monocyte-derived. In ICI-myositis, we also identify inflammatory macrophages taking a place in tissue destruction, describing further their pathologic role.

P-21

UPREGULATION OF DIFFERENT TOLL LIKE RECEPTORS (TLR) IN DIFFERENT SUBTYPES OF IMMUNE MEDIATED MYOSITIS

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Background. Toll like receptors (TLR) are a family of innate pattern recognition receptors capable of inducing and maintaining inflammation. Various ligands lead to an activation of a MyD88 dependent or independent signalling pathway, resulting in NFκB mediated increased production of inflammatory cytokines, such as Interferon β (IFNβ). Skeletal muscle biopsies from patients affected by immune mediated myositis (IMM) present an expression of TLR on muscle fibres, together with an inflammatory infiltrate containing macrophages and lymphocytes. The influence of TLR expressing muscle fibres in the inflammatory milieu as well as the interplay with invading immune cells is unclear. We hypnotized that TLR on muscle fibres contribute, maintain, and aggravate the degree of muscular inflammation.
Methods. Immunofluorescence (IF) stainings were used to evaluate the distribution of TLR 3, 4, 7 and 9 in 11 dermatomyositis (DM), 6 anti-synthetase-syndrome (ASyS), and 6 immune-mediated necrotizing myopathy (IMNM) biopsies. Vimentin was used as a marker for regenerative muscle fibers. To elucidate macrophage polarization, Arg1, iNOS and CD68 IF staining were performed. An IFNß riboprobe was used for in-situ-hybridization. Laser-Capture-Microdissection (LCM) was used to isolate muscle fibers from seven DM patients, two ASyS patients, five IMNM patients, and 14 age and gender matched healthy donor biopsies. RT-qPCR experiments were performed for genes associated with the TLR pathway (MyD88, ß2 microglobulin, NFκB), two housekeeping genes served as control (ACTB, CSN2KA2).
Results. TLR expression on muscle fibres remarkably differs between myositis entities. TLR3 recognizing foreign single stranded RNAs is upregulated in DM and IMNM, but not in ASyS. TLR4 binding bacterial dsDNA expression is strongly expressed in DM biopsies, with only a small expression in ASyS and IMNM, while TLR7 is mainly present on muscle fibres of ASyS and IMNM patients but absent in DM biopsies. For all entities, TLR9 expression on muscle fibres is generally rare. In-situ-hybridization for INFβ showed no expression in muscle fibres. INFβ producing cells were mainly found in DM biopsies, with a smaller number in ASyS and IMNM biopsies. In DM, INFβ expression was mostly found in CD68 positive macrophages. In addition, expression of MyD88 was higher in atrophic perifascicular fibres compared to normal appearing fibres of the same DM patient, while ß2m and NFκB expression showed no clear trend comparing atrophic and healthy appearing muscle fibres. For IMNM, necrotic fibres showed a higher expression of all these genes compared to healthy appearing muscle fibres of the same patient. We will further investigate the difference between necrotic and healthy muscle fibres for ASyS and compare it to healthy controls. Also, we will evaluate the dominating macrophage polarization for each entity by using IF staining.
Conclusion. TLR expressing muscle fibres are present in ASyS, DM and IMNM. For each entity different sets of TLR are expressed, suggesting different pathways leading to an upregulation. For DM, TLRs are mainly expressed on atrophic fibres, while in ASyS and IMNM, they are predominantly found on regenerative muscle fibres (0% of the TLR expressing fibres are Vimentin positive in DM, 85% in ASyS and 77% in IMNM). These TLR expressing fibres also showed an upregulation of genes involved in the TLR pathway compared to healthy appearing muscle fibres of the same biopsy.
Acknowledgements. M. S. received a scholarship from the Else Kröner Fresenius Foundation. This study was approved by the ethical committee of the Universal Medical Center Göttingen (permit No. 7/2/20).

P-22

MUSCLE FIBRES PLAY A CRITICAL ROLE IN THERAPEUTIC RESPONSE OF MYOSITIS TO GLUCOCORTICOIDS BY POLARISING THE INFLAMMATORY INFILTRATE

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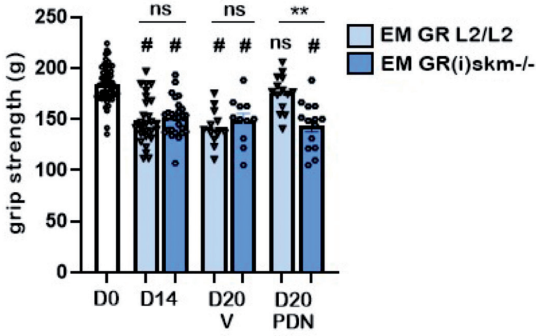
Background. Myositis are rare autoimmune diseases characterized by chronic inflammation of skeletal muscle causing muscle weakness, decreased quality of life and increased mortality. Glucocorticoids (GC) are the first line treatment of myositis. They improve muscle strength (therapeutic effect), yet muscle recovery is generally only partial and long lasting treatment has an iatrogenic effect on skeletal muscle fibre leading to steroid myopathy. Thus, myositis care has to be improved. GC effects are mediated by the glucocorticoid receptor (GR), which is expressed in various cell types including immune cells and myofibres, but the cells mediating therapeutic responses remain to be determined. Our team has recently shown that muscle fibres themselves develop immuno-metabolic modifications that participate to muscle weakness and perpetuation of the disease (Meyer A *et al*. *Acta Neuropathol*. 2017). The aim of this study was to unravel the role of skeletal muscle fibres in the therapeutic effect of GC in myositis.
Methods. To investigate whether the PDN effects are mediated by GR in myofibres, we generated transgenic mice carrying two LoxP sites within the GR gene and expressing the tamoxifen-dependent Cre-ERT2 recombinase selectively in skeletal muscle fibre (HSA-CreERT2/GR L2/L2). Experimental myositis (EM) was induced in eight to ten week-old C57BL/6J female mice by a single intradermal injection of a polypeptide of skeletal muscle fast-type C protein along with Freund's adjuvant and an intraperitoneal (IP) injection of pertussis toxin, as previously described (Sugihara T *et al*. *Arthritis Rheum*. 2007). Tamoxifen, 1 mg/day for 5 days (D) by IP injection, was administered 9 D after immunization to induce GR ablation selectively in skeletal muscle fibres (GR(i)skm-/- mice). Then, prednisone (PDN) was administered 14 D after immunization at 1 mg/kg/day for 7 D by gavage. Mice were euthanized 21 D after EM induction. Similar treatments were applied to GR L2/L2 mice that do not express Cre-ERT2, and served as controls. 4 groups of mice, EM-GR L2/L2 treated by PDN or vehicle and EM-GR(i)skm-/- treated by PDN or vehicle, were compared. Muscle strength was assessed by grip test at D0, before the 1st PDN administration (D14) and the day before sacrifice (D20). Creatine-kinase (CK) activity assay in serum, hematoxylin-eosin (HE) staining on muscle cryosections, immune-cell phenotyping using flow cytometry and transcriptomic analysis of gastrocnemius were performed. Tunel assay and annexin V staining by flow cytometry were conducted to investigate apoptosis.
Results. Muscle strength was decreased by 20% from D14 to D20 in vehicle-treated EM-GR L2/L2 and EM-GR(i)skm-/- mice. At D20 muscle strength of PDN-treated EM-GR L2/L2 mice was similar than that at D0, showing that they recovered muscle strength after PDN treatment. Conversely, PDN did not improve muscle strength in EM-GR(i)skm-/- mice (Figure 1). Consistently, at the end of experiment, CK serum levels were increased in both vehicle-treated EM-GR L2/L2 and EM-GR(i)skm-/- mice. In EM-GR L2/L2 mice, PDN restored CK normal values. This therapeutic effect was abolished in EM-GR(i)skm-/- mice treated by PDN. The top 10 deregulated genes identified at transcriptomic level by comparing EM-GR L2/L2 and EM-GR(i)skm-/- mice treated by PDN or vehi-

cle belonged to muscle fibre metabolism and T cells recruitment pathways. These genes were deregulated in a GR fibre-dependent way further indicating a role of skeletal muscle fibre in GC therapeutic response in myositis. Muscle HE staining did not reveal quantitative differences in the inflammatory infiltrate. However, flow cytometry analysis of muscle showed a 3-fold decrease in $CD8^+$ T-cells in the EM-GRL2/L2 mice treated by PDN compared to vehicle group (p=0.003). This effect of PDN was suppressed in EM-GR(i)skm-/- mice. In addition, Tunel assay, annexin V staining and transcriptome analysis indicated that PDN induces T-cells apoptosis.

Conclusion. Skeletal muscle fibres play a critical role in the GC therapeutic effect in a murine model of myositis through a polarization of inflammatory infiltrate toward an anti-inflammatory response.



P-22. Fig. 1. Grip test. $^{**}p<0.005$ versus (vs) comparator indicated by the line, $^{\#}p<0.0001$ vs D0, ns: not significant, $p>0.05$ vs D0. The bars represent mean ± SEM. N>10 per group. The results of different cohors were pooled.

P-23

IMMUNOMODULATORY FUNCTION OF GM-CSF IN IDIOPATHIC INFLAMMATORY MYOPATHIES

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Background. Idiopathic inflammatory myopathies (IIMs) are characterized by chronic inflammation of the muscle, resulting in muscle weakness and pain. The pathogenesis is driven by the cellular interaction of skeletal muscle, muscle endothelial and immune cells. Cytokines play a central role in the regulation of these cellular interactions. Granulocyte-macrophage colony-stimulating factor (GM-CSF) is a cytokine, which is significantly involved in the development of autoimmune diseases and is currently being investigated in clinical trials for therapy of several inflammatory and autoimmune disorders, such as multiple sclerosis and rheumatoid arthritis. The role of GM-CSF in the inflammatory processes of IIMs is largely unknown. Therefore, the aim of this work is to investigate its immunomodulatory function in the context of IIMs.

Methods. Primary murine skeletal muscle and primary murine microvascular endothelial cells were cultured and stimulated with GM-CSF and other pro- and anti-inflammatory cytokines. To analyze the impact of these conditions, flow cytometric analysis were performed. Furthermore, the immunological relevance of GM-CSF on immune cell migration and adhesion were investigated. The expression of GM-CSF was also evaluated in human muscle biopsies of IIM patients.

Results. The stimulation with pro- and anti-inflammatory cytokines regulates the expression of GM-CSF and the GM-CSF receptor in skeletal muscle and endothelial cells. Vice versa, GM-CSF stimulation resulted in an increased expression of costimulatory molecules on skeletal muscle cells, as well as a decreased expression of tight junction molecules on endothelial cells. Moreover, the activation of GM-CSF signaling leads to an increased adhesion and migration of immune cells in an *in vitro* model of the skeletal muscle endothelial cell barrier. In human muscle biopsies of IIM patients, histological analysis revealed high expression of GM-CSF, mainly in immune cells, located in the perimysial regions of the muscle.

Conclusion. Overall, our findings indicate that GM-CSF signaling is significantly involved in the pathogenic processes and regulated by the inflammatory milieu found in IIMs. These results could contribute to a better understanding of the autoimmune mechanisms in IIMs and help to identify new therapeutic targets.

Acknowledgements. This work was funded by the Deutsche Gesellschaft für Muskelkranke e.V. (DGM). We thank Johanna Schubert for excellent technical assistance.

P-24

MUSCLE-SPECIFIC MICRORNAS IN PLASMA, SKELETAL MUSCLE AND MUSCLE CELLS OF PATIENTS WITH IDIOPATHIC INFLAMMATORY MYOPATHY: THE EFFECT OF 6 -MONTH TRAINING

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Background. Idiopathic inflammatory myopathies (IIM) are systemic autoimmune diseases characterized by proximal muscle weakness and damage as well as metabolic and mitochondrial dysfunction which can contribute to disease symptoms. Physical activity improves muscle function and energy metabolism in parallel with shifts in muscle-specific microRNAs (myomiRs). MyomiRs are involved in the regulation of myogenesis, muscle regeneration and metabolism, and their levels can be modulated by inflammation, muscle degeneration as well as by exercise.

Methods. Samples of m. vastus lateralis were obtained by Bergström needle biopsy under local anesthesia from IIM patients (n=12, 2M/10F, 62.08y±11.26) and sedentary healthy controls (n=13, 2M/11F, 52.64y±11,15). In a subpopulation of IIM patients, muscle and plasma samples have been obtained also before and after 6-month training intervention (n=7/7). Training consisted of supervised individually tailored stretching and strengthening exercise 2x/week (1 h/week activities-of-daily living (ADL), 1 h/week strength training). Patients were encouraged to keep home-based exercise routine for the remaining 5 weekdays (0.5 h/day ADL). Primary muscle cell cultures were established (from muscle of patients with IIM before and after 6-month training intervention as well as from muscle of sedentary healthy controls; n=7/7/7). MicroRNA was isolated from samples of plasma, skeletal muscle and differentiated muscle cells (myotubes). Selected myogenic myomiRs were quantified by qPCR.

Results. We observed lower levels of miR-133b in samples of vastus lateralis muscle of IIM patients compared to healthy controls (p=0.04), with a similar expression pattern for miR-133a, miR-1, miR-206. Interestingly, levels of myomiRs miR-133a,-133b,-1,-206 were substantially higher (2.6, 2.1, 3.3, 0.5 fold, $p>0.05$ for all) in differentiated muscle cells from IIM patients compared to healthy controls. Six-month training intervention in patients with IIM did not modulate in vitro myomiR levels in patients‘ myotubes. However, levels of miR-133b in the muscle of IIM patients were downregulated (p=0.03) and plasma levels of miR-133b & -206 were upregulated in response to 6-month training (p=0.02 & p=0.01). Expression of miR-133a & miR-133b in myotubes tended to negatively correlate with their expression in muscle (R=-0.523, $p<0.1$; R=-0.499, p=0.1).

Conclusion. Lower levels of specific myomiRs in skeletal muscle of patients with IIM indicate reduced regenerative potential of muscle in IIM. It can be speculated that higher levels of myomiRs in differentiated muscle cells in vitro suggest the activation of a potential compensatory mechanism which is not opposed by the presence of inflammation or other systemic factors. The training-induced changes of specific myomiRs in muscle and plasma point at their reciprocal regulation, which could contribute to the adaptive response underlying positive effects of exercise in IIM.

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P-24-1

USP18 A NOVEL REGULATOR OF MUSCLE CELL DIFFERENTIATION AND MATURATION, POTENTIALLY REGULATING REGENERATION IN DERMATOMYOSITIS

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Abstract. USP18 negatively regulates the IFN-1 signalling pathway by removing ISG15, a di-ubiquitin analog, from substrate proteins and plays a role in immune related pathologies. Dermatomyositis (DM), a rare muscle degeneration disease, is characterised by an excessive immune response and IFN-1 signaling. In DM muscles we found USP18 expression within myofibers at regenerating regions, suggesting a role in muscle cell biology. Surprisingly, we observed that USP18 depletion induced muscle cell differentiation under nutrient-rich conditions. USP18 expression and function was independent of ISG15 and IFN-1 signalling, but concomitant with reduced cell cycle and sarcomeric gene networks. USP18 depletion let to altered expression of myogenic (co-)transcription factors, indicating that USP18 tightly regulates the muscle cell differentiation program. Moreover, USP18-depletion impacted physiological features in differentiated muscle cells, suggesting a role in differentiation maintenance. Our results revealed USP18 as a critical regulator of multiple steps during muscle cell differentiation independent of the IFN-1 pathway.

Autoantibodies and biomarkers

P-25

MULTIPARAMETER LINEBLOT IMMUNOASSAY FOR AUTOIMMUNE INFLAMMATORY MYOPATHIES: ADDITION OF CN-1A AS A TARGET FOR DETECTION OF AUTOANTIBODIES ASSOCIATED WITH INCLUSION BODY MYOSITIS

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Background. Autoantibodies against cN-1A (Mup44) are primarily used as a biomarker for inclusion body myositis (IBM), they also occur with lower prevalence in systemic lupus erythematosus (SLE) and Sjögren's Syndrome (SjS). cN-1A has been included as a parameter on the multiparameter lineblot Autoimmune Inflammatory Myopathies 16 Ag et cN-1A (EUROIMMUN), allowing the detection of 17 myositis-specific and myositis-associated autoantibodies. The prevalences of anti-cN-1A autoantibodies were determined in different patient collectives and healthy blood donors.
Methods. A lineblot immunoassay containing a highly purified, recombinant cN-1A expressed in *E. coli* was incubated according to the instructions. Sera of 197 patients with IBM, 48 with collagenosis (systemic sclerosis, undifferentiated collagenosis and mixed tissue collagenosis), 52 with polymyositis/dermatomyositis and 75 with SLE/SjS were screened for cN-1A autoantibodies. Additionally, 151 apparently healthy blood donors as well as a disease control collective comprising sera of 20 patients with thyroiditis, 26 with neuromuscular disorders, 24 with primary biliary cholangitis (PBC), 19 with Wegener's Disease, 17 with Coeliac disease, and 2 with autoimmune liver disease (ALD) were analyzed. Signal intensities were automatically evaluated using the EUROLineScan software (EUROIMMUN).
Results. Prevalences of cN-1A autoantibodies were 34.5% in IBM, 10.4% in collagenosis, 7.7% in polymyositis/dermatomyositis, 13.3% in SLE/SjS, 2% in the blood donor cohort and 4.6% in the disease control collective.
Conclusion. The addition of cN-1A to a multiparametric lineblot immunoassay now reduces the risk of underdiagnosing IBM in patients with autoimmune inflammatory myopathies and increases the overall diagnostic sensitivity.

P-26

MYOSITIS AUTOANTIBODIES DETECTED BY LINE BLOT IMMUNOASSAY: CLINICAL ASSOCIATIONS AND CORRELATION WITH ANTIBODY TITERS

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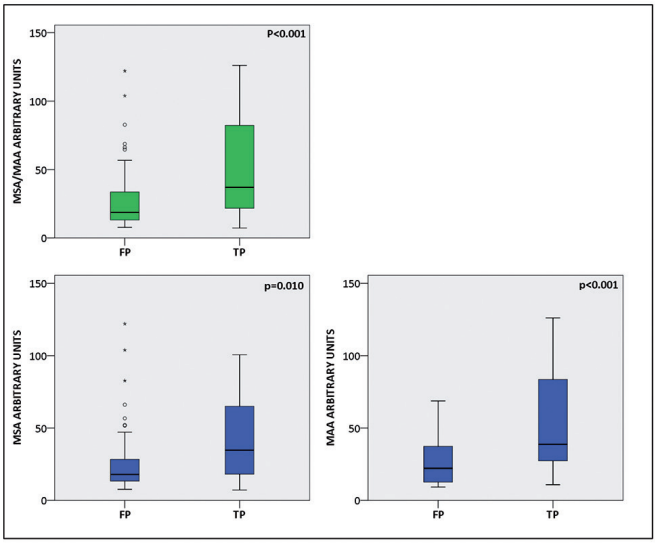
Objectives. The aim of this study is to assess the relationship between MSA and MAA and diagnosis (including IIM and other AID), and to explore the impact of antibody titers in diagnostic accuracy.
Methods. We retrospectively review all the serum samples obtained from patients tested for MSA/MAA by line immunoassay (LIA) between 01/01/2018 and 31/12/2020 in Ramón y Cajal University Hospital (Spain). Positivity was stablished according to absorbance titer (AU) and adjusted by positive control of each test. True positive (TP) MSA and MAA were defined as those patients with IIM or AID with phenotypes expected of that MSA/MAA, according to the available information. The patients that did not have a phenotype compatible with that antibody were regarded as false positive (FP).
Results. Two-hundred-twenty-three positive LIA samples were detected in our lab between 2018 and 2020, 65 were excluded from analysis because they were duplicate tests and 28 were excluded because there was not enough clinical data for accurate classification. The remaining 130 samples corresponded to 130 patients, 85 were women and mean age was 55.08 years (SD 17.92). Forty-four patients (33.8%) were classified as IIM, 43 (33.1%) were classified as AID, and 43 (33.1%) were classified as non-IIM/AID. Among these 130 patients, 164 MSA/MAA were detected (30 patients had a dual positivity, and 2 patients were positive for 3 antibodies). Eighty-three (50.6%) positive MSA/MAA were regarded as TP, and 81 (49.4%) as FP (positive predictive value [PPV] 50.6%). Antibodies regarded as TP had a higher antibody titer compared to FP (49.19 AU vs 26.96 AU, $p<0.001$). This difference was statistically significant for MSA and MAA when analysed separately (Figure 1). According to pre-specified thresholds, 3 antibodies were categorised as borderline, 65 antibodies were categorised as +, 49 as ++ and 47 as +++. Strongly positive antibodies (+++) were more frequently TP (35/47, 74.4%), compared to moderately positives (++) (25/49, 51%) and low positives (+) (22/65, 33.8%), $p<0.001$. The association between MSA/MAA, diagnosis and antibody titer is represented in Table I. ANA were more frequently positive in the TP group compared to the FP group (100% vs 70.3%, $p<0.001$). Besides, ANA titer was higher in TP group compared to FP group ($p<0.001$). Samples that were positive for multiple antibodies were analysed, after excluding those that were positive for one MSA/MAA and anti-Ro52 (as it often co-exists with other MAA/MSA). Multiple positive antibodies (antibodies included in samples that were positive for >1 MSA/MAA) were more frequently FP (19/21, 90.4%) in comparison with isolated positive MSA/MAA (49/101, 48.5%), $p<0.001$. The distribution between MSA/MAA and diagnosis is represented in Table I.



P-26. Fig. 1. Autoantibody titers comparison between FP and TP. MSA: myositis specific antibody; MAA: myositis associated antibody; FP: false positive; TP: true positive.

Conclusions. MSAs and MAAs are associated with IIM and AID. LIA is increasingly used to assess MSA and MAA, although in previous studies a relatively high number of FP results was observed. In this study we confirm that FP results using LIA are relatively frequent, and are associated with lower titer MSA/MAA, negative ANA, lower titer ANA, and with multiple positive samples. This information will be useful for interpreting positive MSA/MAA results in clinical practice.

P-26. Table I. MSA/MAA and diagnosis.

Antibody	TP	TP titer (AU, mean)	TP diagnosis	FP	FP titer (AU, mean)	FP Diagnosis
Anti-Jo1 (n=4)	3 (75%)	91.35	3 ASyS	1 (25%)	15.21	1 non-IIM/AID
Anti-PL7 (n=19)	8 (42.1%)	24.63	8 ASyS	11 (57.9%)	20.70	5 AID (1 SjS, 1 sarcoidosis, 1 PMR, 2 other), 6 non-IIM/AID
Anti-PL12 (n=8)	5 (62.5%)	34.89	5 AsyS	3 (37,5%)	19.57	1 AID (1 SjS), 2 non-IIM/AID
Anti-EJ (n=1)	1 (100%)	99.45	1 AsyS	-	-	-
Anti-OJ (n=6)	-	-	-	6 (100%)	23.75	1 AID (1 SLE), 5 non-IIM/AID
Anti-TIF1γ (n=10)	5 (50%)	31.26	5 DM	5 (50%)	20.77	3 AID (2 SLE, 1 SSc), 2 non-IIM/AID
Anti-NXP2 (n=5)	1 (20%)	12.95	1 DM	4 (80%)	13.78	4 AID (1 SLE, 1 SjS, 1 SSc, 1 PMR) 1 non-IIM/AID
Anti-Mi2A (n=1)	1 (100%)	12.94	1 DM	-	-	-
Anti-Mi2B (n=9)	1 (11.1%)	59.35	1 DM	8 (88.9%)	23.98	1 DM, 2 AID (1 UCTD, 1 other), 5 non-IIM-AID
Anti-Mi2a and anti-Mi2b (n=4)	4 (100%)	32.12	4 DM	-	-	-
Anti-SAE (n=5)	-	-	-	5 (100%)	20.64	2 AID (1 SLE, 1 sarcoidosis), 3 non-IIM/AID
Anti-MDA5 (n=4)	3 (75%)	25.10	3 DM	1 (25%)	82.72	1 non-IIM/AID
Anti-SRP (n=13)	4 (30.8%)	63.18	1 IMNM	9 (69.2%)	48.93	5 AID (2 SLE, 2 sarcoidosis, 1 other), 4 non-IIM/AID
PM-Scl75 (n=13)	5 (38.5%)	28.72	5 AID (3 UCTD, 2 SSc)	8 (61.5%)	24.36	1 DM, 2 AID (1 SLE, 1 RA), 5 non-IIM/AID
PM-Scl100 (n=5)	3 (60%)	24.51	1 OM-CTD, 2 AID (2 SSc)	2 (40%)	15.46	2 non-IIM/AID
PM-Scl75 and PM-Scl 100 (n=2)	2 (100%)	70.45	1 OM-CTD, 1 UCTD	-	-	-
Anti-Ku (n=26)	12 (46.2%)	58.87	3 OM-CTD, 9 AID (5 SLE, 1 SjS, 3 UCTD)	14 (53.8%)	16.50	10 non-IIM/AID, 4 AID (3 sarcoidosis, 1 other)
Anti-Ro52 (n=29)	26 (89.7%)	57.13	6 ASyS, 1 ASyS + SjS, 4 DM, 2 PM, 11 AID (3 SLE, 4 SjS, 2 SSc, 2 UCTD), 2 non-IIM/AID (1 PBC, 1 AIH)	3 (10.3%)	55.65	3 non-IIM/AID

TP: true positive; FP: false positive; AU: arbitrary units; IIM: idiopathic inflammatory myopathy; AID: systemic autoimmune disease; ASyS: antisynthetase syndrome; DM: dermatomyositis; IMNM: immune-mediated necrotising myopathy; SLE: systemic lupus erythematosus; PMR: polymyalgia rheumatica; SjS: Sjögren syndrome; SSc: systemic sclerosis; UCTD: undifferentiated connective tissue disease; PBC: primary biliary cirrhosis; AIH: autoimmune hepatitis; RA: rheumatoid arthritis; MSA: myositis specific antibodies; MAA: myositis associated antibodies.

P-27

B CELL RECEPTOR PROFILING BEFORE AND AFTER IVIG MONOTHERAPY IN NEWLY DIAGNOSED IDIOPATHIC INFLAMMATORY MYOPATHIES

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Objective. To gain more insight into B cell receptor (BcR) repertoire changes in muscle biopsies and peripheral blood in idiopathic inflammatory myopathies (IIMs), and to study how this correlates to the clinical response to intravenous immunoglobulin (IVIg).
Methods. Nineteen treatment naïve patients with newly diagnosed IIM were prospectively treated with IVIg monotherapy. RNA-based BcR repertoire sequencing was performed in muscle biopsies collected before, and in peripheral blood (PB) collected before and nine weeks after IVIg treatment. Results were correlated to patients' clinical improvement based on the total improvement score (TIS).
Results. Amongst the included patients, eight (42%) had dermatomyositis, five (26%) had non-specific/overlap myositis, five (26%) had an immune mediated necrotizing myopathy, and one patient (5%) had antisynthetase syndrome. Prior to IVIg treatment, BcR clones found in muscle tissue could be retrieved in peripheral blood. Nine weeks after IVIg treatment, new patient-specific dominant BcR clones appeared in peripheral blood while pre-treatment dominant BcR clones disappeared. The cumulative frequency of all dominant BcR clones before treatment was significantly higher in individuals who responded to IVIg compared to those who did not respond to IVIg, and correlated with a higher CK. During follow up, a decrease in the cumulative frequency of all dominant clones correlated with a higher TIS.
Conclusion. In naïve patients with newly diagnosed IIM, muscle tissue and peripheral blood share expanded BcR clones. In our study a higher cumulative frequency of dominant BcR clones in blood before treatment was associated with a higher CK and better treatment response, suggesting that response to IVIg may depend on the composition of the pre-treatment BcR repertoire.

P-28

SUPPRESSION OF HDL-ASSOCIATED APOLIPOPROTEIN A-I (APOA-I) LEVELS IN PATIENTS WITH IDIOPATHIC INFLAMMATORY MYOPATHIES

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Background. Patients with idiopathic inflammatory myopathies have accelerated vascular disease, which contributes to higher disease morbidity and mortality. Apolipoprotein A-I (apoA-I) is the major protein component of HDL, which suppresses vascular inflammatory responses through promotion of cholesterol efflux and prevention of low density lipoprotein (LDL) oxidation. The current work assessed HDL-associated ApoA-I levels (HDL-apoA-I) in IIM patients compared to healthy controls, and evaluated associations of HDL-apoA-I with specific IIM disease characteristics.
Methods. HDL-apoA-I levels were measured by sandwich ELISA using a primary HDL antibody. HDL-apoA-I levels, demographic variables and traditional cardiovascular risk factors were compared in 122 IIM patients and 110 healthy controls (HC). HDL-apoA-I levels were also assessed separately in a large IIM extended patient cohort (n=274) in relation to clinical and laboratory IIM disease characteristics. Multivariate linear regression analyses were performed to further assess predictors associated with HDL-apoA-I while adjusting for statistically significant univariate variables.
Results. HDL-apoA-I levels were significantly lower in IIM patients compared to HC and the association between low HDL-apoA-I and IIM diagnosis remained strong after multivariate adjustment. In linear regression analysis of the extended IIM patient group (Table I), higher MD global disease activity scores by visual analog and likert scales as well as the presence of dermatomyositis (vs polymyositis or inclusion body myositis) and the presence of certain myositis specific autoantibodies (ab) (MDA5 and TIF1γ ab) were associated with lower HLD-apoA-I levels. In multivariate analysis, the presence of MDA5 or TIF1γ ab remained significantly associated with lower HDL-apoA-I levels (regression coefficient $\beta = -1.35$, $p<0.001$ and $\beta = -0.81$, $p=0.01$ respectively).

Conclusions. HDL-apoA-I levels were significantly lower in IIM patients compared to HC, and inversely associated with the presence of MDA5 and TIF1γ ab. Our results indicate a potential mechanism for the microvascular inflammation and damage in IIM, particularly in patients with MDA5 and TIF1γ ab.

P-28. Table I. Univariate Linear regression Analysis of variables associated with HDL-apoA-I† levels in Patients with IIM including IIM disease specific variables (n=274)

	IIM (n=274)	Regression coefficient (95%CI)
Age, years	50 ± 15	-0.004 (-0.02,0.01)
Sex, Female	195 (71)	0.31 (-0.13, 0.75)
Race, Caucasian	205 (75)	0.10 (-0.36,0.56)
Ethnicity, Hispanic	53 (20)	**0.36 (0.06,0.65)***
CVD RF		
MI	6 (2)	0.49 (-0.86, 1.85)
Stroke/TIA	6 (2)	-0.51 (-1.87,0.85)
HTN	83 (30)	**0.67 (0.24, 1.09)***
Dyslipidemia	61 (22)	**0.71 (0.24, 1.18)***
Diabetes	38 (14)	0.49 (-0.08, 1.06)
BMI	27 ± 6	0.02 (-0.02, 0.05)
Ever smoker	53 (19)	0.23 (-0.27, 0.73)
FHx of premature MI	29 (11)	0.18 (-0.46, 0.82)
Cholesterol medication use	33 (12)	0.03 (-0.59, 0.64)
Lipid panel, 10mg/dl		
Total cholesterol	211 ± 55	-0.01 (-0.05, 0.03)
LDL-C	125 ± 49	-0.02 (-0.06, 0.02)
HDL-C	62 ± 31	0.01 (-0.05, 0.08)
Triglyceride	176 ± 175	-0.004 (-0.01, 0.01)
IIM type		
Dermatomyositis	195	**-0.06 (-0.99, -0.12)***
Polymyositis	63	0.40 (-0.07, 0.87)
Inclusion body myositis	15	0.64 (-0.20, 1.49)
Disease duration, months, median (IQR)	14 (3-62)	0.001 (-0.001,0.004)
Myositis Autoantibodies		
Antisynthetase	43 (16)	-0.05 (-0.60,0.50)
MDA5	21 (8)	**-1.47 (-2.20, -0.75)***
SRP	18 (7)	-0.63 (-1.43,0.17)
HMGCR	5 (2)	-1.25 (-2.73, 0.23)
Mi2	10 (4)	0.21 (-0.85, 1.27)
TIF1r	32 (12)	**-0.83 (-1.44, -0.22)***
NXP2/MJ	15 (5)	-0.03 (-0.90, 0.85)
RNP	3 (1)	1.09 (-0.82, 3.00)
Ro/SSA	14 (5)	-0.60 (-1.50, 0.30)
SAE	5 (2)	-0.50 (-1.99, 0.99)
Ku	2 (1)	-1.80 (-4.12, 0.53)
PM-scl	3 (1)	-1.41 (-3.31, 0.49)
Unidentified ab	17 (6)	-0.78 (-1.60, 0.04)
None	13 (5)	-0.09 (-1.02, 0.85)
ILD	79 (34)	-0.12 (-0.58, 0.34)
Cancer	19 (25)	0.59 (-0.25, 1.42)
MD global activity VAS, 1-10cm	41 ± 21	**-0.12 (-0.22,-0.02)***
MD global activity likert, median (IQR)	2 (1-2)	**-0.31 (-0.57,-0.05)***
MD global damage VAS, 1-10	31 ± 22	0.03 (-0.07,0.12)
MD global damage likert, median (IQR)	1 (1-2)	-0.06 (-0.30,0.17)
HAQ, median (IQR)	0.88 (0.25-1.5)	-0.11 (-0.42, 0.21)
CK, median (IQR)†	121 (62-352)	0.02 (-0.12, 0.17)
Aldolase	6.4 (4.9-9.5)	0.25 (-0.04, 0.53)
ESR, median (IQR)†	23 (9-33)	-0.10 (-0.28, 0.07)
hsCRP, median (IQR)†	1.6 (0.6-5.7)	0.09 (-0.04, 0.23)
Medications		
IVIG	54 (20)	**-0.90 (-1.37, -0.44)***
MMF	61 (22)	**-0.89 (-1.33,-0.44)***
AZA	22 (8)	0.57 (-0.12, 1.27)
MTX	51 (19)	0.01 (-0.48, 0.50)
HCQ	42 (15)	0.15 (0.37, 0.68)
TNFi	6 (2)	0.52 (-0.74, 1.77)
RTX	17 (6)	-0.04 (-0.81, 0.73)
CYC	10 (4)	**3.17 (1.90,4.45)***
Prednisone, yes	151 (55)	-0.22 (-0.68, 0.23)
Prednisone daily dose, median (IQR)	15 (5-35)	0.003 (-0.01, 0.01)

Values are mean ± SD or N(%) unless specified *p<0.05 † Log transformation was used for skewed variables to fit linearity assumption, apoA1, CK, ESR, hsCRP
Abbreviations: MI: myocardial infarction; TIA: transient ischemic attack; BMI: body mass index; FHx: family history; VAS: visual analog scale; HAQ: health assessment questionnaire.

P-29

ADRENOMEDULLIN EXPRESSION IS ASSOCIATED WITH SEVERITY AND POOR PROGNOSIS OF INTERSTITIAL LUNG DISEASE IN DERMATOMYOSITIS

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Objective. This study aimed to evaluate the adrenomedullin mRNA levels in peripheral blood mononuclear cells (PBMCs) of patients with dermatomyositis (DM) and determine the correlation between the adrenomedullin mRNA levels and the severity of interstitial lung disease (ILD) in DM.
Methods. A total of 41 DM patients, 7 immune-mediated necrotizing myopathy (IMNM) patients, and 21 healthy controls (HCs) were recruited. The adrenomedullin mRNA levels in PBMCs from these samples were measured by quantitative reverse-transcription real-time polymerase chain reaction (qRT-PCR). Associations with major clinical, laboratory and pulmonary function test parameters or prognosis in DM patients with ILD were also analysed. Immunohistochemistry was performed to analyze the expression of adrenomedullin in lung tissues from DM patients with ILD.
Results. Compared with IMNM patients and HCs, adrenomedullin mRNA levels in PBMCs were significantly higher in DM patients (p=0.007, p<0.001, respectively). In DM patients, the levels were significantly higher in patients with RP-ILD than in those with chronic ILD (p=0.002) or without ILD (p=0.003). The adrenomedullin mRNA levels in DM patients with ILD were positively correlated with lung VAS (r=0.354, p=0.039), but negatively correlated with the pulmonary function test results, including FVC% (r = –0.496, p=0.036), FEV1% (r = -0.592, p=0.003), and DLco% (r = -0.505, p=0.032). Furthermore, elevated adrenomedullin mRNA levels in DM patients with ILD were positively associated with the serum ferritin, lactate dehydrogenase (LDH) and C3. In addition, in DM patients with ILD, 6 decedents exhibited a greater level of adrenomedullin compared with 28 survivors (p=0.042). The cumulative survival rate was significantly lower (57.1% vs 100%, p=0.001) in the group with an adrenomedullin level >0.070 than that in the group with an adrenomedullin level <0.070. Immunohistochemistry revealed increased adrenomedullin expression in the lung tissues of patients with DM and RP-ILD.
Conclusions. An elevated adrenomedullin mRNA level in PBMCs is common in DM patients with ILD, and a higher adrenomedullin mRNA is an important biological predictor of RP-ILD and poor prognosis in those patients.

P-30

ANTIGENIC TARGETS IN ANTI-SRP IMMUNE-MEDIATED NECROTIZING MYOPATHY

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Background. Immune-mediated necrotizing myopathy (IMNM) is characterized by a specific phenotype combining subacute and severe muscle weakness with high serum creatine kinase level, specific autoantibodies (anti-SRP or anti-HMGCR antibodies), and muscle fiber necrosis and regeneration with few or absent inflammatory infiltrates on muscle biopsy. SRP is an intracellular ribonucleoprotein complex with 7 SL RNA molecule and six proteins dedicated to target proteins to the endoplasmic reticulum membrane. A direct pathogenic effect of anti-SRP antibodies through a complement-dependent antibody-mediated mechanism has been suggested to explain muscle fiber necrosis supported by in vitro and in vivo models. In murine model, the passive transfer of autoantibodies from patients induced muscle necrosis and muscle weakness which is less important in case of C3-deficient mouse model. Though SRP is a ubiquitous intracellular molecule, IMNM is almost a muscle-specific autoimmune disease raising

the issue of the pathological process leading to antigen recognition and break of tolerance specifically in muscle tissue. Through the identification and production of monoclonal anti-SRP antibodies, we aim to first, confirm the antigenic targets, then identify the pathogenic mechanisms leading to IMNM.
Methods. Anti-SRP B cells were single-cell sorted from frozen PBMC of anti-SRP IMNM patients. Paired V(D)J sequences of heavy and light chains were amplified, cloned into plasmids with constant part sequences, and transfected in CHO cell system to produce monoclonal antibodies (mAb). Supernatants were purified on protein G columns to recover fully human recombinant monoclonal antibodies. Antigenic targets were identified with western blots and immunoblots. In silico predictions using SabPred were performed to create a Fv modelling with ABodyBuilder then a prediction of antigen/antibody interactions with Antibody-i-Patch.
Results. Thirteen monoclonal antibodies were identified, eleven were produced and five antibodies recognized SRP54 using two different immunoassays (Dot blot or ALBIA and Western blot). Analysis of the V(D)J sequences showed a long CDR3 amino acid sequence in several heavy chain, a characteristic of autoreactive clone. In western blots with muscle protein extracts, mAb recognized SRP54 and other proteins. More specifically, when membrane and cytoplasmic proteins are separated, mAb recognized a 50Kd-protein in cytoplasmic fraction of myoblasts and myotubes. In membrane myoblast proteins, it identified a 50 Kd protein and other proteins (~250kDa). In membrane myotube proteins, mAb only recognized proteins with high molecular weight and no band was seen at 50 Kd (Figure 1). This result suggests the expression of SRP54 at the surface membrane or the recognition of another protein with a shared epitope. Immunoprecipitation experiments with mass spectrometry analysis will be developed to identify this protein. *In vitro* model development with live-imaging experiment is being set up to characterize the interaction of the complex mAb/antigen on muscle cells.
Conclusion. The identification of this potential new target is important to better understand the pathogenic role of mAb. The development of *in vitro* model will increase our knowledge on the recognition of the antigenic target in the muscle tissue.
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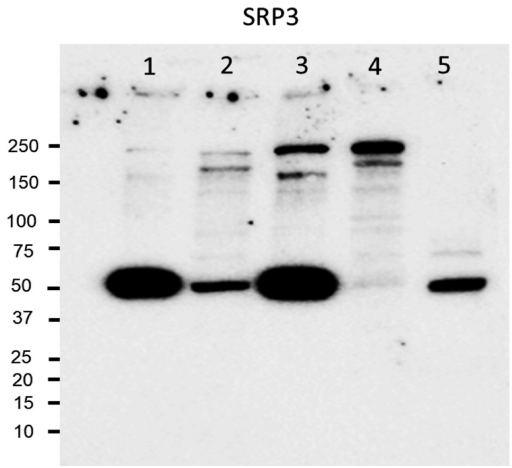

P-30. Fig. 1. Identification of proteins by SRP3 monoclonal antibody in myoblast or myotube protein extracts. Different protein extracts were loaded: lane 1 corresponding to cytoplasmic proteins from myoblasts, lane 2: membrane proteins from myoblasts, lane 3: cytoplasmic proteins from myotubes, lane 4: membrane proteins from myotubes, and lane 5: recombinant commercial SRP54. The primary antibody was SRP3 monoclonal antibody in the culture supernatant and secondary antibody HRP-conjugated goat anti-human IgG, $F(ab')_2$ fragment specific.

P-31

EVALUATION AND VALIDATION OF THE PROGNOSTIC VALUE OF ANTI-MDA5 IGG SUBCLASSES IN DERMATOMYOSITIS-ASSOCIATED INTERSTITIAL LUNG DISEASE

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Objective. To investigate the association between the anti-melanoma differentiation associated gene 5 (MDA5) IgG subclasses and prognosis of patients with dermatomyositis (DM)-associated interstitial lung disease (ILD).
Methods. This retrospective study included 122 Anti-MDA5 positive DM-ILD patients admitted from October 2017 to October 2020 as training cohort, and additional 68 patients from August 2014 to September 2017 as validation cohort. The levels of anti-MDA5 total IgG and IgG subclasses were measured using in-house enzyme-linked immunosorbent assays, and analysed in association with the patient prognosis.
Results. In the training cohort, the concentrations of anti-MDA5 IgG1 and IgG3 in non-survivors were significantly higher than survivors ($p<0.05$), whereas there were no significant differences in the IgG2 and IgG4 levels. Kaplan–Meier survival analysis revealed that the levels of anti-MDA5 total IgG, IgG1 and IgG3 were associated with mortality ($p<0.05$). Multivariate analysis revealed anti-MDA5 IgG1 >13 U/mL and anti-MDA5 IgG3 >11 U/mL were independent risk factors for death of DM-ILD patients ($p<0.05$). Anti-MDA5 IgG1 was confirmed as an independent risk factor in the validation cohort, while anti-MDA5 IgG3 was not. Anti-MDA5 IgG1 showed greater discriminable power for patient prognosis (Youden index 0.494) than anti-MDA5 total IgG, IgG3 or the combination of IgG1 and IgG3 (Youden index as 0.356, 0.32, 0.447, respectively).
Conclusion. Anti-MDA5 IgG1 and IgG3 are significantly associated with poor prognosis in DM-ILD patients, and anti-MDA5 IgG1 is more efficient as a prognostic biomarker in DM-ILD patients.

P-32

PERFORMANCE OF URINARY SUBCLINICAL KIDNEY INJURY BIOMARKERS- NEUTROPHIL GELATINASE ASSOCIATED LIPOCALCIN (NGAL), KIDNEY INJURY MOLECULE (KIM1), CD 163, ACTIVIN A, AND CYSTATIN C IN IDIOPATHIC INFLAMMATORY MYOSITIS: DATA FROM MYOCITE COHORT

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Background. Renal involvement in idiopathic inflammatory myositis (IIM) is rarely reported. Traditional markers of renal injury may not detect very early renal injury
Objective. We aimed to assess the levels of urinary subclinical renal tubular injury biomarkers- (A) Neutrophil gelatinase associated lipocalin (NGAL), (B) kidney injury molecule (KIM1), (C) Activin A, (D) CD163, and (E) Cystatin C in activity and damage stratified subsets of IIM.
Methods. We extracted data of IIM (2017 ACR/EULAR criteria) patients from the MyoCite cohort on clinical and laboratory variables, HAQ-DI and other core set measures [Patient global assessment (PtGA), Physician global assessment (PhGA), MMT8, MDAAT, MDI, muscle enzymes] from baseline and at each follow up (FU) visits. MDAAT>1 (0-10) and MDI extent of severity score >1 (0-38) defined active myositis and damage respectively. Urine was evaluated for A, B, C, D, E, protein and creatinine excretion and normalised for urine creatinine for comparison between active/inactive disease, subtypes of IIM. Their correlation (Pearson r) with core set outcome measures for disease activity and damage were assessed. Sixteen AKI patients defined by KDIGO definition and twenty healthy controls urine sample were compared with. eGFR (unit ml/min/1.73m2) was calculated by Cockcroft-Gault formula (CG) and CKD-EPI formula (EPI). The units of normalized biomarkers are expressed in ng/mg.
Results. 201 visits of 110 adult patients (110 baseline, 63 FU) aged 41 (31-51) years, 84 females, disease duration 5 (3-13.5) months were analyzed. Dermatomyositis (DM) was the most common subset (42%), with a baseline MDAAT and MDI damage scores of [0(0-0.89), and 8.5(3.6-13.7)]. Normalized urinary biomarker concentrations were B 1.23, A 316, C 83, D 233, E 935. The median

eGFR was 92 (70-112) (CG) and 107 (90-119) (EPI). IIM patients had higher normalized biomarkers compared to HC (A 327 vs 184 p 0.024, B 1.2 vs 0.1 p<0.001, C 80 vs 23 p<0.001, D 202 vs 34 p<0.001, E 935 vs 229 p<0.001) (Figure 1). Except for normalized NGAL (327 IIM vs 937 AKI, p 0.009), rest all four biomarkers were equally elevated as seen in AKI patients (B 1.2 VS 1, C 80 VS 72, D 193 VS 226, E 931 VS 1649 IIM VS AKI). Seventy-two (49%) of IIM had eGFR<90 (35% had 30-60, 11% had 15-30, 2% had <15 eGFR). Normalized urinary biomarkers were comparable between active and inactive IIM (A 357 vs 245 p 0.052, B 1.2 vs 1.1 p 0.301, C 72 vs 82 p 0.374, D 181 vs 224 p 0.112, E 896 vs 1101 p 0.264) with 88%, 90% having elevated markers. Further these biomarkers were similar across subtypes of IIM suggesting comparable kidney injury. Change in these normalized biomarkers on follow-up did not correlate with change in eGFR. Further sensitivity to change with change in disease activity couldn't be assessed as patients mostly had no change in disease activity on follow up. Further, these biomarkers correlated poorly with core set measures of myositis.

Conclusions. Patients with IIM have higher renal tubular injury markers compared to HC and comparable to AKI patients. However, this does not seem to be related to disease activity or subset of IIM, and merits further investigation. Key messages:1. Normalized Urine NGAL, KIM1, Activin A, sCD163, Cystatin C are elevated in most of the IIM. 2. These biomarkers were more in IIM than HC and are as high as in AKI patients. 3. These biomarkers did not correlate with disease activity or subsets of IIM.

P-33

ABUNDANT AUTOANTIBODY ISOTYPES IN IDIOPATHIC INFLAMMATORY MYOPATHIES

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Background. Anti-synthetase syndrome (ASSD), a sub-group of idiopathic inflammatory myopathies (IIM), is characterized by the presence of autoantibodies targeting aminoacyl tRNA synthetases (aaRS) and specific clinical manifestations such as myositis and interstitial lung disease (ILD) (1). Some of the most common anti-aaRS autoantibodies in ASSD are anti-Jo1, -PL7, -PL12, and -EJ. In addition, many anti-aaRS positive patients are also positive for anti-Ro52. Having the combination of anti-Jo1 and anti-Ro52 increases the risk of developing ILD (2). The presence of autoantibodies is an integral part of the classification of ASSD. However, only autoantibodies of IgG isotype are usually analyzed in the clinical setting. In rheumatoid arthritis (RA), there is evidence that anti-citrullinated protein/peptide antibodies (ACPA) can be found as IgG, IgA, and IgM, and significantly, specific isotypes might correlate with disease activity (3, 4). Therefore, our objectives were to verify if other autoantibody isotypes, besides IgG, might also be present in sera of patients with IIM/ASSD and compare with the corresponding frequencies in population controls (PC).

Methods. Stored sera collected from 366 IIM patients and 156 age and gender-matched non-rheumatic population controls (PC) at Karolinska University Hospital were retrospectively selected and included in the study. The serum samples were screened for the presence of autoantibodies of isotypes IgG, IgA, and IgM, against a panel of 20 antigens representing Jo1 (HisRS), PL7 (ThrRS), PL12 (AlaRS), EJ (GlyRS), and Ro52 (TRIM21) using a multiplex bead array assay.

Results. We identified IIM patients with autoantibodies of different isotypes (Figure). For anti-Jo1 autoantibodies, we could detect patients with only IgG (n=13), only IgM (n=8), and only IgA (n=4), but the majority did have a combination of two (n=32) or three isotypes (n=16). For the other anti-aaRS autoantibodies, the distribution was more equal to each of the three isotypes, with anti-PL12 and anti-PL7 being represented by a slightly higher frequency of IgG. Only a few patients had antibodies of more than one isotype targeting PL12, PL7, or EJ. The majority (n=52) of anti-Ro52 positive IIM patients only harbored IgG isotype. The combination of anti-Ro52 and anti-aaRS autoantibodies was identified in 28 patients (anti-Jo1 (n=19), -PL12 (n=2), -PL7 (n=3), and -EJ (n=4)). Most patients with such combination had anti-Ro52 IgG and anti-aaRS IgG or IgG combined with IgA and/or IgM. The exception was observed for three anti-Jo1 positive patients who had the combination anti-Ro52 IgG with only anti-Jo1 IgM and one anti-PL7 positive patient who had anti-Ro52 IgA together with anti-PL7 IgA and IgG. A low frequency of autoantibodies was also found in population controls, and for some of the isotypes, these were similar to the IIM cohort (Figure 1).

Conclusions. The frequency of the different autoantibody isotypes seems autoantigen dependent. Our results suggest that for anti-aaRS autoantibodies, it could be essential to investigate additional autoantibody isotypes, as some patients only harbor autoantibodies of IgM or IgA isotypes but not IgG. The clinical relevance of the different antibody isotypes still needs to be determined.

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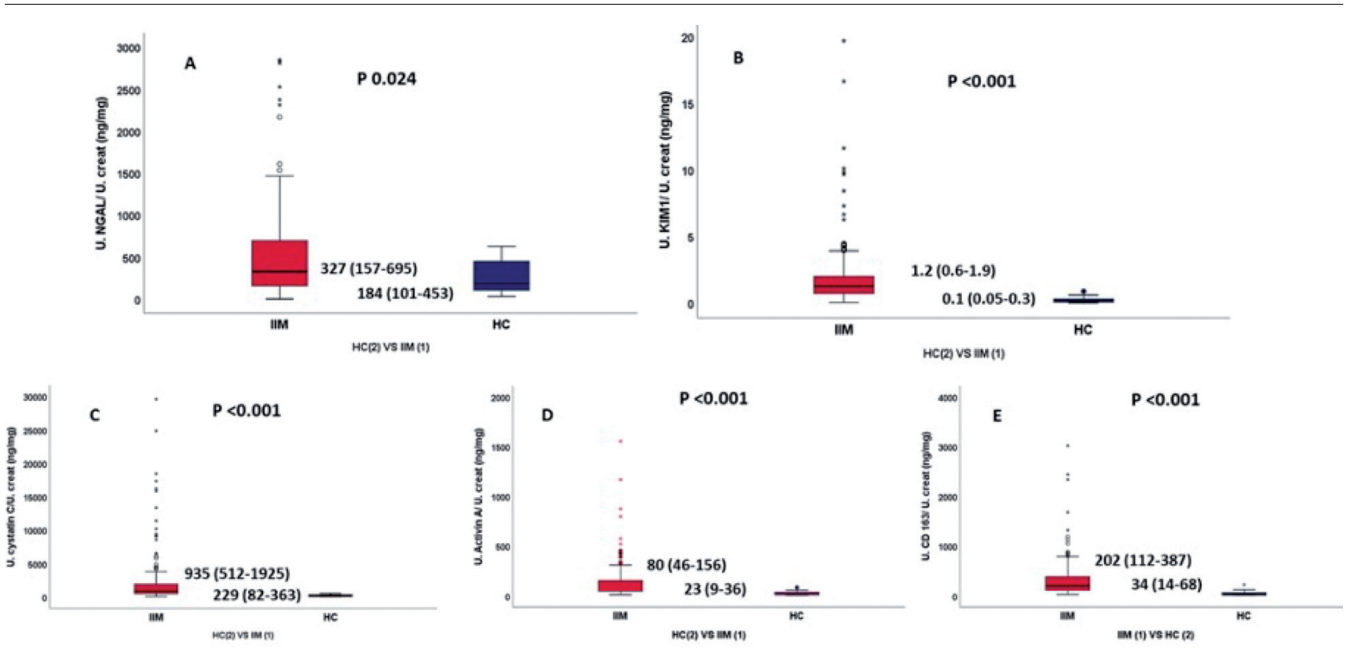
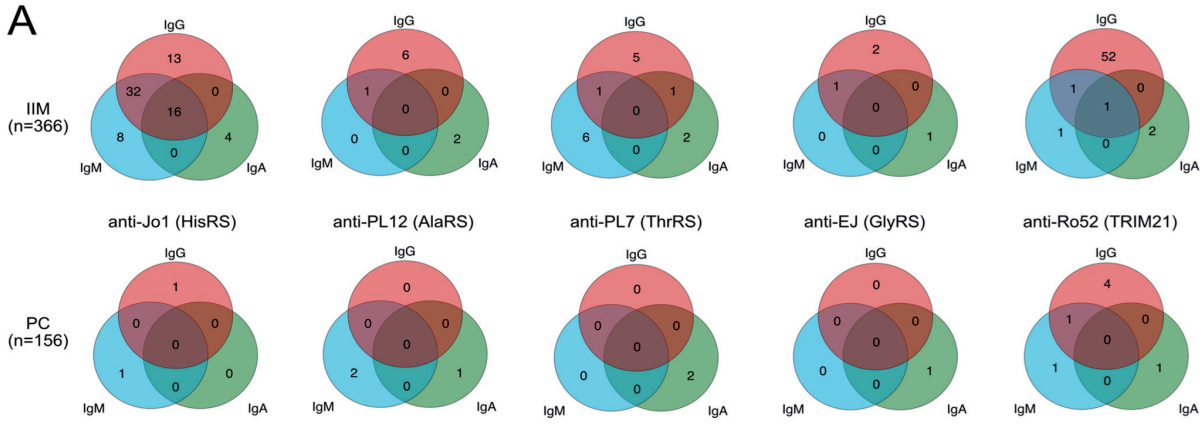


P-32. Fig. 1. Performance Of Urinary Subclinical Kidney Injury Biomarkers- Neutrophil Gelatinase Associated Lipocalcin (NGAL), Kidney Injury Molecule (KIM1), CD 163, Activin A, and Cystatin C In Idiopathic Inflammatory Myositis: Data From Myocite Cohort.

A



B

	anti-Jo1 (HisRS)		anti-PL12 (AlaRS)		anti-PL7 (ThrRS)		anti-EJ (GlyRS)		anti-Ro52 (TRIM21)	
	IIM	PC	IIM	PC	IIM	PC	IIM	PC	IIM	PC
IgG	61 (16.7)	1 (0.6)	7 (1.9)	0 (0.0)	7 (1.9)	0 (0.0)	3 (0.8)	0 (0.0)	54 (14.8)	5 (3.2)
IgA	20 (5.5)	0 (0.0)	2 (1.2)	1 (0.6)	3 (0.8)	2 (1.3)	1 (0.3)	1 (0.6)	3 (0.8)	1 (0.6)
IgM	56 (15.3)	1 (0.6)	1 (0.3)	2 (1.3)	7 (1.9)	0 (0.0)	1 (0.3)	0 (0.0)	3 (0.8)	2 (1.3)

P-33. Fig. 1. Individuals positive for the three autoantibody isotypes IgG, IgA and IgM against five myositis autoantigens: Jo1 (HisRS), PL12, (AlaRS), PL7 (ThrRS), EJ (GlyRS) and Ro52 (TRIM21). **A**) Venn diagrams showing the number of positive individuals divided into two groups: idiopathic inflammatory myopathies (IIM) (top) population controls (PC) (bottom). **B**) Total number positive of individuals and percentage (n (%)) in each group for each of the isotypes and antigens.

P-34

NEGATIVE ANTI-JO ANTISYNTHETASE SYNDROME: ARE THERE DIFFERENCES IN THE CLINICAL PHENOTYPE?

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Background. The antisynthetase syndrome is a type of immune-mediated myopathy defined by the presence of inflammatory myopathy and extramuscular findings including interstitial lung disease, "mechanic's hands", inflammatory arthritis, and Raynaud phenomenon with an antibody directed against an aminoacyl-transfer RNA (tRNA) synthetase. Among these antibodies, the most frequent is anti-Jo, although antibodies against the following antigens have also been described: PL-12, PL-7, OJ, KS, EJ, Zo and Ha. Some clinical differences between some antibodies and others have been described, but definitive data in this diverse group are lacking. The purpose of this study was to examine the clinical phenotype of non-anti-Jo-1 antisynthetase antibodies.
Methods. Retrospective descriptive study on 9 cases with anti-Jo negative antisynthetase syndrome were identified from databases at the Virgen del Rocio Hospital of Seville. The following data were recorded: demographic information; pulmonary and rheumatologic symptoms; serologic autoantibody findings; CT scan results; pulmonary function test results; muscle histopathology and treatment interventions.
Results. The median age at symptom on set was 55.2 years; 77.8% were women. Four patients presented anti-PL-7, three anti-PL-12, one anti-EJ and one anti-OJ. All of them were antisynthetase syndrome except the anti-OJ case which was diagnosed as juvenile dermatomyositis and had anti-Mi2 positivity too. Eighty eight percent presented arthritis and the same percentage had interstitial lung disease (ILD), with a median of 40% in DLCO at diagnosis. Seventy-seven percent presented proximal muscle involvement. Fever occurred in 55% of patients, Raynaud phenomenon in 44% of patients and mechanic's hands 22% of patients. Fifty-five percent of patients had dermatomyositis-like skin involvement.
Conclusions. Non-anti-Jo-1 antisynthetase antibodies are strongly associated with the presence of ILD and proximal muscular involvement without great differences in frequency. Analysis aimed at detecting these antibodies may be essential when approaching the differential diagnosis in myopathies, especially in patients with ILD and skin involvement.

P-35

EFGARTIGIMOD RESTORES MUSCLE FUNCTION IN A HUMANIZED MOUSE MODEL OF IMMUNE-MEDIATED NECROTIZING MYOPATHY (IMNM)

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Introduction. Immune-mediated necrotizing myopathy (IMNM) is a severe form of myositis characterized by muscle weakness and elevated creatine kinase levels in serum. On biopsy, necrosis/regeneration of skeletal muscle fibers and deposition of C5b-9 membrane attack complex (MAC) are associated with varying levels of immune cell infiltration. The most frequent autoantibody (aAb) in IMNM patients is directed against hydroxymethylglutaryl-Coenzyme A reductase (HMGCR). Anti-HMGCR aAb are pathogenic and induce disease after adoptive transfer to mice by a mechanism partly involving complement. Efgartigimod is an engineered human IgG1 Fc fragment which antagonizes the neonatal Fc receptor (FcRn). We evaluated the therapeutic effects of IgG reduction following efgartigimod treatment in a humanized murine model of IMNM.
Methods. Groups of n=8 complement C5-deficient B10 (C5def) or Rag2 deficient (Rag2-/-) mice received daily intraperitoneal injections of IgG-depleted human serum as a source of human complement. To prevent xenoimmunization against human proteins, C5def mice were pretreated with a single injection of cyclophosphamide (day -1). Disease was induced by injections of 2 mg IgG purified from an anti-HMGCR aAb+ IMNM patient or from a healthy donor as control (day 0, 4 ± day 8, 12, 16). C5def mice were treated in a preventive setting with subcutaneous injections of 20 mg/kg efgartigimod (day -1, 2, 4 and 6). Rag2-/- mice were treated in a curative setting (day 8, 11, 15) after disease was induced by IgG injections. Muscle force was assessed by grip test or measurement of gastrocnemius strength upon sciatic nerve electrostimulation (anesthetized animals). Levels of total IgG or anti-HMGCR+ IgG aAb were monitored in mouse serum by ELISA and ALBIA, respectively. Histological analysis of muscle tissue sections was performed after staining with hematoxylin/eosin or fluorochrome-labeled antibodies.
Results. In the preventive setting, administration of efgartigimod prevented decrease in muscle strength induced by anti-HMGCR+ IgG in C5def mice ($p<0.05$). Total IgG levels decreased and anti-HMGCR+ IgG aAb became undetectable at day 7. In a therapeutic setting, the level of the muscle deficit induced

by anti-HMGCR+ IgG (p<0.05) returned to normal following efgartigimod administration. Total IgG levels decreased and anti-HMGCR+ IgG aAb became undetectable on day 18, *i.e.* 9 days after efgartigimod administration. Results of histological analyses (in progress) will be presented.
Conclusion. Efgartigimod dramatically reduces circulating IgG levels and rapidly eliminates pathogenic anti-HMGCR+ aAb in a humanized mouse model of IMNM, preventing disease onset or treating overt IMNM. These results support investigating the therapeutic efficacy of efgartigimod through a clinical trial in IMNM patients.

P-36

HYPOGAMMAGLOBULINEMIA AFTER RITUXIMAB TREATMENT IN AN ITALIAN REAL-LIFE COHORT OF IIM

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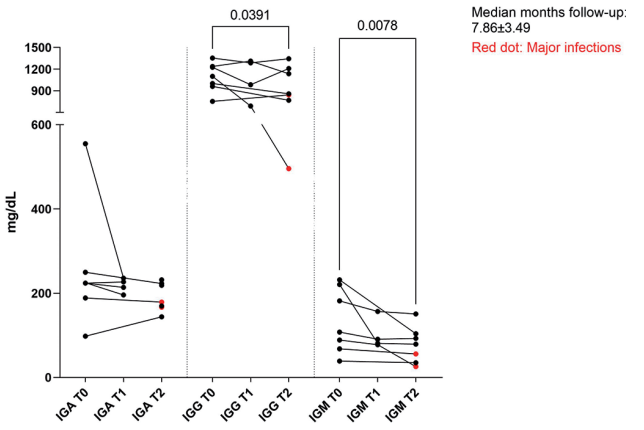
Background. Rituximab (RTX) is a chimeric monoclonal antibody that binds the CD20 molecule on the surface of B cells and leads to B cell depletion. RTX is recommended by the European League Against Rheumatism (EULAR) as off-label in patients affected by idiopathic inflammatory myopathies (IIM). The real-world experience has shown that hypogammaglobulinemia occurring early after anti-CD20 treatment can be multifactorial (active disease, effect of other drugs) and usually transient, with a minimal increase in the risk of infections. The present study aimed to analyse the differences in the rate of RTX-associated hypogammaglobulinemia in a cohort of IIM patients in clinical practice, as well as the onset of major infections and its correlation with hypogammaglobulinemia.
Methods. Patients followed at Rheumatology Unit of Siena University Hospital from January 2020 to September 2021 were retrospectively enrolled. Inclusion criteria were as follows: fulfilment of disease-specific classification criteria 2017 EULAR criteria and /or Peter and Bohan criteria for dermatomyositis (DM) and polymyositis (PM), positivity of anti-synthetase antibody and typical clinical features for anti-synthetase syndrome (ASS) and the measurement of serum Ig levels at the time of RTX administration (maximum 2 weeks before) (T0) and 6 (T1) to 12 (T2) months later, consistently with previous studies. Ig serum levels, measured by standard nephelometry (normal ranges: IgG 700–1600 mg/dL, IgM 40–240 mg/dL, IgA 70–400 mg/dL) were assessed as part of routine clinical care. Hypogammaglobulinemia was defined as moderate (serum IgG <600 mg/dL) and severe (IgG <400 mg/dL), as previously reported.
Results. Seven patients (mean±SD, 57.3±19.7 years; 7 female) were enrolled. Three of them had diagnosis of DM, three ASS and one PM. Two patients showed MDA5-positivity, two JO1-positivity, one TIF1-gamma-positivity, one PL7-positivity and the other one PM/Scl-positivity. All patients had at least two organs involved, and 4 out of 7 (57%) suffered from interstitial lung disease. Before starting RTX treatment, three and four patients underwent at least one and two synthetic immunosuppressants. All patients underwent low dosage of corticosteroids, and four patients underwent concomitant synthetic immunosuppressants (2 hydroxychloroquine and 2 MTX). IgG concentrations were statically lower at T2 compared to those at baseline (p=0.0391). None of them showed severe hypogammaglobulinemia. Similarly, IgM concentration significantly decreased at T2 compared to those at baseline (p=0.0078). Two patients showed major infections and two patients had paucisymptomatic COVID-19 (one of them had twice). Corticosteroids dosages were inversely correlated with IgG T2 concentrations (p=0.040, r=-0.919).
Conclusion. Hypogammaglobulinemia following RTX is uncommon in IIM and is more likely in patients with high glucocorticoids, immunosuppressants and CYC exposure. IgG monitoring at least 6 months after RTX treatment may be useful in stratifying patients to identify those who require closer monitoring. These results shine a spotlight for increased awareness of the role of immunoglobulin measurement before maintenance doses of RTX.



P-36. Fig. 1.

P-37

MYOSTATIN IN IDIOPATHIC INFLAMMATORY MYOPATHIES: SERUM ASSESSMENT AND DISEASE ACTIVITY

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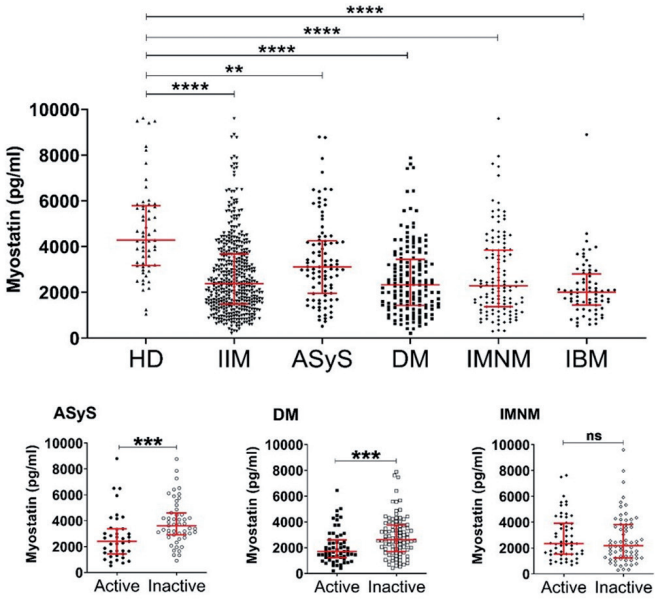
Background. In Idiopathic Inflammatory Myopathies (IIM) disease activity is difficult to assess and IIM may induce severe muscle damage, especially in immune-mediated necrotizing myopathies (IMNM) and inclusion body myositis (IBM). We hypothesize that myostatin, a negative regulator of muscle mass, could be a new biomarker of disease activity and/or muscle damage.
Methods. Prospective assessment of myostatin protein level in 447 IIM sera samples (dermatomyositis (DM), n=157; IBM, n=72; IMNM, n=125; antisynthetase syndrome (ASyS), n=93) and 59 healthy donors (HD) was performed by ELISA (R&D Systems DGDF80, Minneapolis, USA). A gene transcript analysis was also carried out on 18 IIM muscle biopsies and 6 controls to analyze myostatin and myostatin pathway-related genes expression.
Results. IIM patients had lower myostatin circulating protein levels and gene expression compared to HD (2379 [1490; 3678] pg/ml vs 4281 [3169; 5787] pg/ml; p<0.0001 and log2FC=-1.83; p=0.0005 respectively). Myostatin-related genes expression varied in accordance with myostatin protein decrease. We then divided IIM patients into active and inactive patients based on the Physician Global Assessment (PGA). Inactive IIM patients showed higher myostatin levels than active ones. This was the case for all IIM subgroups, except IMNM where low myostatin levels were maintained (2186 [1235; 3815] vs 2349 [1518; 3922] pg/ml; p=0.4). A linear multivariate regression model was finally used to determine the association of myostatin, creatine kinase or creatinine levels with the PGA or the Manual muscle testing of 8 muscles. Only myostatin was a significant independent factor in both models.



P-37. Fig. 1. Quantification of circulating myostatin levels in IIM and IIM subgroups. Myostatin circulating levels in IIM patients' serum and comparison between active and inactive disease state. Patients with a PGA>5 were considered active.
**p<0.01, ***p<0.001, ****p<0.0001, ns non-significant.
HD: healthy donors; IIM: Idiopathic inflammatory myopathies; ASyS: anti-synthetase syndrome; IMNM: immune-mediated necrotizing myopathy; DM: dermatomyositis; IBM: inclusion body myositis.

Conclusion. Myostatin protein and RNA levels are decreased in all IIM patients and protein levels correlate with disease activity. Inactive ASyS and DM patients have higher myostatin levels than active patients. Myostatin could be a disease activity marker in these subgroups. However, IMNM patients do not have significant myostatin levels increase after disease remission. This may highlight a new pathological disease mechanism in IMNM patients.

Acknowledgements. We would like to thank Franck Letourneur and Benjamin Saintpierre at GENOM'IC facility Core for their help with RNA-seq experiment and analysis, the Myobank for samples preservation and the Association Française contre les Myopathies for their support.

P-38

CLINICAL CHARACTERISTICS AND PROGNOSIS OF PATIENTS WITH ANTI-MELANOMA DIFFERENTIATION-RELATED GENE 5 (MDA5) RELATED DISEASES

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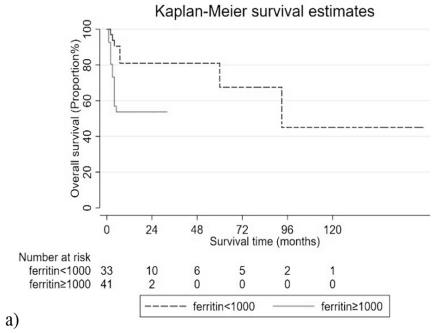
Background. Idiopathic inflammatory myopathy (IIM) is a group of heterogeneous systemic autoimmune diseases, of which patients with anti-melanoma differentiation-associated gene 5 (MDA5) antibody are of specific clinical characteristics. Our study is aimed to propose the concept of patients with anti-MDA5 related diseases (Anti-MDA5-RD), and to describe the clinical characteristics and prognosis of these patients.

Methods. Patients with anti-MDA5 admitted to Peking Union Medical College Hospital from November 2015 to December 2018 were retrospectively studied. Patients were divided into either remission or progression group according to their prognosis. Demographic data and clinical outcomes were compared between the two groups. A multivariate Logistic regression model was applied to explore independent risk factors for poor prognosis. Furthermore, the clinical manifestations and prognosis of patients with both anti-MDA5 and anti-Ro-52 were compared with patients with only anti-MDA5.

Results. A total of 126 patients were included. Rash is the most common initial symptom (65.1%) and clinical amyopathic dermatomyositis (CADM) is the most common clinical subtype (74.8%). Logistics analysis showed anti-Ro-52 (OR 9.17, 95%CI 1.97-42.62, p=0.005), serum ferritin > 1000ng/ml (OR 2.91, 95%CI 1.03-8.21, p=0.044), age >50 (OR 7.78, 95%CI 1.75-34.66, p=0.007) and hypoxemia at diagnosis (PaO2 <60 mmHg) (OR 30.68, 95%CI 6.48-145.33, p<0.001) were independent risk factors for poor prognosis. Patients with anti-MDA5 combined with anti-Ro-52 had a higher risk of rapidly progressive interstitial lung disease (RP-ILD) (42.0% vs 24.6%, p=0.04) and a worse response to intensive immunosuppressive therapy.

Conclusions. Anti-MDA5 related disease is a high-risk clinical subtype. Patients with anti-Ro-52 are prone to RP-ILD and have a poor response to traditional immunosuppressive therapy. Early combination therapy with biologics may improve the prognosis of these patients.



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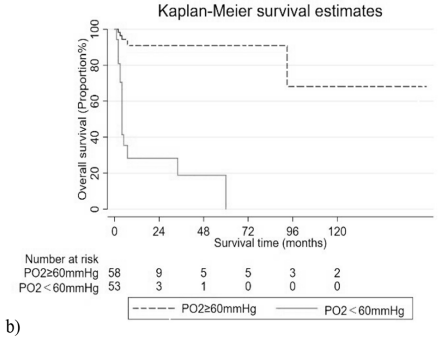

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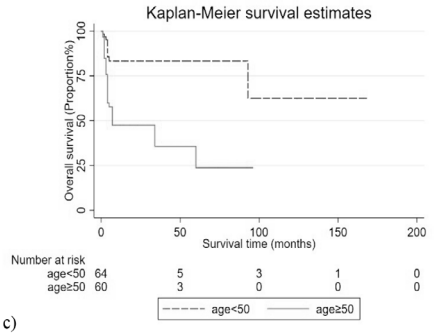

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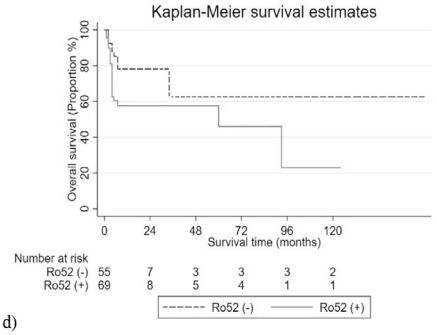

d)

P-38. Fig. 1. Overall survival. Kaplan-Meier estimates of overall survival based on serum ferritin levels, arterial oxygen partial pressure at onset, and age status are shown a) Serum ferritin; b) Arterial partial pressure of oxygen <60mmHg; c) Age >50 years old; d) Combined with anti-Ro-52 antibody.

P-39

CLINICAL PHENOTYPE OF ANTI-SAE DERMATOMYOSITIS IN A SPANISH COHORT

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Background. Several myositis specific antibodies (MSA) have been described, some of them associated with specific features such as interstitial lung disease (ILD), cancer or joint involvement. Antibodies against the small ubiquitin-like modifier activating enzyme (anti-SAE), described in 2007, are one of the rarer specificities associated with dermatomyositis (DM). Various cohorts from Europe, Asia and America have described this group of patients, characterized by an extensive skin involvement. Interestingly, lung and joint involvement differs from each cohort, as well as cancer association. In this study, we aim to describe the clinical features in DM with anti-SAE antibodies in a Spanish cohort.

Methods. A REDCap® form was distributed through the Spanish group of autoimmune and systemic diseases to obtain demographics, clinical characteristics, blood tests, muscle biopsy, CT imaging, pulmonary function tests (PFT) and cancer history of patients with anti-SAE. Cancer-associated myositis (CAM) was defined as myositis occurring within 3 years of cancer diagnosis, as well as myositis developing in a patient with active cancer, independently of the time from a cancer diagnosis. Sera of each patient was tested by immunoblot at the center of origin. Those patients who have more than one MSA or a non-concordant ANA

pattern were excluded. Data was analyzed with Stata/IC 16.
Results. Fifty-five patients were collected. Forty-four were anti-SAE positive by immunoblot and negative for the rest of MSA: of these, five patients with cytoplasmic or mitotic ANA pattern were also excluded. Among the 39 study patients, 59% females, mean age was 60.9y (SD 16.8). According to ACR/EULAR 2017 classification criteria, 64.1% were definite DM, while 25.6% were probable and only 10.3 do not fulfill the criteria. CK analyses showed a wide variability of results (median 245 UI/L, IQR 131-900) and 57.9% reported myalgia. Muscle biopsy was performed in 28 patients, 20 of them (51.3%) with characteristic DM findings. Regarding myositis associated antibodies, we found ro52 in 35.3%. ANAs were found in 24 patients (61.5%), predominantly nuclear fine speckled pattern (70.1%). Skin involvement was the most representative feature: 64.1% had Gottron papules, 52.6 heliotrope rash, 54.1% malar rash, 46.1% V sign and 48.7% shawl sign. Periungual erythema was seen in 33.3% and patients reported pruritus in 19 cases (50%). Other skin involvements were less frequent, such as Raynaud's phenomenon, mechanic's hands or panniculitis (Table I). Arthritis was reported in 18.4% and dysphagia in 34.2%. ILD was found in 7 patients (2 nonspecific interstitial pneumonia, 2 cryptogenic organizing pneumonia, 1 usual interstitial pneumonia and 2 unclassifiable findings) with mean FVC of 62.6% (SD 6.3) and KCO 73.8% (SD 15.3). In this study, malignancy was reported in 5 cases, 4 out of them (10.3%) considered CAM.
Conclusions. This study shows that anti-SAE DM is mainly characterized by an extensive skin involvement along with pruritus, a differential feature with respect to other DM. Dysphagia was present in one third of patients, highlighting the importance of evaluating its presence. In contrast with other cohorts, this study shows articular and muscle involvement, with myalgia and a wide range of CK levels. Regarding lung involvement, a mild interstitial lung disease is a well-known manifestation. Our study shows similar results in terms of cancer association. The relationship of this antibody with malignancy is yet to be determined, and cancer screening strategy should be individualized.
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P-39. Table I. Demographics, clinical and serological features.

Patients characteristics (n=39)	Results
Age, mean (SD)	60.9 (16.8)
Sex, female (%)	23 (59.0)
Follow up, months (SD)	46.7 (50.3)
CK range (min-max UI/L)	36-20568
CK, median (IQR)	245 (131-900)
ACR/EULAR criteria 2017, n (%)	
• No criteria	4 (10.3)
• Probable	10 (25.6)
• Definite	25 (64.1)
Ro52 (n=34), n (%)	12 (35.3)
Ro60 (n=34), n (%)	1 (2.9)
ANA, n (%)	24 (61.5)
Gottron papules, n (%)	25 (64.1)
Heliotrope rash (n=38), n (%)	20 (52.6)
Malar rash (n=37), n (%)	20 (54.1)
V sign, n (%)	18 (46.1)
Shawl sign, n (%)	19 (48.7)
Mechanic's hands (n=37), n (%)	4 (10.8)
Periungual erythema, n (%)	13 (33.3)
Raynaud's phenomenon (n=37), n (%)	8 (21.6)
Panniculitis (n=37), n (%)	3 (8.1)
Lipoatrophy (n=37), n (%)	1 (2.7)
Calcinosis (n=37), n (%)	1 (2.7)
Poikiloderma (n=38), n (%)	4 (10.5)
Pruritus, n (%)	19 (50.0)
Fever (n=38), n (%)	4 (10.5)
Arthritis (n=38), n (%)	7 (18.4)
Dysphagia (n=38), n (%)	13 (34.2)
Myalgia (n=38), n (%)	22 (57.9)
Muscle biopsy, n (%)	
• DM	20 (51.3)
• MNIM	1 (2.6)
• Amyopathic DM	1 (2.6)
• Nonspecific	6 (11.8)
ILD, n (%)	7 (18.0)
• Initial FVC (n=6), mean (SD)	77.7 (10.4)
• Worst FVC (n=5), mean (SD)	62.6 (6.3)
• Initial KCO (n=4), mean (SD)	81.2 (12.2)
• Worst KCO (n=5), mean (SD)	73.8 (15.3)
Malignancy, n (%)	5 (12.8)
Cancer-associated myositis, n (%)	4 (10.3)

P-40

DETECTION OF ANTI-ZO AND OTHER RARE ANTI-SYNTHETASE SYNDROME AUTOANTIBODIES ON RESEARCH LINEBLOT IMMUNOASSAYS

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Background. Detection of different myositis specific autoantibodies (MSA) and myositis associated autoantibodies (MAA) is an important aspect of diagnosis for different types of idiopathic inflammatory myositis (IIM) (1). MSA's are detected in 60% of patients and can be directed against both nuclear and cytoplasmic autoantigens. The most common group of MSA in adult patients are directed against aminoacyl-transfer RNA synthetases (ARS) associated with the anti-synthetase syndrome. Immunoprecipitation (IP) is widely considered the gold-standard for the identification and evaluation of myositis specific autoantibodies (2). However, IP is not readily available and only a few facilities can perform these tests and performing the test requires technical expertise (3) Line blot immunoassays (LIA's) have become increasingly available and small studies have demonstrated that LIA is an appropriate substitute to IP for MSA/MAA detection. A strong positive result and high pre-test diagnosis of IIM is associated with the highest true positive result, emphasising the importance of the clinician's initial impression in reaching an IIM diagnosis. Results for LIA should be interpreted in caution in patients with low diagnostic suspicion for IIM (4). False positives and false negative autoantibody results remain a concern (5) The purpose of this study was to evaluate the accuracy of a new myositis research LIA in detecting antibodies to anti-synthetase autoantibodies anti-Zo, Ha and Ks.
Methods. Sera samples utilised had all previously been investigated for autoantibodies by immunoprecipitation by our research group. Samples known to contain the autoantibodies of interest were selected from research and diagnostic cohorts (9 anti-Zo samples, 2 anti-KS and 1 anti-Ha). All were tested by research profile LIA, EUROIMMUN according to manufacturer's instructions. This aims to detect the three autoantibodies of interest, in addition to those included in the standard commercially available assay (anti- cN-1A, anti- Ro52, anti- OJ, anti- EJ, anti- PL-12, anti- PL-7, anti- SRP, anti- Jo-1, anti- PM-Scl100, anti- PM-Scl75, anti- Ku, anti- SAE, anti- NXP2, anti- MDA5, anti- TIF1-gamma, and anti- Mi-2). Interpretation of antibodies was defined as per the manufacturer's instructions, with negative results being defined as (-), borderline ((+)), positive (+ or ++) or strongly positive (+++).
Results. Using the EUROLINE immune blot, sensitivity for detecting Zo-antibodies was 100% in this case series. All Zo-antibodies were strongly positive. Five sera samples for anti-Zo also tested positive for Ro52 antibodies. LIA was not able to detect the few anti-KS and anti- Ha antibodies positive by IP.However, some antibodies detected on LIA were not detected on IP. This included one positive KS antibody, one positive Pm-Scl75 and two positive Mi-2α.
Conclusions. Our case series demonstrates that the new commercial LIA can reliably detect anti-Zo antibodies with 100% sensitivity. Expanding the repertoire of MSA detectable by LIA should facilitate the diagnosis of patients with the anti-synthetase syndrome.
Acknowledgements. AL Arthritis Australia; EUROIMMUN provided blots.

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DETECTION OF MYOSITIS AUTOANTIBODIES IN PATIENTS LABELLED WITH 'IDIOPATHIC' INTERSTITIAL LUNG DISEASE

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Background. Idiopathic inflammatory myositis (IIM) is a heterogeneous disease for which there are several known myositis specific antibodies (MSA) and myositis associated antibodies (MAA). Interstitial lung disease (ILD) is the leading cause of morbidity and mortality for patients suffering from connective tissue disease (CTD). ILD can be the dominant manifestation in unrecognised CTD and is detectable in 20-65% of IIM patients. There has been increased utilisation of commercial immunoassays as they can be performed without clinical expertise and are widely available. However, commercial assays have not always performed well in real-world cohorts when assessing all MSA and MAA, with common false positives and negative results for different MSA; 16.1% of patients tested positive for an MSA with incongruent ANA patterns in a healthy population. Differentiating idiopathic ILD and CTD-ILD can be challenging as there is often overlap between radiographic and histological findings. We have previously investigated a UK cohort of patients with idiopathic ILD for CTD associated autoantibodies by immunoprecipitation (IP) and identified relevant autoantibodies in approximately 10% of those with idiopathic NSIP and Cryptogenic Organising pneumonia. It is not clear whether these autoantibodies were not tested for by local treating physicians, if testing methods had provided false-negative results or if autoantibody results had been discounted as not clinically relevant. We re-evaluated twenty-three autoantibody positive iILD patient sera by line blot and compared the results obtained previously by immunoprecipitation (IP).
Methods. All patients were enrolled in the UK Biomarkers of Interstitial Lung Disease Cohort and had previously been investigated for autoantibodies by immunoprecipitation. Twenty-three sera samples were further analysed: three with anti- Jo-1 antibodies, three with anti- Ku-antibodies, one with anti- OJ-antibody, eight with anti-PL-12 antibodies, two with anti-Pm-Scl antibodies, three with anti-topoisomerase and three with anti-U1RNP antibodies. Autoantibodies were tested for by line immunoassay (LIA) according to the manufacturer's instructions. The LIA was selected based on the known autoantibody result from IP; either Myositis research profile (detects anti- Zo, anti- Ha, anti- Ks, anti- cN-1A, anti- Ro52, anti- OJ, anti- EJ, anti- PL-12, anti- PL-7, anti- SRP, anti- Jo-1, anti- Pm-Scl, anti- Ku, anti- SAE, anti- NXP2, anti- MDA5, anti- TIF1-gamma, and anti- Mi-2), nucleoli profile (detects anti- PDGFR, anti- Ku, anti- PM75, anti- PM100, anti-Th/To, anti-NOR90, anti-Fib, anti-Fib, anti-RP155, anti-RP11, anti-CB, anti-CA and anti-Scl70) or ANA profile 3 (detects M2, RIB, HI, NUC, DNA, PCNA, CB, anti-Jo, anti-PM100, anti-Scl, anti-SSB, anti- Ro52, anti-SSA, anti- Sm and anti-RNP/Sm). Interpretation of antibodies was defined as per the manufacturer's instructions, with negative results defined as (-), borderline ((+)), positive (+ or ++) or strongly positive (+++).
Results. Results are shown in the table below. In addition to the known IP proven antibodies, positive results were also demonstrated for anti-SRP, anti-PmScl75, anti-Mi2, anti-PL-12, anti-PL-7 and anti-EJ. However, these antibodies were not detected on IP and are likely to be false positives. The degree of positivity varied from positive (+/++) (EJ, PM75, TIF1γ, Mi2α/Mi2β, SRP, Fib, Th/To, Fib and CA) to strongly positive (+++) (PM100, SRP).
Conclusions. Identifying an autoantibody is not diagnostic of CTD or myositis, but the presence of an ILD associated autoantibody in a patient presenting with ILD is highly suggestive. The ability of the line blot to detect relevant autoantibodies strongly suggests that better autoantibody testing strategies are needed in this patient group to ensure accurate diagnosis and appropriate immunosuppressive treatment.
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P-41. Table I.

True Positives	
Autoantibody by immunoprecipitation (n)	Line blot result
Anti-Jo1 (3)	3 (100%) positive
Anti-PL12 (8)	8 (100%) positive, 6/8 Ro52 (Positive)
Anti-PmScl (2)	2 (100%) but both positive to PmScl100 antigen only
Anti-Ku (3)	2 (66.67%), 1/3 Ro52 (strongly positive)
Anti-Oj (1)	0 (0%)
Anti-Topo (3)	2 (66.67%)
Anti-U1RNP (3)	2 (66.67%)

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NEITHER CANCER NOR MYOSITIS ARE COMMON IN PATIENTS TESTING POSITIVE FOR TIF1γ BY LINE IMMUNOBLOT ASSAY

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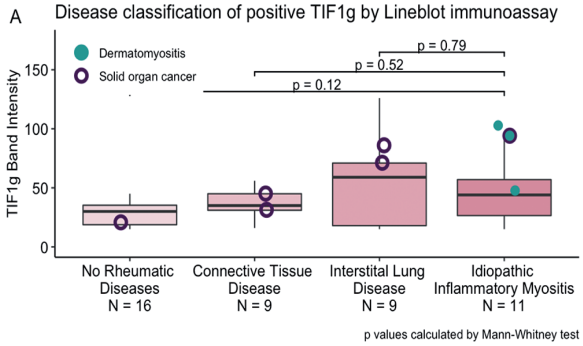
Aims. Autoantibodies to transcriptional intermediary factor 1-gamma (TIF1γ) have been identified in patients with malignancy and idiopathic inflammatory myopathies (IIM), in particular dermatomyositis. However, commercial assays may yield non-specific results. We sought to determine the disease associations of anti-TIF1γ antibodies identified by current line immunoassay technology in a South Australian population.
Methods. All positive anti-TIF1γ (band Intensity, BI, >15) results from SA Pathology, Flinders Medical Centre, between January 2018 and December 2020 were included and available medical records reviewed. Patients were categorised by diagnoses of IIM, interstitial lung disease (ILD), other connective tissue disease (CTD), and no rheumatic diseases (NRD).
Results. Of 2736 LIA's evaluated, 113 (4%) tested positive for TIF1γ; of these 45 cases had accessible records. A diagnosis of IIM was confirmed or suspected, in 8 and 3 patients respectively (24%). Eight of 15 (53%) patients who underwent biopsy demonstrated histological evidence of myositis (dermatomyositis in 3, necrotising myositis in 3 and inclusion body myositis in 2). Eleven of 45 (27.5%) had a cancer diagnosis; 5 cases with solid organ malignancy (SOC), 5 cases of skin cancer and 1 diagnosis of coexisting DM and SOC. Nine of 45 had ILD in absence of IIM and were significantly older than patients without ILD (median age 61 vs 80 years, p=0.02). Antinuclear antibody (ANA) was consistent with TIF1γ (speckled) in 67% of IIM and 28% of non-IIM diagnoses (p=0.05). BI values were not significantly different between groups (Figure A), however all patients with dermatomyositis and malignancy had BIs >45 and >20 respectively.
Conclusion. Most patients testing positive for TIF1γ by commercial LIA have neither IIM nor malignancy, but their risk increases with increasing BI. ANA consistency may be helpful to identify true positive anti-TIF1γ antibodies. Clinicians should be aware of the low specificity of LIA in detection of clinically relevant TIF1γ autoantibodies.



P-42. Fig. A.

P-43

EVALUATION OF MAJOR HISTOCOMPATIBILITY COMPLEX CLASS II IN IDIOPATHIC INFLAMMATORY MYOPATHIES

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Background. Idiopathic inflammatory myopathies (IIMs) is a group of acquired muscular diseases with IIM diagnosis built on clinical, serological, and histological data. Muscle pathological analysis gives relevant elements for the diagnosis. In normal muscle, myofibers are negative for major histocompatibility complex

class (MHC-II) expression. This study aims to analyze the pattern of MHC-II expression in various IIMs and to further define the involvement of such marker in IIM pathogenesis.

Patients & Methods. A historical cohort was designed using the MYOLYON register. Inclusion criteria were IIM diagnosis without treatment before biopsy. A centralized, standardized, and blind analysis was conducted to define the patterns of MHC-II immunostaining by myofibers. In vitro experiments were performed using CD56+ human muscle stem cells (MuSC). MuSC were expanded in growth medium for 48 hours in the presence or not of the following cytokines: IFNβ, IFNβ, IL-1β, IL-6, TNF-α. Human MuSC were trypsinized and analyzed by flow cytometry for MHC-II membrane expression (HLA-DR mouse anti-human antibodies, FITC, BD pharmingen, ref 555811).

Results. Muscle sections from biopsies of seventy-four IIMs patients were included: 22 dermatomyositis (DM), 9 anti-synthetase syndrome (ASyS), 13 immune-mediated necrotizing myopathies (IMNM), 17 inclusion body myositis (IBM), and 13 overlap myositis (OM). By IHC, we observed that MHC-II expression was abnormal in 93.2% of the biopsies analyzed, staining localized on myofibers and/or on capillaries. The analysis of MHC-II expression on myofibers revealed distinguishable patterns: the labeling was diffuse in IBM (88.2%, n=15/17), perifascicular in ASyS (66.7%, n=6/9), variable in OM (patchy for 30.8% n=4/13 or clustered for 30.8%, n=4/13). MHC-II expression was negative in IMNM (84.6%, n=11/13) and in DM (50.0%, n=11/22) (Figure 1.I). DM exhibiting positive MHC-II myofibers (n=11) were associated with the presence of anti-TIF1γ, anti-NXP2 and anti-SAE auto antibodies (n=5, n=3 and n=1, respectively). Among the 11 patients, there were juvenile cases (n=5, 45.5%) or DM associated with ongoing neoplasia (n=4, 36.4%). Regarding the vascular domain, in comparison to usual staining on healthy muscle, 3 main architectures were described for capillaries: giant, leaky and capillary dropout (Figure 1.I). Patterns of MHC-II positive capillaries were the following: DM was characterized by capillary dropout (71.4%), IMNM showed leaky capillaries (75.0%), IBM giant capillaries (75.0%), ASyS exhibited both giant (66.7%) and/or leaky (50.0%) capillaries, while OM showed giant (53.8%) or/and leaky (83.3%) capillaries and capillaries dropout (50.0%).

In vitro, we observed that human CD56+ MuSC did not express MHC-II. A significant increase of MHC-II expression was only showed following 48h stimulation with IFNγ. Other cytokine tested had no effect on MHC-II expression (Figure 1.II-III)

Conclusion. The present work establishes the usefulness of MHC-II immunostaining for IIM diagnosis, and gives additional elements on the impairment of myofibers and capillaries in the various IIM subgroups. These results also support the implication of vasculopathy in IIM pathogenesis, with various structural and cellular consequences regarding the different subgroups. MHC-II immunostaining in IIM muscle biopsies enables a foremost analysis of myofibers and capillaries, and represents an additional biomarker to distinguish IIM subgroups. Finally, our in vitro results on human MuSC show that IFNγ could play an important role in the induction of MHC-II expression by myogenic cells.

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DO WE OVERLOOK ANTISYNTHETASE SYNDROME? - RETROSPECTIVE ANALYSIS OF CLINICAL PHENOTYPES AND THE COMPLIANCE WITH CRITERIA IN PATIENTS WITH ANTISYNTHETASE ANTIBODIES

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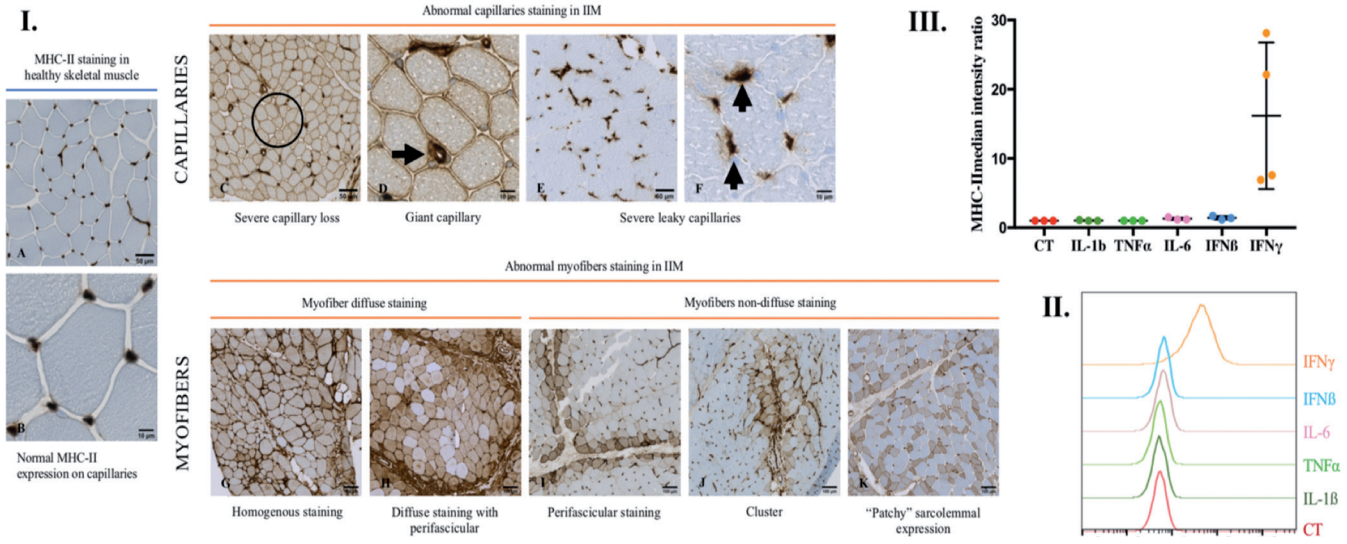
Background. Antisynthetase syndrome (ASS) is a rare subtype of idiopathic inflammatory myopathies (IIM), characterised by the unique clinical phenotype and the presence of antisynthetase antibodies (ARS). Due to the heterogeneity of symptoms, many patients with ASS remain misdiagnosed.

Methods. We have analysed the digital database of patients, who have been tested for the presence of antinuclear antibodies (ANA) during hospitalization in the USK-WAM Hospital in Lodz or during the appointments in the associated outpatient clinic in the years 2015-2019. Serum titters and ANA profiles were evaluated with the line immunoassay method. Consecutive patients with ARS were identified. Data on the demographical features, clinical symptoms, diagnoses and the results of selected laboratory tests were collected retrospectively based on the patients' medical history. The prevalence of different clinical symptoms was evaluated and compared in patients with distinct serological profiles. The range of diagnoses stated in the ARS-positive patients as well as the compliance with available criteria for ASS and IIM (Solomon's criteria, Connors'criteria, EULAR/ACR classification criteria for adult and juvenile IIM and their major subgroups, the modified version of the EULAR/ACR classification criteria proposed by Greco *et al.*) were evaluated. Data were analysed with STATISTICA 13.1 software. ANA tests were performed in 3215 patients with positive results observed in 86,16% of them. In 1,71% of the cohort (n=55) ARS were identified. Due to the lack of data on the clinical symptoms in 5 patients, further analysis was performed on the group of 50 ARS-positive patients. The mean age of the study group was 57±17 years old and 68% of them were female.

Results. The most common ARS type was anti-Jo-1 detected in 70% of the patients, followed by anti-PL-12 in 18% and anti-PL-7 in 8%. In 6% of the patients co-occurrence of different ARS was observed. Anti-Ro-52 were the most frequent type of accompanying antibodies, identified in 30% of the cohort. The most common clinical manifestation was arthralgia or/and arthritis, affecting 58% of the patients. Myalgia or/and myositis occurred in 48% and was particularly common in the subgroup with anti-PL-12 autoantibodies. Interstitial lung disease and the Raynaud phenomenon were observed in respectively 32% and 12% of the patients. A surprisingly high prevalence of xerostomia or xerophthalmia was observed. Cutaneous lesions were



P-43. Fig. 1. Major histocompatibility complex class II (MHC-II) in idiopathic inflammatory myopathies (IIMs).

I. MHC-II immunostaining on muscle biopsies of IIMs. In normal skeletal musk, major histocompatibility complex class II (MHC-II) is expressed on capillaries and highlights their regular and ''round'' shape on axial sections, while there is no sarcolemmal MHC-II expression ((A, scale bar 50µm and B, scale bar 10µm). In idiopathic inflammatory myopathies (IIM), MHC-II staining highlights either capillary loss (C, circle, scale bar 50µm)), giant capillaries ((D, arrow scale bar 10µm) characterized by a widen lumen and a thickened wall, as well as leaky capillaries characterized by a blurred staining with undefined borders (E, scale bar 50µm, and F, arrow, scale bar 10µm). Sarcolemmal expression of MHC-II can be diffuse (G, scale bar 100µm).With for scene cases perifascicular reinforcement (H, scale bar 100µm), or non-diffuse: perifascicular (I, scale bar 100µm), cluster (sarcolemmal expression around inflammatory infiltrates) (J, scale bar 100µm), or ''patchy'' (K, scale bar 100µm). **II & III.** ***In vitro*** **experimentations**. Evaluation of induction of MHC-II by muscle stem cells (muSC) by cytokines (interleukine 1b (IL-1β), interleukine 6 (IL-6). Tumor necrosis factor alpha (TNF-α), interferon (IFN) beta (IFNβ) et gamma (IFNγ) in comparison to control MuSC. II. modelisation on FlowJo. III. median intensity ratio of MHC-II expression by MuSC incubated with various cytokine and unstimulated MuSC.

described in 34% of the patients. Noteworthy, muscle enzymes were rarely assessed. A high prevalence of thrombocytopenia and anaemia was noted. Only in 26% of the patients diagnosis of IIM was posed. Other frequently stated diagnoses included non-specified connective tissue disease in 24%, various types of arthritis in 10% and myopathies other than IIM in 6%. Noteworthy, 10% of the cohort was diagnosed with disorders not associated with musculoskeletal symptoms. Solomon's criteria were met by 20% of the patients, while Connors' criteria by 72%. According to the EULAR/ACR classification criteria, 64% of the patients could have been classified as having IIM, including probable IIM in 48% and definite IIM in 16% of the patients. The EULAR/ACR criteria were met mostly by the patients with anti-Jo-1 antibodies. Following the modification proposed by Greco et al., 68% of the patients could be classified as having probable IIM and 20% as definite IIM.

Conclusion. Patients with ARS present a variety of symptoms and myopathy may not necessarily be the predominant manifestation. An alarming disproportion between the compliance with distinct IIM/ASS criteria and the diagnoses stated by the clinicians was observed. Rare diagnostics for the antisynthetase syndrome, including the assessment of muscle enzyme concentrations or muscle biopsy, indicate that in many cases ASS is not even considered in the differential diagnosis. Detailed examinations and watchful observation are needed in patients with ARS to minimalize the risk of misdiagnosis.

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P-45

ANTI-KU ANTIBODY SYNDROME: IS IT A DISTINCT CLINICAL ENTITY? A CLUSTER ANALYSIS OF 75 PATIENTS

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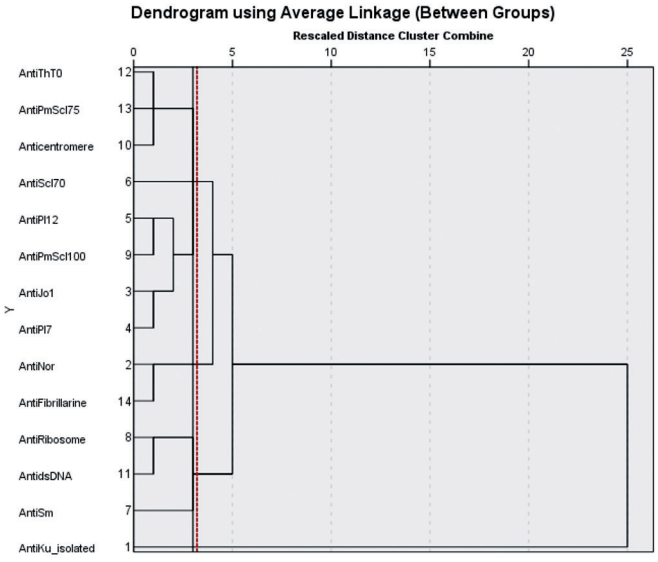
Background. Anti-Ku antibodies are rare among patients with Connective Tissue Diseases (CTD) (1). Their potential role as a disease biomarker is not well established. The objective of this work is to identify subgroups of anti-Ku positive patients according to their spectrum of anti-nuclear antibody (ANA) specificities and analyze their clinical and analytical features.

Methods. Multicenter, cross-sectional study of anti-Ku positive patients, irrespective of their diagnosis, followed at eight Rheumatology outpatient clinics. Patients were spontaneously identified according to the local work-out for suspected autoimmune diseases. Anti-Ku and other ANA specificities were determined at each hospital's Immunology lab according to the local methodology and strategy to decide on which auto-antibodies to check when faced with a positive ANA immunofluorescence. Clinical, analytical and treatment cumulative features were identified following a dedicated structured questionnaire. Hierarchical cluster analysis (method: between-groups linkage, squared Euclidian distance) for ANA specificity variables was performed to identify subgroups.



P-45. Fig. 1. Hierarchical cluster analysis of ANA specificities in anti-Ku+ patients.

Results. Seventy-five anti-Ku positive patients were included (female: 73.3%, mean age at diagnosis: 50.5±17.9 years, mean disease duration: 4.7±5.4 years). Their clinical diagnosis were undifferentiated connective tissue disease (UCTD) (21.3%), systemic lupus erythematosus (17.3%), Sjögren's syndrome (16.0%), inflammatory myositis (14.7%), systemic sclerosis (10.7%), overlap CTD syndrome (8.0%), other connective tissue diseases (17.3%), healthy anti-Ku carrier (17.3%). Six autoantibody clusters were identified and included most patients (Fig.1): Cluster 1 - anti-Ku without any other ANA specificities (36.0%); cluster 2 - Anti-nor90 and anti-fibrillarin (8.0%); cluster 3 - anti-Jo1, PL-7, PL-12, and PM-Scl100 (9.3%); cluster 4 - anti-Scl70 (4.0%); cluster 5 - anti-Sm, anti-ribosome, and anti-dsDNA (13.3%); cluster 6 - anti-centromere, Th/To, PM-Scl75 (8.0%). The remaining patients were outliers (21.3%) not fitting in any cluster. In patients of cluster 1, presenting anti-Ku antibodies without any other ANA specificities, the most frequent clinical manifestations were: Raynaud's phenomenon (40.7%), arthritis (25.9%), sicca syndrome (25.9%), myositis (14.8%), and interstitial lung disease (ILD) (14.8%); 25.9% were healthy anti-Ku carriers. Patients from cluster 1 were most frequently treated with low dose glucocorticoids (51.9%), hydroxychloroquine (37.0%), or methotrexate (18.5%). Among the whole study population (n=75), major organ involvement was present in 18.7%, with ILD in 10.7% and renal involvement in 8.0%. None of the patients in cluster 1 presented nephritis.

Conclusion. Anti-Ku positive patients without any other ANA specificities is the largest subset and may represent a distinct entity among the differentiated CTD (2). Patients with this anti-Ku syndrome may develop ILD. In addition, anti-Ku antibodies can be found in patients with a diversity of other ANA specificities and heterogeneous CTD diagnosis.

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P-46

IDENTIFICATION OF ANTI-FLAGELLIN ANTIBODIES IN JUVENILE DERMATOMYOSITIS USING AN ANTIBODY PROFILING TECHNOLOGY

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Background. Idiopathic inflammatory myopathies (IIMs) are a heterogenous group of autoimmune muscle diseases. While they are all characterized by chronic progressive muscle weakness, autoantibodies can be used to clinically stratify patients with different myopathies. In juvenile dermatomyositis (JDM), examples of such autoantibodies are anti-TIF1γ, anti-NXP2, and anti-MDA5. Despite existing clinical stratification, the causes of these autoimmune myopathies, including juvenile dermatomyositis are unknown. Currently, a prevailing hypothesis is that environmental triggers can precipitate disease in individuals with genetic susceptibility. In JDM studies thus far, group A Streptococcus may be associated with disease, but this association is limited to case-reports and small sample size. To characterize environmental exposures and associations in an unbiased and high-throughput manner in larger disease cohorts, an antibody profiling technique was employed.

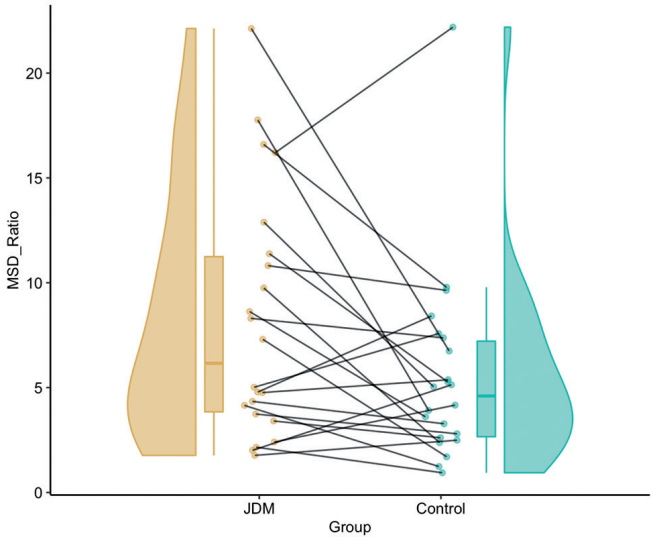
Methods. We used Phage ImmunoPrecipitation Sequencing (PhIP-Seq) to profile antibody reactivities in 23 JDM patients and age-matched controls, which included twin and non-twin siblings. The methodology uses oligonucleotide library synthesis (OLS) to encode proteomic-scale peptide libraries for display on T7 bacteriophages. These libraries are then immunoprecipitated, using an individual's antibodies, for subsequent analysis by high-throughput DNA sequencing. We used a library of overlapping peptides, that covers all known protein toxin and virulence factors ("ToxScan"), to identify environmental IgG antibody reactivities in the JDM and control cohorts. Candidate antigens were identified via comparison of JDM samples to controls using a custom case-control analysis software. The most significant reactivity in cases compared to controls, targeting bacterial flagellin, was validated using Mesoscale Diagnostics (MSD), a technique which is similar to an ELISA, but demonstrates improved sensitivity and a wider dynamic range of target detection.

Results. PhIP-Seq with the ToxScan library identified increased anti-flagellin antibodies in juvenile dermatomyositis (JDM). The anti-flagellin antibodies displayed reactivity to several flagellin peptides from various bacterial species with

conserved epitopes. Increased flagellin reactivity in JDM patients, compared to age-matched controls (including sibling and twin controls), were validated by MSD (paired t-test, p-value = 0.03). Additionally, 4 age-matched control samples were positive for flagellin reactivity, and all were siblings of flagellin seropositive JDM patients (1 was a monozygotic twin and 3 were non-twin siblings). Additionally, this flagellin reactivity in JDM patients is associated with an age of 10 years or younger (Fisher's test, *p*-value = 0.037). Furthermore, 9 of the 11 (82%) JDM patients with flagellin reactivity were also anti-TIF1γ positive, versus only 5 of the 12 (42%) without flagellin reactivity.

Conclusions. Profiling antibody reactivities targeting environmental antigens may be useful for identifying triggers of autoimmune diseases, such as IIMs. This study identifies a novel environmental antibody reactivity in JDM patients. Ultimately, these types of efforts will deepen our understanding of the complex interplay between the microbiota, host immunity, and the development of JDM.

Acknowledgements. PNF was instrumental for providing the demographic and clinical data about JDM patients. LR and AM provided samples. MW and TS provided flagellin antigen that was used for MSD validation. HBL oversaw study design and analysis.



P-46. Fig. 1.

P-47

HUMAN EPIDIDYMIS SECRETORY PROTEIN 4 AS A BIOMARKER FOR IDIOPATHIC INFLAMMATORY MYOPATHIES-ASSOCIATED INTERSTITIAL LUNG DISEASE

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Background. Human epididymis protein 4 (HE4) is a biomarker of inflammation and fibrosis, but the association between HE4 and idiopathic inflammatory myopathies-associated interstitial lung disease (IIM-ILD) has not been investigated.

Methods. Sera and clinical data were collected from 139 patients with IIM and 135 healthy controls. The comparison of the clinical parameters between high and low HE4 group, and the relationship between HE4 levels and clinical parameters were determined. Moreover, the dynamic changes of HE4 levels and the expression of HE4 in the lung tissue were accessed.

Results. HE4 level was significantly higher in the serum of IIM patients than in the controls (median 69.3 versus 33.5 μg/L, $p<0.001$). Patients in the high HE4 group had higher ferritin (median 559 versus 83.7 μg/L, $p=0.006$), frequencies of ILD (94.4% versus 56.1%, $p<0.001$) and anti-Jo-1 autoantibodies (25.5% versus 5.7%, $p=0.018$) compared with the low HE4 group. The dynamic changes reveled that the HE4 levels in the non-survivors with IIM-ILD dramatically increased as death approached. The immunohistochemical staining of HE4 in lung tissues was positive in IIM-ILD and negative in controls.

Conclusion. Our findings suggest that serum HE4 may be a clinically useful biomarker for IIM-ILD.

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CHARACTERIZATION OF ANTI-MDA5 AUTOANTIBODY BINDING SITES AND CORRELATION WITH CLINICAL FINDINGS IN SWEDISH DERMATOMYOSITIS PATIENTS

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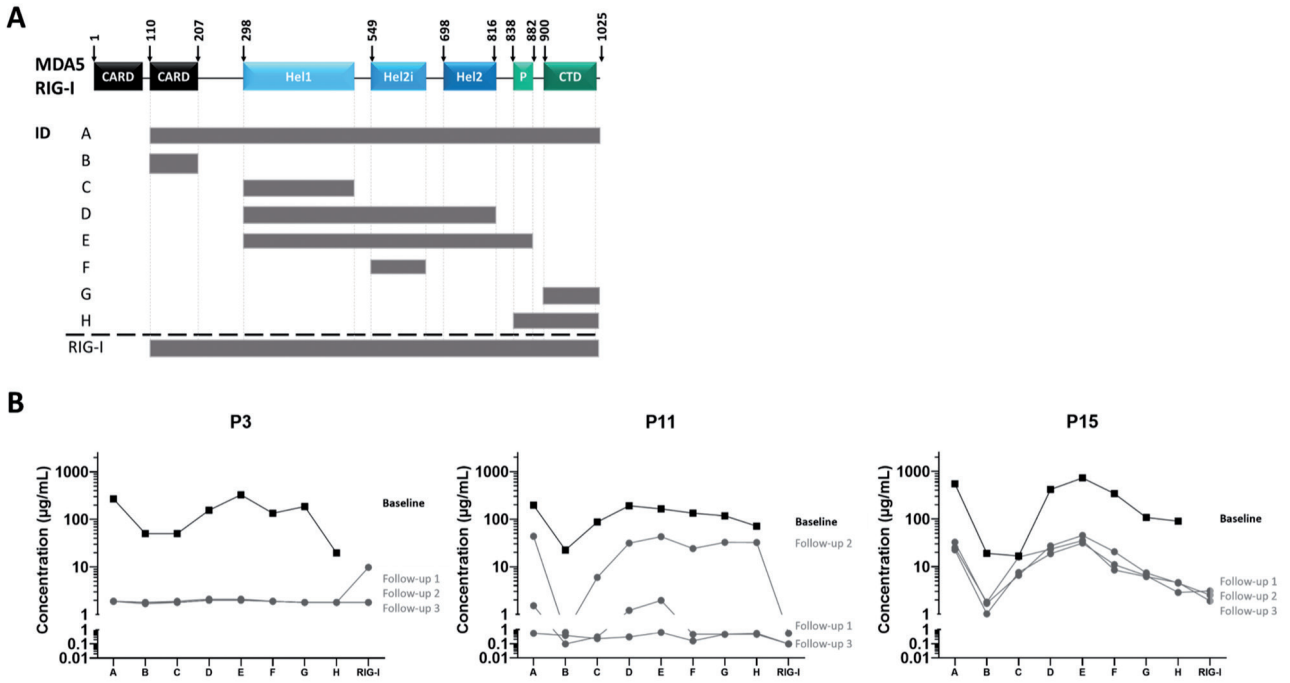
Background. The presence of autoantibodies against melanoma differentiation associated protein 5 (MDA5) has been associated with (rapidly progressing) interstitial lung disease (RP-ILD) in myositis cohorts from different ethnicities. This association suggests an active role for the anti-MDA5 autoantibodies (aMDA5) in the pathogenesis, but to date the molecular mechanisms are unknown. Moreover, there are large differences in symptom severity, with some patients showing no or mild lung involvement while others are in respiratory distress. This clinical heterogeneity suggests that different molecular mechanisms are leading to pathology. We hypothesize that identifying the main immunogenic domain on the MDA5 protein could lead to a better insight into the origin of the pathology. The aims of this study are to 1) identify the different epitopes on the MDA5 protein using baseline and longitudinal serum samples and 2) to correlate the reactivities with clinical parameters.

Methods. We included patients attending Karolinska University Hospital from 1999 to 2021 fulfilling ACR/EULAR IIM classification criteria, with documented positive aMDA5 autoantibody status and sera available at the time of diagnosis (n=21) and/or during follow-up (n=16). An in-house ELISA was developed to measure the reactivity of serum samples against different MDA5-derived protein constructs (UniProt ID Q9BYX4), each comprising of one MDA5 domain or a combination of domains (Figure 1A), allowing to map the reactivity throughout the MDA5 protein. The retinoic acid-inducible protein I (RIG-I) was used as a negative control and all protein constructs were produced in E. Coli. Reactivity against construct A is reported as median concentrations (μg/mL), based on a standard curve of polyclonal patient-derived aMDA5 autoantibodies. Clinical parameters including pulmonary function tests (diffusing capacity for carbon monoxide, DLCO; total lung capacity, TLC; and forced vital capacity, FVC) were collected retrospectively.

Results. The aMDA5 autoantibody level among all 21 patients at baseline was 186.02 μg/mL (IQR 372.71 μg/mL -109.63 μg/mL). All samples at baseline consistently showed reactivity towards constructs D and E, (the helicase domains) but the reactivity towards other domains was less consistent among patients. Analysis of longitudinal samples (n=16) revealed a significant decrease of aMDA5 autoantibody levels during follow-up compared to baseline (1.875 μg/mL vs 227.0 μg/mL, $p<0.0001$), with follow-up dates from 0.2 to 14 years after diagnosis. Highest reactivity during follow-up is still measured against constructs D and E. Analysis of aMDA5 autoantibody levels during follow-up (Figure 1B) revealed 3 different scenarios: 1) autoantibodies disappear during follow-up, 2) autoantibodies disappear and reappear during follow-up and 3) autoantibodies are consistently present during follow-up, even years after diagnosis. Finally, we observed a negative correlation between aMDA5 autoantibody titers and DLCO (Spearman coefficient -0,718, $p=0,006$) at baseline, but there was no significant correlation between aMDA5 autoantibody titers and TLC or FVC.

Conclusion. Our findings indicate epitopes are spread throughout the MDA5 protein, but the high and consistent reactivity against the helicase domains suggest they are the main immunogenic domains of the protein. The negative correlation between aMDA5 autoantibody titers and DLCO indicates antibody levels could reflect disease severity at baseline, but further analysis is needed. Our results also show that aMDA5 autoantibodies may remain present in the circulation even years after diagnosis, although at lower levels compared to baseline.



P-48. Fig. 1. Anti-melanoma differentiation associated protein 5 (aMDA5) autoantibodies target epitopes throughout the MDA5 protein and persist during follow-up. **A**: Graphical representation of the different constructs used in ELISA to map the epitopes. **B**: Analysis of longitudinal aMDA5 autoantibody reactivity to constructs A-H shows the autoantibodies disappear during follow-up (P3 and P11), autoantibodies can reappear during follow-up (P11) and autoantibodies are consistently present during follow-up (P15).

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ANTI-CYTOSOLIC 5'-NUCLEOTIDASE 1A IN PRIMARY SJÖGREN'S SYNDROME: DATA FROM THE MULTICENTER PROSPECTIVE ASSESS COHORT

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Background. Primary Sjögren's syndrome (pSS) is a heterogeneous disease with multisystem involvement including muscle involvement. Recent data showed that anti-cytosolic 5'-nucleotidase 1A (anti-cN1A), which is known for its association with sporadic inclusion body myositis (sIBM), have an increased prevalence in pSS. However, the clinical significance of the anti-cN1A in pSS is currently unknown.
Objectives. To assess the prevalence and the clinical significance of anti-cN1A antibodies in pSS.
Methods. Between 2006 and 2009, 395 consecutive adult patients with pSS (according to revised American-European criteria) were recruited in the French nationwide multicenter prospective Assessment of Systemic Signs and Evolution in Sjögren's Syndrome (ASSESS) cohort. During a 5-year follow-up, data were collected by case-report file tracked on a centralized computer database after monitoring. Patient serum at baseline was tested for anti-cN1A in a central laboratory using ELISA (Euro-Immun, Lübeck, Germany).
Results. Baseline serum was available for 378 patients (96% of the cohort). Thirty pSS patients tested positive for anti-cN1A [7.9% (95% CI: 0.05, 0.11)]. The characteristics of pSS patients with anti-cN1A vs. without out anti-cN1A antibodies were compared. Patients with anti-cN1A had higher rates of lymphadenopathy (27.6% vs. 12.7%, p=0.026) and hematologic involvement (33.3% vs. 15.2%, p=0.01), although there was no significant difference in lymphoma rate (6.7% vs. 4.6%, p=0.61). The unique patient with myositis in the anti-cN1A group (3.3%) was diagnosed with sIBM (vs. 0.24% in the anti-cN1A negative group, p=0.027). Corticosteroids were more rarely used in the anti-cN1A patients (37.9% vs. 56.9%, p=0.048).
Conclusions. In pSS, anti-cN1A positive patients have a higher prevalence of sIBM and hematologic involvement. Corticosteroids were more rarely used in these patients. This data suggests that anti-cN1A may delineate a sub-type of pSS patients.

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HALIP: FIRST LINE BIOMARKER FOR STATIN IMMUNE-MEDIATED NECROTIZING MYOPATHY

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Background and aims. Patients exposed to statins may develop a statin-associated immune mediated necrotising myopathy (IMNM) with antibodies against 3-hydroxy-3-methylglutaryl-coenzyme A reductase (anti-HMGCR). These autoantibodies are highly specific of this distinct type of myositis. However, not all laboratories have adequate technologies for its determination. In 2016, a new and distinct indirect immunofluorescence (IIF) pattern, named HMGCR Associated Liver IIF Pattern (HALIP), was described in association with HMGCR-IMNM on liver tissue of triple rat autoimmune serology test (Inova Diagnostics) (1). Statistical concordance between HALIP and anti-HMGCR antibody specific tests was 98.7%, kappa 0.95. HALIP pattern was confirmed to be due to human anti-HMGCR in a second confirmatory study (2). Since the HALIP pattern was described in triple tissue from a particular manufacturer, the reproducibility of this pattern in tissues from other manufacturers must be confirmed in order to establish if HALIP could be a universally first line biomarker in these patients.
Methods. The performance of HALIP by two different manufacturers was compared with the determination of anti-HMGCR antibodies by chemiluminescent immunoassay (CLIA). Archived sera from 96 patients formed the study population. Thirty-two cases sera from clinically confirmed anti-HMGCR positive myositis patients and 64 anti-HMGCR negative sera from patients with myalgia and/or weakness. Thirty control sera were selected from patients with antibodies against hepatitis C virus. Anti-HMGCR autoantibodies were quantified by CLIA (Inova Diagnostics). HALIP was detected by IIF on liver rat sections as per the manufacturer's instructions (Inova Diagnostics and Euroimmun).
Results. In the method comparison study, 84 of the 96 samples were concordant (kappa = 0.73) between CLIA and Inova-IIF; whereas 50 of the 55 samples were concordant (kappa = 0.82) between CLIA and Euroimmun-IIF. The concordance between both IIF manufactures were excellent (Kappa=0.8).
Conclusions. HALIP determination by IIF is virtually universally available and it can be considered an accessible first line method to classify myopathic patients exposed to statins. In case of negative HALIP and highly clinical suspicion, specific methods, such as CLIA, to determine anti-HMGCR antibodies should be performed.

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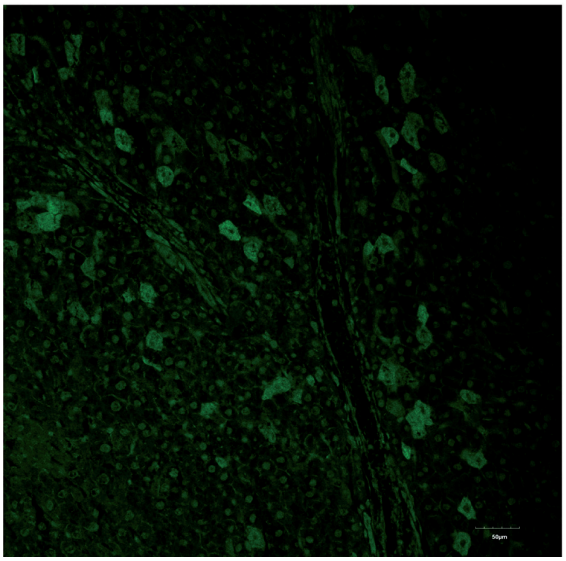

P-50. Fig. 1. Representative image of the HALIP pattern on rat liver section. It is showed some isolated stained hepatocytes on liver rat sections after incubation with a human serum positive for anti-HMGCR antibodies.

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CLINICAL MANIFESTATIONS PREDICTED BY ANTISYNTHETASE ANTIBODIES IN PATIENTS WITH INFLAMMATORY MYOPATHIES: WHAT SHOULD WE LOOK FOR?

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Background. Idiopathic inflammatory myopathies (IIM) are a group of rare multisystemic disorders. Autoantibody expression significantly impacts the clinical features and prognosis of IIM, influencing the follow-up plan and treatment choices. Antisynthetase antibodies are positive in 11-39% of patients with IIM and are usually associated with antisynthetase syndrome classically characterized by the triad of arthritis, myositis and interstitial lung disease (ILD). This work aimed to define the clinical characteristics of IIM patients positive for antisynthetase antibodies, compared to IIM patients negative for these autoantibodies, regardless of IIM subtype.
Methods. Multicentre open cohort study, including patients registered in the IIM module of the Rheumatic Diseases Portuguese Register (Reuma.pt/Myositis) until January 2022. Only patients who had information regarding the results of the myositis-specific (MSA) and associated antibodies (MAA) testing were included. Univariate analysis was performed using chi-square, Fisher's exact, Mann-Whitney or t-test, as appropriate. Independent predictors of different clinical manifestations, adjusted for sex and age at diagnosis, were identified through binomial logistic regression modelling. The linearity of the continuous variables with respect to the logit of the dependent variable was assessed via the Box-Tidwell procedure. Correlated variables, cases with missing information and outliers were excluded from the multivariate analysis in order to fulfil all assumptions necessary to assure the validity of the regression.
Results. From the 280 patients registered at Reuma.pt/Myositis, 237 were included, 71.7% females, with a mean age at diagnosis of 49.27±18.40, out of which 72 (25.7%) were positive for either anti-Jo1 (n=56), anti-PL7 (n=10), anti-PL12 (n=8), anti-EJ (n=4) or anti-OJ (n=4). These patients' most common clinical manifestations were myositis (n=54/70, 77.1%), arthritis (n=20/29, 69.0%), and lung involvement (40/65, 61.5%). Compared to other IIM patients, patients positive for antisynthetase antibodies more frequently had arthritis (20/29 vs 15/61, $p<0.001$), lung involvement (40/65 vs 36/149, $p<0.001$), mechanic's hands (12/36 vs 11/88, $p=0.010$), and heart involvement (7/65 vs 3/148, $p=0.010$). On the contrary, this group less frequently had Gottron's sign (13/51 vs 55/119, $p=0.016$) and papules (18/69 vs 66/152, $p=0.017$), heliotrope rash (16/71 vs 76/170, $p<0.001$), malar rash (2/36 vs 27/89, $p=0.002$), erythema (11/49 vs 49/105, $p=0.005$), photosensitivity (3/36 vs 24/89, $p=0.029$) and the shawl sign (3/36 vs 22/88, $p=0.047$). In the multivariate analysis, antisynthetase antibodies (OR 19.34, 95%CI: 2.99-125.04, $p=0.002$) and mechanic's hands (OR 9.86, 95%CI: 1.15-84.28, $p=0.037$) were identified as predictors of ILD in IIM patients independently of sex, age at diagnosis, arthritis, and neoplasia. Aditionally, antisynthetase antibodies (OR 12.31, 95%CI: 2.41-62.81, $p=0.003$) and mechanic's hands (OR 21.41, 95%CI: 3.10-147.74, $p=0.002$) were also predictors of arthritis in IIM patients independently of sex, age at diagnosis, ILD, and neoplasia. On the other hand, no independent predictors of heart involvement were identified.
Conclusions. Patients positive for antisynthetase antibodies are more likely to have arthritis, mechanic's hands, and heart and lung involvements than other IIM patients. Both antisynthetase antibodies and mechanic's hands were identified as independent predictors of ILD and arthritis in IIM patients.

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LONGITUDINAL ASSESSMENT OF ANTI-JO1 AUTOANTIBODY AND HISRS PROTEIN LEVELS IN A LARGE COHORT OF MYOSITIS PATIENTS

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Background. Anti-Jo1 autoantibodies, targeting the histidyl-tRNA synthetase (HisRS) protein, are the most common myositis-specific autoantibodies and the serological biomarker of the anti-synthetase syndrome (ASSD), a subgroup of Idiopathic Inflammatory Myopathies (IIM). The diagnostic role of the anti-Jo1 autoantibodies (aJo1) is well established, while data is limited on the trend of aJo1 levels over the IIM/ASSD disease course. Serum HisRS protein levels have been previously reported to be higher in anti-Jo1 negative than anti-Jo1 positive patients at time of IIM diagnosis, but the evolution of HisRS levels over time is not known. The aim of this study was to analyze the longitudinal variation of levels of both aJo1 and HisRS protein in a large cohort of myositis patients.
Methods. Stored serum samples (n=780) collected at time of diagnosis and during follow-up from patients (n=251) with IIM/ASSD (51 anti-Jo1 positive (+), 197 anti-Jo1 negative (-) and 5 with unknown anti-Jo-1 status), attending the Rheumatology clinic at Karolinska University Hospital, Stockholm, Sweden, were retrospectively identified. Patients were classified as anti-Jo1 (+) if they had ever tested positive for aJo1 by standardized immune assays (commercial ELISA, Line Blot, Immunoprecipitation. An in-house ELISA was used to detect levels of anti-Jo1 autoantibodies (aJo1) and its target HisRS protein at diagnosis and longitudinally. We analyzed whether the anti-Jo1 status could explain variations of serum levels of both aJo1 and HisRS protein overtime using linear mixed models to account for clustering of samplings within patients. We fitted anti-Jo1 status as fixed effect

and each individual ID number as random effect. Logarithmic transformation was applied to normalize both antibody and protein levels.

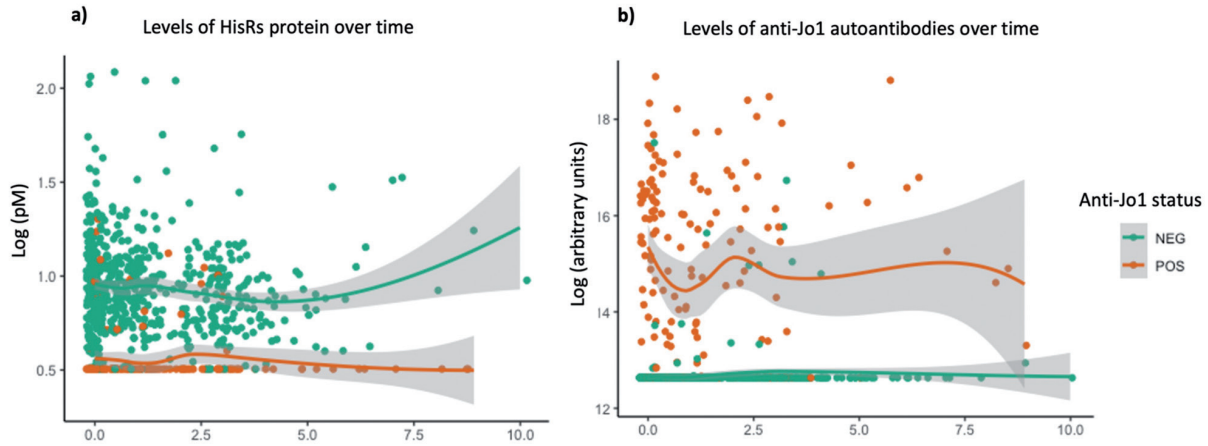
Results. The median number of samples available for each patient was 3 (interquartile range (IQR) 2-4, range 1- 5), covering a mean follow-up time from IIM/ASSD diagnosis of 1.3 years (standard deviation (SD) 1.6, range 0-10). A sixth follow-up sample was available only for one patient and excluded from the analysis as well as the results of aJo1 and HisRS levels obtained from the five patients with unknown anti-Jo1 status. At diagnosis, anti-Jo1 (-) patients had higher mean HisRS levels than anti-Jo1 (+) patients (11.83 (SD 12.8) vs 4.11 (SD 3.5) pM, respectively, $p<0.001$, Fig. 1a). The anti-Jo1 (-) group showed higher mean levels of HisRS than the anti-Jo1 (+) during the entire follow-up (Fig. 1a). On the contrary, both baseline and longitudinal mean aJo1 levels were constantly higher in the anti-Jo1 (+) group than the anti-Jo1(-) group where majority of the aJo1 levels were below the limit of detection (Fig.1b). In the anti-Jo1 (+) group, mean aJo1 titers decreased one year after diagnosis and then increased again at two-three years follow-up, reaching almost the same baseline levels. Thereafter we observed a slightly but steady decrease of autoantibodies. This observation was supported by a predictive model showing that, over ten years, anti-Jo1(+) patients had a significant yearly decrease of levels of aJo1 (p=0.048). Interestingly, only in five anti-Jo1 (+) patients, we found that over time the aJo1 titers reached the same levels as were observed in the anti-Jo-1 (-) group (Fig. 1b). Surprisingly, at follow-up, an increase of aJo1 titers with similar levels of the anti-Jo1 (+) patients was recorded in 12 anti-Jo1 (-) patients (Fig. b). In the predictive model, we also detected a yearly decrease of HisRS protein levels in both anti-Jo1(+) and (-) patients, but only significant in the anti-Jo1 (-) group (p=0.039).

Conclusions. In this study, we observed that, with few exceptions, anti-Jo1 (+) myositis patients displayed stable aJo1 titers over time with similar levels between diagnosis and follow-up times, despite a slight overall trend of annual decrease. Levels of HisRS protein were found constantly higher in the anti-Jo1 (-) group than the anti-Jo1 (+) both at diagnosis and longitudinally and they decreased every year in both groups. The relevance of these findings will be explored by combining serum aJo1 and HisRS levels with clinical data.

P-51. Table I.

	Antisynthetase antibodies positive (n=72)	Antisynthetase antibodies negative (n=165)	Univariate analysis
Age at disease onset, median ± SD (N)	50.51 ± 17.20 (55)	46.88 ± 19.04 (146)	p=0.199
Age at diagnosis, median ± SD (N)	52.51 ± 16.41 (56)	47.98 ± 19.04 (140)	p=0.098
Disease duration (in years), median ± SD (N)	7.81 ± 6.51 (55)	6.50 ± 6.69 (146)	p=0.212
Deceased patients, n/N (%)	5/72 (6.9)	5/165 (3.0)	p=0.177
Clinical data			
Musculoskeletal involvement			
Muscle involvement			
Proximal muscle weakness, n/N (%)	43/55 (78.2)	118/138 (85.5)	p=0.283
Myositis, n/N (%)	54/70 (77.1)	131/153 (85.6)	p=0.128
Muscle weakness (not predominantly proximal), n/N (%)	6/34 (17.6)	10/84 (11.9)	p=0.392
Joint involvement			
Arthralgia (without arthritis), n/N (%)	1/9 (11.1)	1/44 (2.3)	p=0.313
Arthritis, n/N (%)	20/29 (69.0)	15/61 (24.6)	**p<0.001***
Skin involvement			
Gottron' sign, n/N (%)	13/51 (25.5)	55/119 (46.2)	**p=0.016***
Heliotrope rash, n/N (%)	16/71 (22.5)	76/160 (47.5)	**p<0.001***
Gottron's papules, n/N (%)	18/69 (26.1)	66/152 (43.4)	**p=0.017***
Erythema, n/N (%)	11/49 (22.4)	49/105 (46.7)	**p=0.005***
Periungual changes, n/N (%)	13/61 (21.3)	39/146 (26.7)	p=0.484
Malar rash, n/N (%)	2/36 (5.6)	27/89 (30.3)	**p=0.002***
Oedema			
Periorbital oedema, n/N (%)	2/34 (5.9)	13/85 (15.3)	p=0.227
Generalized subcutaneous oedema, n/N (%)	1/35 (2.9)	5/85 (5.9)	p=0.670
Photosensitivity, n/N (%)	3/36 (8.3)	24/88 (27.3)	**p=0.029***
Shawl sign, n/N (%)	3/36 (8.3)	22/88 (25.0)	**p=0.047***
Mechanic's hands, n/N (%)	12/36 (33.3)	11/88 (12.5)	**p=0.010***
Cutaneous vasculitis, n/N (%)	6/54 (11.1)	17/115 (14.8)	p=0.634
Calcinosis, n/N (%)	4/65 (6.2)	16/150 (10.7)	p=0.443
Alopecia, n/N (%)	1/36 (2.8)	11/88 (12.5)	p=0.177
Skin ulceration, n/N (%)	5/65 (7.7)	11/149 (7.4)	p=1.000
Panniculitis, n/N (%)	0/35 (0.0)	6/87 (6.9)	p=0.181
Livedo reticularis, n/N (%)	0/35 (0.0)	6/87 (6.9)	p=0.181
Vascular involvement			
Raynaud's phenomenon, n/N (%)	27/66 (40.9)	43/150 (28.7)	p=0.084
Periungual capillary changes, n/N (%)	5/33 (15.2)	17/76 (22.4)	p=0.447
Digital ulcers, n/N (%)	0/29 (0.0)	1/73 (1.4)	p=1.000
Internal organ involvement			
Heart involvement, n/N (%)	7/65 (10.8)	3/148 (2.0)	**p=0.010***
Lung involvement, n/N (%)	40/65 (61.5)	36/149 (24.2)	**p<0.001***
Gastrointestinal involvement, n/N (%)	12/36 (33.3)	40/95 (42.1)	p=0.426
Dysphagia, n/N (%)	7/33 (21.2)	25/82 (30.5)	p=0.365
Dysphonia, n/N (%)	4/32 (12.5)	8/82 (9.8)	p=0.737
Abdominal pain, n/N (%)	2/31 (6.5)	3/81 (3.7)	p=0.616
Oesophageal involvement, n/N (%)	8/64 (12.5)	31/143 (21.7)	p=0.129
Gastric involvement, n/N (%)	1/63 (1.6)	1/142 (0.7)	p=0.521
Intestinal involvement, n/N (%)	1/63 (1.6)	2/143 (1.4)	p=1.000
Systemic involvement			
Fatigue, n/N (%)	12/34 (35.3)	35/87 (40.2)	p=0.682
Weight loss, n/N (%)	7/34 (20.6)	15/87 (17.2)	p=0.794
Fever, n/N (%)	2/35 (5.7)	4/87 (4.6)	p=1.000
Neoplasia, n/N (%)	2/36 (5.6)	8/87 (9.2)	p=0.295
Complementary diagnostic exams			
Muscle enzymes			
High CK levels, n/N (%)	45/57 (78.9)	99/131 (75.6)	p=0.709
High aldolase levels, n/N (%)	20/37 (54.1)	49/91 (53.8)	p=1.000
High LDH levels, n/N (%)	35/51 (68.6)	81/120 (67.5)	p=1.000
High AST levels, n/N (%)	27/57 (47.4)	68/123 (55.3)	p=0.340
High ALT levels, n/N (%)	24/57 (42.1)	65/123 (52.8)	p=0.202
Electromyogram			
Myopathic pattern, n/N (%)	24/37 (64.9)	73/95 (76.8)	p=0.190
Muscle magnetic resonance			
Muscle oedema (STIR), n/N (%)	4/14 (28.6)	28/45 (62.2)	**p=0.035***

Abbreviations: ACR: American College of Rheumatology; ALT: alanine transaminase; AST: aspartate transaminase; CK: creatine kinase; LDH: lactate dehydrogenase; n: number of patients positive for the variable of interest; N: number of patients without missing information regarding the variable of interest; STIR: short tau inversion recovery.



P-52. Fig. 1.

P-53

CLINICAL PERFORMANCE OF MYOSITIS SPECIFIC AND NOVEL MYOSITIS ASSOCIATED AUTOANTIBODIES IN A COHORT OF DERMATOMYOSITIS PATIENTS FROM FRANCE

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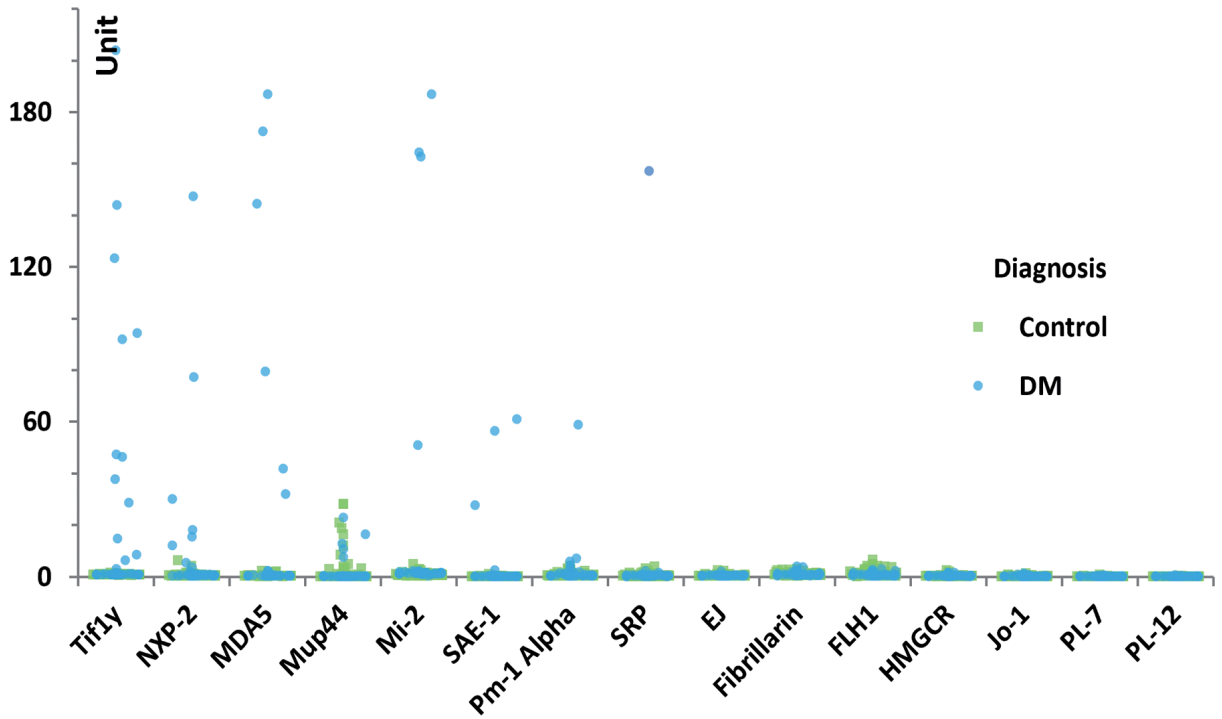
Background. Myositis specific antibodies (MSA) represent not only important diagnostic tools, but also help in the stratification of idiopathic inflammatory myopathy (IIM) patients into particular clinical phenotypes, according to treatment responses, and disease outcomes. In addition, myositis associated antibodies (MAA) have been recognized as useful biomarkers in IIM and several were included in this study to investigate their prevalence in dermatomyositis (DM) patients. The objective of this study was to compare the prevalence of both MSA and MAA in a cohort of dermatomyositis patients collected from France.
Methods. A total of 46 patients with DM and 143 disease control and healthy patient samples were included in the study. The prevalence of MSA and MAA were analyzed as detected using a novel particle-based multi-analyte technology (PMAT) (Inova Diagnostics, San Diego, USA, research use only; Mi-2, TIF1y, PL-12, SAE-1, EJ, MDA-5, HMGCR, Jo-1, PL-7, SRP54, NXP-2, Fibrillarin, PM-1 Alpha, FHL1, Mup44).
Results. The frequency of the established MSA and novel MAA markers are summarized in Table I and II. The standardized unit values for MSA and MAA panels in dermatomyositis patients (n=46) and controls (n=143) are summarized in Figure 1.
Conclusions. The PMAT MSA and MAA panels demonstrated expected prevalence among DM patients. TIF1y, NXP-2 and MDA5 analytes showed the highest prevalence in the MSA panel, while Mup44 and PM1-Alpha had the highest prevalence in the MAA panel. Further investigation into the novel marker reactivity with clinical manifestations is warranted, especially the markers which are mostly associated with SSc.



P-53. Fig. 1. Standardized unit values for MSA and MAA panels among dermatomyositis (n=46) and controls (n=143). TIFγ: transcription intermediary factor 1 gamma; SAE-1: SUMO1 activating enzyme subunit 1; EJ: glycyl-tRNA synthetase; MDA-5: melanoma differentiation-associated protein; HMGCR: 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase; PL-7: threonyl-tRNA synthetase; PL-12: alanyl-tRNA synthetase; SRP: signal recognition particle; NXP2: nuclear matrix antigen 2; Fibrillarin: U3-RNP; PM-1 Alpha: major alpha helical PM/Scl-100 epitope; FHL1: four-and-a-half LIM domain 1; Mup44: cytosolic 5'-nucleotidase 1A (NT5x1A).

P-53 Table I. Prevalence of MSA Analytes Among Dermatomyositis Patients (n=46) in France and Specificity in Controls (n=143).

Disease Group	Sample Size (n)	Mi-2	TIFγ	PL-12	SAE-1	EJ	MDA5	HMGCR	Jo-1	PL-7	SRP54	NXP-2
Sensitivity in DM, No., %	46	4/46 8.7 (3.4-20.3)	12/46 26.1 (15.6-40.3)	0/46 0.0	3/46 6.5 (2.2-17.5)	0/46 0.0	6/46 13.0 (6.1-25.7)	0/46 0.0	0/46 0.0	0/46 0.0	1/46 2.2 (0.4-11.3)	7/46 15.2 (7.6-28.2)
Specificity %	143	100.0 (97.4-100.0)	100.0 (97.4-100.0)	100.0 (97.4-100.0)	100.0 (97.4-100.0)	100.0 (97.4-100.0)	100.0 (97.4-100.0)	100.0 (97.4-100.0)	100.0 (97.4-100.0)	100.0 (97.4-100.0)	100.0 (97.4-100.0)	99.3 (96.2-99.9)

P-53 Table II. Prevalence of MAA Novel Markers Among Dermatomyositis Patients (n=46) in France and Specificity in Controls (n=143).

Disease Group	Sample Size (n)	Fibrillarin	PM-1 Alpha	FHL1	Mup44
Sensitivity in DM, No., %	46	0/46 0.0	3/46 6.5 (2.2-17.5)	0/46 0.0	5/46 10.9 (4.7-23.0)
Specificity %	143	100.0 (97.4-100.0)	100.0 (97.4-100.0%)	99.3 (96.2-99.9)	95.1 (90.2-97.6)

P-54

MYOSITIS SPECIFIC AND NOVEL MYOSITIS ASSOCIATED AUTOANTIBODIES IN DERMATOMYOSITIS SUBPHENOTYPES OF A FRENCH COHORT

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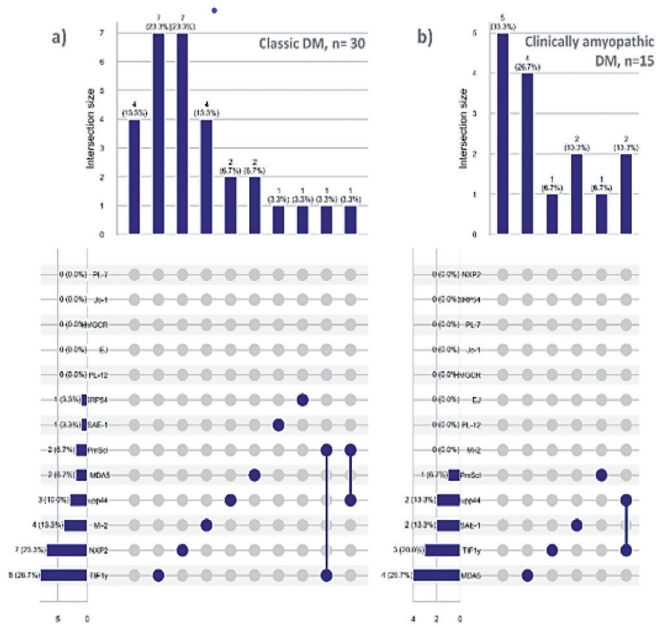
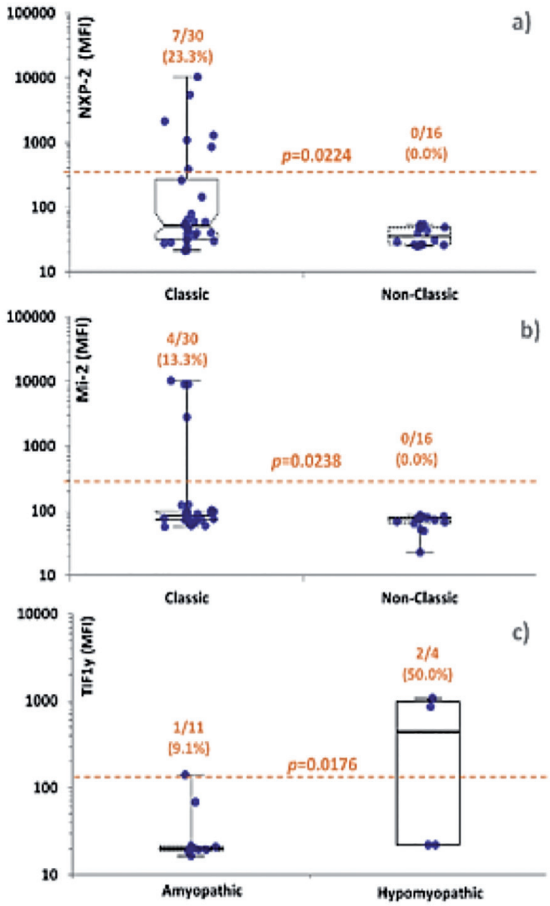
Background. Dermatomyositis (DM) is an idiopathic inflammatory myopathy (IIM) characterized by varying degrees of skin disease with or without muscle involvement and can be categorized as classic (cDM), clinically amyopathic (CADM), and cutaneous. Myositis specific antibodies (MSA) represent important diagnostic and stratification tools for defining IIM clinical subsets, based on treatment responses and disease outcomes. Additionally, myositis associated antibodies (MAA) have been recognized as useful biomarkers in IIM including DM. This study aimed to describe the autoantibody profile of DM sub-phenotypes from patients seen at a French myositis referral center.
Methods. 46 well-characterized DM patients from CHU Montpellier (Montpellier, France) consisting of cDM (n=30, 65.2%), CADM [amyopathic (n=11, 23.9%), hypomyopathic (n=4, 8.7%)], and severe cutaneous (n=1, 2.2%) DM patients were tested on particles coated with MSA and MAA related autoantigens using a novel particle-based multi-analyte technology (PMAT, research use only, Inova Diagnostics, San Diego, USA). The autoantibody prevalence and levels of the DM patients were assessed.
Results. The prevalence of relevant MSA and MAA in this cohort are summarized in Figure 1. Anti-NXP2 and anti-Mi-2 antibody levels were found to be significantly higher in cDM vs. non-cDM (p=0.0224 and p=0.0238, respectively) (Figure 2). Among the CADM patients, anti-TIF1γ antibody median levels are significantly different between amyopathic and hypomyopathic DM (p=0.0179) (Figure 2). Despite the small numbers, the anti-TIF1γ (+) hypomyopathic DM patients (n=2) notably exhibited arthritis, digestive symptoms, and late onset muscle weakness during follow up.
Conclusion. Multiparametric autoantibody profiling of DM patients can aid in identifying distinct clinical features and profiles different from "classic" dermatomyositis. MSAs such as anti-NXP2, anti-Mi-2 and anti-TIF1γ antibodies show potential in differentiating classic DM with CADM. Further studies with larger sample sizes are needed to solidify this new clinical utility of DM markers.



P-54. Fig. 1. UpSet plot showing the frequency and overlap of MSA and MAA markers on classic dermatomyositis (DM, n=30) (a) and clinically amyopathic DM (CADM, n=15) (b) patients.



P-54. Fig. 2. Box plots illustrating autoantibody levels between classic and non-classic dermatomyositis (DM) (a-b), and between the two groups of clinically amyopathic DM (CADM) (c) patients. Dotted line represents the cut-off.

P-55

ANTISYNTHETASE: FROM SYNDROME TO INDIVIDUALIZED IMMUNOLOGICAL PROFILES

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Background. Antisynthetase syndrome (ASyS) is a systemic autoimmune disease characterized by the presence of specific antibodies, arthritis, Raynaud's phenomenon (RP), mechanic's hands (MH), myositis, fever, and typical skin lesions. Interstitial lung disease (ILD) is the hallmark manifestation of ASyS. It is one of the most common clinical features and is the major contributor to morbidity and mortality. ASyS is included within the group of idiopathic inflammatory myopathies (IIM), although not all patients have a classic presentation and may be either hypomyopathic or amyopathic. ASyS has unique serological and pathological features and is a separate entity within the IIMs. In addition, antisynthetase autoantibodies can condition different clinical profiles. Objectives: Our objective was to evaluate the clinical, immunological, and radiological profiles of the 4 most prevalent autoantibodies (Anti-Jo1, anti-PL12, Anti-PL7, and anti-EJ) in a Spanish single-center cohort.
Methods. Single-center retrospective observational study of autoantibody profiles in ASyS. We included all ASyS patients who fulfilled Connors and Solomon's classification criteria between 2017 and 2021.
Results. Thirty-six patients with a mean age at diagnosis of 54.8 years (88.9% women) were analyzed. The mean follow-up time was 3.9 years. Most of the patients were of Hispanic origin (91.7%): Spanish (80.6%) or Latin American (11.1%). The most frequent antibody was anti-Jo1 (n=16, 44.4%), followed by anti-PL7 (n=8, 22.2%), anti-PL12 (n=8, 22.2%), anti-EJ (n=4, 11.1%). Median time from onset to diagnosis was approximately 12 months (range 3-39). The first symptom at onset was arthritis (37.1%), followed by ILD (22.8%) defined by high-resolution CT scan (HRCT). Myopathy was present in 57.8% of patients, arthritis in 55.6%, RP in 41.7%, MH in 36.1%, and non-MH skin lesions in 36.1%. Myocarditis only occurred in 2 patients (both anti-PL12). From the immunological point of view, antinuclear antibodies (ANA) were found in 38.9% of cases, anti-Ro (Ro52) 27.8%, anticardiolipin 11.1%, rheumatoid factor (RF) 11.1%, and anti-cyclic citrullinated peptide (anti-CCP) 8.3%. However, there were clinical and immunological differences in the presentations of the autoantibodies (Figure 1). Anti-Jo1 was characterized by the classical triad: myositis, arthritis (p=0.036) and ILD, followed by MH; anti-PL12 by ILD and RP (p=0.030) followed by arthritis, and was the only autoantibody associated with myocarditis (p=0.006); anti-PL-7 by ILD and skin lesions, and anti-EJ by myositis and skin lesions with less frequency of ILD (p=0.025). Anti-Jo1 patients were younger (p=0.018). Anti-PL12 was the antibody most associated with positive ANA (and higher titles) and with anti-Ro52 (p<0.001). Anti-PL7 was the one that most frequently presented with negative ANA and anti-ENA (p=0.018). Regarding myositis, the mean CK was 1045 U/L. However, there were large differences between groups with the highest levels in anti-Jo1 and the lowest levels in anti-PL12 (p=0.018). Five patients (13.9%) presented cancer during follow-up, there were no differences between autoantibodies (p=0.380). Four (11.1%) patients died during follow-up, two due to ASyS complications and two due to cancer progression.
Conclusion. ASyS is a systemic autoimmune disease with typical manifestations. This single-center Spanish cohort defined different clinical, immunological, and radiological presentations of anti-Jo1, anti-PL12, anti-PL7, and anti-EJ. It is essential to know them in order to individualize follow-up, better adapt treatments and anticipate potentially lethal complications in these patients.

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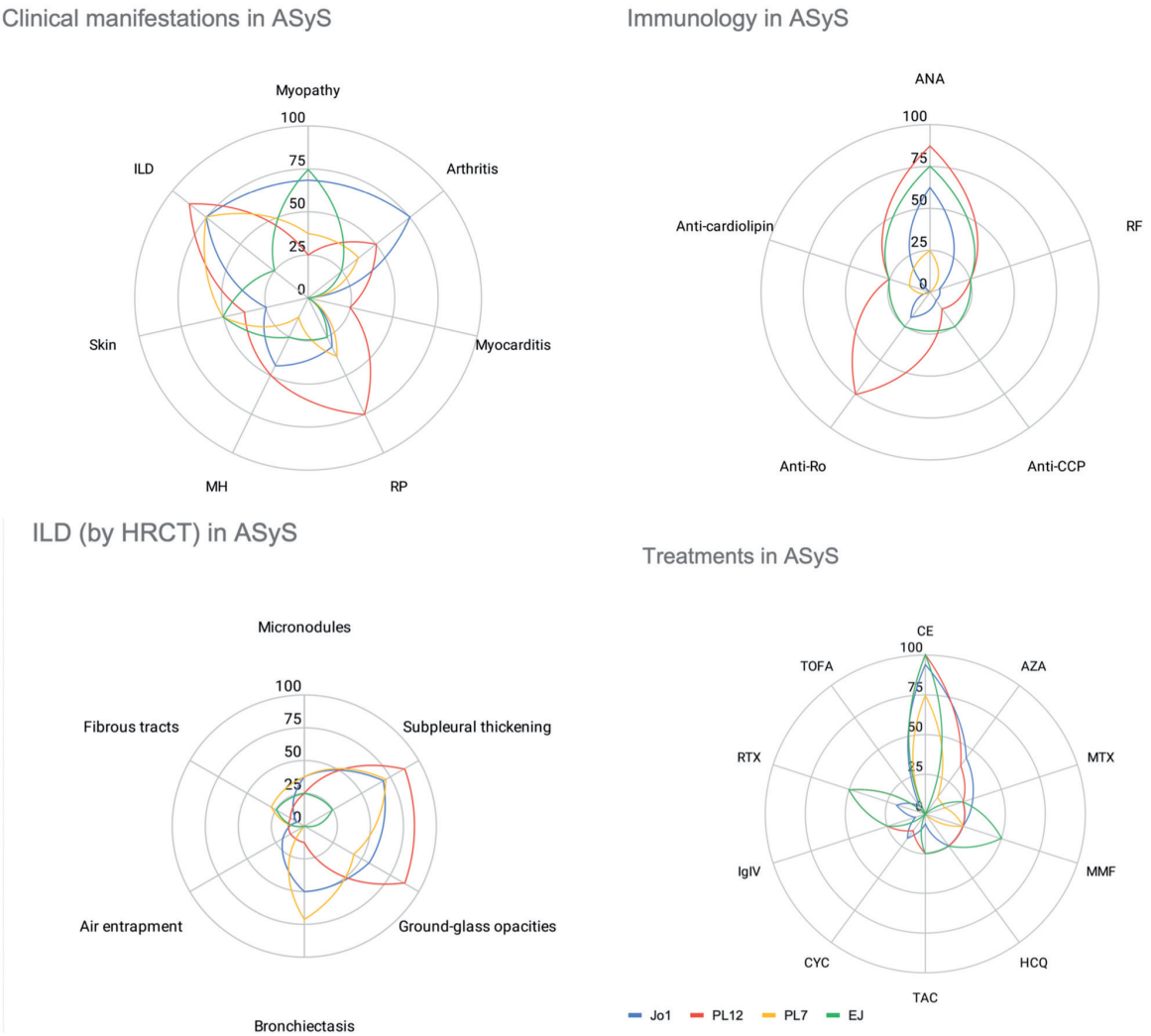

P-55. Fig. 1.

COVID-19 and myositis

P-56

IMPAIRED PROMIS PHYSICAL FUNCTION IN IDIOPATHIC INFLAMMATORY MYOPATHY PATIENTS: RESULTS FROM THE MULTICENTER COVAD PATIENT-REPORTED E-SURVEY

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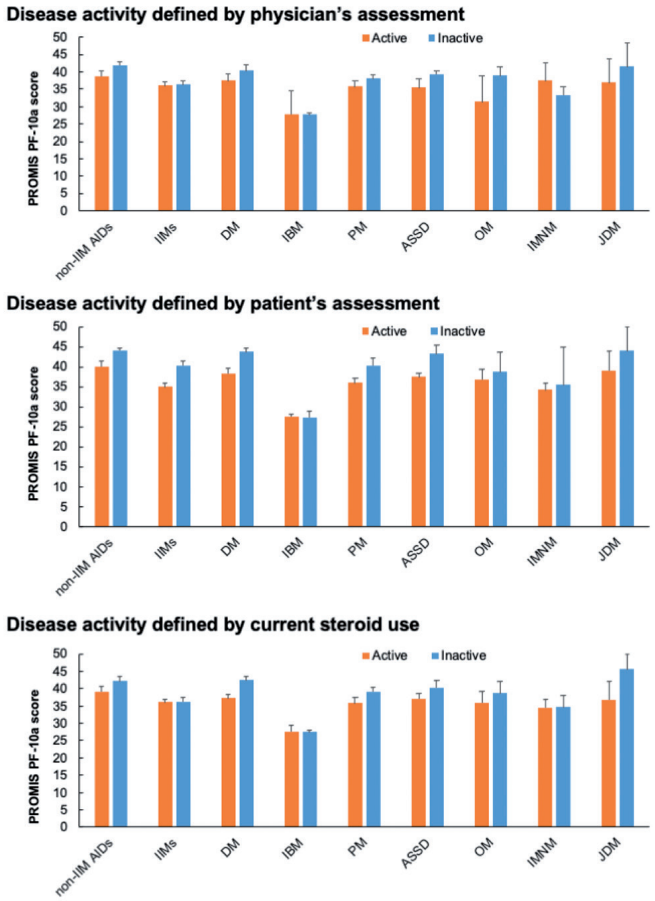
Background. Evaluation of physical function is fundamental in the management of idiopathic inflammatory myopathies (IIMs). Patient-Reported Outcome Measurement Information System (PROMIS) is a National Institute of Health initiative established in 2004 to develop patient-reported outcome measures with improved validity and efficacy. The present study aims to investigate the physical function status of IIM patients compared to those with non-IIM autoimmune diseases (AIDs) and healthy controls (HCs) utilizing PROMIS Physical Function (PF) data obtained in the coronavirus disease-2019 (COVID-19) Vaccination in Autoimmune Diseases (COVAD) study, a large-scale, international self-reported e-survey assessing the safety of COVID-19 vaccines in AID patients.
Methods. The survey data regarding demographics, IIM and AID diagnosis, disease activity, fatigue and pain VAS, and PROMIS PF short form-10a were extracted from the COVAD study database. The disease activity (active vs inactive) of each patient was assessed in 3 different ways: (1) physician's assessment (active if there was increased immunosuppression), (2) patient's assessment (active vs inactive as per patient), and (3) current steroid use. These 3 definitions of disease activity were applied independently to each patient. PROMIS PF-10a scores were compared between each disease category (IIMs vs non-IIM AIDs vs HCs), stratified by disease activity based on the 3 definitions stated above, employing negative binomial regression model, and the predicted PROMIS PF-10a score adjusted for age, gender, and ethnicity was calculated. Factors affecting PROMIS PF-10a scores other than disease activity were identified by multivariable regression analysis in the patients with inactive disease (IIMs or non-IIM AIDs). The association between fatigue or pain VAS and PROMIS PF-10a scores was also assessed.
Results. 1057 IIM patients, 3635 non-IIM AID patients, and 3981 HCs responded to the COVAD survey until August 2021. The median age of the respondents was 43 [IQR 30-56] years old, and 74.8% were female. Among IIM patients, dermatomyositis was the most prevalent diagnosis (34.8%), followed by inclusion body myositis (IBM) (23.6%), polymyositis (PM) (16.2%), anti-synthetase syndrome (11.8%), overlap myositis (7.9%), and immune-mediated necrotizing myopathy (IMNM) (4.6%). The predicted mean of PROMIS PF-10a scores was significantly lower in IIMs compared to non-IIM AIDs or HCs (36.3 [95% (CI) 35.5-37.1] vs 41.3 [95% CI 40.2-42.5] vs 46.2 [95% CI 45.8-46.6], $p<0.001$), irrespective of disease activity (Figure 1). The results were consistent across analyses using different disease activity definitions (physician's assessment, patient's assessment, and steroid use), while the largest difference between active IIMs and non-IIM AIDs was observed when the disease activity was defined by patient's assessment (35.0 [95% CI 34.1-35.9] vs 40.1 [95% CI 38.7-41.5]). Considering the subgroups of IIMs, the scores were significantly lower in IBM in comparison with non-IBM IIMs ($p<0.001$). The independent factors associated with low PROMIS PF-10a scores in the patients with inactive disease were older age, female gender, and the disease category being IBM, PM, or IMNM. Higher fatigue or pain VAS was associated with lower PROMIS PF-10a scores in each disease category ($p<0.001$), while the scores were still lower in IIMs compared to non-IIM AIDs even after being adjusted for fatigue and pain.
Conclusion. Physical function is significantly impaired in IIMs compared to non-IIM AIDs or HCs, even in patients with inactive disease. The elderly, women, and IBM groups are the worst affected, suggesting that developing targeted strategies to minimize functional disability in certain groups may improve patient-reported physical function and disease outcomes.
Acknowledgements. The authors are grateful to all respondents for filling out the questionnaire. The authors also thank The Myositis Association, Myositis India, Myositis UK, Global Myositis Network, Cure JM, Cure IBM, Sjögren's India Foundation, EULAR PARE for the dissemination of this e-survey.



P-56. Fig. 1.

P-57

COVID-19 SEVERITY AND VACCINE BREAKTHROUGH INFECTIONS IN IDIOPATHIC INFLAMMATORY MYOPATHIES, OTHER SYSTEMIC AUTOIMMUNE AND INFLAMMATORY DISEASES, AND HEALTHY INDIVIDUALS: RESULTS FROM THE COVID-19 VACCINATION IN AUTOIMMUNE DISEASES (COVAD) STUDY

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Background. Significant gaps are present in the evidence of the spectrum and severity of COVID-19 infection in idiopathic inflammatory myopathies (IIMs). Patients with IIMs typically require immunosuppressive therapy, may have multiple disease sequelae, and frequent comorbidities, and thus may be more susceptible to severe COVID-19 infection and complications. The possibility of attenuated immunogenicity and reduced efficacy of COVID-19 vaccines due to concomitant immunosuppressive medication is a major concern in these patients, and there is little data available on COVID-19 vaccine breakthrough infections (BI) in IIMs
Methods. We developed an extensive patient self-reporting electronic-survey (COVAD survey) featuring 36 questions to collect respondent demographics, SAID details, COVID-19 infection history, COVID-19 vaccination details, 7-day post vaccination adverse events and patient reported outcome measures using the PROMIS tool. After pilot testing, validation, translation into 18 languages on the online platform surveymonkey.com, and vetting by international experts, the COVAD survey was circulated in early 2021 by a multicenter study group of >110 collaborators in 94 countries. BI was defined as COVID-19 infection occurring more than 2 weeks after receiving 1st dose of a COVID-19 vaccine. We analysed data from the baseline survey for descriptive and intergroup comparative statistics based on data distribution and variable type.
Results. Data from 10,900 respondents [42 (30-55) years, 74% females, 45% Caucasians] were analysed. Most were HCs (47%), followed by SAIDs (42%) and IIMs (11%). All respondents included in the final analysis had received a single dose of the vaccine and 69% had received 2 primary doses. Pfizer (39.8%) was the most common vaccine received, followed by Oxford/AstraZeneca (13.4%), and Covishield (10.9%). IIM patients were older, had a higher Caucasian representation and higher Pfizer uptake than other SAIDs, and HC. A higher proportion of IIM patients received immunosuppressants than other SAIDs. After adjustment for covariates, COVID-19 severity and BIs were comparable among patients with IIMs, SAIDs, and HCs, except for all-cause hospitalisation prior

to vaccination (IIMs vs. HCs, OR=2.5, 95%CI 1.1-5.8) and COVID-19 cases prior to vaccination (IIMs vs. SAIDs, OR=0.6, 95%CI 0.4-0.8, and IIMs vs HCs, OR=0.4, 95%CI 0.3-0.5). BIs in IIMs were uncommon, with only 17 (1.4%) patients reporting BIs, of whom 13 were on immunosuppressants, and 3 required hospitalisation. Unvaccinated individuals with IIMs were at 4.6 (95%CI 2.7-8.0) times higher odds for developing COVID-19, and the 2nd vaccine dose had a protective effect on BI occurrence (Figure 1).

Conclusion. IIMs patients reported fewer COVID-19 prior to vaccination than SAIDs and HCs, but had higher odds of all-cause hospitalisation than HCs. Vaccination protected patients with IIMs against COVID-19. COVID-19 breakthrough infections were uncommon in IIMs, with a similar symptom profile, disease duration, and severity in comparison to patients with SAIDs and HCs.

Acknowledgements. The authors thank all members of the COVAD study group for their invaluable role in the collection of data. The authors thank all respondents for filling the questionnaire. The authors thank The Myositis Association, Myositis India, Myositis UK, the Myositis Global Network, Cure JM, Cure IBM, Sjögren's India Foundation, EULAR PARE, and various other patient support groups and organisations for their invaluable contribution in the dissemination of this survey among patients which made the data collection possible.

P-58

UNUSUAL MYOSITIS OF THE TEMPORALIS MUSCLE OCCURRING WITH ACUTE COVID-19

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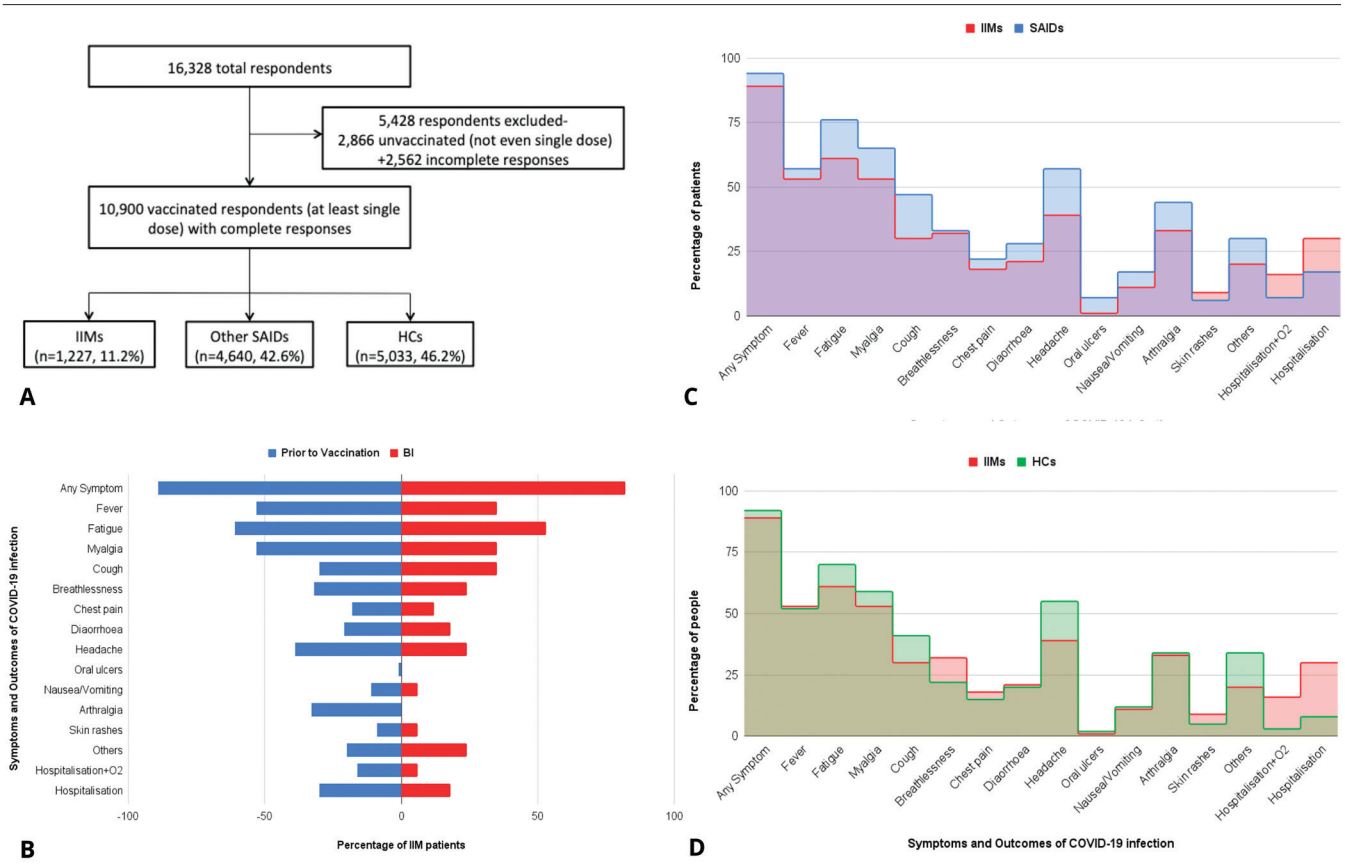
Background. SARS-CoV-2 infection can be accompanied by neuromuscular disorders. Rhabdomyolysis and Guillain-Barré syndrome have been described repeatedly. There are case reports of inflammatory myopathies manifesting during COVID-19, presenting as dermatomyositis, polymyositis or immune-mediated necrotizing myopathy, with dermatomyositis-like presentations most commonly reported. Larger cases series are from postmortem examinations of COVID-19 patients, where variable inflammatory pathology of the skeletal muscle has been found frequently but without local detection of the actual virus. Thus, autoimmune mechanisms or the systemic interferon response are discussed as causes. We report a case of focal inflammatory myopathy with perimysial pathology of the temporalis muscle occurring with acute, but mild COVID-19.

Methods. Case report of clinical observations, cranial MRI, histopathological, and laboratory findings. 3T cranial MRI was performed with gadolinium contrast. Open temporalis muscle biopsy was performed. The sample underwent standard cryohistological studies as well as immunohistochemistry with antibodies against MHC-I and II, CD3, CD4, CD19, CD68, anti-MAC, p62 and MxA. Testing for auto-antibodies was based on immunoblots or ELISA. RT-PCR for SARS-CoV-2 was run with RNA extracted from cryopreserved muscle.

Results. A Caucasian woman in her 60s with no history of autoimmune or muscle complaints developed swelling and pain of the right jaw musculature five days after testing positive for SARS-CoV-2 due to respiratory tract symptoms. In addition, she experienced trismus, but no further neuromuscular complaints. The course of respiratory tract symptoms stayed mild. She had been vaccinated previously with single shot SARS-CoV-2 vector vaccine. Due to persistent swelling and complaints, giant cells arteritis was excluded by unresponsiveness to five days oral steroids and sonography of the temporal artery. Cranial MRI was performed nearly four weeks after the SARS-CoV-2 infection and showed marked swelling and oedema of the temporalis muscle. Its biopsy showed numerous CD68 and acid phosphatase positive cells infiltrating from perimysial perivascular foci towards the endomysium with perimysial damage but little damage of adjacent, perifascicular muscle fibres. Muscle fibres did not react with anti-MHC-II, anti-MAC or -MxA. Capillaries did not react with anti-MAC or -MxA. SARS-CoV-2 RNA was not detected in muscle tissue. Serum creatine kinase was not elevated in the subacute phase. Slightly elevated ANA titre led to detection of autoantibodies against proliferating cell nuclear antigen (PCNA). No pathological results for other autoantibodies, including myositis-specific antibodies and anti-ds-DNA, were found in blood. Neither were antibodies against hepatitis C and B viruses. Retesting 15 weeks after infection, anti-PCNA immunoblot was still positive, but ELISA did not indicate a pathologic titre. The swelling, myalgia and trismus regressed spontaneously a month after onset, yet the latter still persists at the time of reporting.

Conclusion. Our case diverges from the majority of COVID-19 associated my-



P-57. Fig. 1. A. Flow diagram of study participants. **B.** Symptomology of COVID-19 infection in IIM prior to vaccination compared to BI. **C.** Symptomatology of COVID-19 infection prior to vaccination in IIMs compared to other SAIDs. **D.** Symptomatology prior to vaccination in IIMs compared to other HCs. IIMs: idiopathic inflammatory myopathies; SAIDs: systemic autoimmune inflammatory diseases; HCs: healthy controls; BI: vaccine breakthrough COVID-19 infections.

ositis reports in the unusual location of the focal myositis and the histopathological pattern of predominantly perimysial damage and histiocytic infiltration. It concurs with the literature as no SARS-CoV2 RNA could be detected in the muscle. Anti-PCNA is associated very rarely with myositis. Other associated disorder (systemic lupus erythematosus, chronic viral hepatitis B or C) were not found. Increased levels of autoantibodies are reported in COVID-19 and mostly attributed to loss of self-tolerance during the acute disease phase. Interestingly, the structural protein M of SARS-CoV-2 appears to interact notably with PCNA in infected cells. Still, the causal connection between the myositis and COVID-19 in this case is based on the close temporal association in the absence of alternative, competing explanations from the medical history and findings.

P-59

EXPERIENCES OF COVID19 DISEASE AND VACCINATION IN HUNGARIAN MYOSITIS PATIENTS: ANTI-JO-1 IS A RISK FACTOR FOR HOSPITALIZATION

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Background. Pandemic caused by severe acute respiratory syndrome coronavirus 2 (COVID19) raises a smash barrier for clinicians and patients since 2 years. Limited information is available on disease course after COVID19 infection or vaccination in patients with idiopathic inflammatory myopathies (IIM). Objectives: The primary goals of the current research were to assess frequency and outcome of COVID19 disease and to determine the vaccination rate and effect in our IIM cohort. Secondary objectives were to search for risk factors of infection, predictive factors of hospitalization and to assess incidence of pots-vaccination adverse events and breakthrough infections.
Methods. We identified the confirmed COVID19 positive patients and assessed disease course and outcome on 01/06/2021 in our cohort then patients were prospectively followed. Incidence and complications of infection and vaccination were determined by questionnaires and using the database. Anti-SARS-CoV-2 spike protein electrochemiluminescent immunoassay has been used to assess seroconversion. Disease activity was determined by physician global activity.
Results. A total of 176 patients were screened and 101 participated in the study. By 01/06/2021, the COVID infection rate was 34.7%, which was significantly higher than the national prevalence at that time (8.2%). A third of these infections occurred asymptomatically or mild, but 20% of the infected patients were hospitalized, one patient died. Longer disease duration (8.67 vs. 17.87 years; p=0.003) and higher incidence of anti-Jo-1 antibody (57% vs. 10%; p=0.018) were significantly associated with hospitalization. All patients became seropositive after COVID19 infection regardless of immunosuppressive therapy or symptoms severity, meanwhile 72.3% of patients became seropositive after vaccination. Different vaccines induced various titer of antibody against the spike protein. Significantly higher antibody titers was detected after Pfizer-BioNTech (177.1 U / ml vs. 81.1 U / ml; p=0.001) and numerically lower ones after AstraZeneca (45.05 U/ml vs. 126.93 U/ml p=0.054) vaccination compared to others. Patients receiving steroid therapy had significantly decreased post-vaccination antibody response compared to those without steroid treatment (94.03 U/ml vs. 165.6 U/ml; p=0.008). We did not found short term vaccine related major adverse events. Long term data by 15/02/2022 revealed more infections (42.57%), where anti-Jo1 positivity still showed significant association with hospitalization (50% vs. 9%; p=0.0103). Breakthrough infection was detected in 9,25 % of the vaccinated patients, which was significantly more often after Astra Zeneca vaccination (40 % vs. 7%, p=0.017). All the fatal (n=3) COVID infections occurred in patients with seronegativity to anti-spike protein regardless vaccination. We identified 7,4 % post vaccination disease relapse needing therapy changes and 24,7% new autoantibody positivity.
Conclusions. Based on our results, myositis may be associated with an increased risk of COVID19 disease. Independent risk factor for hospitalization for unvaccinated people is anti-Jo1 positivity. Anti-SARS-CoV2 vaccines are safe, tolerable, could prevent complicated infections and strongly recommended for IIM population. Further investigation is required to assess clinical significance of post-vaccination disease flare.

P-60

DERMATOMYOSITIS WITH SPECIFIC AUTOANTIBODIES APPEARING AFTER SARS-COV-2 INFECTION OR MRNA VACCINATION: HINTS AT A SHARED PATHOGENETIC MECHANISM

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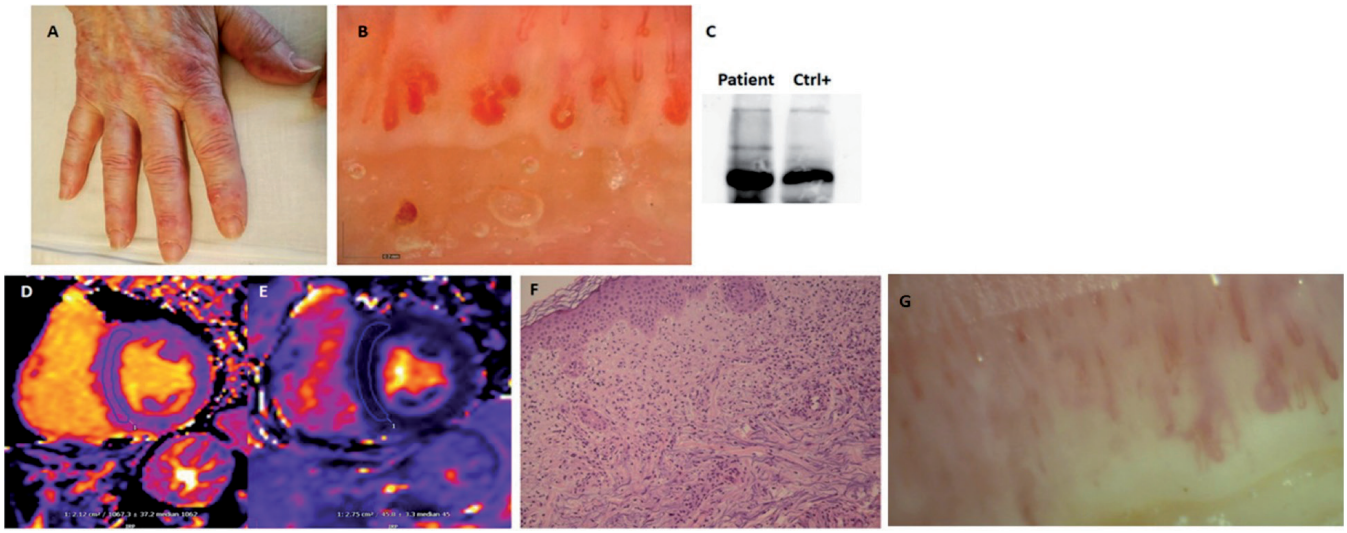
Background. Environmental factors such as infections and vaccines are known to trigger dermatomyositis (DM), and during the recent SARS-CoV-2 pandemic this has become even clearer. SARS-CoV-2 infection may share features with anti-MDA5 DM, such as rapidly progressive lung involvement, cutaneous lesions and cytokine release syndrome. A few case reports of DM following SARS-CoV-2 vaccination have been published, suggesting the onset of an aberrant immune response leading to DM with specific autoantibody signatures and severe organ impairment.
Methods. Clinical and laboratory data of the 2 case reports were obtained from electronic clinical charts in Humanitas Research Hospital (Rozzano, Milan, Italy). Autoantibody analysis was performed by protein-immunoprecipitation for anti-MDA5 and immunoblot for anti-Ro52 and TIF1gamma antibodies as per protocol.



P-60. Fig. 1. Manifestations of SARS-CoV-2 associated DM case reports.
Case report 1 (anti-MDA5 DM) panels A-F. *Panel A*: cutaneous manifestations of DM: violaceous, maculo-papular lesions on both dorsal and volar sides. *Panel B*: nailfold videocapillaroscopy showing reduced capillary density, neoangiogenesis, tortuos, ectasic and giant capillaries. *Panel C*: anti-MDA5 antibodies detected by protein-immunoprecipitation. *Panel D and E*: T1-weighted cardiac magnetic resonance images showing increased signal intensity [native T1=1067±37msec (NV<1015)], which, in association with ECV=30±4% (NV<29) and normal T2 intensity [native T2=46±3 msec (NV<50)], indicate interstitial myocardial fibrosis and are consistent with previous myocarditis. *Panel F*. Skin punch biopsy of a Gottron-like lesion on the left hand showing patchy mixed superficial inflammatory infiltrated with leukocytoclastic vasculitis features (EE 20X).
Case report 2 (anti-TIF1gamma DM) *Panel G*: nailfold videocapillaroscopy showing neoangiogenesis, giant capillaries and avascular areas.

Results. Case report 1 is a 71-year-old woman who developed fever, cough, and anosmia, which resolved spontaneously in two weeks, but did not undergo a nasopharyngeal swab, while her relatives were diagnosed with SARS-CoV-2 infection. When symptoms improved, she developed arthralgia and skin lesions on her face, chest, and hands for which she started topical treatment, with negative SARS-CoV-2 nasopharyngeal swab and positive serum test for IgG against SARS-CoV-2 spike protein. For the persistence of the skin rash and arthralgia, she was admitted to our Department in March 2021. Blood tests showed mild elevation of C reactive protein (2.1 mg/L –normal value NV<5), aspartate (84 UI/L) and alanine aminotransferase (133 UI/L –NV<35), ferritin (595 ng/ml –NV<306), troponin I (19 ng/L –NV<14), and BNP (251 pg/ml –NV<100) with normal complete blood cell count, creatine kinase, C3 and C4. IgG antibodies for SARS-CoV-2 spike protein were confirmed to be elevated (96 AU/ml –NV<15). Autoantibodies associated with connective tissue diseases were tested and only anti-MDA5 antibodies were positive at immunoprecipitation. A punch biopsy of a Gottron-like lesion on the left hand showed leukocytoclastic vasculitis. We observed reduced capillary density with neoangiogenesis and ectasic capillaries at the nailfold capillaroscopy. EKG and ecocardiography were normal, while cardiac magnetic resonance detected abnormalities in the parametric sequences, consistent with signs of previous myocarditis. A lung CT scan revealed pulmonary emphysema while respiratory function tests demonstrated reduced volumes (FVC 82%, FEV1 64%, inadequate compliance CO diffusion test). Based on the biochemical and clinical findings, a diagnosis of anti-MDA5-associated DM with skin and heart involvement was made and treatment with low-dose methylprednisolone (0.25 mg/kg daily) and azathioprine 100 mg was started, then switched to mycophenolate because not effective on skin lesions. Case report 2 is an 84-year-old woman with history of colon cancer (surgical treatment) and oral lichen treated with low doses steroids in the last 2 years. After the 2nd dose of SARS-CoV-2 mRNA vaccination, in March 2021 she developed skin rash with V-sign, Gottron's papules, periungueal ulcers, muscle weakness and fatigue, thus she performed a rheumatologic evaluation. Blood tests showed mild elevation of creatine kinase (484 UI/L, NV <167), CK-MB (9.6ng/ml, NV <3.4), BNP (215 pg/ml –NV<100) with normal values of complete blood cell count, C3 and C4. Anti-Ro52kDa and TIF1gamma were positive at immunoblot, thus we confirmed a diagnosis of DM. The clinical evaluation also showed active scleroderma pattern at nailfold capillaroscopy, normal echocardiography, bronchiectasia but not interstitial lung disease at lung CT, and normal respiratory function tests (FVC 99%, FEV1 99%, DLCO 63%, DLCO/VA 81%). A PET-CT scan was performed to exclude paraneoplastic DM, and treatment with steroids and mycophenolate was started.
Conclusions. SARS-CoV-2 may induce mechanisms for escaping the innate immunity surveillance and causing autoimmune diseases, but more clinical and functional studies are needed to demonstrate this possible association.

P-61

CHANGES IN JUVENILE DERMATOMYOSITIS AFTER THE COVID-19 PANDEMIC

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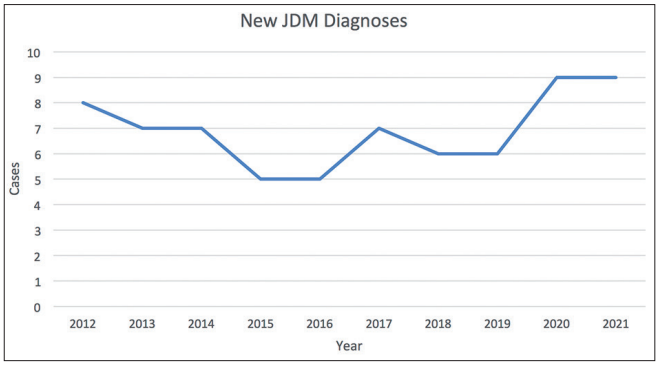
Background. Prior research has shown that viruses may trigger JDM, although the degree to which COVID-19 may serve as a trigger for JDM remains unknown. We present two case reports of JDM occurring after COVID-19 infection. We also provide case numbers of new JDM diagnoses pre-and post-COVID-19 as well as an analysis of JDM population characteristics pre-and post-COVID-19. A 5year-old female developed upper respiratory infection (URI) symptoms and was diagnosed with COVID-19 in December of 2020. She developed Gottron's sign, heliotrope rash, and weakness resulting in admission in February of 2021. She had elevated CK, AST, ALT, LDH, and aldolase. Her CMAS (childhood myositis assessment scale) was 24. An MRI showed diffuse myositis. Myositis specific antibody (MSA) testing revealed a positive MJ antibody. She was diagnosed with JDM and started on steroids, methotrexate, hydroxychloroquine, and IVIG with improvement. The second patient was a 4year-old female who was diagnosed with COVID-19 in October 2020. In January 2021, she developed heliotrope rash and Gottron's papules. She developed decreased exercise tolerance in May 2021 found to have elevated Aldolase and LDH. Her CMAS was 34. An MRI showed diffuse myositis. MSA testing was significant for a positive P155/140 antibody. She was started on hydroxychloroquine, steroids, IVIG and methotrexate with improvement. Due to the aforementioned cases a retrospective analysis was performed assessing the characteristics of JDM pre-and post-COVID-19 at Lurie Children's Hospital.
Methods. The Cure JM biorepository houses clinical data, laboratory data, and patient samples obtained at the onset of JDM. The following information was obtained from newly diagnosed JDM patients: MSA, DAS (disease activity score), flow cytometry results, vWF antigen, neopterin, CMAS, capillary end row loop(ERL), LDH, Aldolase, ESR, CRP, IgG, complements, ANA, and age at diagnosis. We identified 10 patients with a diagnosis of JDM from January 1st 2020 - July 1st 2021 who were designated as the post-COVID-19 group. This population was compared to a total of 51 patients diagnosed with JDM between Jan 1st 2010 and December 31st 2019 who were designated as the pre-COVID-19 group. Data analysis was performed using Welch T-testing. Research enrollment was impacted due to the COVID-19 pandemic. To better assess JDM rates, chart review and EMR reports were obtained to determine the total number of JDM diagnoses.
Results. T-testing showed no significant change in DAS, ERL count, T or B cell flow cytometry, vWF antigen, CK, CMAS, CRP, Aldolase, LDH, IgG, complements or ANA titer between the pre-and post-COVID-19 JDM groups. The analysis showed a significant change in NK cell population with a decrease in the absolute NK cell number (pre 163, post 90.75. P value 0.03), and NK cell percentage (pre 6.6%, post 3.625%, P value 0.008). Both of the patients presented in this case report showed a low NK cell number (1% and 3% respectively). The total number of new JDM cases rose from an average of 6.3 cases per year to an average 9 cases per year from January 1st 2020 to December 31st 2021.
Conclusion. This study provides two case reports of COVID-19 likely triggering JDM. This study also shows a modest increase in the number of new JDM cases since the onset of the pandemic. Interestingly, the NK cell population in the post-COVID-19 JDM patients were significantly decreased. NK cells have multiple roles in not only immune regulation, but also the immune response to viruses. This study suggests that NK cells play a role in the development of in virally mediated JDM, specifically in cases triggered by COVID-19. Future studies will be important to further delineate the function of NK cells in these patients. Markers of JDM disease severity, including DAS, Neopterin, CK, and CMAS, did not significantly change in our institution's JDM population after the onset of the COVID-19 pandemic.
Acknowledgements. This work is supported our donors and the Cure JM foundation through use of the Cure JM Biorepository.



P-61. Fig. 1.

P-62

MENTAL HEALTH ISSUES AND LIFE CONDITIONS OF ADOLESCENTS WITH JUVENILE DERMATOMYOSITIS AND OTHER AUTOIMMUNE RHEUMATIC DISEASES DURING COVID-19 QUARANTINE

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Background. Autoimmune rheumatic diseases (ARD) include various chronic conditions with high morbidity and mortality rates, and an increased risk of infections, including the new COVID-19. It is possible that adolescents with ARD have higher levels of psychological distress which may affect their mental health and life conditions. The objectives were to assess mental health and life conditions in adolescents with autoimmune rheumatic diseases (ARD) and healthy controls in social isolation, emphasizing some demographic aspects and daily routine of adolescents with juvenile dermatomyositis (JDM) during the COVID-19 quarantine.
Methods. A cross-sectional study, performed from July 2020 to October 2020, included 155 ARD adolescents and 105 healthy controls. Online survey composed by self-reported strengths and difficulties questionnaire (SDQ) and a semi-structured questionnaire was filled in regarding demographic data, daily home and school routine, physical activities and COVID-19 information during the pandemic.

Results. The patients included in the study presented the following underlying diseases: 15% JDM, 29% juvenile systemic lupus erythematosus (JSLE) and 56% juvenile idiopathic arthritis (JIA). Among adolescents with JDM, 71% were female, 54% Caucasian and the median age was 14 years (range 10-18). Regarding school data, 92% JDM participants attended school before pandemic, 75% studied in public schools and up to 17% did not present home schooling during the quarantine. All JDM patients agreed with stay-home policy after pandemic outbreak, and they reported change in life routine (96%), sleep problems (29%), sleep after midnight (75%) and increased screen time (87%). Worsening of family financial situation (37%) and increased family violence (8%) were also observed. Concerning mental health assessment, it was verified that one third of JDM subjects presented abnormal total difficulties and emotional scores of SDQ. No differences were found regarding sex, ethnicity and current age between ARD patients and controls ($p>0.05$). The frequencies of abnormal SDQ total (32% vs. 32%, $p=0.901$) and emotional (38% vs. 35%, $p=0.653$) were similar in both groups. Logistic regression analyses in ARD patients demonstrated that female (OR=2.4; 95%CI 1.0-6.0; $p=0.044$) was associated with severe emotional SDQ dysfunction, whereas poor sleep quality was considered risk factor for both worse total SDQ (OR 2.6; 95% CI 1.2-5.5; $p=0.009$) and emotional SDQ scores (OR=4.6; 95%CI 2.2-9.7; $p<0.001$). Comparisons between ARD patients with and without current prednisone use showed higher median scores of peer problems in the first group [3(0-10) vs. 2(0-7), $p=0.049$]. The median and frequencies of SDQ scores and domains were similar between JDM, JSLE and JIA ($p>0.05$).
Conclusions. Approximately one third of JDM, JSLE and JIA patients presented abnormal total difficulties and emotional scores of SDQ. Female sex and poor sleep quality were the main factor associated with emotional impact in these ARD adolescents.
Acknowledgements. Our gratitude to Ulysses Doria-Filho for the statistical analysis support. We would like to recognize the work of Lívia M. Lindoso, Debora N. D. Setoue, Nicolas Y. Tanigava, Alberto C. Helito, Camilla A. A. Pedroso, Sofia M. Sieczkowska, Caio B. Casella, Guilherme V. Polanczyk, Dandara C. C. Lima, Lorena V. M. Martiniano, Luana C. A. Miranda, Moisés F. Laurentino, Sofia S. M. Lavorato, Deborah F. P. Roz, Ligia P. Saccani, Amanda Y. Iraha, Bruna C. Mazzolani, Claudia R. P. Santos, Claudia B. Fonseca, Fabiana I. Smaira, Hamilton Roschel, Helena T. Miyatani, Isabela G. Marques, Jane Oba, Juliana C. O. Ferreira, Luiz E. V. Silva, Neusa K. Sakita, Louise Cominato, Patrícia Palmeira, Paulo R. A. Pereira, Ruth R. Franco, Simone S. Angelo, Tamires M. Bernardes, Tathiane C. Franco, Vera P. M. F. R. Barros, Yingying Zheng.

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PATIENTS WITH MYOSITIS CONTRACT SARS-COV2 INFECTION: TWO DIFFERENT CASES

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Background. Mortality risk of the COVID-19 is marked elevated in high-risk patients. In our series of 78 patients with inflammatory myopathies (IIM), we documented two patients who died after being infected with SARS-CoV2: we here describe our experience in these unfortunate cases.
Case 1: A 45-years-old Caucasian man was diagnosed with PM in 2012 and was treated with prednisone (PDN) associated with intravenous (IVIg) and subcutaneous (SCIg) immunoglobulin. In January 2020, when in remission with a low-dose PDN, he performed a routine control, including a completely negative echocardiogram. In March 2020, he presented with fever and headache from occult SARS-CoV2 infection. Although myositis was in remission, and home treatment had given him with paracetamol and NSAIDs, after two days he had a sudden death. The cause was an acute myocardial ischemia in COVID-19 interstitial pneumonia revealed by autopsy investigation.
Case 2: An 87-years-old Caucasian woman came to our attention with severe-onset PM in 2017. She responded well at treatment with high-dose IVIg, PDN and methotrexate. In April 2020, she presented with SARS-CoV2 infection, who slowly complicated with an interstitial lung disease until the death due to respiratory failure 25 days after the COVID-19 infection.
Conclusions. The two cases are opposite: the man, who had an acute thrombotic event during SARS-CoV2 infection, was in remission since 2012 and he did not have comorbidities. Unlikely, the woman, who had respiratory failure, was a high-risk patient due to old age, high cardiovascular risk, chronic obstructive pulmonary disease (COPD) and intraductal papillary mucinous neoplasms.

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ASYMPTOMATIC SARS-COV-2 INFECTION IN PEDIATRIC PATIENTS WITH JUVENILE DERMATOMYOSITIS AND OTHER RHEUMATIC DISEASES OF ONE TERTIARY REFERRAL HOSPITAL

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Background. Several studies and cohorts with adult populations with rheumatic diseases (RD) were performed since pandemic outbreak. RD patients were more susceptible to infections and may develop severe forms of COVID-19, since they present immunosuppressive mechanisms inherent to the disease itself and to its treatment. Healthy children and adolescents seem to be less infected and present milder diseases. However, juvenile dermatomyositis patiets and immunosuppressed children have not been extensively studied. The objectives of the study are to evaluate asymptomatic SARS-CoV-2 infection in pediatric RD patients, to identify the risk factors related to contagion and to describe demographics and the profile of COVID-19 in juvenile dermatomyositis (JDM) patients followed.
Methods. A cross-sectional study was conducted in March 2021, including 77 pediatric RD patients followed at a Brazilian tertiary hospital and 45 healthy controls. Data was obtained through a questionnaire applied to outpatients during the month of March 2021, before the vaccine, and contained demographic data, symptoms compatible with COVID-19 over the past year, and contact with people with confirmed COVID-19. Patients' medical records were reviewed to access data regarding disease and current medications. A qualitative immunochromatographic SARS-CoV-2 test was performed in all participants. All patients who were using rituximab or intravenous human immunoglobulin, or had symptoms of COVID-19, were excluded.
Results. Patients' group included 11 (14.3%) JDM patients, 31 (40.2%) JIA, 25 (32.4%) JSLE, six patients with vasculitis, two with SS, one MCTD and one with autoinflammatory syndrome. Patients and controls were similar in terms of female gender (70.1% vs. 57.8%, $p=0.173$), median age (14 vs. 13 years, $p=0.269$) and SARS-CoV-2 serology positivity (22% vs. 15.5%, $p=0.481$). 80.5% of rheumatic patients were in use of immunosuppressive drugs, 27.3% of them using corticosteroids, 33.3% in high doses, and 7.8% on immunobiologicals. No statistical differences were found between positive (n=17) and negative serology (n=60) patients regarding demographic/socioeconomic data, contact with people with confirmed COVID-19, use and number of immunosuppressive drugs, use and dose of corticosteroids, use of hydroxychloroquine and immunobiological drugs ($p>0.05$). Regarding the profile of JDM patients, 6/11 (54%) were female, the median age was 13 years (range 9-17) and 3/11 (27%) presented COVID-19 serology positivity. 2/11 were in immunosuppressive treatment, however none of them were in use of glucocorticoids and biologic agents.
Conclusions. Pediatric JDM and other rheumatic diseases patients were infected at the same rate as healthy ones. Neither the underlying pathology nor its treatment seemed to interfere with the contagion risk.

P-65

KAISER PERMANENT (KP) MID-ATLANTIC STATES (MAS) EXPERIENCE WITH COVID RELATED HOSPITAL ADMISSIONS IN ADULT PATIENTS WITH MYOSITIS

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Background. Myositis is a group of rare systemic disease and may be treated with immunosuppressives which increase the risk for poor outcome with the COVID19 pandemic. Patients with this condition may have higher rates of admission to the hospital.
Methods. KP is a health insurance plan and provides care to about 800 thousand people (including Medicare and Medicaid population) in Maryland, District of Columbia and Northern Virginia. As part of quality improvements, we randomly looked at 40 patients from our larger cohort with myositis who are diagnosed

and followed by a board-certified rheumatologist. We noted hospitalizations and Covid infection from March 1, 2020 to December 31, 2021.
Results. Of the 40 patients, 29 (72%) were female and 11 were male. 19 (47%) were Blacks, 18 whites (including 6 Latino), and 3 Asians. Age ranged from 25 to 80 years with a mean age of 59.6 years. 25 (62%) patients had Dermatomyositis, 14 had polymyositis and 1 was IBM. The mean age at diagnosis was 55.9 years (range 23-80 years). 12 (30%) had myositis specific antibodies (4 Jo-1, 4 Mi-2, 1 PL 7, 1 PL 12, 1 PL7 plus PL12, 1 TIF Gamma). 22 (55%) were negative. Six did not have antibody testing. During this time, 11 (27.5%) were admitted to the hospital, 2 patients tested positive for COVID 19. One tested positive in the hospital and was asymptomatic. The other person was admitted for symptomatic COVID 19 infection. Other reasons for admission were cardiac, pulmonary (non-covid 19 related), infections, Gastrointestinal issues (including GI bleeding). One admission was for accidental bleach ingestion, and one for psychiatric admission. Of these 40 patients, 38 (95%) patients have received the COVID vaccinations, one patient refused, and for one person we do not have any record of vaccination.
Conclusion. The admission rates to the hospital do appear to be higher for this group of patients with myositis, as is generally postulated. However, the reasons for admission were largely related to reasons other than COVID 19 infection and were related to general medical conditions.

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IMPACT OF SARS-COV-2 ON THE CLINICAL PRESENTATION OF JUVENILE IDIOPATHIC INFLAMMATORY MYOPATHIES

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Background. Viruses are thought to play a role in triggering juvenile idiopathic inflammatory myopathies (JIIM), which include juvenile dermatomyositis (JDM), juvenile polymyositis (JPM), and overlap myositis. There is growing evidence that infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can trigger autoimmune diseases in genetically susceptible individuals, including idiopathic inflammatory myopathies (IIM). Studies have shown similarities between SARS-CoV-2 infection and anti-melanoma differentiation-associated gene 5 (MDA5) antibody-related dermatomyositis, suggesting possible shared underlying autoimmune and/or inflammatory mechanisms. To date, there are few studies describing individual cases of JIIM following SARS-CoV-2 infection, and, to our knowledge, none have explored the effects of SARS-CoV-2 on the clinical presentation of JIIM. In this study, we aim to investigate the impact of SARS-CoV-2 on JIIM by comparing the onset of new JIIM cases, as well as clinical and laboratory characteristics at disease onset, in patients diagnosed before and after onset of the Coronavirus Disease 2019 pandemic (COVID 19).
Methods. Patients diagnosed with JIIM prior to age 19 at The Children's Hospital at Montefiore were eligible for study inclusion. Demographic, clinical, and laboratory data, as well as evidence of exposure to SARS-CoV-2, were collected retrospectively by manual chart review. Patients were grouped into pre-COVID 19 (defined as prior to January 1, 2020) and post-COVID 19 (defined as January 1, 2020, or later). Descriptive statistics were used to summarize each variable. Given the small sample size, non-parametric testing was performed using Fischer's exact test and Wilcoxon rank sum test.
Results. Forty-four patients were included in the analysis (Table I). Thirty-four patients (77.3%) were diagnosed pre-COVID 19 and ten patients (22.7%) were diagnosed post-COVID 19. Of the ten patients diagnosed post-COVID 19, five (50%) had known exposure to or infection with SARS-CoV-2. Patients diagnosed with JIIM post-COVID 19 were more likely to be of non-Hispanic Black or Asian descent (p=0.041), develop disease at an older age (p=0.009), and present with non-classic cutaneous manifestations (as opposed to classic findings of Gottron's papules/sign or Heliotrope rash) (p=0.031), despite similar frequencies of JDM versus overlap myositis. While presence of muscle weakness did not differ between the groups, patients diagnosed post-COVID 19 tended to have more severe weakness, though results were not statistically significant. Interestingly, despite delays to diagnosis reported during the pandemic, there was no difference between time from symptom onset to diagnosis.
Conclusion. This is the first study to explore the effects of SARS-CoV-2 on the clinical presentation of JIIM. In our center, we found that patients diagnosed with JIIM after COVID-19 were more likely to be racial minorities, older at onset, and present with non-classic cutaneous manifestations. While there were no significant differences in myositis specific or associated antibodies, patients diagnosed post-COVID 19 did not have complete autoantibody investigation performed at the time of this study. Clinicians should consider JIIM even in the absence of classic cutaneous manifestations, particularly in the post-COVID 19 era. Patients should be followed longitudinally to explore long-term impacts of SARS-CoV-2 on JIIM. Further investigation is warranted to identify the mechanisms by which SARS-CoV-2 impacts JIIM and how these differ from the effects of other viruses.

Skin in myositis

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PATIENT-REPORTED OUTCOMES AND BIOMARKERS ASSOCIATED WITH THE CUTANEOUS DERMATOMYOSITIS DISEASE AREA AND SEVERITY INDEX ACTIVITY SCORE (CDASI-A) IN A PHASE 2 CLINICAL TRIAL OF LENABASUM IN DERMATOMYOSITIS (DM)

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Background. Retrospective reviews of clinical databases from two sites have identified strong relationships between patient-reported outcomes and skin activity in DM, as measured by CDASI-A. No studies validate these associations in a controlled setting. Additionally, the relationship between the Patient Reported Outcomes Measurement Information System-29 (PROMIS) Short Form and skin activity in DM has not been assessed. Previous investigations have demonstrated a correlation between IL-31 and itch in DM. IFN-β and IFN-γ are known type I and II interferons, which are critical drivers of DM pathogenesis. We assessed correlations between changes in CDASI-A, quality of life (QoL) outcomes, and biomarkers of disease activity in a double-blind, randomized, placebo-controlled clinical trial.
Methods. Data were retrospectively collected from five visits of a Phase 2 trial evaluating lenabasum, a cannabinoid receptor type 2 agonist, for treatment of DM. Quality of life assessments collected in the trial included Patient Global Assessment (PtGA) scores, PROMIS domains, and Skindex domains. Skindex question 10, regarding itch, was included as a separate domain. Physician Global Assessment scores were evaluated. Cytokines measured in skin samples using immunohistochemistry/polymerase chain reaction collected at baseline and week 12 were assessed for predictors of CDASI-A response and association with disease activity. Analyses used linear mixed effect models to account for within subject variability and repeated measures, where applicable. Analyses were performed without regard to treatment arm, to correlate CDASI, QoL, and biomarkers among all subjects.
Results. Clinical trial data from 22 subjects at 110 visits and cytokine data from pre- and end-of-treatment skin biopsies from 12 of these subjects were analyzed. Improvement in CDASI-A correlated with improvement in: Skindex Symptoms, Emotions, Function, and Itch domain scores; PtGA global disease activity, skin activity, pain, and itch scores; and Physician Global Assessments of overall disease activity, skin activity, and global skin scores, each p<0.001; and PROMIS Social Role domain, p=0.046. Improvement in CDASI-A correlated with reduction in IL-31 protein area (p=0.047). CDASI-A improvement also correlated with reduction in IFN-β (p=0.081) and IFN-γ (p=0.134) protein areas in skin biopsies, but $p > 0.05$. Surprisingly, improvement in CDASI-A correlated with increases in PROMIS fatigue (p=0.019) and pain (p<0.001) domain scores.
Conclusion. The results extend previous similar findings in observational databases and support the use of CDASI-A as an efficacy outcome in DM clinical trials that reflects both physician- and patient-assessed changes in skin disease. These results show for the first time in a clinical study that changes in CDASI-A correlate with Skindex domain and PtGA scores, all well-established measures of QoL in DM patients. However, improvement CDASI-A did not correlate well with improvement in overall physical function and symptoms measured using PROMIS-29 domains. This finding suggests, not unexpectedly, that changes in CDASI-A, a measure of skin disease activity in DM, may be more useful in clinical trials to reflect changes in skin-related QoL than overall QoL. The directionally correct correlations of change in CDASI-A with changes in IL-31, a cytokine previously associated with itch in DM, IFN-β, and IFN-γ support the role of these cytokines in the pathogenesis of skin disease in DM.
Acknowledgements. Funding was provided by the National Institute of Health [R21AR066286] and the United States Department of Veterans Affairs (Veterans Health Administration, Office of Research and Development and Biomedical Laboratory Research and Development). Corbus Pharmaceuticals were involved in the collection and management of data.

P-66. Table I. Presenting features in children with juvenile idiopathic inflammatory myopathies (JIIM) diagnosed prior to and after the onset of the COVID-19 pandemic (n=44).*

Variable	Total	Pre-pandemic (n=34)	Post-pandemic (n=10)	*p*-value
Diagnosis				>0.999
JDM	36 (82%)	28 (82%)	8 (80%)	
Overlap	8 (18%)	6 (18%)	2 (20%)	
Race				**0.041**
White	7 (16%)	7 (20%)	0	
Non-Hispanic Black	13 (29%)	8 (24%)	5 (50%)	
Hispanic	21 (48%)	18 (53%)	3 (30%)	
Asian	3 (7%)	1 (3%)	2 (20%)	
Sex				0.310
Female	38 (86%)	28 (82%)	10 (100%)	
Male	6 (14%)	6 (18%)	0	
Age at diagnosis (years)	8.1 [4.3, 12.5]	7.4 [4,10.6]	12.3 [8.9,18.4]	**0.009**
Time from symptom to diagnosis (months)	4 [2,8]	5 [2,9]	2.5 [2,6]	0.291
Delay to diagnosis > 6 months (n=38)	12 (32%)	10 (36%)	2 (20%)	0.453
Weakness ‡				0.684
None	6 (14%)	6 (18%)	0	
Mild	8 (18%)	6 (18%)	2 (20%)	
Mild/moderate	11 (25%)	9 (26%)	2 (20%)	
Moderate	8 (18%)	5 (14%)	3 (30%)	
Moderate/severe	5 (11%)	4 (12%)	1 (10%)	
Severe	6 (14%)	4 (12%)	2 (20%)	
Weakness				0.287
None, mild, mild/moderate	25 (57%)	21 (62%)	4 (40%)	
Moderate, moderate/severe, severe	19 (43%)	13 (38%)	6 (60%)	
CMAS (n=28)	39 [25,47.5]	39.5 [25,49]	37.5 [22,41]	0.457
Cutaneous manifestations †				**0.031**
Classic	32 (74%)	27 (82%)	5 (50%)	
Non-classic	6 (14%)	2 (6%)	4 (40%)	
None	5 (12%)	4 (12%)	1 (10%)	
Constitutional symptoms (n=38)	25 (66%)	17 (61%)	8 (80%)	0.441
Abnormal nailbed capillaries (n=39)	34 (87%)	26 (87%)	8 (89%)	>0.999
Cutaneous ulceration (n=39)	14 (36%)	12 (41%)	2 (20%)	0.279
Raynaud's (n=39)	8 (21%)	7 (24%)	1 (10%)	0.653
Arthritis (n=42)	16 (38%)	12 (38%)	4 (40%)	>0.999
Calcinosis (n=43)	7 (16%)	5 (15%)	2 (20%)	0.656
Lipodystrophy	2 (5%)	2 (6%)	0	>0.999
GI involvement	4 (9%)	4 (12%)	0	0.561
Cardiac involvement	2 (5%)	2 (6%)	0	>0.999
Pulmonary involvement	8 (19%)	8 (24%)	0	0.171
Abnormal muscle enzymes (n=41)	41 (98%)	31 (100%)	9 (90%)	0.238
Myositis Specific or Associated Autoantibodies				0.214
None	6 (14%)	4 (12%)	2 (20%)	
Anti-MDA5	9 (20%)	8 (24%)	1 (10%)	
Anti-p155/140	7 (16%)	7 (20%)	0	
Anti-MJ	7 (16%)	6 (18%)	1 (10%)	
Anti-Mi2	3 (7%)	1 (3%)	2 (20%)	
Anti-synthetase	2 (4%)	1 (3%)	1 (10%)	
Overlap**	10 (23%)	7 (20%)	3 (30%)	

Categorical values are represented as n (%), and continuous values as median [interquartile percentiles]

CMAS: childhood myositis assessment score, JDM: juvenile dermatomyositis, GI: gastrointestinal

* Presenting features defined as muscle weakness and rash at diagnostic clinical visit; all other clinical features defined as present within first 6 months of diagnosis

‡ Weakness defined by CMAS, with mild = 45-52, mild/moderate = 39-44, moderate = 30-38, moderate/severe = 16-29, severe = <15; subjective assessment used when CMAS unavailable

† Classic rash = Gottron's papules, Gottron's sign, Heliotrope rash; Non-classic cutaneous manifestations = malar or facial erythema, linear extensor erythema, V sign, Shawl sign, non-sun exposed erythema, extensive cutaneous erythema, livedo reticularis, mucus membrane lesions, Mechanic's hands, cuticular overgrowth, subcutaneous edema, panniculitis, alopecia

** Overlap = anti-Ro, anti-RNP, anti-PM/Scl

P-68

A CASE REPORT OF DIGITAL ISCHEMIA AS AN UNUSUAL MANIFESTATION OF ANTISYNTHETASE SYNDROME

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Background. antisynthetase syndrome (ASS) is a rare form of idiopathic inflammatory myopathy (IMM), characterized by positivity of autoantibodies against aminoacyl-tRNA synthetase associated with interstitial lung disease, Raynaud's phenomenon, arthritis, fever and mechanic's hands.
Case presentation: a 40-year-old Caucasian man came to our attention due to arthralgia, transient left eye's amaurosis and acral painful ischemic lesions appeared in the last few days. He suffered from ASS, treated with low-dose prednisone and azathioprine; other immunosuppressants, like methotrexate and mycophenolate mofetil, were poorly tolerated. Physical examination revealed low-grade fever, widespread synovitis, four-limb hyposthenia (MMT8 65/80), ischemic acral lesions in both hands; neurological tests were normal. Blood tests showed a marked increase in inflammatory parameters, while creatine kinase levels were in range. The patients underwent a whole-body CT scan, arterial doppler ultrasound and echocardiography, which ruled out inflammation of the large vessels, macroangiopathy or endocarditic vegetations. Nailfold capillaroscopy documented a characteristic pattern with decreased capillary density, giant and dilated capillaries with microhaemorrhages. Due to microcirculatory and joint active involvement in ASS, high dose intravenous glucocorticoids, acetylsalicylic acid and synthetic analogue of prostacyclin were started. The patient experienced rapid improvement in synovitis and the ischemic lesions presented progressive necrotic demarcation and recovered with good outcome. Although the muscle component was fairly controlled by azathioprine, it was decided to change immunosuppressive therapy with sodium mycophenolate, with clinical benefit.
Conclusions. there are few sporadic reports of digital ischemia during ASS in literature, but this may be considered as a rare manifestation of disease activity.

P-69

DEVELOPING CLASSIFICATION CRITERIA FOR SKIN-PREDOMINANT DERMATOMYOSITIS: REVIEWING THE PROCESS FROM THE DELPHI METHOD TO INTERNAL VALIDATION

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Background. The European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) classification criteria for the idiopathic inflammatory myopathies (IIM) can classify patients who present with cutaneous features of dermatomyositis (DM) (heliotrope rash, Göttron's sign, and Göttron's papules) as amyopathic DM. However, in a single-center retrospective study of prospectively collected skin variables conducted among established DM cases, 26% of patients fail the revised classification. Recognizing the need to improve on current criteria, international experts in the field of Rheumatologic Dermatology aimed to create a more inclusive validated classification criteria in skin-predominant dermatomyositis.
Methods. We performed an extensive literature search to analyze and compare current classification criteria in amyopathic DM and generate candidate items for consensus exercises. These items were subjected to several rounds of Delphi. Participants were asked to rate each candidate item in terms of its specificity in classifying DM via a web-based survey set, using a visual analogue scale. The median score of each item determined if it got retained, and a cutoff score was used to choose which item would move forward to the next round. There were nominal group discussions in between rounds to serve as checkpoints and to discuss items which failed to meet the cutoff score but deserved to be included in subsequent rounds. Several measurement properties were also assessed including the final purpose of the criteria set, population and disease characteristics of cases and controls for study entry, sources of samples, definition of criteria items, methods of item ranking and reduction, and consideration of criteria set validity against a comparator backdrop "gold standard" criteria. In addition, a single-center pilot validity testing was done to determine the prevalence of these items in a DM population.
Results. The Dermatomyositis Delphi Criteria Project created 22 provisional clinical and laboratory classification criteria after an extensive literature search, three rounds of consensus exercises and nominal group discussions. There were 22 resultant items grouped into categories of distribution (scalp, eyelid, nasolabial fold, V of neck, upper back in shawl, elbow/knee, and lateral upper thigh/hip), morphology (erythema to violaceous erythema, erythematous papules/plaques that are often flat-topped with or without scale over the dorsal metacarpophalangeal or interphalangeal joints, macular erythema over the dorsal metacarpophalangeal and interphalangeal joints, nailfold capillary loops by eye or microscopy, nailfold erythema, cuticular dystrophy, poikiloderma, lateral digit fissuring/hyperkeratosis/papules, linear extensor erythema of digits, erythematous palmar macules and papules), symptomatology (scalp pruritus, photosensitivity), and pathology/laboratory (interface dermatitis, increased dermal mucin, presence of DM-specific myositis antibodies). A pilot validity testing of these criteria items showed that nearly all items are prevalent among confirmed cases of DM in the patient database, and therefore have good face validity. These criteria are now being tested in an international case-control international validation study to create a combination of items that will define a more inclusive cohort of DM patients with skin-predominant disease. We are working with colleagues from the International Myositis Classification Criteria Project Steering Committee to externally validate these variables in a larger effort using data from a new set of cases and controls.
Conclusion. This project is a key step in the development of prospectively validated classification criteria that will create a more inclusive population of patients with DM for clinical research. Proper classification of patients with dermatomyositis is indispensable in the appropriate conduct of clinical and translational research in the field.
Acknowledgements. We would like to thank the members of the Skin Myositis Committee and the Rheumatologic Dermatology Society.

Imaging in myositis

P-70

POWER DOPPLER ULTRASONOGRAPHY FOR THE MONITORING OF PATIENTS AFFECTED BY IDIOPATHIC INFLAMMATORY MYOPATHIES

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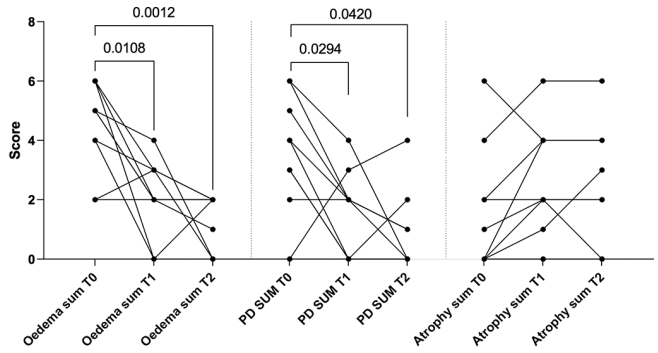
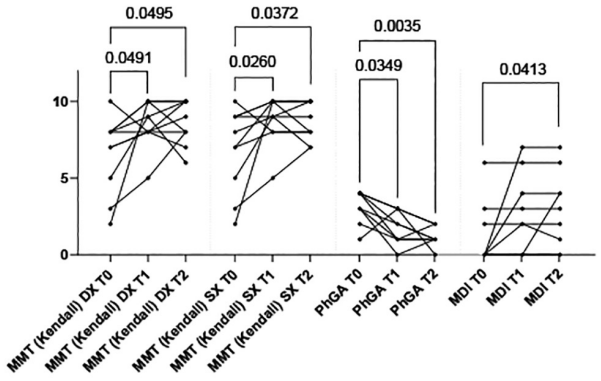
Background. No clear-cut guidelines exist about the use of imaging procedures for the diagnosis of idiopathic inflammatory myopathies (IIM). Similarly, conflicting, and scanty data exist about Power Doppler Ultrasonography (PDUS) in this subset of patients. In this regard, we recently proposed1 a 0-3 grey scale (GS) and Power Doppler (PD) score in a cohort of patients affected by IIM, evidencing a positive, statistically significant, correlation for PD and oedema and disease activity. Similarly, a good diagnostic accuracy was evidenced for this procedure when IIM patients were compared with a control group. Thus, due to the potential role of PDUS in monitoring of IIM, we aimed to assess whether this procedure may be useful not only at diagnosis but also during follow-up. The aim of this study was to assess the diagnostic accuracy of our score in IIM patients compared to a control group.
Methods. All patients evaluated from July 2020 to December 2021 in Vasculitis and Myositis clinic, Rheumatology Unit, University of Siena, with a recent diagnosis of IIM, as well as patients with a previous, definite diagnosis of IIM and evaluated during follow-up or referred from other centres for a second opinion, were prospectively enrolled. All patients underwent US examination of both thighs in axial and longitudinal scans.
Results. Forty-five IIM patients (median age, IQR 55 (45-66) years; 35 female and 12 male) were enrolled. Eleven had a diagnosis of anti-synthetase syndrome, 20 of dermatomyositis, 12 of polymyositis and 2 of scleromyositis. During the observational period, eleven patients underwent PDUS at baseline and during T1 (2.2±2.5 months) and T2 (7.8±4.3 months) follow-up period. Oedema and PD sum was significantly decreased during follow-up evaluation (Figure 1a). Oedema sum was lower at T1 (p=0.0108) and T2 (p=0.0012) compared to T0 values. Similarly, PD was lower at T1 (p=0.0294) and T2 (p=0.0420) compared to T0 values. PhGA values decreased during follow-up at T1 (p=0.0349) and T2 (p=0.0035) compared to those at baseline (figure 1b). Conversely, MMT DX and SX values increased at T1 (DX: p=0.0491 and SX: p=0.00260) and T2 (DX:

p=0.0495 and p=0.0.372) compared to those at baseline. MDI scores increased at T2 compared to T0 (p=0.0413), as well. Assessing the variation rate (delta) between T2-T0 of each clinical variable, a correlation analysis was performed (Figure 1c). ΔPhGA was directly correlated with ΔOedema sum (r=0.909, p=0.001) and ΔPD sum (r=0.844, p=0.003). While ΔPhGA was inversely correlated with ΔMMT-DX and ΔMMT-SX (r=-0.772, p=0.011 and r=-0.674, p=0.037, respectively). Moreover, ΔMMT-DX and ΔMMT-SX were inversely correlated with ΔPD sum (r=-0.909, p<0.001 and r=-0.723, p=0.021, respectively).

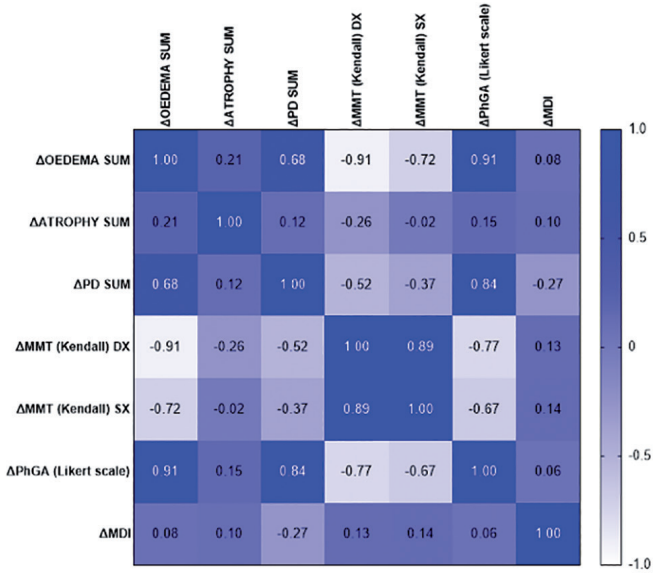
Discussion. Our findings show that PDUS is a reliable procedure also during the follow-up of patients affected by IIM. The reduction of disease activity, measured with PhGA, led to a concomitant decrease of both oedema and PD, which was directly correlated with their variation rate. This remarks the strict connection existing for clinical assessment and PDUS findings, not only at diagnosis but also during monitoring. Conversely, no statistically significant modifications occurred for atrophy, probably due to the reduced observational period; this also confirms the poor correlation, previously reported in our cohort, between muscle atrophy and disease activity.



P-70. Fig. 1. a



P-70. Fig. 1. b



P-70. Fig. 1. c

P-71

PRELIMINARY VALIDATION INTO THE DIAGNOSTIC EVALU-ATION OF PET-CT SCAN IN IDIOPATHIC INFLAMMATORY MYOPATHIES; A PILOT CROSS-SECTIONAL STUDY (MYO-PET)

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Background. Positron emission tomography (PET)-computed tomography (CT) scans are generally used in idiopathic inflammatory myositis (IIM) to exclude malignancy due to its high association in specific IIM subtypes. PET-CT scans are often not protocoled to look at the muscle. Magnetic resonance imaging (MRI) remains the most sensitive test to detect muscle inflammation. Our study aims to begin preliminary validation of PET-CT scan in IIM against commonly used clinical and imaging biomarkers.

Methods. Patients underwent assessment by clinical examination (manual muscle testing 26 scores [MMT 26]), laboratory testing (creatinine kinase and myositis serology), self-reported health assessment questionnaires (HAQ), and imaging (whole-body PET-CT scan and myositis-protocoled lower limb MRI). The SUVmax for four predetermined muscles (deltoid, biceps, gluteus, and quadriceps) and the two most FDG-avid muscles in the upper limbs and lower limbs were tabulated bilaterally and compared against a physiological baseline (the musculus longissimus thoraces [MLT]). PET findings were compared with patient, laboratory, and MRI findings.

Results. Ten patients with myositis were included in the study, 8 (80%) were males, and 2 (20%) were females. The median age was 67 (IQR: 61-72), CK was 972 (129-3538), MMT 26 was 239 (217-255), and HAQ was 1(0-2). Seven participants had necrotising autoimmune myopathy, one with dermatomyositis, one with polymyositis and one with granulomatous myositis. Half of the patients were seronegative. Fifty-four muscles (54/80, 67.5%) with FDG-avid uptake on PET also had muscle oedema on MRI. The median SUVmax of FDG-avid muscles was higher at 1.27 (CI: 1.28-1.63) when muscle oedema was present on MRI, compared to 0.96 (CI:0.83-1.08) when muscle oedema was absent on MRI (p<0.001). The mean SUVmax of 16 muscles showed no significant correlation with CK (r=0.467, p=0.174), MMT 26 (r=-0.192, p=0.620) and HAQ (r=-0.478, p=0.162).

Conclusion. PET-CT scan appears comparable to MRI when analysing muscle in IIM in most cases. This is a promising alternative when MRI scans are contraindicated or not available. Future studies could focus on comparative analysis with muscle biopsies, differentiating IIM phenotypes, and exploring visceral involvement.

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P-72

A COMPARISON STUDY OF DIFFERENT IMAGING TECHNOLOGIES IN INCLUSION BODY MYOSITIS

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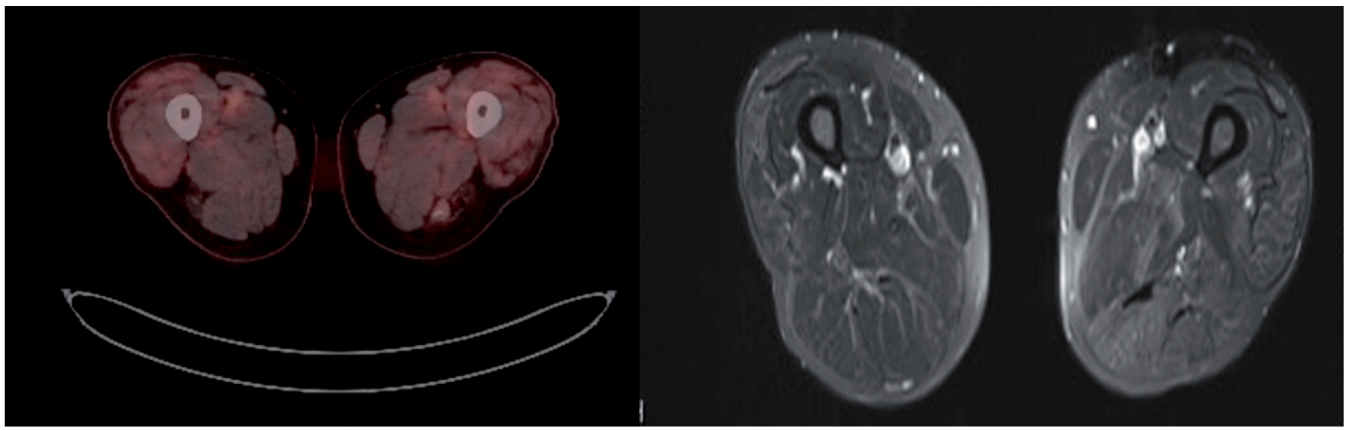
Background. Imaging studies such as EIM, QUS, and muscle MRI can reflect on muscle health and correlate well with clinical outcome measures of IBM. However, a direct comparison between these technologies is lacking.

Methods. We performed EIM scanning and ultrasound imaging of extremity muscles in patients with IBM. EIM parameters at 50kHz (EIM50) and the ratio of phase values at 50kHz and 211kHz (EIMPR) were recorded. We recorded grayscale levels (GSL) for muscles on ultrasound images, performed Z-score normalization for all parameter values, and compared qualitative assessment of MRI imaging to EIM and GSL.

Results. To date, we have recruited seven patients with IBM. All the subjects were men with an average age of 71.4±6.0 years. Clinical outcome measures showed an average IBM-FRS score of 26.7±5.5, 6-minute-walk test of 1030±186.4 feet, grip strength of 17.0±8.2 kg, and total manual muscle testing score of 138±9.6. Preliminary analysis revealed a strong correlation between the EIMPR and GSL values from the averaged lower extremity muscle groups (r = 0.812, p=0.027). We noted a moderate correlation between the EIM and QUS



P-71. Fig. 1. PET-CT scan showing mild diffuse FDG-avid uptake in the quadriceps (vastus lateralis and rectus femoris predominantly) with corresponding MRI showing muscle oedema in the vastus lateralis and rectus femoris in a 71-year-old man with chronic immune-mediated necrotising autoimmune myopathy.

parameters in the medial gastrocnemius. Only four patients had muscle MRI, and we noticed a trend between EIM50 phase value and fatty infiltration of muscles tissues on muscle MRI.
Conclusion. EIM and QUS parameters in IBM are related, and large-scale studies are warranted to validate the relationship between these technologies. These relatively cost-effective technologies may potentially serve as a surrogate for muscle MRI and monitor IBM progression in the clinic setting.

P-73

NAILFOLD VIDEO CAPILLAROSCOPY IN TIF GAMMA POSITIVE PATIENTS WITH AND WITHOUT CANCER

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Background/Purpose. The TIF gamma antibodies have been classified as a myositis-specific antibody and have been associated with dermatomyositis. It is present in 75% of patients with cancer associated dermatomyositis. Nailfold videocapillaroscopy (NVC) represents the best method to assess the microvascular abnormalities. A defined pattern on NVC has been reported in patients with dermatomyositis. This study thought to distinguish the NVC characteristics of TIF gamma positive with and without cancer to see if NVC findings will correlate with the severity of skin lesions and assess for any differences in patient with or without malignancy.
Methods. The NVC was performed in 8 consecutive anti TIF gamma positive patients; Capillaries parameters were scored as reported in literature. NVC were scored in all 8 patients. 5 patients TIF gamma positive without cancer were compared to 3 patients anti TIF gamma positive with cancer. Baseline clinical characteristics and serology were recorded in all patients.
Results. An abnormal pattern was noted in 7 patients. 1 patient treated with IVIG, in complete remission was noted with normal pattern. This later patient's NVC was reported abnormal on the initial presentation 3 years prior. There were no significant differences noted between the 2 groups. A specific pattern with extensive microhemorrhages rather than larger hemorrhages (noted in other scleroderma like diseases) was noted in 3 of 8 patients. 3 patients TIF gamma positive presented with Raynaud's. All patients had skin rash at the initial presentation and 7 patients TIF gamma had periungual erythema, none had mechanics hands. 3 had cancers. None had ILD.
Conclusion. an abnormal pattern on NVC is noted in all DM patients. Patients with vs without cancer do not seem to have a statistically significant different pattern but larger studies would provide better clarity.

Drug induced myositis

P-74

TOXICITY OF PRALSETINIB MIMICKING IDIOPATHIC INFLAMMATORY MYOPATHY

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Background. Pralsetinib (GAVRETO®) is a new kinase Inhibitor indicated for treatment of metastatic RET-mutant medullary thyroid. Pralsetinib toxicities are yet poorly reported. We report the case of a patient who has developed such a musculo-pulmonary toxicity mimicking an idiopathic inflammatory myopathy.
Method. To assess the probability of adverse drug reactions (ADR), we used the Naranjo ADR Probability Scale. To provide additional data, we performed a pharmacovigilance analysis on the World Health Organization global database of individual case safety reports, Vigibase.
Case presentation: A 76 years-old patient, without medical lung or muscular history, was followed over 35 years for medullary thyroid cancer (MTC). She was first treated by thyroidectomy until she relapsed as a subclavicular lymphadenopathy. Due to the presence of RET-mutation on a metastatic biopsy sample, she was treated by Vandetanib (CAPRELSA®) - a Tyrosine Kinase Inhibitor (TKI) - for 6 months. This treatment was switched to Pralsetinib because of the known risk of renal toxicity. Four weeks after the introduction of Pralsetinib, the patient was admitted in our institution for deterioration of her performance status with an increasing general weakness: the patient was complaining of an inability to stand up on her own. Blood analysis -performed at day 9 of the onset of symptoms- showed acute renal failure (serum creatinine= 209 µmol/L), liver cytolysis (aspartate aminotransferase (AST) and alanine aminotransferase (ALT) = 6 & 2 times the normal range (nr), respectively). It was associated with hypocalcemia (1,59 mmol/L) and hyperphosphatemia (1,98 mmol/L). Pralsetinib was immediately stopped. During her hospitalization, at day 12, she presented with fever and dyspnea (oxygen saturation = 89%) with diffuse crackles. A thoracic CT-scan showed ground-glass opacities mainly in the right lung associated with confluent micronodules in the right upper lobe, not identified on the thoracic CT-scan 3 months before. Bactarial or viral pneumonias were ruled out. Transthoracic-echocardiography did not show signs of heart failure. Although Natriuretic Peptides (BNP) was slightly increased, (to a maximum of 2551 ng/L), the patient was suspected of diffuse interstitial pneumonia. Concurrently, general weakness persisted, but no myalgia nor significant weakness (MRC muscle scale = 5) occurred. In contrast, creatine kinase reached 14 times nr. At this time, temporality and clinical features were suggestive of either Pralsetinib lung and muscle toxicities or an overlap myositis/a cancer-associated inflammatory myopathy. However, electromyogram did not show a myogenic pattern and muscle-MRI indicated no signs of inflammatory myopathy. Additionally, dyspnea and general weakness were regressive a month after treatment discontinuation. Thoracic CT-scan and creatine kinase normalized within 14 days. Indeed, with a 3 month follow-up (including thoracic CT-scan, PET-CT, abdominal and pelvic MRI-scan), the patient showed global stability under the previous TKI (Vandetanib). Finally, these latter events ruled out the diagnosis of inflammatory myopathy and Pralsetinb toxicity was established. The French cases reported on the WHO database related 3 cases of lung toxicity without muscular history. In addition, the ARROW phase 1/2 study of Pralsetinib reported dyspnea for 22% of the 138 patients included with CMT. Moreover, 42% had low grade musculoskeletal pain without any details on

the presence of rhabdomyolysis. The Naranjo ADR probability scale confirms an association between lung and muscle toxicities and Pralsetinib at probable level.
Conclusion. The patient had an unusual presentation of Pralsetinib toxicity, which was also evocative of an idiopathic inflammatory myopathy in the first place. Clinicians must be aware that in addition to previously reported lung toxicity, there are also specific muscle adverse events of Pralsetinib, i) mimicking inflammatory myopathy when associated together and ii) inviting all to perform dosage of creatine kinase.

P-75

IMMUNOGENETICS FEATURES OF DERMATOMYOSITIS-ASSOCIATED MALIGNANCIES

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Background. The development of immune checkpoint inhibitors (ICI) has reshaped the prognostic of several tumor types such as melanoma, non-small cell lung cancer, and others. Several response predictive biomarkers have been proposed such as high tumor mutational burden (TMB), PDL1 expression, or high tumor-infiltrating lymphocytes. As ICI works unleashing the immune system, its administration in patients with autoimmune diseases is a matter of concern because of the potential theoretical risk of exacerbated immune-adverse events. Considering the frequent co-occurrence of dermatomyositis (DM) and cancer, it is a clinical need to understand whether patients with cancer-associated DM (CADM) could be suitable for treatment with ICI. Our objective was to analyze the presence of those biomarkers in a series of patients with CADM and report the outcome of two DM patients treated with ICI.
Methods. We performed immunogenomics and immunophenotyping analyses to profile the tumors samples from 14 patients (9 females) diagnosed in our Centre with CADM during the last decade (2009-2021). Immunohistochemistry was used to assess TILs (markers FOXP3, CD3, CD4, CD8) and PD-L1 expression in 10 tumors. Whole-exome sequencing was performed in for the analysis of TMB. Clinical data and tumor response histories were evaluated in two patients treated with ICI.
Results. Immunophenotyping analysis showed high levels of TILs in 4 patients. High and moderate expression of PD-L1 protein were seen in one and two tumors, respectively, and one tumor showed high TMB (>10 muts/Mb). Two patients with paraneoplastic DM (one with high TMB and other with high PD-L1 expression) were treated with ICI (anti-PD1) with meaningful clinical improvement (progression-free survival of 12 and 20 months). None of these patients developed either immune adverse events or DM flare.
Conclusions. The results in this small series demonstrate that a previously unrecognized proportion of tumors from DM patients may have immune infiltration and high TMB, predictors of good response to ICI. Such features could be the molecular basis for the antitumor activity unleashed by ICI seen in the two treated patients.

P-76

ANTI-ACETYL CHOLINE RECEPTOR ANTIBODIES IN IMMUNE CHECKPOINT INHIBITOR-RELATED MYOSITIS: SPECIFIC CLINICAL PROFILE AND/OR RISK FACTORS?

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Background. Immune checkpoint inhibitor (ICI) had markedly changed the prognosis of many diseases during the last years. However, this treatment could induce serious side effects such as myocarditis, «myasthenia-like disease» and myositis. Anti-acetyl choline receptor antibodies (AchRab), which are highly associated with myasthenia Gravis, had been found in some patient's sera with ICI-related myositis. There clinical and prognostic signification are not clear. The purpose of this study is to describe clinical and biological characteristics of patients diagnosed with ICI-related myositis, with positive AchRab (Group1) and, to compare them to patients with negative AchRAb (Group 2).
Methods. It is a retrospective monocentric study that compares male patients with positif AchRab to négative ones, from 2018 to 2021. Myositis was diagnosed on histological data (10/12 cases) or the association of myalgia, elevated CPK, and electromyogram and muscle MRI features. Myasthenia was suspected in front of dysphonia or dysphagia or diplopia and/or ptosis. Myocarditis was defined as certain, presumed or possible according to clinical, biological and morphologic criteria (Bonaca MP 2019). AchRab and anti Musk antibodies were systematically investigated by ELISA routine.
Results. Twelve men were included. Mean age at diagnosis was 73 years (50-87). Patients were treated with Nivolumab (n=4), Nivolumab + Ipilimumab (n=3), Pembrolizumab (n=3), Cemiplimab (n=1) and Avelumab (n=1) for melanoma (n=9), cutaneous Squamous cell carcinoma (n=1=, renal cell carcinoma (n=1) and Merkel cell carcinoma (n=1). ICI's toxicity occurred between the first and the third course of the treatment with a mean period of three weeks (2-6). AchRab were positive in 5/12 patients. Anti Musk antibodies were always negative. In patients with AchRab group, 3/5 patients had myasthenia Gravis symptoms, none patient signaled fatigue, and a decrement pattern was observed in 1/5 case. AchRab were positive in two patients' sera before treatment with ICI. There was no significant difference between patients in group 1 and 2 in muscle involvment severity (median MRC score was 4 : (3-5) vs (3-5)), axial manifestations (2 cases vs 2) or CPK level (7 times vs 8 times, p=0,87). The Clinical manifestations related to Myasthenia Gravis were similar in the two groups : Dysphonia (2 case vs 2), dysphagia (2 case vs 3), diplopia (2 case vs 1) or ptosis (no case vs 3). Although myocarditis symptoms were more frequent in group 1 (3 case vs 1 case), prevalence of presumed and certain diagnosis was similar. (p=0,22). Admission to intensive care unit was more frequent in group 1 (4 cases vs 1) (p=0,07). Treatment was similar in both groups. ICI treatment has been stopped or suspended in all patients. Treatment by corticosteroids depended on disease severity (bolus methylprednisolone in 5 cases) even if AchRab were positif (n=3). Three patients received an immunomodulatory therapy: Two patients from group 1 (Abatacept or intravenous immunoglobulin therapy) and one from group 2 (intravenous immunoglobulin therapy). Mean duration corticosteroids therapy (median followup time of 255 days, 60-800) was similar in both groups : 3 months vs 3 (2-7). Two patients, recently treated, were in partial remission during corticosteroids tapering after one month of follow-up.
Conclusion. Positive AchRab is common in ICI-related myositis and must be systematically investigated. AchRab does not seem associated with a specific clinical, biological or prognostic profile, mainly in relation to associated myasthenia signs. Nevertheless, more studies are required to characterize the clinical profile of these patients in terms of severity, management and follow-up. Other specific antibodies observed in myasthenia Gravis must be investigated in particular those not routinely researched such as LRP4 antibodies. Positivity of AchRab in two cases before ICI treatment suggest the role of these antibodies in ICI-related myositis pathogenesis (Mammen AL, 2019).

P-77

DIAGNOSIS ACCURACY OF MUSCLE MRI FOR AUTOIMMUNE MYOPATHIES: MULTICENTRIC PROSPECTIVE STUDY (DARWIM)

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Introduction. Peripheral musculoskeletal signs are a common for seeing neurologists or rheumatologists. While autoimmune myopathy (IIM) is a rare disease, its diagnosis has important prognostic and therapeutic implications. Myositis are heterogeneous pathologies characterized by muscular impairment whose diagnosis is based on muscle biopsy (gold standard). Myositis-specific antibodies also play a decisive role in diagnosis but 30-40% of MAI are seronegative. The diagnostic contribution of other non-invasive tools remains poorly evaluated. This is the case of muscular MRI while it is widely used in routine. Objective: To determine the diagnostic accuracy of muscle MRI.
Methodology. Multicentre prospective study including adult patients with either (i) proximal motor deficiency with elevated creatine kinase enzymes or with specific myositis antibodies or (ii) erythema suggesting dermatomyositis and (iii) <3 years. The results of the muscular MRI of the 4 limbs (proximal and distal) and the limbs girdle were compared with those of the muscle biopsy. The 2 procedures were analyzed blindly by 2 pairs of experts. Myositis was defined clinico-histologically according to the ENMC criteria. MRI was considered positive if there were T2 STIR hypersignals in at least 2 muscle groups symmetrically.
Results. One hundred and forty-three patients were included and 25 excluded (wrongly included: n=12; biopsy not performed: n=5; incomplete MRI: n=8). Patients (n=118; female: 56.8%) had an average age of 52 [38 - 63] years. The motor deficit was 4 [3 - 4] on the MRC 5 scale and the creatine kinase level was 1456 [593 - 5756] U.I/L. Skin signs were present in 51 (43.2%) patients, and 39 (33.3%) had joint signs. Forty-three (36.4%) patients had myositis-specific antibodies. In 79 (66.9%) patients the diagnosis of myositis was retained. Thirty-

three (28%) patients were classified as dermatomyositis, 20 (16.9%) as auto-immune necrotizing myopathies, 18 (15.3%) as polymyositis, 6 (5.1%) as inclusion body myositis, and 2 (1.7%) non-specific myositis. Muscle MRI was positive in 70 (59.3%) patients, 63 (79.7%) patients in the myositis group and 7 (17.9%) patients in the myositis-free group. Of note 75 and 86 patients had at least one T2 hypersignal according to radiologist 1 and 2 respectively. Muscle MRI has a sensitivity of 79.7% [69.2 - 88.0] and a specificity of 82.1% [66.5 - 92.5] for myositis diagnosis. The positive predictive value is 90% [80.5 - 95.9], the negative predictive value is 66.7% [51.6 - 79.6]. The coefficient k of concordance for MRI is 0.79 [0.67 - 0.90] for the upper limbs and 0.79 [0.66 - 0.88] for the lower limbs. The coefficient k of concordance for histological myositis diagnosis is 0.77 [0.59 - 0.88].

Conclusion. This unique prospective study shows that muscular MRI is a powerful examination for the diagnosis of IIMs but the result must be interpreted with clinical-biological data to limit the risk of misdiagnosis.

P-78

USEFULNESS OF MUSCLE BIOPSY IN THE FOLLOW-UP OF PATIENTS WITH IMMUNE MEDIATED NECROTIZING MYOPATHY

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Background. Immune-mediated necrotizing myopathy (IMNM) is one of the most severe forms of inflammatory myopathy. It is characterized by severely elevated creatine kinase (CK) levels and muscle weakness. Anti-3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR) and anti-signal recognition protein (SRP) autoantibodies have been associated with IMNM. Muscle biopsy is the cornerstone of the diagnosis of IMNM showing as the most characteristic finding the presence of necrotic fibers. Other findings include sarcoplasmic p62 aggregation, presence of the membrane attack complex (MAC) in the sarcolemma and expression of major histocompatibility complex (MHC) class I in muscle fibers. Although the role of a first muscular biopsy for a correct diagnosis is well established, a second biopsy to monitor response to treatment is not usually performed. The aim of this study was to assess the usefulness of performing a second muscle biopsy in the follow up of anti-HMGCR positive IMNM to evaluate the response to the treatment.

P-78. Table I. Main features of the patients and muscle biopsy before and after treatment in 15 patients with HMGCR positive immune-mediated necrotizing myopathy.

Variables	First biopsy (n=15)	Second biopsy (n=12)
Age at diagnosis (years), mean ±SD	70.4 ± 6.6	71.6 ± 4.6
Sex (women), n (%)	4 (26.7%)	3 (25)
Treatment, n (%)		
- MTX	15 (100)	12 (100)
- Intravenous glucocorticoids	5 (33.3)	4 (33.3)
- Oral glucocorticoids	12 (80)	10 (83.3)
- IVIG	12 (80)	9 (75)
- RTX	1 (6.7)	1 (8.3)
Muscle biopsy findings		
Necrotic fibers		
- Presence	15 (100)	0
- Absence	0	12 (100)
- Not assessed	0	0
MHC-I expression		
- Positive	15 (100)	1 (8.3)
- Negative	0	8 (66.7)
- Not assessed	0	3 (25)
P62 expression		
- Positive	7 (46.7)	2 (16.7)
- Negative	1 (6.7)	3 (25)
- Not assessed	7 (46.7)	7 (58.3)
MAC expression in muscle fibers		
- Positive	7 (46.7)	3 (25)
- Negative	1 (6.7)	3 (25)
- Not assessed	7 (46.7)	6 (50)

IVIG: Intravenous immunoglulins; MAC: Membrane attack complex; MHC: Major histocompatibility complex; MTX: Methotrexate.

Methods. Patients consecutively diagnosed with statin induced IMNM at Karolinska University Hospital, Stockholm, Sweden, from January 2018 to November 2021, and followed for at least 3 months were included in this study. Clinical data were extracted retrospectively from SweMyoNet (Swedish myositis network register). All patients were tested for anti-HMGCR antibodies at diagnosis. All patients underwent a first muscular biopsy prior to the start of the treatment and the second biopsy was performed after 3-28 months. Percutaneous conchotome muscle biopsy was used as biopsy method. Muscle samples were obtained from tibialis anterior muscle and second biopsy was performed in the contralateral side. The samples were stained for Hematoxylin eosin, MHC class I, p62 and MAC. All muscle biopsies were examined by a single muscle pathologist.

Results. Fifteen anti-HMGCR positive patients with IMNM were included, mean age 70.4±6.6 years. All patients underwent a first muscle biopsy. Thirteen patients (86%) also underwent a second muscle biopsy after treatment. One of the biopsies was reported as non-conclusive and excluded from the study. Main data of our patients regarding general features, treatments and muscle biopsy can be seen in Table I. 13 of 15 patients achieved clinical remission after a mean time of 5.5±2.7 months. Time between the first and second biopsy varied between 3 and 28 months, with a mean of 15.8±9.3 months. In the first biopsy, all patients had presence of necrotic fibers and expression of MHC-I in muscle fibers. There was also positivity in most cases for p62 and MAC in the muscle fibers. Regarding the second biopsy findings, no sign of muscle fiber necrosis was found in any patient. Regarding immunohistochemical markers, MHC-I and p62 and MAC expression was lower in the second biopsy. We found good correlation between clinical outcome and second muscle biopsy.

Conclusion. In IMNM, performing a control biopsy during the follow-up can be useful to verify that there is an adequate response to the treatment based on the absence of muscle fiber necrosis.

P-79

ACHIEVING CLINICAL REMISSION IN ANTI-HMGCR POSITIVE IMMUNE-MEDIATED NECROTIZING MYOPATHY WITH A CORTICOSTEROID-FREE TREATMENT: REPORT FROM A SINGLE CENTER

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Background. Statin-induced immune mediated necrotizing myopathy (IMNM) is a recently identified rare autoimmune condition associated with anti-3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR) autoantibodies. This condition is characterized by progressive weakness of muscles leading to severe disability. As in other subgroups of myositis, treatment of Statin-induced IMNM includes high doses of glucocorticoids in combination with other immunosuppressive drugs, mainly methotrexate (MTX) or azathioprine. The effects are often disappointing on muscle strength. Side effects are commonly related to the high doses of glucocorticoids. Intravenous immunoglobulins (IVIG) have also proved to be effective in the treatment of IMNM. There have been some reports suggesting that clinical remission in IMNM can be achieved without the use of glucocorticoids, with treatment regimens based on the use of IVIG. The aim of this study was to compare the outcome of IMNM between patients treated with glucocorticoid-free protocols and patients receiving conventional immunosuppressive treatments, including glucocorticoids.

Methods. Patients consecutively diagnosed with statin induced IMNM at Karolinska University Hospital from January 2018 to November 2021 and followed for at least 3 months were included in this study. IMNM was diagnosed according to the definition of the European Neuromuscular International Workshop 2016 (1). Clinical data was extracted retrospectively from SweMyoNet (Swedish myositis network register) from time of diagnosis, after 3,6 and 12 months and then yearly, using validated outcome measures including a core set measure (CSM), patient and physician disease activity score, health assessment questionnaire, manual muscle test (MMT) in 8 muscle groups, serum levels of creatine kinase and an extra-muscular score. Based on the CSM a total improvement score (TIS) was calculated as proposed by 2016 ACR/EULAR Myositis Response Criteria for Minimal, Moderate, and Major Clinical Response in Adult Dermatomyositis and Polymyositis. Remission was defined as no disease activity by expert physicians. Treatment was assigned to the patients considering the current evidence and possible contraindications of the therapies available. In patients with signifi-

P-79. Table I. General features of 15 patients diagnosed with HMGCR positive immune-mediated necrotizing myopathy.

Variables	Total (n=15)	Gluco-corticoid group (n=12)	Gluco-corticoid-free group (n=3)	P (steroids vs steroid-free)
Age (years), mean ± SD	70.4 ± 6.6	71.3 ± 5.8	67 ± 9.5	0.33
Sex (women), n (%)	4 (26.7)	4 (33.3)	0	0.33
Mean time of follow up (months), mean ± SD	21.1 ± 12.4	24.7 ± 11.2	7 ± 4	**0.02***
Time from symptoms to diagnosis (months), mean ± SD	4.8 ± 3.4	4.3 ± 3	6.7 ± 5	0.3
Comorbidities (n, %)				
- HTA	10 (66.7)	8 (66.7)	2 (66.7)	1
- Diabetes mellitus	8 (53.3)	6 (50)	2 (66.7)	0.6
- Ischemic heart disease	6 (40)	5 (41.7)	1 (33.3)	0.79
Extramuscular manifestations, n(%)				
- Dysphagia	8 (53.3)	7 (58.3)	1 (33.3)	0.44
- Weight loss >10%	5 (33.3)	5 (41.7)	0	0.18
Presence of other autoantibodies, n(%)				
- Anti-Ro-52	2 (13.3)	2 (16.7)	0	
- Anti-Mi 2	1 (6.7)	1 (8.3)	0	
- Anti-SAE	1 (6.7)	0	1 (33.3)	
Analytical values at diagnosis, mean ± SD				
- CK (ukat/L)	121.5±125.1	143.9±129.9	32±42.4	**0.03***
- Myoglobin (ng/ml)	4029.3±3831.5	4972±3846	727±796	**0.03***
- LDH (ukat/L)	13.6±6.5	15.3 5.7	6.5±5	**0.048***
- Anti-HMGCR autoantibody titer	214±137	231±149	148±48.8	0.37
Treatments received, n (%)				
- Intravenous corticosteroids	5 (33.3)	5 (41.7)	0	0.17
- Oral GC // mean dose ± SD (mg/day)	12 (80) // 50.4±14.8	12 (100) // 50.4±14.8	0	**0.0001***
- MTX	15 (100)	12 (100)	3 (100)	1
- IVIG	12 (80)	9 (75)	3 (100)	0.33
- RTX	1 (6.7)	1 (8.3)	0	0.6
Muscle strength assessment				
- MMT-8 at diagnosis	60.9±12	59.5±8	66.3±23.7	0.46
- MMT-8 after remission	77±5.1	76.2±5.5	80±0	0.29
Remission				
- Patients achieving remission, n (%)	13 (86.7)	10 (83.3)	3 (100)	0.45
- Time from diagnosis to clinical remission (months), mean ± SD	5±2.7	5.5±3	3.5±0.5	0.28
- Time to CK normalization (months), mean ± SD	3.5±1.5	3.3±1.4	4.8±1.8	0.23

CK: Creatine kinase; GC: Glucocorticoids; HTA: Hypertension; IVIG: Intravenous immunoglobulins; LDH: Lactate dehydrogenase; MTX: Methotrexate; RTX: Rituximab Upper limit for analytical values were: CK <4.7 ukat/L for men and 3.5 ukat/L for women; LDH <4.2 ukat/L; Myoglobin <73 ng/ml and anti-HMGCR < 20; *: $p<0.05$.

cant comorbidities that limit the use of glucocorticoid treatment, through shared decision between the physician and the patient, a steroid-free regime was agreed.
Results. We included fifteen anti-HMGCR positive patients. The main features of the patients are summarized in Table I. Three patients (20%) received a glucocorticoid-free regimen based on MTX 15 to 20 mg/week in combination with IVIG 2g/kg every month for 3 months. The rest (n=12, 80%) received treatment with glucocorticoids in combination with MTX and/or IVIG at the same dose mentioned before. Major improvement according to the TIS was observed in 13 out of 15 patients after a median of 4 months. None of the patients who achieved low disease activity or remission presented flares of the disease during the follow-up. All 3 patients who did not receive glucocorticoids achieved low disease activity or remission after a median of 3.5 months. Two of the 12 patients receiving glucocorticoids did not achieve remission. There were no statistically significant differences regarding the time to remission or CK normalization between both groups. Two of the three patients who did not receive glucocorticoids had lower CK levels at time of diagnosis, which might indicate a milder disease when compared to the other group. However, there were no statistically significant differences regarding MMT-8 between groups at baseline.
Conclusion. Despite our limitations, in our series of patients with anti-HMGCR positive IMNM, we found that patients can achieve low disease activity/ remission without glucocorticoid treatment.

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P-80

18-FDG PET-CT DIAGNOSTIC VALUE IN IMMUNE CHECKPOINT INHIBITOR INDUCED MYOSITIS

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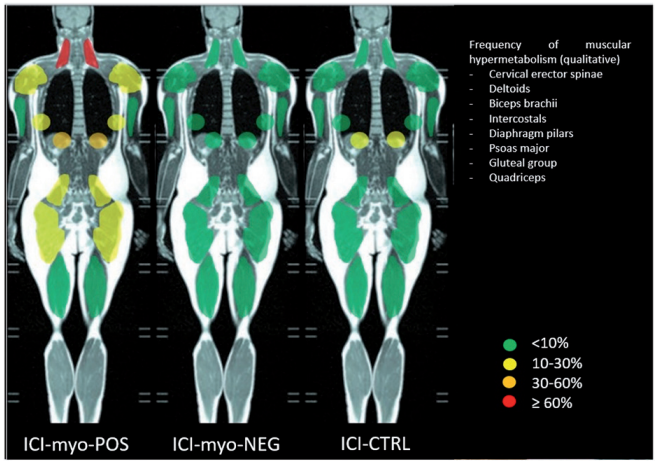
Introduction. Positron Emission Tomography (PET-CT) marked with 18-FDG is one of the key exams for assessing tumor mass and therapeutic response in oncology. Cancer treatment has been dramatically improved by immune checkpoint inhibitors (ICI) development. Among the immune-mediated side effects of ICI, muscle toxicity (ICI-myo-POS) has the highest mortality rate. Early management of this side effect determines the prognosis. The purpose of our study was to define the diagnostic value of PET-CT in ICI induced myositis.
Methods. In this retrospective monocentric study we compared the PET-CT of a group of ICI-myo-POS patients, defined by the presence of inflammation on the muscle biopsy (gold standard) to the PET-CT of patients with suspected ICI induced myositis ruled out by negative muscle biopsy (ICI-myo-NEG) and patients on ICI treatment without suspicion of myositis (ICI-CTRL). All PET-CT underwent single examinator second lecture blinded from diagnosis. Eight muscle groups (cervical erector spinae, deltoids, biceps brachii, intercostal muscles, diaphragm pillars, psoas major, gluteal group and quadriceps) were analysed bilaterally, qualitatively (visual evaluation) and then quantitatively (highest SUVmean, SUVmean normalized on the mediastinal vessels SUVmean). Qualitatively PET-CT was considered positive if there was at least one visually hyper-metabolic muscle group bilaterally. The highest SUVmean positivity threshold was defined by ROC curve using the Youden method.
Results. A total of 84 patients were analysed. In the group of suspected myositis (n=42), 28 patients were in the ICI-myo-POS group, 14 in the group ICI-myo-NEG. ICI-CTRL included 42 patients. Mean ages in ICI-myo-POS, ICI-myo-NEG and ICI-CTRL were respectively 66±15; 63±13 and 65±12 years. In ICI-myo-POS 68%. Anti PD1/PDL1 was the most represented therapy with 86% in ICI-myo-POS and ICI-myo-NEG groups (respectively n= 24 and n=12) and 100% in ICI-CTRL (n=42). Qualitative examination showed that 75% (n=27) of PET-CT were visually positive in the ICI-myo-POS group. Positivity in the control group was found in 7% (n=1) of ICI-myo-NEG and 19% (n=8) of ICI-CTRL with a significant difference between ICI-myo-POS vs controls ($p<0.0001$). In ICI-myo-POS patients, the most frequently hyper-metabolic muscles were the cervical erector spinae (64%, n=18) and diaphragm pilars (39%, n=11). In the controls (ICI-myo-NEG and ICI-CTRL) these same groups were represented but in lower proportion with cervical erector spinae in 7% (n=4) and diaphragm pilars in 7% (n=5). Sensitivity for ICI induced myositis diagnosis when a visual hypermetabolism was found (regarding all muscle groups) was 75%, Specificity was 84% ($p<0.0001$). Quantitatively the highest SUVmean of all muscular groups in ICI-myo-POS was 2.8 [2.2-3.4] and higher than controls (ICI-myo-NEG and ICI-CTRL) measured at 1.7 [1.3-2.2] with a significant difference ($p<0.0001$). Quantitatively PET-CT at the 2.3 threshold of highest SUVmean normalized had a Sensitivity of 75% and a Specificity of 80% for ICI induced myositis diagnosis.
Conclusion. PET CT seems to be a good examination to exclude ICI induced myositis diagnosis, both qualitatively and quantitatively, a visual hypermetabolism on the cervical erector spinae seems to be suggestive for this kind of myositis.



P-80. Fig. 1.

Juvenile Myositis / Juvenile to adult transition

P-81

KEY FEATURES FOR MORPHOLOGICAL CLASSIFICATION OF IDIOPATHIC INFLAMMATORY MYOPATHIES IN JUVENILE PATIENTS

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Background. In adult patients, the classification of idiopathic inflammatory myopathies (IIM) has been well described, and distinct morphological features have been associated with clinical subtypes and myositis specific autoantibodies (MSA). Although there are certain clinical and serological similarities, there may be important differences in pathogenesis of myositis between adults and children. In juvenile IIM, the classification and morphological characteristic features of distinct subgroups are not well-defined. New treatment strategies require a precise diagnosis of the subgroups in IIM, and, therefore knowledge about pathomorphology of juvenile IIM is warranted.

Methods. Muscle biopsies from 15 patients (mean age 8.9±4.6, range 3-19 years, 73% female) with IIM and 7 controls were analysed by standard methods, immunohistochemistry and transmission electron microscopy (TEM). Detailed clinical and laboratory data were accessed retrospectively.

Results. The leading clinical symptom was proximal muscle weakness and skin symptoms. Dermatomyositis (DM) was diagnosed in 9/15, antisynthetase syndrome (ASyS) in 4/15 and overlap-myositis (OM) in 2/15. Analysis of skeletal muscle tissues showed inflammatory cells and upregulation of MHC class I in all IIM-subtypes. Morphological key findings were COX-deficient fibres as a striking pathology in DM and perimysial alkaline phosphatase positivity in anti-Jo-1-ASyS. Vascular staining of the type 1 IFN-surrogate marker MxA correlated with endothelial tubuloreticular inclusions in both groups. None of these specific morphological findings were present in anti-PL7-ASyS or OM.

Conclusions. Morphological key features are helpful to discriminate IIM subtypes in juvenile patients underlining differences in their aetiopathogenesis and therefore individual and targeted therapeutic strategies may be applied to these children.

P-82

IMPROVEMENT IN DISEASE ACTIVITY IN REFRACTORY JUVENILE DERMATOMYOSITIS FOLLOWING ABATACEPT THERAPY: RESULTS OF THE ABATACEPT IN DERMATOMYOSITIS (AID) TRIAL

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Background/purpose. Insufficient data exist on the therapeutic potential of biologic agents in the treatment of refractory juvenile dermatomyositis (JDM). The aim of this study was to assess the safety and efficacy of weekly subcutaneous abatacept in patients with refractory JDM.

Methods. Ten patients of ≥7 years of age with refractory probable or definite JDM (inadequate response to corticosteroids and at least one other immune suppressive agent for ≥3 months) were enrolled in an open label trial to receive subcutaneous (SQ) abatacept weekly for 6 months (125 mg weekly for subjects weighing >50 kg or 87.5 mg weekly for subjects <50kg). Clinical response was assessed using the International Myositis Assessment and Clinical Studies Group (IMACS) Definition of Improvement (DOI) (primary endpoint, 24 weeks): 3 of any of the 6 core set measures (CSMs) improved by ≥20%, with no more than 2 CSMs worsening by >25% (worsening measures cannot include muscle strength). The Pediatric Rheumatology International Trial Organization (PRINTO) DOI and the American College of Rheumatology (ACR)- European League Against Rheumatism (EULAR) response criteria were also assessed as well as change in the CSMs. Patients not improved by ≥5% in the DOI at week 12 were offered an increase in abatacept dose (212.5 mg weekly for subjects weighing ≥50 kg or 137.5 mg weekly for subjects <50 kg). Muscle edema (STIR hyperintensity and percentage of compartment involvement using a 0-3 scale) for thigh Magnetic Resonance Imaging (MRI) was assessed by two radiologists blinded to clinical data and visit, at baseline and 24 weeks. IFN gene score was performed on RNA from whole blood by nanostring. Adverse events were evaluated using the NCI Common Terminology Criteria (CTCAE) version 5.0. Statistical analysis was conducted using SAS version 9.4. Differences in means between visits were evaluated for significance via longitudinal analysis by paired t-test.

Results. Ten refractory JDM patients (8 female, 8 Caucasians, 1 African-American, 1 Asian) with mean age 12.0 (range 7.0-17.0) years, mean weight 49.4 (25-83) kg at baseline and mean disease duration of 2.7 (0.7-5.3) years received study medication: 6 patients received 125.0 mg abatacept weekly and 4 patients 87.5 mg weekly. The dose of abatacept was increased to 212 mg at week 12 in one subject due to non-response. Five patients achieved DOI at week 12 and nine achieved DOI at week 24. Among them, 2 reached minimal improvement, 4 moderate, and 3 major improvement at week 24 by ACR-EULAR response criteria using IMACS CSMs, and 1 patient reached minimal, 1 moderate, and 7 patients had major improvement using PRINTO CSMs at week 24. All CSMs improved from baseline at weeks 12 and 24, except muscle enzymes (Table). Mean daily corticosteroid dose was 16.7 (6-30) mg at baseline and 10.2 (4-20) mg at 24 weeks (p=0.002), following a standardized tapering regimen. The mean MRI muscle edema score was 5.9 (0-12) at baseline and 2.6 (1.1-6.3) at week 24 (p<0.003). Six patients had down-trending IFN gene scores at week 24, although

P-82. Table I.

	W0 Mean (Std Dev)	W12 Mean (Std Dev)	Difference in Means (Relative % Change)	W0 vs. W12 *p* value	W24 Mean (Std Dev)	Difference in Means (Relative % Change)	W0 vs. W24 *p* value
Physician Global Activity (PGA), VAS*†	5.0 (1.0)	3.5 (1.2)	-1.5 (-30.0%)	0.001	2.6 (1.48)	-2.4 (-48.0%)	<0.0001
Patient/Parent Global Activity (PPGA), VAS*†	5.3 (1.2)	3.5 (1.8)	-1.7 (-34.0%)	0.001	2.3 (2.4)	-3.0 (-56.6%)	0.001
Manual Muscle Testing (MMT)*	121.8 (14.8)	135 (11.0)	13.2 (10.8%)	0.010	137.2 (10.7)	15.4 (12.6%)	0.001
Childhood Health Assessment Questionnaire (CHAQ)*†	1.84 (0.58)	1.16 (0.54)	-0.68 (37.0%)	0.003	0.88 (0.63)	-0.96 (-52.2%)	<0.0001
Muscle Enzymes / Upper Limit Normal*Δ	0.46 (0.59)	0.10 (0.77)	-0.36 (-78.3%)	0.131	0.25 (0.82)	-0.21 (-45.7%)	0.149
Physician Extramuscular Activity*	4.1 (1.5)	2.8 (1.4)	-1.3 (-31.7%)	0.015	2.4 (1.7)	-1.7 (-41.5%)	0.0002
Childhood Myositis Assessment Scale (CMAS)†	33.9 (9.5)	41.0 (6.9)	7.1 (20.9%)	0.020	44.2 (5.7)	10.3 (30.4%)	0.001
CHQ-PF50 Physical Summary Score (PhS)†	17.9 (12.6)	31.9 (12.9)	14 (78.2%)	0.009	37.3 (12.7)	19.4 (108.4%)	<0.0001
Disease Activity Score (DAS)†	14.0 (1.7)	11.65 (2.1)	-2.35 (-16.8%)	0.005	10.6 (2.8)	-3.4 (-24.4%)	0.001
MRI Score							
Total Muscle Edema (0-12)	5.9 (3.5)	NA	NA		2.6 (3.1)	-3.3 (-55.9%)	0.003

*IMACS, International Myositis Assessment & Clinical Studies Group.
†PRINTO, Pediatric Rheumatology International Trials Organization
ΔLog_2 Transformed
Abbreviations: W: week; Std Dev: standard deviation; VAS: visual analog scale.

they were not significantly changed overall. Eleven Grade 2 and 3 treatment-emergent adverse events were observed, including worsening ILD requiring hospitalization (1 subject), worsening calcinosis (in 2), compression fracture (1), febrile episodes (2) and skin infection, E. coli diarrhea, and urticaria (1 subject each). Four subjected developed a positive ANA and one positive anti-Ro autoantibodies.
Conclusions. In this investigational pilot study, treatment of patients with refractory JDM with abatacept resulted in lower disease activity, decreased muscle edema, and clinically significant responses in the majority of patients. Abatacept was generally well tolerated. These data suggest that abatacept may be beneficial in the treatment of refractory JDM, and a larger clinical trial is needed to further investigate its efficacy.
Acknowledgements. Patients and their families, Cure JM Foundation, Bristol Myers Squibb, IRP of NIH, NIEHS, NIAMS, including TIS of NIAMS.

P-83

ASSOCIATION OF NAILFOLD CAPILLARY END ROW LOOP (ERL) PATTERN AND MYOSITIS SPECIFIC ANTIBODIES IN JUVENILE DERMATOMYOSITIS

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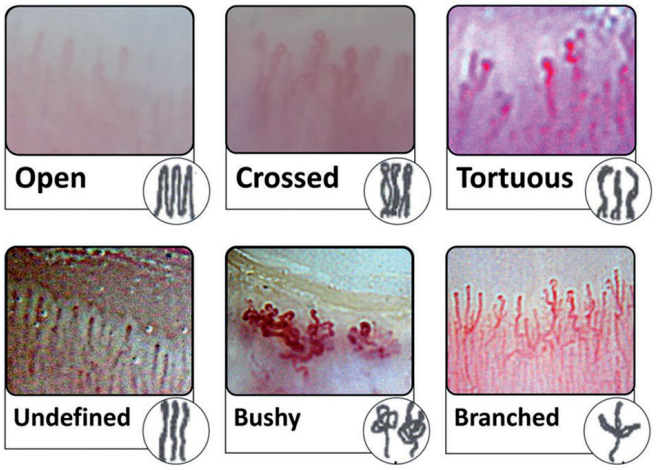
Background. Juvenile Dermatomyositis (JDM) is a pediatric autoimmune disease that affects both skin and muscle and is characterized by small vessel inflammation. Evidence of small vessel involvement is provided by the loss of nailfold capillary end row loops (ERL) which can be assessed by a capillaroscope at the patient bedside. In this study, we examined the association between various nailfold capillary patterns and JDM disease characteristics, such as duration of untreated disease, Myositis Specific Antibodies (MSA), and disease activity markers.
Methods. This is a retrospective chart review study (IRB# 2010-14117, 2011-14651) conducted at the Ann & Robert H. Lurie Children's Hospital of Chicago. We included all subjects with definite or probable JDM diagnosis based on Bohan and Peter criteria who had nailfold assessment prior to treatment, and who also had an up-to-date MSAs evaluation. Patients with overlap syndrome were excluded from the analysis. A digital camera (Nikon Coolpix p6000) equipped with a Dermlite2 ProHR provided standardized images of the periungual nailfold capillary for the 2nd-5th digits of both hands. ERL/mm was quantified by counting the number of end row capillary loops per 3mm section on each of the 8 fingers, dividing this by three, transforming this count into ERL/mm. The nailfold capillary pattern was assigned by a single observer for all the patients based on the most prominent shape (open, crossed, tortuous, bushy, branched and undefined) (Fig 1). MSAs were evaluated via immunoprecipitation and immunodiffusion by the Oklahoma Medical Research Foundation.
Results. 92 untreated children with definite/probable JDM (79% female, 76% Caucasian, 15% Hispanic, 3% Asian, 3% African American, 2% multiracial mean age of onset 6.8 +/- 3.8 years) were included in this study. Their initial nailfold capillary patterns were as follows: 41% open, 38% undefined, 12% crossed, 7% bushy, and 2% tortuous. Untreated Children with MSA P155/140 have more of their capillary end row loops that are open than the other MSAs (Chi-square *p*-value <0.0001). The undefined pattern was associated with the shorter duration of untreated disease (DUD) with a median of 3.6 months in comparison to crossed (median of 10.6 months) and open (median 5.8 months) and *p*-value of 0.036 by Kruskal-Wallis test. The undefined pattern was associated with the highest ERL capillary density with a median of 5.6 /mm in comparison to 3.8 /mm for the crossed group and 4.2/mm for the open group (*p*-value of 0.002 by Kruskal-Wallis test). Of note, 13% of the study groups had periungual hemorrhages on 1st nailfold assessment and that group was associated with more dysphagia on presentation (Chi-Square *p*-value 0.004). There was no association between the presence of periungual hemorrhages and MSA, DUD or disease activity markers.
Conclusions. Although ERL patterns did not predict disease severity, these patterns can provide useful clues to the clinician before more comprehensive laboratory results are available. For example, the presence of periungual hemorrhages in our study correlated with dysphagia. Therefore, the physician may want to consider obtaining a swallow study in that population. Of importance, the undefined pattern was associated with a shorter duration of untreated disease, which is an important indicator of disease outcome.
Acknowledgements. The authors like to acknowledge the CureJM Foundation's support of this study. The data in this project is entered in REDCap, which is supported by NUCATS, and funded in part by a Clinical and Translational Science Award (CTSA) grant from the National Institutes of Health (NIH), UL-1TR001422.



P-83. Fig. 1.

P-84

ASSOCIATION OF DECREASED NAILFOLD CAPILLARY END ROW LOOP (ERL) DENSITY AND DISEASE COURSE IN JUVENILE DERMATOMYOSITIS

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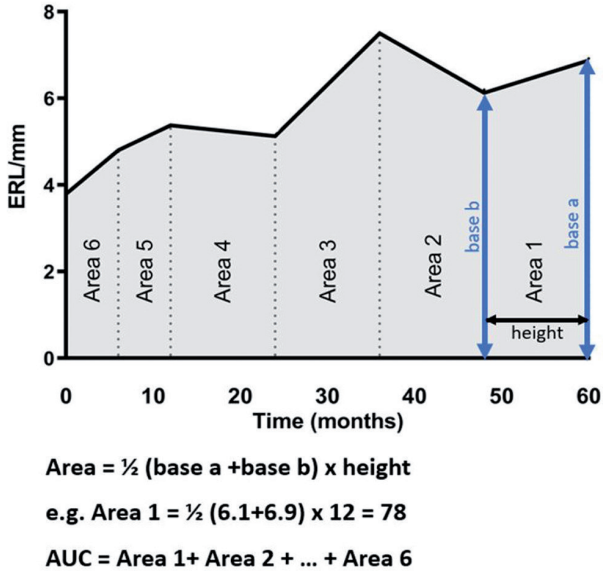
Background. Juvenile Dermatomyositis (JDM) is autoimmune vasculopathy characterized by skin and muscle inflammation. One evidence of the small vessel involvement in JDM is the loss of nailfold capillary end row loops (ERL) which can be assessed at the bedside using a capillaroscope. In this study, we want to examine the association between ERL over time using the area under the curve (AUC) method and various disease courses (monocyclic short, monocyclic long, polycyclic, and chronic) and indicators of disease damage (lipodystrophy, calcification, and fractures).
Methods. This is a retrospective chart review study (IRB# 2012-14858) conducted at Ann & Robert H. Lurie Children's Hospital of Chicago. We included all subjects with definite or probable JDM diagnosis based on Bohan and Peter criteria who had at least five years of follow-up data and had at least 4 or ERLs assessment at a prespecified time point (0,6,12,24,36,48, and 60 months). Patients with overlap syndrome were excluded from the analysis. GraphPad Prism was used to calculate the area under the curve (AUC) to measure the ERL cumulatively across the study duration. First, the curve was created by plotting the ERL data over time. Then, Prism divides AUC into multiple small trapezoid areas, which are measured individually, using the trapezoid rule [area = ½ (base a + base b) x height], and added up to get the total AUC (Fig. 1). Disease courses were



P-84. Fig. 1.

defined as the following. a) monocyclic short if medical therapy was completed by 36 months, b) monocyclic long if completed after 36 months, c) polycyclic if completed therapy, but a disease flare with re-initiation of treatment occurred within 60 months, and d) chronic, if the clinical resolution was not obtained over the 60 months.

Results. 68 untreated children with definite/probable JMD (84% female, 75% Caucasian, 19% Hispanic, 1.5% Asian, 3% African American, mean age of onset 6±3.1 years) were included in this study. Their MSAs were as follows: 41% P155/140+, 3% MJ+, 7.5% Mi-2+, 3% MDA-5+, 7.5% multiple MSAs, 31 % MSA negative and 7.5% lack up to date MSA. The disease course distribution was: 17.6 % monocyclic short, 42.6% monocyclic long, 20.6% polycyclic and 19.1% chronic. There was a significant difference between the ERL AUC for monocyclic short vs Chronic (389 vs 313, *p*-value 0.001) and monocyclic long vs Chronic (359 vs 313 *p*-value 0.01). Also, JDM with lipodystrophy of any type (generalized, partial or localized) has lower ERL AUC, *p*-value 0.04. There is no association of ERL AUC with calcifications or fractures.

Conclusions. ERL AUC can be used to assess ERL cumulatively across a prolonged period of time and it reflects the disease course (monocyclic vs chronic). This association could be due to decreased bioavailability of oral medication in patients with persistently low ERL as documented by our group in a prior study. Intravenous or subcutaneous medication might be the preferred option in patients with persistently low ERL counts. Also, these data suggest that loss of microvasculature may impact fat metabolism and the development of lipodystrophy.

Acknowledgements. The authors like to acknowledge the CureJM Foundation's support of this study. The data in this project is entered in REDCap, which is supported by NUCATS, and funded in part by a Clinical and Translational Science Award (CTSA) grant from the National Institutes of Health (NIH), UL-1TR001422.

P-85

ANTI-HMGCR AUTOANTIBODIES IN JUVENILE IDIOPATHIC INFLAMMATORY MYOPATHIES: A CASE SERIES

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Background. Patients with weakness and autoantibodies directed against 3-hydroxy-3-methylglutaryl-coenzyme reductase (HMGCR) define a subtype of Immune-mediated necrotizing myopathy (IMNM), which has been described mainly in adults after statin exposure. We herein present three statin naïve pediatric patients with an anti-HMGCR autoantibody related IMNM. None took statin medication or had dietary statin exposures.

Case discussions:

Patient 1: A 10-year-old girl presented with right upper extremity weakness with inability to raise her arm above her head, along with multiple falls due to bilateral lower extremities weakness. Her creatine kinase (CK) was 17,470 U/L. A pelvic MRI showed T2 hyperintensity throughout the adductor magnus and minimus muscles. Muscle biopsy showed myofiber necrosis and regeneration, without an inflammatory infiltrate. Anti-HMGCR autoantibody was positive. She received IV methylprednisolone, then was maintained on prednisone, methotrexate, and IVIG. Later, methotrexate was discontinued due to elevated transaminases and rituximab was added with significant improvement.

Patient 2: A 7-year-old girl developed difficulty riding her bike and standing from sitting over a four-month period before she developed dysphagia. Her CK was found to be 16,871 U/L. Pelvic MRI showed a patchy increased T2 signal within all the muscles. Muscle biopsy showed myofiber necrosis and atrophy. Anti-HMGCR autoantibody was positive. She was treated with IV methylprednisolone, then maintained on monthly IVIG, tacrolimus, and prednisolone. Despite treatment, she continued to have persistent muscle weakness, and rituximab was added with 80% improvement in her symptoms: she became able to climb stairs and run after 6 months on treatment.

Patient 3: A 3-year-old girl presented with slowly progressing weakness, with difficulty getting up from the floor, inability to lift her arms, and muscle pain. She also had a pale butterfly-like rash over her cheeks, rash overlying the knuckles and around her eyes. Her CK was 7,210 U/L. Muscle biopsy was reported to be consistent with muscular dystrophy. She was treated with prednisone for nine years, which was then discontinued after multiple osteoporotic fractures. The patient remained without treatment for 26 years. Her disease progressed, developing joint contractures and generalized muscle atrophy, and she became wheelchair bound. Anti-HMGCR autoantibody was then obtained and found to be detectable. Whole-body MRI showed pronounced and diffuse muscle atrophy, without muscle edema. Following monthly IVIG and physical therapy, she was able to sit up independently and stand with some assistance, but remained wheelchair bound due to significant muscle atrophy.

Discussion. Anti-HMGCR autoantibody associated IMNM has been reported in 1% of juvenile patients with idiopathic inflammatory myopathies. Two main phenotypes have been described: subacute-onset myopathy with elevated CK 1,000-20,000 IU/L and biopsy typically showing myofiber degeneration and necrosis with a variable density of regenerating fibers, which is typical for IMNM. A second phenotype is limb-girdle muscular dystrophy, with asymptomatic elevation of CK years before developing weakness and a chronic course. Although the pathology is not fully understood, the presence HLA-DRB1*07: 01, has been reported in pediatric patients with the disease. Pediatric patients tend to have more severe disease with poor response to immunotherapies, compared to the statin exposed adults. Often, more than one immunosuppressive agent is needed, with IVIG being the most effective therapy, especially in patients with refractory disease.

Conclusions. Pediatric anti-HMGCR autoantibody associated IMNM might not be as rare as previously reported. Early detection of anti-HMGCR autoantibodies may be required to initiate early treatment and slow disease progression. The absence of exposure to statins in these children and a distinct HLA association may suggest an alternative disease trigger.

P-86

ANTI-FHL1 AUTOANTIBODIES IN JUVENILE MYOSITIS ARE ASSOCIATED WITH MYOSITIS-ASSOCIATED AUTOANTIBODIES BUT NOT DISTINCTIVE CLINICAL FEATURES

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Background. The idiopathic inflammatory myopathies (IIM) are a heterogeneous group of systemic autoimmune diseases characterized by chronic muscle inflammation, frequent multi-system involvement, and autoantibodies. Four-and-a-half LIM domains 1 (FHL1) is a muscle-specific protein found predominantly in skeletal muscle. Autoantibodies recognizing FHL1 were recently reported in 25% of adult IIM patients, where they were associated with a more severe phenotype that included an increased frequency of muscle atrophy, dysphagia, and myofiber damage. Since anti-FHL1 autoantibodies have not been described in children, the prevalence and clinical features associated with anti-FHL1 autoantibodies were examined in a large North American cohort of juvenile IIM patients.

Methods. Sera from 339 patients with juvenile IIM and 91 juvenile healthy controls were screened for anti-FHL1 autoantibodies by ELISA, as previously described (DOI: 10.1093/rheumatology/keac003). Results were transformed to arbitrary units, and threshold for positivity was defined as three standard deviations above the healthy control mean. Clinical features of those with and without anti-FHL1 autoantibodies were compared among those with juvenile IIM. Other myositis autoantibodies were tested by immunoprecipitation and immunoblotting. Wilcoxon rank sum test was used for continuous variables and Chi-squared or Fisher's exact test was used for dichotomous variables as appropriate. $P < 0.05$ was considered significant. RStudio (version 1.4.1717, RStudio, PBC, Boston, MA) was used for statistical analyses.

Results. Anti-FHL1 autoantibodies were present in 10.9% (n=37) of patients with juvenile IIM and 1.1% (n=1) of healthy controls. There was no difference in the frequency of anti-FHL1 autoantibodies among the clinical and serologic subgroups of IIM (Table). There was a higher percentage of Asian patients with anti-FHL1 autoantibodies (11% v 0.7%, p=0.002) but no other differences in demographic variables. Speed of onset from first symptoms to diagnosis was also different between the groups, with a higher percentage of those with anti-FHL1 autoantibodies presenting within 1 week of first symptoms (8.1 v 0.3%, p=0.005). Those with anti-FHL1 autoantibodies had a higher frequency of other myositis-associated autoantibodies (MAAs) (57% v 38%, p=0.026) and specifically anti-Ro52 autoantibodies (35% v 13%, p<0.001). Among clinical features only, V-sign rash was present significantly more often in patients with anti-FHL1 autoantibodies (41% v 25%, p=0.041). There were no differences in other disease manifestations, including distal weakness, muscle atrophy, and dysphagia, or in measures of disease severity. Additionally, the types of medications and responses to treatment did not differ between patients with and without anti-FHL1 autoantibodies. A subgroup analysis of patients with no other MSA or MAA revealed that anti-FHL1

autoantibodies were isolated to the JDM subgroup and that there was an increased frequency of Asians patients with these autoantibodies (33% v 0%, p=0.024).
Conclusions. Anti-FHL1 autoantibodies were present in approximately 11% of juvenile IIM patients and commonly co-occurred with other MAAs. In contrast to adult IIM patients, anti-FHL1 autoantibody-positive juvenile IIM patients did not have more severe disease or other distinctive clinical features.
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P-86. Table I. Clinical features and outcomes of juvenile myositis patients with and without anti-FHL1 autoantibodies.

		Anti-FHL1 positive, N=37[1]	Anti-FHL1 negative, N=302[1]	p-value[2]
General characteristics	Clinical subgroup			
	Juvenile dermatomyositis	81% (30 / 37)	82% (248 / 302)	0.9
	Juvenile polymyositis	8.1% (3 / 37)	6.6% (20 / 302)	0.7
	Juvenile connective tissue-disease myositis	11% (4 / 37)	11% (34 / 302)	>0.9
	Female	76% (28 / 37)	72% (217 / 302)	0.6
	Race			
	Caucasian	70% (26 / 37)	64% (194 / 302)	0.5
	Black	11% (4 / 37)	17% (50 / 302)	0.4
	Hispanic	5.4% (2 / 37)	6.6% (20 / 302)	>0.9
	Asian	11% (4 / 37)	0.7% (2 / 302)	**0.002**
	Other	2.7% (1 / 37)	12% (36 / 302)	0.1
	Age at diagnosis (years)	7.8 (4.5)	8.9 (4.2)	0.095
	Delay in diagnosis (months)	6.0 (8.3)	8.6 (14.6)	0.13
	Follow up duration (months)	49.1 (41.9)	53.9 (52.0)	0.8
	Speed of onset			
	Very rapid (<1 week)	8.1% (3 / 37)	0.3% (1 / 298)	**0.005**
	Rapid (<1 month)	11% (4 / 37)	12% (35 / 298)	>0.9
	Moderate (<3 months)	27% (10 / 37)	23% (69 / 298)	0.6
	Slow (3-6 months)	30% (11 / 37)	28% (83 / 298)	0.8
	Very slow (>6 months)	24% (9 / 37)	37% (110 / 298)	0.13
	Severity at onset			
	Mild	8.1% (3 / 37)	11% (34 / 299)	0.8
	Moderate	57% (21 / 37)	54% (162 / 299)	0.8
	Severe	27% (10 / 37)	32% (95 / 299)	0.6
	Very severe	8.1% (3 / 37)	2.7% (8 / 299)	0.11
Autoantibodies	Positive MSA	73% (27 / 37)	81% (245 / 302)	0.2
	Anti-p155/140	30% (11 / 37)	37% (111 / 302)	0.4
	Anti-NXP2	24% (9 / 37)	27% (81 / 302)	0.7
	Anti-MDA5	11% (4 / 37)	7.9% (24 / 302)	0.5
	Anti-Mi2	0% (0 / 37)	5.0% (15 / 302)	0.4
	Anti-synthetase autoantibodies	5.4% (2 / 37)	4.0% (12 / 302)	0.7
	Positive MAA	57% (21 / 37)	38% (114 / 302)	**0.026**
	Anti-Ro52	35% (13 / 37)	13% (38 / 302)	**<0.001**
	Anti-NT5c1A	30% (11 / 37)	26% (78 / 302)	0.6
Muscle enzymes	Peak creatine kinase (IU/L)	3,243.7 (4,882.2)	5,852.2 (13,381.3)	0.5
	Peak aldolase (IU/L)	28.7 (37.1)	23.7 (35.0)	0.084
Musculoskeletal	Distal weakness	51% (18 / 35)	47% (140 / 298)	0.6
	Asymmetric weakness	11% (4 / 36)	16% (49 / 301)	0.4
	Myalgia	58% (21 / 36)	65% (193 / 295)	0.4
	Muscle atrophy	38% (14 / 37)	36% (109 / 299)	0.9
	Arthritis	57% (21 / 37)	50% (149 / 301)	0.4
Extra-muscular	Dysphagia	35% (13 / 37)	41% (124 / 302)	0.5
	Dysphonia	32% (12 / 37)	34% (101 / 299)	0.9
	Dyspnea on exertion	31% (11 / 36)	31% (93 / 299)	>0.9
	Interstitial lung disease	11% (4 / 37)	8.3% (25 / 301)	0.5
	Mechanic's hands	8.1% (3 / 37)	6.4% (19 / 298)	0.7
	V-sign	41% (15 / 37)	25% (75 / 302)	**0.041**
	Shawl sign	19% (7 / 37)	17% (52 / 301)	0.8
	Skin ulcer	19% (7 / 37)	20% (61 / 302)	0.9
	Raynaud's phenomenon	19% (7 / 37)	14% (41 / 301)	0.4
Outcomes	Course			
	Monocyclic	16% (5 / 31)	21% (51 / 240)	0.5
	Polycyclic	29% (9 / 31)	22% (54 / 240)	0.4
	Chronic continuous	55% (17 / 31)	56% (135 / 240)	0.9
	Hospitalized ever	64% (23 / 36)	56% (163 / 289)	0.4
	Wheelchair use	20% (7 / 35)	19% (56 / 294)	0.9
	Calcinosis	32% (12 / 37)	31% (93 / 302)	0.8
	Mortality	2.7% (1 / 37)	3.3% (10 / 302)	>0.9
	Complete clinical response	26% (9 / 34)	31% (82 / 261)	0.6
	Remission	18% (6 / 34)	22% (58 / 265)	0.6

[1] % (n / N); Mean (SD). [2] Pearson's Chi-squared test; Fisher's exact test; Wilcoxon rank sum tes.
Complete clinical response was defined as no evidence of active disease by for 6 continuous months duration remaining on therapy.
Remission was defined as no evidence of active disease for 6 continuous months duration off all therapy.

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COMPLICATED JUVENILE DERMATOMYOSITIS PATIENT WITH REPEATED COMPLIANCE PROBLEMS AND SEVERE COMPLICATION- DUODENAL PERFORATION

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Background. Juvenile dermatomyositis (JDM) is a rare disease with incidence 1,9 to 4,1 per million children per year (Mendez, Lipton, Ramsey-Goldman *et al*., 2003). Early and agressive treatment is important to get the remission and to avoid complications. Gut vasculopathy is a rare complication that can cause death.
Methods. Patient data was collected from the year 2013-2022. Consent was obtained from the patient and parents for the use of the data.
Results. In 2013 patient presented with proximal muscule weakness and malar rash in 2013. Kendall's score was 41/80. Creatinine kinase (CK) 3295 units per liter (U/L), lactate dehidrogenase (LDH) 788 U/L. Whole body magnetic resonance imaging was done, the biopsy confirmed the diagnosis of JDM. Treatment with methotrexate (MTX) and glucocorticoids (GC) was initiated. Patient stopped the treatment after 6 month. She came back in 2014 with the same symptoms+ Gottron's papules, hoarse voice, the same treatment was initiated but after 6 month she discontinued the treatment again. In 2018 she came back in sever state- malar rash, erythematous rash on the chest, livedo reticularis on the foot, subcutaneous calcifications on the right foot. Kendall's score 41/80, CK 6529 U/L, LDH 907 U/L. She got the same treatment and this time compliance was good. In February 2019 she had exacerbation with abdominal pain, endoscopy was done- without pathology. Aditionaly to the previous treatment adalimumab was started. On April 13 she had severe abdominal pain- duodenal perforation was diagnosed and treated surgically but she had reperforation after 2 days. During the laparathomy necrotic duodenal wall was detected, the defect was corrected and jejunostomy was done, she had nasogastral feeding. Cyclophoshamide (CP) was initiated- she got 5 CP courses after she had remission and treatment was switched to mycophenolate mofetil (MMF). She still got methylprednisolon (MP) 4 mg. In September 2020 she had exacerbation- the rash on the face and Gottron`s papules, Kendall`s score was 46/80, CK 2812 U/L, LDH 450 U/L. She got solumedrole pulse additionally. On a May 2021 intravenous immunoglobulin 70 g (the maximum dose) monthly was initiated and she got 6 infusions. On a June 2021 cyclosporin was added and MMF gradually tappered. On February 2022 she still gets the treatment with cyclosporin A, MP 2 mg per day. Her Kendall's score is 80/80, LDH is normal, CK little bit elevated 224 U/L.
Conclusions. Compliance problems observed at the beginning of the treatment probably affected the very complicated course of the disease. Duodenal perforation is a very rare complication what can be controlled with CP but needs team work (rheumatologists, surgeons, gastroenterologists etc.). Finding the better treatment for concrete patient with JDM can be challenging.
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VALIDATION OF THE 2016 ACR/EULAR MYOSITIS IMPROVEMENT CRITERIA IN JUVENILE DERMATOMYOSITIS (JDM) CLINICAL TRIALS AND CONSENSUS PROFILES

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Background. Juvenile dermatomyositis (JDM) is a heterogenous systemic autoimmune disease resulting in weakness and characteristic rashes. ACR/EULAR myositis response criteria (MRC) were developed based on absolute percent changes (abs%) in 6 core set measures (CSM) differentially weighted to calculate a total improvement score (TIS), with improvement categories (minimal, moderate, major) based on TIS cutoffs. MRC TIS performance has not been well-characterized. Whether patients can achieve MRC with worsening in CSMs is unknown. Of the 6 CSMs, specificity to muscle disease vs. extra-muscular disease is varied. It is unclear whether patients can achieve response without improvement in strength, a concern of regulatory agencies. Only a few CSMs are patient-reported (PRO) (Childhood Health Assessment Questionnaire (CHAQ), Parent Global Disease Activity (ParGA), and Childhood Heath Questionnaire-PF50 Physical Function Score (CHQ-PF50 PhS)). How changes in IMACS vs. Paediat-

ric Rheumatology INTernational Trials Organization (PRINTO) CSMs compare, and clinical significance of MRC categories is unclear. In this study, we aimed to assess the contribution of each CSM to TIS, frequency of worsening CSMs, frequency of muscle improvement among improved patients, representation of PRO in the TIS, relationship of IMACS vs. PRINTO CSMs, and clinical significance in examining MRC performance.

Methods. Data from JDM patients enrolled in Rituximab in Myositis trial (n=48), PRINTO methotrexate trial (n=139), and consensus profiles from natural history studies (n=273) were included. TIS and number of improving/worsening CSMs by improvement category were examined. Abs% change of each CSM is (final value-baseline value)/CSM range)*100. Observed % contribution of each CSM to TIS was calculated as: (CSM Improvement Score/TIS)*100. Sign test was performed to compare the observed vs. expected contribution of each CSM. Frequency of improvement with: a) muscle-related CSMs (MMT/CMAS, CHAQ, and/or muscle enzyme (CK)/ CHQ-PF50 PhS, and without muscle-related CSMs, and b) PRO (ParGA, CHAQ and/or CHQ-PF50) improvement, was calculated. Wilcoxon tests with Bonferroni-adjusted p-values were performed comparing improvement categories. Change in IMACS and PRINTO CSM and TIS were compared by correlation analysis. Physician rating of change category was compared to MRC improvement categories.

Results. Of 457 total JDM patients with IMACS CSM and 380 with PRINTO CSM, 13% and 9% had minimal improvement, 23% and 19% had moderate improvement, and 41% and 50% had major improvement (Table). The number of improved CSMs significantly increased with higher MRC improvement categories. As the level of improvement increased from minimal to major, abs% change in all CSMs significantly increased (Table). Patients with no improvement had a median of 1 CSM worsening, whereas patients with moderate-major improvement had median zero CSM worsening. With minimal improvement, most CSMs contribute to TIS as expected (Table). Of patients who had at least minimal improvement, 90-93% had improvement in MMT/CMAS, while only 15% had no improvement in IMACS (MMT/CHAQ/CK) or PRINTO (CMAS/CHAQ/CHQ-PF50 PhS) muscle-related measures. Of the patients with at least minimal improvement, 77% had improvement in ParGA or CHAQ (IMACS) and 71% had improvement in ≥1 PRO (ParGA, CHAQ, CHQ-PF50) (PRINTO). TIS and change in CSM for IMACS vs. PRINTO significantly correlated for most measures. Most of the physician-rated categories of change were in agreement with the TIS improvement categories (Table).

P-88. Table I. Frequency and distribution of patients, median TIS, improving and worsening CSMs, CSM contribution to TIS by the TIS categories from IMACS and PRINTO CSM for Combined Juvenile Trial and Profile Consensus Data.

IMACS (n=457)	**Total Improvement Score Categories**			
	No improvement	**Minimal improvement**	**Moderate improvement**	**Major improvement**
N (%)	102 (22.3%)	60 (13.1%)	106 (23.2%)	189 (41.4%)
Median TIS (IQR)	12.5 (2.5 - 20)	37.5* (32.5 - 42.5)	57.5*† (52.5 - 65)	82.5*†‡ (75 - 92.5)
Median Number of CSM Improved (Range)	1 (0 - 4)	4* (2 - 5)	5*† (3 - 6)	6*†‡ (4 - 6)
Median Number of CSM Worsened (Range)	1 (0 - 6)	1 (0 - 2)	0 (0 - 2)	0 (0 - 1)
Median Absolute Percent Change in each CSM [IQR]				
MMT	0 [(-8) - 3]	5* [0.5 - 10]	16*† [8 - 25]	39*†‡ [26 - 53]
MDGA	0 [(-9) - 8]	15.5* [10 - 23]	26*† [16 - 40]	52*†‡ [40 - 69]
EMGA	-1 [(-13) - 0]	9.5* [0 - 18.5]	10* [0 - 25]	30*†‡ [10 - 48]
ParGA	0 [(-10) - 12]	10* [0 - 24]	24.5*† [10 - 38]	50*†‡ [37 - 68]
CHAQ	0 [(-4) - 4]	8* [0 - 21]	25*† [8 - 38]	54*†‡ [33 - 75]
Muscle Enzyme	4.5 [0 - 14]	11* [2 – 23.5]	12.5* [3 - 31]	45*†‡ [19 - 111]
Median Percent Contribution of each CSM to TIS [IQR]				
MMT (32.5% expected contribution)	0§ [0 – 36.4]	25.8§ [0 – 32.1]	37.2 [20 - 47.8]	35.1§ [32.5 - 39.4]
MDGA (20% expected contribution)	0§ [0 - 27.3]	30.1§ [20 – 41.2]	28.6§ [22.2 - 33.3]	22.2§ [21.1 - 25]
EMGA (20% expected contribution)	0§ [0 - 20]	18.8 [0 - 29.4]	11.8§ [0 - 25]	16.7§ [9.4 - 20.5]
ParGA (10% expected contribution)	10 [0 – 14.3]	7.1 [0 – 15.4]	11.1 [4.4 - 14.8]	10.5§ [9.4 - 12.5]
CHAQ (10% expected contribution)	0§ [0 - 10]	11.8 [0 - 19.4]	12§ [9.1 - 14.8]	10.7§ [10 - 11.8]
Muscle Enzyme (7.5% expected contribution)	7.5 [0 – 33.3]	6.3 [0 – 15.4]	4.7 [0 - 11.1]	7.9§ [6.3 - 9.1]
Physician Rated Change Categories from the RIM trial (N (%))				
No Improvement or worsened (n=10)	8 (80%)	1 (10%)	1 (10%)	0 (0%)
Slight Improvement (n=14)	7 (50%)	4 (28.6%)	3 (21.4%)	0 (0%)
Moderate Improvement (n=15)	3 (20%)	2 (13.3%)	7 (46.7%)	3 (20%)
Marked Improvement (n=9)	0 (0%)	1 (11.1%)	3 (33.3%)	5 (55.6%)
PRINTO (n=380)	**No improvement**	**Minimal improvement**	**Moderate improvement**	**Major improvement**
N (%)	83 (21.8%)	34 (8.9%)	72 (18.9%)	191 (50.3%)
Median TIS (IQR)	7.5 (0 - 15)	37.5* (32.5 - 40)	55*† (50 - 61.2)	92.5*†‡ (82.5 - 97.5)
Median Number of CSM Improved (Range)	1 (0 - 4)	4* (2 - 5)	5*† (2 - 6)	6*†‡ (4 - 6)
Median Number of CSM Worsened (Range)	1 (0 - 6)	0 (0 - 3)	0 (0 - 2)	0 (0 - 1)
Median Absolute Percent Change in each CSM [IQR]				
CMAS	0 [(-12) - 0]	8* [4 - 10]	14*† [7 - 21]	46*†‡ [31 - 63]
MDGA	0 [(-11) - 9]	19.5* [13 - 27]	26* [15 – 38.5]	50*†‡ [38 - 68]
DAS	0 [(-10) - 5]	15* [5 - 25]	25*† [15 - 35]	50*†‡ [35 - 60]
ParGA	0 [(-13) - 6]	4* [0 - 20]	20* [8.5 – 30.5]	50*†‡ [32 - 66]
CHAQ	0 [(-12) - 0]	2* [0 - 17]	17*† [4 - 31]	58*†‡ [38 - 75]
CHQ-PF50 (PhS)	0 [(-4) - 3]	2 [(-4) – 10]	5.5* [0 - 17]	29*†‡ [16 - 43]
Median Percent Contribution of each CSM to TIS [IQR]				
CMAS (32.5% expected contribution)	32.5§ [0 - 32.5]	25.8 [23.5 - 33.3]	33.3 [19.1 - 42.3]	34.2§ [32.5 - 36.1]
MDGA (20% expected contribution)	20 [0 - 37.5]	37.5 [18.8 - 43.8]	29.8§ [19.4 - 34.1]	20.7§ [20 - 22.2]
DAS (20% expected contribution)	20§ [0 - 20]	23.1 [0 - 35.3]	22.9 [15.8 - 27.3]	20 [17.7 - 21.1]
ParGA (10% expected contribution)	10 [0 - 10]	0 [0 - 13.3]	8.9 [4.1 - 13]	10 [8.3 - 10.7]
CHAQ (10% expected contribution)	0§ [0 - 10]	0 [0 - 17.7]	11.3 [0 - 14.3]	10.3§ [10 - 10.8]
CHQ-PF50 (7.5% expected contribution)	7.5§ [0 - 7.5]	0§ [0 - 6.7]	1.9§ [0 - 7.6]	7.5 [5.1 - 7.9]

Abbreviations: CSM: core set measure; MMT: Manual Muscle Testing; MDGA: Physician Global Disease Activity; EMGA: Extramuscular Global Disease Activity; ParGA: Parent Global Disease Activity; CHAQ: Childhood Health Assessment Questionnaire; RIM: Rituximab in Myositis Trial; DAS: Disease Activity Score; CHQ-PF50: Physical Summary Score of the Child Health Questionnaire-Parent Form 50.

Improvement categories: No Improvement: 0 ≤Total Improvement Score ≤30: Minimal Improvement: 30 ≤Total Improvement Score <45; Moderate Improvement. 45 ≤Total Improvement Score <70; and Major Improvement: 70 ≤Total Improvement Score.

A CSM was considered imptoving (or worsening) if Abs% change was >5% (<-5% for worsening) for all CSMs except for Manual Muscle Testing (MMT), which was considered improving if the Abs% change is >2% (<-2% for worsening) per points assigned in the Total Improvement Score.

Expected contribution was based on (CSM maximum TIS point contribution/100).

Bonferroni-adjusted *p*-value cutoff for significance was *p*-value was <0.008 for all comparisons other than median number of improving CSM and median TIS, which had a cutoff adjusted *p*-value cutoff of <0.006.

*Statistically significant difference from the No Improvement category.

†Statistically significant difference from the Minimal Improvement category.

‡Statistically significant difference from the Moderate Improvement category.

§Statistically significant difference from the expected contribution (Sign Test).

Conclusions. Most JDM patients who improve by the MRC show improvement in muscle disease; it is uncommon to meet improvement criteria without improvement in muscle disease. Among those who improve, worsening of CSM is infrequent. The ACR/EULAR MRC improvement reflects improvement in PRO. TIS and most changes in CSM are significantly correlated between IMACS and PRINTO CSM. MRC TIS categories generally agree with clinically significant changes by physician assessment. The ACR-EULAR MRC are robust for the assessment of JDM, and perform consistently across studies.

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CALCINOSIS IN JUVENILE DERMATOMYOSITIS: AN UNSOLVED PROBLEM

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Background. Juvenile Dermatomyositis (JDM) is the most prevalent Idiopathic Inflammatory Myopathy (IIM) affecting children, and although the mortality has declined over time, it contributes to significant morbidity. The latter is influenced by disease related factors like dystrophic calcinosis and contractures as well as treatment related adverse effects. In this study, we aimed to study the prevalence and predictors of calcinosis in JDM.

Methods. Medical records over 20 years at a tertiary care rheumatology center in Northern India were reviewed to identify patients with JDM and clinical details were recorded. Demographic factors, clinical course, laboratory investigations and treatment details were noted. Additionally, frequency of calcinosis, plausible associations, specific treatment and its outcomes were studied. Statistical analysis was done using GraphPad prism version 8.4.2. Data are expressed as median and interquartile range with p value <0.05 deemed as statistically significant.

Results. In eighty-six patients of JDM [Age 10 (5.7-14.5) years, 46 girls], the frequency of calcinosis was 18.2% (8.5% at presentation). Two-thirds were diagnosed clinically and the remaining radiographically. Five (33%) each had circumscripta and mixed type of calcinosis; tumoral calcinosis was present in four (26%); superficial in one. Younger age at presentation, longer follow-up duration, heliotrope rash [OR 11.4 (1.4-92.12)], chronic or polycyclic course [OR 4.4 (1.2-15.5)] and cyclophosphamide use [OR 8.2(1.6-41.9)] were associated with calcinosis. Dysphagia [OR 0.14 (0.02-1.2)] and elevated muscle enzymes [0.14 (0.04-0.5)] were negatively associated with calcinosis. MSA/MAA were

P-89. Table I. Comparison of patients with and without calcinosis.

	With calcinosis, N=15	Without calcinosis, N=71	Univariate Analysis P, <0.05* OR (CI)	Multivariate Analysis P, <0.05# OR (CI)
Median age at presentation in years	8.2 (3-11)	10.5 (6.5-14.8)	0.03*	
Gender, M:F	1.1:1	1:1.16	0.56	
Median delay in diagnosis in months	6 (5-24)	6.25 (3.75-18)	0.56	
Median duration of follow up in months	40 (30-96)	24 (6.25-54)	0.02*	
Arthritis, *n (%)*	2 (13.3%)	15 (21.4%)	0.47	
Joint contractures, *n (%)*	4 (26.7%)	10 (14.1%)	0.20	
Dysphagia, *n (%)*	1 (6.7%)	23 (32.4%)	0.04*,0.14 (0.02-1.2)	0.03# 0.06(0.01-0.78)
Gottron rash/papules	11 (73.3%)	49 (69.0%)	0.7	
Heliotrope Rash	14 (93.3%)	39 (54.0%)	0.005* 11.4 (1.4-92.12)	
Cutaneous Ulcers, *n (%)*	4 (26.7%)	19 (26.8%)	0.99	
ANA positivity (IIF), *n (%)*	5 of 9 (55.5%)	35 of 54 (64.8%)	0.60	
Elevated muscle enzymes, *n (%)*	4 (26.7%)	51 (71.8%)	0.001* 0.14 (0.04-0.5)	0.01# 0.07(0.01-0.5)
Baseline CPK (IU/L)	76 (57-470)	390(113=1459)	0.01*	
Baseline AST (IU/L)	49.7 (35-79)	93.5 (52.7-226.75)	0.01*	
Baseline ALT (IU/L)	24 (20-49)	69.5 (43-119)	0.001*	
Baseline LDH (IU/L)	869 (593.5-1066)	1088 (754.5-1939)	0.07	
Treatment				
Methotrexate	12 (80%)	61 (86%)	0.56	
Azathioprine	3 (37.5%)	5 (62.5%)	0.12	
Cyclophosphamide	4 (26.7)	3 (4.2%)	0.004* 8.2(1.6-41.9)	0.03#
Rituximab	2 (13%)	4 (5.6%)	0.29	29(1.42-619)
Course				
Monocyclic	4	42	0.01*	
Chronic/Polycyclic	11	30	4.4 (1.2-15.5)	

SD: Standard Deviation; IIF: Indirect Immunofluorescence; CPK: Creatine Phosphokinase; AST: Aspartate Transaminase; ALT: Alanine Transaminase; LDH: Lactate Dehydrogenase; OR: Odds Ratio.

present in 19(54%) of the 35 tested, and anti-MDA 5 was the most common type 4(11%) (Table I). Calcinosis resulted in ulceration of overlying skin in 4 (26.6 %), secondary infection with pyoderma or cellulitis in 1 (6.67 %) and limitation of movement in 5 (33.3 %). Eight children were treated with bisphosphonates of which the best results were seen with pamidronate, three of five (60%) had a partial or complete response in calcinosis.
Conclusions. Calcinosis in JDM is associated with long standing, poorly controlled disease and use of bisphosphonates like pamidronate offer promise in the future for its treatment.

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THE INFLUENCE OF ENVIRONMENTAL FACTORS RELATING TO JUVENILE DERMATOMYOSITIS´S COURSE AND REFRACTORINESS TO TREATMENT

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Background. Environmental factors may act as triggers in the immune system of genetically predisposed individuals, leading to Juvenile Dermatomyositis (JDM) and influencing its course. In this context, the aim of this study is to assess the influence of environmental factors relating to JDM's course and refractoriness to treatment.
Methods. This is an exploratory case-control study with JDM patients followed up at the Pediatric Rheumatology Unit of Faculdade de Medicina de São Paulo. All resided in São Paulo, in areas with pollution monitoring. They were classified according to monocyclic, polycyclic or chronic disease courses and refractoriness to treatment.The daily concentrations of pollutants (inhalable particulate matter-PM10, sulfur dioxide-SO2, nitrogen dioxide-NO2, ozone-O3 and carbon monoxide-CO) were provided by the Environmental Company of São Paulo, considering the period between 4 pm of the previous day and 3 pm of the current day. Data on the population was obtained from a questionnaire regarding the pregnancy period, from birth to JDM onset and up to two years after the onset. Control group: Healthy children/adolescents residents of that area with pollution monitoring. The study was approved by the Ethics Committee.
Results. Thirty-five patients participated, 15(42.85) had monocyclic course, and 19(54.28%) chronic/polycyclic courses. Mean age of JDM diagnosis was 5.8(±2.5) years. Eighteen patients (51%) were refractory to treatment and 50% (p=0.49) were female. Maternal smoking rate was higher in JDM patients compared to control group (12.12% vs. 2.4%, p=0.036, respectively). There was an association between maternal smoking (OR 5.58; CI 1.18-26.23; p=0.03), paternal (OR 2.64; CI 1.04 – 6.71; p=0.041) or others household residents(OR 3.55; CI 1.58-7.96; p=0.002) in the univariate logistic regression model. Maternal work during pregnancy was a protective factor (OR: 0.18; CI 0.08 – 0.42; p<0.001). However, only 5.94% of mothers in the control group had occupational exposure to one of the inhalation agents (demolition/construction/quarry dust or school chalk dust and volatile compounds) while 26.6% of JDM patients' mothers were exposed to these agents (p=0.024), presenting a risk for JDM (OR: 5.76, CI: 1.40 – 23.60, p=0.015). As well as the presence of a factory/quarry less than 500 meters from home (OR: 5.92; CI: 2.52 – 13.90; p<0.001) and work during pregnancy (OR: 5; CI: 1.40 – 17.87; p=0.013). There was a difference between both groups regarding prematurity (4% of patients in the control group vs 14% in the JDM group, p=0.042), remaining a risk factor in the univariate analysis (OR: 3.97; CI: 1 .08 - 14.59; p=0.038). We found that exposure to O3 in fifth year after birth, PM10 in sixth year after birth, O3 in six months after birth were risk factors for JDM, while exposure to O3 during pregnancy was a protective factor. Mean age at diagnosis and frequency of females were compared between patients with monocyclic and polycyclic/chronic courses (p>0.05). Univariate analysis in the logistic regression model revealed that exposure to NO2 showed a tendency to be a risk factor for a polycyclic or chronic course in the third year of life(third tertile: > 98.82µg/m3; OR: 8; CI: 1.001 – 63.96, p=0.05), as is PM10(third tertile: > 46.87 µg/m3; OR: 9; CI: 1.14–71.04; p=0.037). Exposure to CO (second tertile = 1.79 – 2.73 ppm; OR 0.11; CI 0.01-0.88; p=0.037) and NO2 (second tertile = 84.83 – 101.64µg/m3; OR 0.13; CI 0.02-0.90; p=0.039) in the second trimester of pregnancy was a protective factor for refractoriness. The remaining data did not show statistic relevance (p>0.05).
Conclusions. Risk factors for JDM were exposure to tobacco, maternal occupational exposure; presence of factories near residence; prematurity; exposure to O3 and PM10. Pregnancy exposure to NO2 was related to monocyclic course. However, its exposure during third year of life and exposure to PM10 were risk factors for the polycyclic/chronic course. Exposure to inhalable pollutants at 500 meters from daycare/school and to O3 during pregnancy were protective factors for JDM. CO and NO2 exposure in second trimester of pregnancy protected refractoriness.

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ASSESSING DISEASE ACTIVITY IN JUVENILE DERMATOMYOSITIS: COMPARISON BETWEEN A STANDARDIZED ELECTROMYOGRAPHY SCORING PROTOCOL AND WHOLE-BODY MAGNETIC RESONANCE

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Background. Juvenile Dermatomyositis (JDM) is the most common pediatric inflammatory myopathy (IM), predominantly affecting proximal muscles and skin. One of the major challenges in the clinical management of JDM is to accurately assess disease activity to optimize therapeutic strategies. Since JDM is still associated with significant morbidity, earlier detection of flares and precise measuring of disease activity are crucial. Recently a standardized electromyography (EMG)-scoring protocol for the assessment of disease activity in juvenile IM has been developed. The aim of our study is to assess the reliability of the EMG scoring protocol and whole-body magnetic resonance imaging (WB-MRI) in evaluating disease activity in JDM, and to provide preliminary data about their discriminative power.
Methods. All patients diagnosed with JDM and referred to our Centre between 01 Jan 2018 and 31 Oct 2021 were enrolled. Clinical, laboratory, neurophysiological and radiological data were collected if performed within a period of 30 days. The complete assessment consisted of: 1) standardized clinical evaluation through hybrid MMT8/CMAS (hMC); 2) laboratory exam including creatinine kinase (CK), aspartate aminotransferase (AST) and lactic dehydrogenase (LDH) levels; 3) WB-MRI; 4) EMG. WB-MRI signal intensity was scored using a 0-2 point scale in 42 muscular groups; myofascial and subcutaneous tissue inflammation were assessed on the upper and lower extremities using a 0-1 point scale. The EMG score was calculated as the sum of two subsets, evaluating acute denervation signs (fibrillation potentials) and reinnervation signs (motor unit remodeling) respectively, each with a score ranging from 0 (maximal muscle inflammation for the fibrillation potentials score or no reinnervation for the remodeling score) to 8 (no muscle inflammation or maximal reinnervation). Inactive disease was defined according to PRINTO definition. Correlations were assessed by Spearman's rank order correlation coefficient (rs). Comparison of quantitative variables in the analysis of discriminant validity was made by Mann–Whitney U Test.
Results. Seventeen patients (82,3% female) were included in the study for a total of 27 examinations analyzed. Seven episodes were observed at disease onset, and 20 during follow-up visits. The median age at JDM diagnosis was 6.59 years (interquartile range [IQR]: 3.49-10,1). In 15 patients JDM satisfied Bohan and Peter's criteria, while 2 patients were classified as amyopathic juvenile dermatomyositis. The hMC revealed a high correlation with the EMG score (rs=0.63), compared to the moderate correlation observed with MRI muscle score (rs=-0.47) and MRI myofascial score (rs=-0.43), and to the poor correlation with MRI perifascicular score (rs=-0.11). The EMG score, and its single subsets (fibrillar potentials and remodeling), as well as the MRI muscle score were not significantly increased in active JDM patients when compared with the group with clinically inactive disease (p=0.1380, p=0.0821, p=0.7041, p=0.0909).
Conclusions. This pilot study proves a good association between the newly standardized EMG score and clinical evaluation of muscular disease activity, endorsing the role of EMG in the management of children with JDM. The discriminative power of both EMG and WB-MRI could have been hampered by the inclusion of dermatologic involvement in the definition of inactive disease. Further prospective analysis on larger sample cohorts could contribute to better assess the role of both EMG and WB-MRI in evaluating muscular disease activity in JDM.

P-91. Table I.

	hMC	EMG score	EMG fib	EMG remod	RMN musc	RMN myo	RMN subc	VES	Log CPK
hMC	1.0000								
EMG score	0.6301	1.0000							
EMG fib	0.5195	0.6321	1.0000						
EMG remod	0.4095	0.7157	0.0504	1.0000					
RMN musc	0.4730	-0.3161	-0.3298	-0.1696	1.0000				
RMN myo	-0.4382	-0.2223	-0.3185	-0.0015	0.7846	1.0000			
RMN subc	-0.1121	-0.0088	-0.0937	0.0907	0.6620	0.7649	1.0000		
VES	-0.1092	-0.0088	-0.0937	0.0907	0.6620	0.7649	1.0000		
Log CPK	-0.5834	-0.5160	-0.3417	-0.3542	0.5942	0.4184	0.2562	-0.0098	1.0000

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THE USE OF RITUXIMAB IN CHILDREN WITH JUVENILE DERMATOMYOSITIS AND ANTI-MDA5 ANTIBODIES

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Background. Juvenile Dermatomyositis (JDM) is an autoimmune condition characterized by inflammation of muscle and pathognomonic rashes. Patients can have a varied clinical presentation, with differing degrees of gastrointestinal, musculoskeletal, mucocutaneous, and cardiopulmonary involvement. Recent research has expanded our understanding of the association of autoantibodies with various clinical phenotypes and long-term outcomes. Antibodies against melanoma differentiation associated gene 5 (MDA5) have been reported in 7-33% of JDM patients with studies reporting mild muscle involvement, characteristic rashes, and rapidly progressive interstitial lung disease (ILD). ILD is rare in children with JDM, but a serious complication. Diagnosis of ILD is made by pulmonary function tests (PFTs) and high-resolution computed tomography (HRCT), as children with ILD typically have mild to absent respiratory symptoms at time of diagnosis. The mainstay of treatment in JDM is high-dose corticosteroids and methotrexate. Given that B cells are believed to play an immunopathogenic role in JDM, rituximab (RTX), a B cell depleting anti-CD20 monoclonal antibody has been suggested for the treatment of JDM. Few studies in adults have evaluated the use of rituximab specifically in the treatment of patients with anti-MDA5 associated dermatomyositis (DM), however there are no studies to date that examine the use of RTX in the treatment of children with JDM and anti-MDA5 positive autoantibodies. This case series aims to review the clinical features of this specific population before and after the use of RTX with a focus on its impact on the pulmonary, cutaneous, and musculoskeletal features of the disease.
Methods. Children and adolescents (age 2-21 years) seen in the pediatric rheumatology clinic at the Children's Hospital at Montefiore between July 2012 and August 2021, with a diagnosis of probable or definite JDM (as defined by Bohan and Peter criteria), positive anti-MDA5 antibodies, and who were treated with rituximab were identified. Retrospective clinical and laboratory information was reviewed in the electronic medical record system. Data reviewed included demographics, date of diagnosis, duration of disease, medication usage, side effects of medication usage, and disease manifestations as evident by clinical, laboratory, and imaging findings.
Results. Four patients were identified who met inclusion criteria, with the median age at diagnosis of 8-years-old (range 3-12). Patients' laboratory results, clinician's assessment of muscle strength using childhood myositis assessment scale (CMAS), PFT results and HRCT reports are shown in Table I. All four patients had at least 5 courses of RTX infusions, with an average difference of 6.5 months between infusions. Concurrent medications with RTX include hydroxychloroquine, intravenous immunoglobulin (IVIG), mycophenolate mofetil (MMF), methotrexate (MTX), prednisone, and solumedrol. Two out of four patients demonstrated complete normalization of CMAS, muscle enzymes, HRCT findings and discontinuation of steroids (patients B and A). One patient demonstrated notable improvement in strength, muscle enzymes and normalization of HRCT, however, continues to have mild cutaneous findings and elevation in LDH (patient C). The final patient developed signs of ILD while receiving rituximab (patient D). Cutaneous manifestations and strength improved, along with the discontinuation of steroids. However, repeat imaging has not yet been performed.
Conclusions. To our knowledge, this is the first case series specifically examining anti-MDA5 positive JDM patients before and after the use of RTX. As this is a small case series, more studies are required to better understand the impact of RTX on this specific population and its role in the prevention and treatment of JDM associated ILD.

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INCREASED PREVALENCE OF DEPRESSION IN JUVENILE DERMATOMYOSITIS DURING THE COVID-19 PANDEMIC

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Background. Juvenile Dermatomyositis (JDM) is a chronic systemic vasculopathy of unknown etiology characterized by symmetrical proximal muscle weakness, raised serum concentration of muscle enzymes and pathognomonic skin rashes. Although JDM is the most common pediatric idiopathic inflammatory myopathy, it is still quite rare with an annual incidence of 3.2 cases per million children in the US. Youth with chronic disease are reported to have a higher prevalence of mental health disorders compared to healthy peers, with some research reporting up to a fourfold increase in risk. The COVID-19 pandemic has raised psychological distress among youth; data from the first year of the pandemic suggests that 1 in 4 youth globally are experiencing clinically elevated depression symptoms. The primary aim of this study is to describe the prevalence of depression in a cohort of patients with JDM to help providers better understand the mental health issues that arise in this population. This is critically important as early intervention for depression in youth with JDM has the potential to improve both medical and psychosocial outcomes.
Methods. This was a cohort study measuring depression in youth with JDM at Children's Healthcare of Atlanta (CHOA). Subjects were recruited during routine outpatient visits to CHOA rheumatology clinics from August to December 2020. Subjects had a diagnosis of JDM for at least 3 months, were between 5-20 years old, and had no cognitive deficit precluding questionnaire completion. Parent completed a proxy questionnaire if the child was 5-7 years old. Depression was assessed using the Patient Questionnaire-9 (PHQ-9). Of 15 eligible subjects, all consented to the study. Informed consent/assent was obtained. CHOA Institutional Review Board approved the study. Upon identification of depression, an educational handout was offered, which also included mental health care providers. Identified suicide risk was addressed with immediate direct questioning of suicidal intent, plan or attempt within the prior week; endorsement of any of these prompted enactment of a safety plan and urgent psychiatric evaluation. Statistical comparisons were performed using SAS. Medians and interquartile ranges (IQR), mean and standard deviation and frequencies were calculated for demographic and disease related variables. The presence of depression symptoms were analyzed as binary covariates for positive screens on the PHQ-9.
Results. Demographics of the 15 participants included 53% female, median age of 12 years (IQR 10.0, 19.0; range 5-20) with a range of 5-20 years. The sample was heterogeneous with respect to race/ethnicity, with 8 (53.3%) Black, 6 (40%) White and 1 (6.7%) Asian participant. Median disease duration was 4.1 years (IQR 2.2, 6.9). Calcinosis was present in 10 (67%) of patients. Five (33%) participants had active disease at the time of completing PHQ-9, all of whom had mild disease with median Physician Global Score of 0.6 (IQR 0, 0.9). Depression was identified in 6 subjects (40%): 5 subjects (33%) were classified as having mild depression and 1 subject (7%) was classified as having moderate depression. No subjects had severe depression nor endorsed suicidal ideation. There was no significant difference in depression prevalence in patients with active disease versus inactive disease. The prevalence of depression in this small cohort is similar to previously reported rates of depression in patients with JIA and SLE; notably, it is higher than rates of depression in healthy children in the US.
Conclusions. This pilot study adds to our understanding of the relationship between JDM diagnosis and psychosocial functioning in children and youth. The COVID-19 pandemic has been associated with a rise in depression in all children. Our findings suggest that regardless of disease status, there is a higher prevalence of depression in JDM patients compared to their healthy peers. Given the small sample size, further studies are needed to assess depression in paediatric rheumatology clinics.

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THE ASSOCIATION OF DELAY IN DIAGNOSIS OF JUVENILE DERMATOMYOSITIS WITH VARIOUS AND CLINICAL AND LABORATORY PARAMETERS: EXPERIENCE OF A CENTRE IN NORTH INDIA

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Introduction. Juvenile dermatomyositis (JDM) is the most common type of inflammatory myopathy seen in children. The incidence of JDM in North India is around 3.3 % of all the rheumatological diseases. When predicting the course, activity and outcome of the disease, it has been found that early age of onset and female sex are important factors. Most patients have good outcome with mortality being around 3 percent. Delayed diagnosis and inadequate treatment are harbingers of poor outcome in these patients. This is the first study from a tertiary care centre in a developing nation like India comparing delay in diagnosis with various clinical and laboratory findings.
Materials and Methods. In this retrospective cross-sectional study, 140 children with a diagnosis of JDM according to modified Bohan and Peter criteria were enrolled from 1992-2022. The children were divided according to the delay in their diagnosis (from the onset of symptoms) into 4 groups; 0-3 months, 3-6 months, 6-12 months and ≥12 months. These groups were compared with various clinical and laboratory parameters like age at onset, calcinosis, interstitial lung disease (ILD), mortality, lipodystrophy, gastrointestinal (GI) vasculitis, respiratory weakness and myositis specific autoantibodies. Statistical analysis was done using the SPSS (Statistical package of the social sciences)
Results. The total number of patients were divided according to the duration of delay in diagnosis into 4 categories- 0-3 months, 3-6 months, 6-12 months and ≥12 months and these groups were compared on the basis of different variables like the age at onset and various complications of chronic disease like calcinosis, ILD (interstitial lung disease), lipodystrophy, GI vasculitis, respiratory muscle weakness and mortality outcomes as given in the table below:

P-92. Table I. Patients' Clinical and Laboratory Information Surrounding Courses of Rituximab.

	Diagnosis	Course 1	Course 2	Course 3	Course 4	Course 5
CMAS	37	44	48	48	47	-
CK total	**25**	**<20**	**38**	**38**	**94**	**-**
LDH	364 (H)	318 (H)	201	157	181	-
AST	36	<20	<20	<20	<20	-
Aldolase	9.1 (H)	8.5	4.2	5.1	7	-
FVC	-	53	-	-	78	-
TLC	-	59	-	-	77	-
DLCO	-	75	-	-	81	-
Concurrent Medications	-	MMF, MTX, pred, solumedrol	MMF, MTX, pred	MMF, pred	MMF	MMF
Steroid Use	-	yes	yes	yes	no	no
CT impression	-	Findings of ILD. No evidence of advanced fibrosis	-	Findings of ILD, with improved opacities compared to prior. No evidence of advanced fibrosis	-	-
Patient B						
CMAS	49	48	50	52	-	51
CK total	66	88	72	270 (H)	113	91
LDH	295	245	257	265 (H)	260 (H)	234
AST	37	28	23	27	26	25
Aldolase	11.9 (H)	12.3 (H)	8.5	12.1 (H)	7.1	6
FVC	103	101	-	-	105	-
TLC	-	137	91	-	94	-
DLCO	-	73	88	-	70	-
Concurrent Medications	-	HCQ, MTX, pred	HCQ, MTX, pred	HCQ, MTX, pred	HCQ, MTX	HCQ, MTX
Steroids	-	yes	yes	yes	no	no
CT impression	-	Mild peripheral groundglass and nodular opacities in the bilateral upper lobes and basilar lower lobes, likely ILD	-	-	Normal, no evidence of ILD	-
Patient C						
CMAS	37	44	47	51	47	50
CK total	38	93	183	223 (H)	114	-
LDH	440 (H)	327 (H)	40	312 (H)	290 (H)	-
AST	126 (H)	36	321 (H)	38	28	-
Aldolase	17.3 (H)	7.3	-	8.4	6.9	-
Concurrent Medications	-	MTX, pred, solumedrol	HCQ, IVIG, MTX, solumedrol	HCQ, IVIG, MTX, solumedrol	HCQ, IVIG, MTX, solumedrol	HCQ, IVIG, MTX, solumedrol
Steroid Use	-	yes	yes	yes	yes	yes
CT impression	-	Interstitial opacities in a peripheral distribution, likely secondary to ILD	-	Previously seen lower lobe subpleural opacities have resolved. No evidence of ILD	-	-
Patient D						
CMAS	42	49	50	47	50	51
CK total	84	105	122	135	168	130
LDH	416	350 (H)	346 (H)	309 (H)	317 (H)	296 (H)
AST	40	41	32	31	28	25
Aldolase	12.9 (H)	7.7	8.3	6.7	7.2	6.1
FVC	-	131	-	108	-	-
TLC	-	96	-	76	97	-
DLCO	-	-	-	74	67	-
Concurrent Medications	-	HCQ, MTX, IVIG, pred	HCQ, MTX, IVIG, pred	HCQ, MTX, IVIG, pred	HCQ, IVIG, MMF	HCQ, IVIG, MMF
Steroid Use	-	yes	yes	yes	no	no
CT impression	-	Normal, no evidence of ILD	-	-	Mild lower lobe groundglass opacity, atelectasis vs early ILD. No evidence of fibrosis	-

AST: Aspartate Aminotransferase; CK: Creatine Kinase; CMAS: Childhood Myositis Assessment Scale; C: Computed Tomography; DLCO: Diffusing Capacity for Carbon Monoxide; FVC: Forced Vital Capacity; H: high; HCQ: Hydroxychloroquine; ILD: Interstitial Lung Disease; IVIG: intravenous immunoglobulin; LDH: Lactate Dehydrogenase; MMF: Mycophenolate Mofetil; MTX: Methotrexate; Pred: Prednisone; TLC Total Lung Capacity.

P-94. Table I. Delay in diagnosis with clinical parameters.

Delay in diagnosis (months)	Age at onset (years)	Calcinosis	ILD	Lipodystrophy	GI vasculitis weakness	Respiratory muscle	Mortality
0-3	7±3.4	7	2	4	5	3	5
3-6	6±3.9	6	4	1	1	4	3
6-12	6.5±3.4	4	3	2	1	3	2
≥12	6.4±3.1	18	5	10	0	3	2

These 4 groups were also compared on the basis of myositis specific autoantibodies (out of the 34 patients that were tested)

P-94. Table II. delay in diagnosis with muscle specific antibodies

Delay in diagnosis (months)	1 or more Ab*	Anti NXP2	Anti TIF1γ	Anti MDA5	Anti SAE	Anti Ro	Anti Mi2	Anti Ku	Anti PL	Anti PmScL
0-3	1	1	0	1	0	1	0	0	0	0
3-6	3	3	0	1	1	1	0	0	0	1
6-12	3	1	3	1	1	1	2	2	1	1
≥12	1	2	0	2	1	1	1	0	0	1

ab*- antibodies

Conclusions. This retrospective analysis of data shows that chronic complications of JDM like calcinosis, ILD and lipodystrophy are more commonly seen in patients where delay in diagnosis ≥12 months with calcinosis and lipodystrophy being statistically significant.

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LONG-TERM FOLLOW-UP OF JANUS-KINASE INHIBITOR (JAKI) AND NOVEL ACTIVE-DISEASE BIOMARKER IN JUVENILE DERMATOMYOSITIS

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Objective. To evaluate the use of JAKi in treating JDM and develop potential cytokine biomarkers of active disease.
Methods. The study measured cytokines in 128 JDM patients treated with JAKi and 30 normal controls. 101 JDM patients participated in the follow-up to evaluate the benefits and side effects of JAKi. A receiver operating characteristic curve (ROC) was used in the biomarker test.
Results. The median follow-up was 19 months. In 65.5% of the patients, rashes improved, and CAT-BM scores decreased. 39.6% of JDM patients eliminated glucocorticoids. Muscle strength was improved in all patients who exhibited abnormal muscle strength before JAKi use. Most parents thought that JAKi was effective and believed it did not increase infections. Potential side effects of JAKi included abnormal leukopenia and cough, which affected over 10% of the JDM patients. In terms of cytokine signatures, 35.3% of cytokines were significantly elevated in active JDM patients. Among all increased cytokines, IL-1RA changed most dramatically, reaching over 793 times the mean of normal values. Compared to active JDM patients with multiple phenotypes, active JDM patients with only rashes demonstrated lower cytokine levels. Most importantly, we developed a panel composed of 6 cytokines to efficiently differentiate between active and stable disease (AUC=0.8486, $p<0.05$).
Conclusions. Preliminary evidence suggested that JAKi is a safe, effective alternative for JDM patients. Cytokine profiles could well reflect the inflammatory status of JDM patients, especially for patients with different subtypes, such as NXP2+ active patients and patients with multiple symptoms.

Toward personalized treatment

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CLINICO-PATHOLOGICAL PHENOTYPES OF SYSTEMIC SCLEROSIS ASSOCIATED MYOPATHY: ANALYSIS OF A MULTICENTER LARGE COHORT

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Background. To analyze the clinico-serological and histological phenotype of patients with systemic sclerosis (SSc) with associated myopathy.
Methods. From November 2002 to September 2020, 52 patients with SSc underwent a muscle biopsy for suspected myopathy. We established two subgroups according to the histological findings based on the presence of isolated fibrosis or fibrosis together with significant inflammation. These patterns were designated as fibrosing and inflammatory, respectively. Clinical data, antibody profile, electrophysiologic studies, muscle biopsy findings and data regarding treatment, mortality and survival were compared between the 2 groups.
Results. Fourteen biopsies had a fibrosing pattern whereas 26 showed an inflammatory pattern that could be classified attending the predominant pattern into dermatomyositis (DM) (n=7), necrotizing myopathy (n=4) and non-specific myositis (n=15). Additionally, 12 muscle biopsies were reported as neurogenic atrophy (n=2) and normal muscle or minimal changes (n=10). Compared with the inflammatory group, SSc patients with fibrosing pattern presented a higher prevalence of ischemic heart disease (38.5% vs 3.8%, $p=0.011$), conduction abnormalities or arrhythmias (61.5% vs 26.9%, $p=0.036$), anti-topoisomerase I antibodies (42.9% vs 11.5%, $p=0.044$), greater median erythrocyte sedimentation rate (53.5mm/h vs 32.5mm/h, $p=0.013$), with poor response to treatment and a higher mortality (42.9% vs 3.8%, $p=0.004$) and lower cumulative survival ($p=0.035$).
Conclusions. Patients with SSc associated myopathy require a comprehensive approach that encompasses clinical, serological, and histopathological aspects given their outcome predictive capacity. At least two different phenotypes can be drawn considering clinic-pathological features. Significant differences are delineated between both a fibrotic and an inflammatory phenotype.

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USING SMARTPHONE-BASED APP COLLECTED DAILY SYMPTOM DATA TO IDENTIFY AND INVESTIGATE CHARACTERISTICS OF MYOSITIS FLARES - TOWARDS REAL-TIME FLARE DETECTION AND PERSONALISED MANAGEMENT

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Background. "Flares" of idiopathic inflammatory myopathy (IIM) are frequently reported by patients and associated with increased symptom severity. Research into IIM flares and the association with symptoms remains limited. Further, flares are typically identified late in real-world settings, resulting in irreversible muscle damage and disability. The ability to identify the occurrence of an IIM flare in "real-time" could prevent accrual of irreversible muscle damage, and facilitate personalised management. Technological advances and ubiquity of smartphones provides the ability to detect IIM flares and to investigate the associations with symptoms using daily patient reported outcome measurements (PROMs).
This study aimed to use daily smartphone app-collected data from an adult IIM cohort to:
1) Demonstrate the ability of smartphone app-collected data to allow IIM flare identification
2) Investigate the frequency of patient-reported IIM flares
3) Characterise "symptom-based" flares (using an a priori definition)

Methods. UK adults with a verified IIM answered PROMs every day via a smartphone-based app during a 91 day study. Patient-reported flares were recorded via a weekly app binary question ("Have you experienced a flare of myositis in the last seven days?"). Daily symptom PROMs addressed global activity, overall pain, myalgia, fatigue, and weakness (0-100 visual analogue scale [VAS]). Mean symptom scores across the cohort were compared between patient-reported flare and non-flare weeks. "Symptom-based" flares were de-

P-97. Table I. Profiles of symptom-based flares.

	Median number of flare events per participant (IQR)	Total number of flare events across cohort (%†)	Incidence rate / 100 person-days (95% CI)*	Median (IQR) symptom 4 day trailing mean on first day of flare	Median (IQR) magnitude of symptom score increase on first day of flare	Median (IQR) score of "peak" of flare	Median (IQR) flare duration / days
Global activity	5.5 (2.8, 8.0)	107 (20.0)	18.8 (15.4, 22.7)	31.0 (22.4, 43.8)	15.8 (12.0, 21.8)	52.0 (38.0, 71.3)	3.0 (2.0, 4.0)
Fatigue	6.0 (3.8, 9.3)	128 (24.9)	23.0 (19.2, 27.3)	36.8 (25.8, 52.6)	18.6 (13.2, 27.2)	64.0 (51.0, 76.0)	2.0 (2.0, 4.0)
Weakness	4.5 (2.0, 8.0)	107 (20.0)	17.8 (14.6, 21.5)	36.8 (25.8, 46.4)	17.5 (12.8, 30.5)	62.0 (46.5, 77.5)	3.0 (2.0, 4.0)
Myalgia	3.0 (1.8, 6.3)	87 (16.3)	13.2 (10.5, 16.2)	25.8 (20.9, 40.6)	17.3 (13.6, 24.0)	47.0 (36.0, 66.0)	3.0 (2.0, 4.0)
Overall pain	5.0 (1.8, 8.3)	106 (19.8)	17.3 (14.2, 20.9)	28.4 (21.1, 42.6)	17.3 (13.3, 23.2)	49.0 (36.5, 69.0)	3.0 (2.0, 4.0)

†Calculated as percentage of all symptom-based flares identified. *Denominator was number of eligible person-days (*i.e.* available 4 day trailing mean and resolution of previous flare). IQR: interquartile range; CI: confidence interval.

fined via an *a priori* definition of a symptom score increase of more than 10 points higher than the four day trailing mean; this definition was based on previous qualitative work, where participants identified that flares were characterised by brief increases in symptoms compared to their recent "baseline". Characteristics, including incidence and duration, of detected symptom-based flares were calculated for each symptom separately (global activity, overall pain, myalgia, fatigue, weakness). The synchronicity of patient-reported flares and symptom-based flares was calculated.

Results. Twenty participants (65% female) participated. A total of 78 (33% of 233 eligible responses submitted) flare weeks and 155 (67% of 233 responses submitted) non-flare weeks were reported across the cohort. Patient-reported flares occurred on a median of five weeks (IQR 3, 7) per participant, out of a possible 13. The mean of each symptom score was significantly higher in flare weeks, compared to non-flare weeks (e.g. mean flare week myalgia score 34/100, vs 21/100 during non-flare week, t-test p-value <0.01). A total of 535 individual symptom-based flares were identified and began on 269 individual eligible person-days. One hundred and forty (52%) symptom-based flares occurred without the co-occurrence of another symptom-based flare and 129 (48%) identified symptom-based flares occurred concurrently with at least one other. Fatigue symptom-based flares occurred most frequently, had the highest score increase on the first day of a flare, and the highest peak score (Table I). Myalgia flares were least common and had the lowest peak score. Flares typically resolved after three days, however fatigue flares were shorter, typically lasting two days. Out of the 78 patient-reported flare weeks, 54 (69%) coincided with at least one symptom-based flare of any of the five symptoms. Of the 155 patient-reported non-flare weeks, 61 (39%) coincided with no symptom-based flare.

Conclusions. Smartphone app-collected daily symptom data can be used to detect IIM flares. IIM symptom-based flares are frequent, of short duration, and most commonly characterised by increased fatigue. This study has also demonstrated the utility of frequent smartphone-based data collection and the ability of such data to facilitate insights into the characteristics of IIM flares, paving the way towards personalised treatment and real-time flare identification, thus facilitating instigation of flare-mitigating/terminating interventions.

P-98

EFFECT OF AN 8-WEEK PHYSICAL THERAPY PROGRAM ON SEXUAL FUNCTION IN FEMALE PATIENTS WITH IDIOPATHIC INFLAMMATORY MYOPATHIES AND SYSTEMIC SCLEROSIS: A PILOT CONTROLLED STUDY

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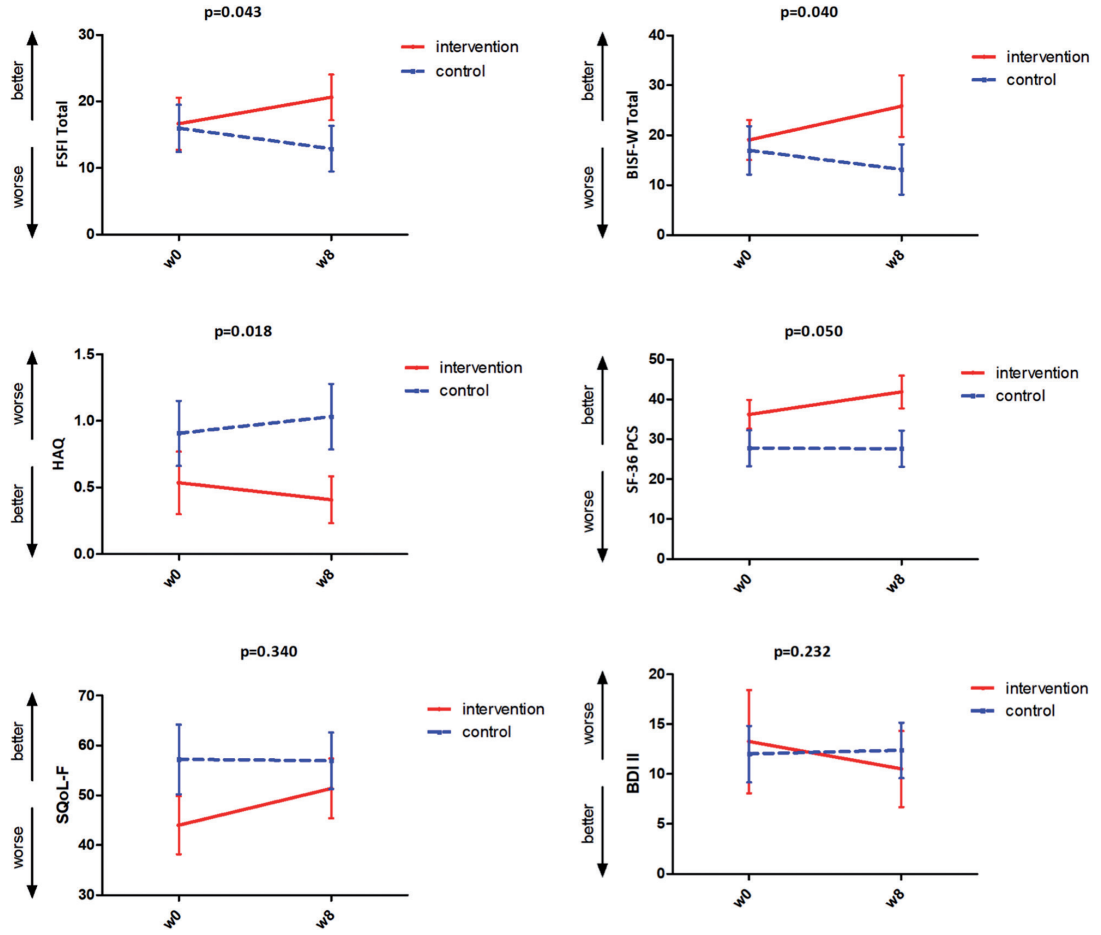
Background. Rare systemic autoimmune rheumatic diseases like idiopathic inflammatory myopathies (IIM) and systemic sclerosis (SSc) may affect all aspects of life, including sexual health. However, no non-pharmacological treatment has been proposed to date addressing these issues. This pilot project aims to investigate the effect of an 8-week physical therapy program on sexual function in women with IIM and SSc.

Methods. In total, 8 female patients with IIM and 8 with SSc, who fulfilled the 2013 ACR/EULAR criteria for SSc and the 2017 EULAR/ACR criteria for dermatomyositis/polymyositis, were enrolled in the study. Based on patients' possibilities and willingness to participate in the program, they were divided into an intervention group (IG) (4 IIM/4 SSc, mean age: 46.8±3.1 years) and a control group (CG) (4 IIM/4 SSc, mean age: 46.3±3.0 years). The IG underwent an 8-week tailored physiotherapy program, including the pelvic floor exercise and physiotherapy aimed at musculoskeletal problems subjectively limiting the patients' sexual function (1 hour of supervised physiotherapy twice weekly), whereas the control group received no physiotherapy. At weeks 0 and 8, all patients filled in questionnaires assessing sexual function: Female Sexual Function Index (FSFI), Brief Index of Sexual Functioning for Women (BISF-W); sexual quality of life: Sexual Quality of Life-Female (SQoL-F); functional ability: Health Assessment Questionnaire (HAQ); quality of life: Medical Outcomes Short Form-36 (SF-36), and depression: Beck's Depression Inventory-II (BDI-II). At the

P-98. Fig. 1.



baseline, patients were assessed by a physician (medical history, MITAX, MYOACT, mRSS, ESSG activity score) and by a physiotherapist (pelvic floor function assessment–PERFECT scheme, MMT-8, Functional Index-2). Normality of data was tested, and inter-group analysis was performed with 2-way ANOVA, and intra-group analysis by Friedmann's test.
Results. Significant deterioration was observed in CG over the period of 8 weeks, whereas in the IG, we found a statistically significant improvement in both sexual function questionnaires [FSFI (p=0.043) and BISF-W (p=0.040)], in functional status [HAQ (p=0.018)], and in quality of life [SF-36 Physical Component Score (p=0.050)]. Only numerical improvement in IG compared to numerical deterioration in CG, which has not reached statistical significance, was observed in SQoL-F, BDI-II, and SF-36 Mental Component Score.
Conclusions. Our physiotherapy program not only prevented the natural course of progressive deterioration of functional abilities but also led to a significant improvement in sexual function, disability, and overall quality of life in women with SSc and IIM. Thus, physical therapy might become one of the possible therapeutic modalities for sexual problems in women with SSc and IIM.
Acknowledgements. Supported by MHCR 023728, SVV–260523, GAUK-1578119.

P-99

DESIGN OF A GLOBAL PHASE 2/3 RANDOMIZED, PLACEBO-CONTROLLED TRIAL OF THE LONG-ACTING ANTI-C5 ANTIBODY RAVULIZUMAB IN ADULT DERMATOMYOSITIS

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Background. The rare and life-altering chronic immune-mediated disease dermatomyositis (DM) is characterized by distinct skin rashes and/or progressive muscle weakness and other systemic manifestations. For many patients, established DM medications (e.g., high-dose systemic steroids and immunosuppressive therapies, frequently prescribed off-label) inadequately control symptoms and/or lead to severe adverse effects, highlighting the need for new DM treatments with improved risk-benefit profiles. The classical complement pathway, including endothelial deposition of the C5b-9 membrane attack complex (MAC), is thought to play a key role in organ damage in DM. The long-acting anti-C5 monoclonal antibody ravulizumab, which is approved for the treatment of several complement-mediated diseases, causes the immediate, complete, and sustained inhibition of C5, thereby preventing its cleavage to form MAC and pro-inflammatory mediators. Given the need for new DM therapies and the evidence implicating terminal complement proteins in DM pathophysiology, we designed a global, double-blind, randomized, Phase 2 (Part A)/Phase 3 (Part B) trial to evaluate the efficacy and safety of ravulizumab compared with placebo in adults with DM (ALXN1210-DM-310; NCT04999020; EudraCT2021-001200-15).
Methods. A total of 180 adults with DM who have active disease with muscle weakness and inadequate responses or intolerances to two or more DM medications will be randomized to receive ravulizumab or placebo, delivered intravenously as a loading dose followed by maintenance dosing once every eight weeks. Parts A and B will contain different participants and each part will consist of a screening period, a randomized, controlled period (Part A; 26 weeks; Part B: 50 weeks), and an open-label extension period. The primary endpoints are the percentage of participants with a ≥20-point improvement from baseline on the ACR/EULAR Myositis Response Criteria Total Improvement Score (TIS20) at 26 weeks (Part A) and 50 weeks (Part B). In addition, a variety of secondary and exploratory outcome measures will be assessed, including mean changes from baseline in the Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI) activity score and a novel participant-reported assessment, the Dermatomyositis-Disease Symptoms Questionnaire (DM-DSQ). Safety evaluations will focus on the incidence rates of treatment-related adverse events (TEAEs), such as those classified as serious and/or leading to treatment discontinuation.
Results. The ALXN1210-DM-310 trial is currently enrolling patients in multiple countries.
Conclusions. ALXN1210-DM-310 is the first global, randomized, placebo-controlled Phase 2/3 trial designed to evaluate the efficacy and safety of a C5 inhibitor in adult patients with DM who have active disease despite treatment with standard medications.
Acknowledgements. The authors would like to acknowledge Korie Handwerger, PhD (Alexion, AstraZeneca Rare Disease) for medical writing support.

P-100

A RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE 3 STUDY EVALUATING THE EFFICACY, SAFETY AND PHARMACOKINETICS OF IGPRO20 (SUBCUTANEOUS IMMUNOGLOBULIN) IN ADULTS WITH DERMATOMYOSITIS: RECLAIIM STUDY DESIGN

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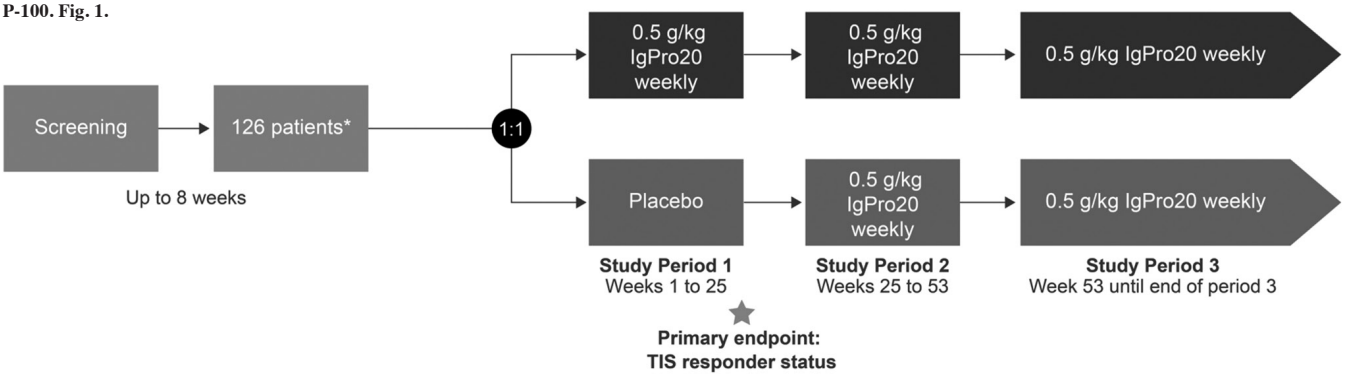
Background. Dermatomyositis (DM) is a chronic systemic autoimmune disease characterised by a distinctive rash and symmetrical proximal muscle weakness. DM affects the joints and organs of the pulmonary, gastrointestinal and cardiovascular systems with varying frequency. Given the multisystem involvement and paucity of therapeutic agents, DM is associated with substantial morbidity and mortality. Approximately 30–40% of patients with DM experience an unsatisfactory response to conventional treatments such as immune-modifying drugs and/or corticosteroids. Human intravenous immunoglobulin (IVIg) is currently available to patients with DM who have experienced a poor response to first-line therapies. Subcutaneous immunoglobulin (SCIg) administration is an alternative to IVIg and may offer fewer bioavailability fluctuations versus IVIg, the potential for home therapy due to a simple infusion technique and no requirement for venous access. The ongoing Phase 3 RECLAIIM study (NCT04044690) aims to assess the efficacy, safety and pharmacokinetics of IgPro20, a normal human immunoglobulin preparation for SC administration versus placebo in adults with DM.
Methods. Adult patients (≥18 years of age) with DM with/without muscle weakness are being enrolled into this Phase 3, multicentre, randomised, placebo-controlled, double-blind study. Inclusion criteria are: meeting DM classification as per 2017 European League Against Rheumatism/American College of Rheumatology Classification Criteria), including confirmation of DM rash/manifestation, disease activity defined by the presence of DM rash/manifestation or an objective disease activity measure; disease severity defined by Physician Global Activity ≥2.0 cm on a 10 cm visual analogue scale (VAS) and Manual Muscle Testing of 8 muscle groups (MMT-8) score ≤142 or Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI) total activity score ≥14; and stable corticosteroid daily dose equivalent to ≤20 mg prednisolone. Key exclusion criteria are

P-100. Fig. 1.



*Expected number of patients enrolled with DM, with or without muscle weakness.
DM, dermatomyositis; TIS, Total Improvement Score.

cancer-associated myositis; evidence of active malignant disease or malignancies diagnosed within the past 5 years; and a Physician Global Damage score ≥3 or clinically relevant improvement between screening visit and baseline. After the initial screening period (≤2 months; Figure 1), patients enter study period 1 (up to Week 25) and receive IgPro20 0.5 g/kg weekly administered subcutaneously or placebo along with concomitant immunosuppressive drug(s). During study period 2 (Weeks 25–53), all patients will enter open-label extension to receive IgPro20 0.5 g/kg weekly. Long-term efficacy and safety data for IgPro20 will be collected during the final study period 3 (starting Week 53) for patients who have shown a treatment benefit at the end of study period 2. The primary efficacy measure is responder status as defined by a Total Improvement Score ≥20 points at Week 25, and at least 1 of the evaluations at Week 17 or 21 in patients who complete 24 weeks of IgPro20 treatment without the use of rescue corticosteroid treatment. Secondary efficacy measures include changes in MMT-8 and CDASI scores, and proportion of patients achieving ≥25% reduction in corticosteroid daily dose at Week 25. Safety assessments include monitoring of adverse events, clinical laboratory assessments, vital signs, 12-lead electrocardiography and physical examination. Blood samples are taken pre-and post-dose for pharmacokinetic analysis.

Conclusions. The RECLAIIM study started in October 2019 and is expected to complete in 2024 with 126 patients randomised. The results will provide evidence for SCIg therapy with IgPro20 in DM, and help to establish its efficacy, safety and pharmacokinetic profile for the treatment of patients with DM.

Acknowledgements. This study is sponsored by CSL Behring. The authors would like to thank the patients who are participating in this study and their families, and to patients who may participate in this study. Writing support was provided by Shannah McGauran, BSc, of OPEN Health (London, UK) and was funded by CSL Behring.

P-101

COMPARATIVE ANALYSIS OF SINGLE VERSUS MULTIPLE DISEASE MODIFYING ANTI-RHEUMATIC DRUGS IN JUVENILE DERMATOMYOSITIS-30-YEAR EXPERIENCE FROM NORTH INDIA

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Background. Juvenile dermatomyositis (JDM) is a rare disorder lacking uniform treatment protocol. The purpose of our study is to evaluate the changes of treatment over time, to determine factors leading to unfavourable outcome and mortality in children receiving single or multiple disease modifying anti-rheumatic drugs (DMARDs) in a resource-limited country.

Methods. Records of 140 children diagnosed to have JDM during 1992-2022 were retrieved. Profile of different DMARDs use and comparison between single and multiple DMARDs were analysed.

Results. Out of 140 cases, 40 received multiple DMARDs. Glucocorticoids with or without methotrexate was the initial treatment in early cohort of our study. Use of cyclophosphamide as initial therapy started after 2015.Number of cases receiving mycophenolate mofetil (MMF), cyclophosphamide (CYC), azathioprine (AZA), rituximab (Rtx) were 14,21,9 and 3 respectively. Most common cause for addition of second DMARD was non-response (18) followed by severe disease (15). Weakness of respiratory muscles, higher manual muscle testing score (MMT8) were significantly associated with requirement of multiple DMARDs. Among multiple DMARDs, cyclophosphamide receiving group had the highest mortality. Age of onset, delay in diagnosis, and presence of calcinosis were not significantly associated with increased DMARDs. Mortality was significantly higher in multiple DMARDs group signifying severe disease.

Conclusions. Multiple DMARDs were required in severe disease and was associated with increased mortality. Low MMT 8 scoring and respiratory weakness at diagnosis are predictors for additional DMARDs.

Acknowledgements. Allergy Immunology Unit, Department of Pediatrics, Advanced Pediatrics Centre, PGIMER Chandigarh, India.

P-101. Table I. Comparison between patients receiving single and multiple DMARDs

Characteristics	Single DMARDs (n=100)	Multiple DMARDs (n=40)	*p* value
Age at onset of symptoms (year) Mean ± SD	6.3±1.3	6.7±2.1	0.534
Delay in diagnosis (months) (Mean ± SD)	8.9±1.1	7.6±2.2	0.466
MMT-8 score at admission (Mean ± SD)	53.1±14.6	38.6±13.1	**0.00001**
Respiratory Muscle weakness	8	8	**0.043**
Calcinosis	27	14	0.173
Follow-up duration (person-years)	7.3±2.9	4.6±1.6	**.008**
Adverse events	9	8	0.088
Mortality	6	5	**0.032**

P-102

CLINICAL RESPONSE AND B CELL PHENOTYPE IN ADULT PATIENTS WITH IDIOPATHIC INFLAMMATORY MYOSITIS (IIM) TREATED WITH BELIMUMAB

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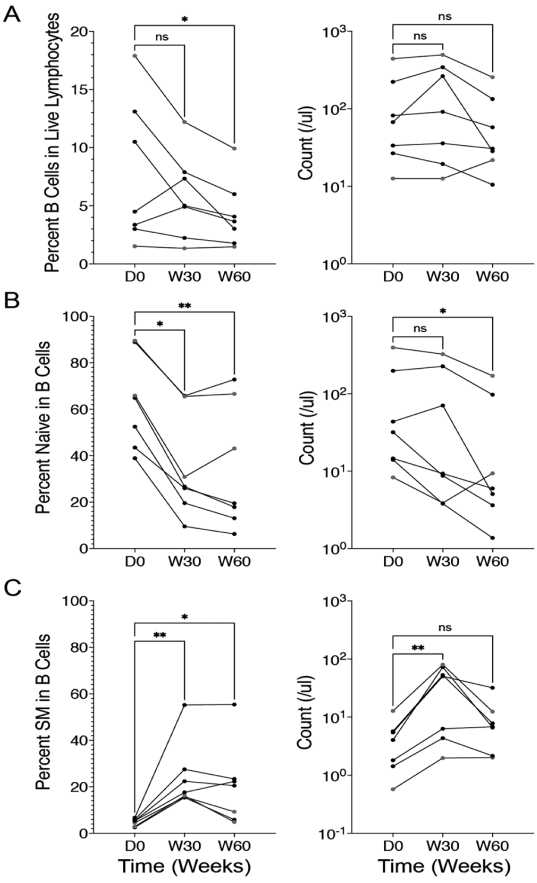
Background. Treatment of Idiopathic Inflammatory Myositis (IIM) includes steroids and immunosuppressive agents. The role of B-cell depleting therapy remains uncertain. B cell activating factor (BAFF) overexpression leads to B cell hyperplasia and autoimmunity. Elevated serum levels of circulating BAFF in patients with myositis independently correlates with markers of myositis disease activity. B and plasma cells in muscle tissues of IIM patients have marked up-regulation of the BAFF transcript, and high expression of BAFF receptors (BAFFR). This study aims to evaluate clinical and biological effect of targeting BAFF pathway in IIM.

Methods. This was a 40-week multicenter randomized, double blind, placebo-controlled trial with a 24-week open label extension of belimumab for adults with refractory IIM, meeting ACR 2017 classification criteria of polymyositis/dermatomyositis (PM/DM) with MMT8 <125/150. Refractory IIM was defined as inadequate response and/or intolerance to 3 months of at least one immunosuppressive agent. Patients were randomized 1:1 to IV belimumab 10mg/kg or placebo for 40w followed by a 24w open label phase with belimumab 10mg/kg. The primary objectives included the proportion of patients reaching Definition of Improvement (DOI) and Total Improvement Score (TIS) at w40. Secondary objectives included clinical response at w64 steroid sparing effect, safety analysis and effect of belimumab on B cell frequency in patients with IIM. To evaluate B cells response, available samples were analyzed at three time points: before starting belimumab (baseline) and after w30-40 and w60-64 of receiving



P-102. Fig. 1. A-C. Plots show percent **(Left)** and number **(Right)** of B cells **(A)**, Naive **(B)** and Switched Memory **(C)** B cells in peripheral blood of IIM patients before (D0), 30-40 (W30), and 60-64 (W60) weeks after Belimumab treatment (n=7). Shown **in red** are patients who reached moderate or major TIS after the treatment. ANOVA Friedman test with Dunn's multiple comparisons, **p*<0.05, ***p*<0.005, ns = p not significant.

belimumab. The number and % of B cells and B cell subsets (transitional, naïve, double negative, memory, and plasmablasts) were analyzed using flow cytometry. Descriptive statistics, the Mann-Whitney test, Fisher's exact, and ANOVA Friedman tests were used to compare groups for continuous and categorical variables, respectively.

Results. 17 subjects were randomized; baseline demographic and clinical characteristics were balanced. 15 subjects received at least 4 doses of study drug and were included in the efficacy analysis (9 belimumab; 6 placebo). By w40 both groups had similar response by DOI (belimumab 37.5%, SoC 16.7%, NS) and mean TIS (belimumab arm 38.3 / SoC 34.5, NS). Moderate or major improvement was more frequent in the belimumab arm (belimumab 62.5%, SoC 33.0%, NS). 2/16 patients, both from the belimumab arm, had a major response (TIS= 72.5) at 40w. After the open label phase (w64) no patients in the original SoC arm achieved DOI, while 42.9% of subjects randomized to belimumab attained DOI (NS). The frequency of moderate or major improvement remained higher in original belimumab arm (belimumab 57%, SoC 40.0%, NS) and no steroid sparing effect was observed in either arm. The baseline B cell count, phenotype and % of B cells in IIM patients were comparable to those reported in healthy donors. Although there was significant drop in % of B cells upon treatment, the absolute count did not change (Fig.1A). There was statistically significant drop in the % and number of naïve B cells (Fig.1B), but the magnitude of the drop was 3-fold less than reported in belimumab treated SLE. Memory B cells were significantly increased 6 months after initiation of belimumab treatment and although they subsequently declined, they did not deplete below baseline even at w64 (Fig.1C). 1 of the 2 patients with major response did not deplete B cells. There was no significant change in the % and number of ANA+B cells, CD3 cells and non-B, non-T cells after treatment.

Conclusions. A higher proportion of patients on belimumab achieved sustained moderate or major TIS compared to SoC, but the study was underpowered to detect significant differences in clinical efficacy. While the baseline B cell phenotype in IIM patients was normal, belimumab induced only modest B cell depletion that was associated with a prolonged increase of memory B cells, distinct from SLE patient's response. These findings suggest that the mechanisms of B cell survival in IIM could be independent of BAFF.

Acknowledgements. Supported by GSK grant and NIH1R21AR070540-01.

P-103

IDIOPATHIC INFLAMMATORY MYOPATHIES: TREATMENT PATTERNS IN AN INTERNATIONAL COHORT OF 1,418 PATIENTS

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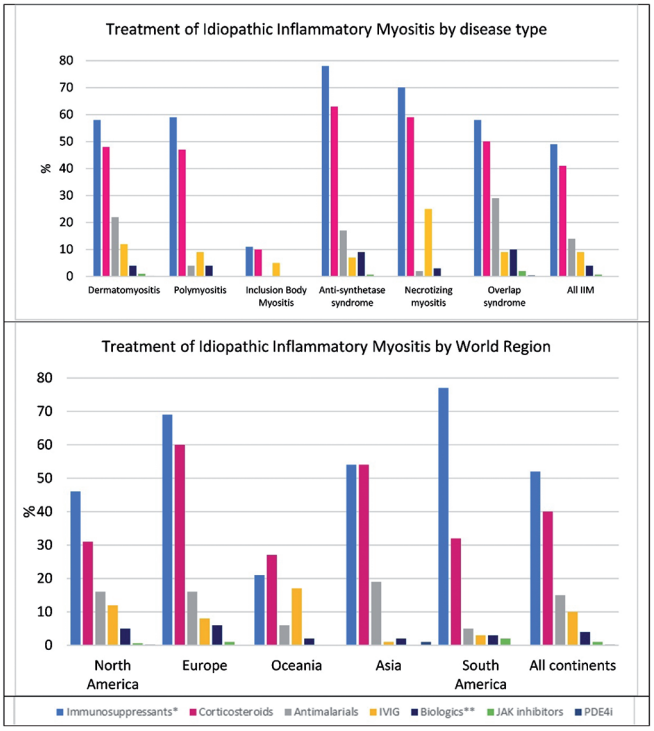
Background. Idiopathic inflammatory myopathies (IIM) are a group of rare and heterogeneous autoimmune disorders with limited standardization of treatment protocols. The objective of the study is to evaluate the frequency and patterns of various treatments used for IIM based on disease subtype, world region, and organ involvement.

Methods. Cross-sectional data from the international CoVAD self-reported e-survey (Parikshit S. et al. Rheumatol Int. 2022 Jan;42(1):23–9) was extracted on Sep 14th, 2021. Patient details included demographics, IIM subtypes (dermatomyositis (DM), polymyositis (PM), inclusion body myositis (IBM), antisynthetase syndrome (ASSD), necrotizing myositis (NM) and overlap myositis (OM)), clinical symptoms, disease duration, disease activity, and current treatments. Treatments were categorized in corticosteroids (CS), antimalarials, immunosuppressants (IS), intravenous immunoglobulins (IVIG), biologics, and others. Typical clinical symptoms (dyspnea, dysphagia) were used as a surrogate for organ involvement. Treatments were presented descriptively according to IIM subtypes, world regions, and organ involvement. Factors associated with the four main treatment categories (IS, CS, antimalarials, IVIG) were analyzed using four separate multivariable logistic regressions, including the treatment as the dependent variable and the following independent variables: IIM subtype, world region, age, disease duration, disease activity, and clinical signs and symptoms with a prevalence >10%.

Results. In 1,418 patients with IIM, the median age was 61 years [IQR 49-70], 62.5% were females, median disease duration was 6 years [IQR 3-11]. The most common subset was DM (32.4%), followed by IBM (24.5%), OM (15.8%), PM (12.8%), ASSD (10.4%), and NM (4.0%). The most used treatments were IS (49.4%, including Methotrexate 19.6%, Mycophenolate Mofetil 18.2%, Azathioprine 8.8%, Cyclosporine 2.7%, Tacrolimus 2%, Leflunomide 1.6%, Sulfasalazine 1%, and Cyclophosphamide 0.6%), followed by CS (40.8%), antimalarials (13.8%) and IVIG (9.4%). Biologics were used in 4.3% of patients (including Rituximab in 3.1%). Other treatments were JAK inhibitors in 0.7% and PDE4 inhibitors in 0.1%. Treatment patterns differed significantly according to the IIM subtypes with a higher frequency of IS (77.7%) and CS (63.4%) use in ASSD, antimalarials (28.6%), and biologics (9.8%) use in OM and IVIG use in NM (24.6%) (Figure). In addition, treatment patterns were different in various regions of the world, with a higher frequency of CS use in Europe (60.5%), antimalarials in Asia (19.4%), and IVIG in Oceania (16.9%) (Figure). Data from Africa (4 patients) and South America (57 patients) was scarce. Dyspnea was associated with higher use of IS (69.9%) and CS (65.8%) (p<0.001), whereas dysphagia was negatively associated with IS (39.7%) and CS (32.7%) likely due to a higher proportion in IBM patients reporting dysphagia (p=0.024 and 0.007, respectively). Multivariable logistic regression analysis confirmed the association of the four treatments with the IIM subtype (treatments were used the least in IBM, whereas IS and CS were mostly associated with ASSD and NM, antimalarials with OM, and IVIG with NM). The association with the world region was also confirmed. Moreover, IS and CS were associated with dyspnea (OR 1.86 [1.09-3.18] and 2.38 [1.46-3.89], respectively). Furthermore, IS, CS, and IVIG were associated with the disease activity (active and improving disease, OR 4.47 [2.45-8.14], 6.92 [3.96-12.09], and 2.75 [1.25-6.07], respectively). In addition, antimalarials were associated with female sex (OR 2.07 [1.13-3.81]), joint pain and swelling (OR 1.60 [1.04-2.47]), and rashes (OR 1.74 [1.04-2.92]), and IVIG were associated with younger age (OR 0.98 [0.96-0.99]) and muscle weakness (OR 2.00 [1.25-3.22]).

Conclusions. IIM treatment patterns differ significantly by disease subtypes, world regions, and organ involvement, highlighting the need for unified international consensus-driven guidelines. Moreover, data from low-income countries is still needed to evaluate the treatment pattern worldwide.



P-103. Fig. 1.

P-104

MORTALITY RISK STRATIFICATION USING CLUSTER ANALYSIS IN PATIENTS WITH MYOSITIS-ASSOCIATED INTERSTITIAL LUNG DISEASE RECEIVING INITIAL TRIPLE COMBINATION THERAPY

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Objective. To identify patients with polymyositis/dermatomyositis-associated Interstitial lung disease (ILD) who benefit from an intensive regimen consisting of high-dose corticosteroids, a calcineurin inhibitor, and intravenous cyclophosphamide (triple-combo therapy) using cluster analysis in a large-scale multicenter retrospective cohort of Japanese patients with myositis-associated ILD (JAMI).
Methods. Unbiased, two-step cluster analysis of pre-clustering and subsequent hierarchical clustering was conducted in 185 patients who received triple-combo therapy in an unbiased way. Predictors of mortality in patients with myositis-associated ILD were used as variables and included age, gender, disease duration, classification of myositis, requirement of supplemental oxygen, anti-aminoacyl tRNA synthetase (ARS) antibody, anti-melanoma differentiation-associated gene 5 (MDA5) antibody, and serum levels of C-reactive protein (CRP) and Krebs von den Lungen-6 (KL-6) at diagnosis. The developed clustering model was applied to 283 patients who received conventional regimens consisting of corticosteroids with or without a single immunosuppressive agent (dual-combo therapy or monotherapy). Cumulative survival rates were compared using Kaplan-Meier analysis and statistical difference between two groups was tested using log-rank test.
Results. We developed a cluster model consisting of 6 clusters, which were categorized by age at disease onset, clinically amyopathic dermatomyositis, CRP, KL-6, requirement of supplemental oxygen, anti-ARS antibody, and anti-MDA5 antibody. This model was judged to be of good quality based on the silhouette measure of cohesion and separation of 0.6. These clusters were re-grouped into three groups based on low mortality rate (<10%), moderate mortality rate (10-50%), and high mortality rate (>50%). The performance of clustering was generally replicated in patients who received initial dual-combo therapy or monotherapy. Survival benefits of triple-combo therapy over dual-combo therapy or /monotherapy were shown in none of the clusters.
Conclusions. We successfully developed a cluster model that divided patients with myositis-associated ILD who were treated with initial triple-combo therapy into subgroups stratified by prognosis, although this model failed to identify a patient subgroup who showed survival benefits in triple-combo therapy over dual-combo therapy or /monotherapy group.

P-105

JAK INHIBITORS IN IDIOPATHIC INFLAMMATORY MYOPATHIES: A CASE-BASED SYSTEMATIC LITERATURE REVIEW

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Background. Idiopathic inflammatory myopathies are a heterogeneous group of rare, autoimmune, diseases, primarily affecting striated muscles. Usually divided into dermatomyositis (DM), polymyositis (PM), juvenile DM (JDM), inclusion body myositis (IBM) and antisynthetase syndrome (ASS), they may also affect lung, skin, joints, heart and gastrointestinal tract with different degrees of severity. Currently, no specific drug is licensed for IIM and treatment relies on conventional immunosuppressants, while the evidence for biologic drugs are de facto limited to Rituximab. Conversely, a growing number of data is reporting a certain degree of efficacy of JAK inhibitors. Thus, the aim of our paper was to report our experience with such drugs and systematically review the current evidence for JAK inhibitors in IIM.
Methods. We retrospectively collected clinical and serological data from all patients who were treated with JAK inhibitors in our "Myositis Clinic" in the last 3 years. Moreover, via Pubmed, we performed an extensive research using the following keywords: "tofacitinib", "baricitinib", "ruxolitinib", "upadacitinib", "filgotinib" and "JAK inhibitors" each combined with "dermatomyositis", "polymyositis", "antisynthetase syndrome", "inclusion body myositis" and "myositis".
Results. In our experience, we employed Tofacitinib and Baricitinib in respectively two and one patients affected by DM. Two were affected by anti-MDA5+ DM with rapidly progressive interstitial lung disease, while the latter by anti-Mi 2+ DM with severe arthritis and skin and muscular involvement, whose onset dated back to the administration of checkpoint-inhibitors for lung carcinoma. Furthermore, we treated with Baricitinib a patient affected by overlap syndrome (rheumatoid arthritis and anti-Jo1+ ASS), who presented with severe skin, muscular and pulmonary involvement. All 4 patients did not respond or suffered from adverse events or had contraindications to other immunosuppressants, but displayed an excellent response to the treatment. Nevertheless, one patient discontinued Tofacitinib due to concomitant thrombophlebitis and Zoster reactivation. Our literature search displayed a total of 30 papers, for a sum of 111 patients (Table I) treated with any JAK inhibitor. The majority was treated with Tofacitinib, which was administered in 67 of them, while 34 received Ruxolitinib and 10 Baricitinib. More robust evidence comes from DM and JDM, which were the disease suffered by 62 and 47 patients, respectively, while only 1 suffered from PM and ASS, each. Autoimmune profile was as follows: 34 were positive for anti-MDA5, 13 for anti-TIF1gamma, 8 for anti-NXP2, 2 for anti-SAE, and 1 for anti-Mi2 and 1 anti-Jo1, each. No data are available for Filgotinib and Upadacitinib, nor for inclusion body myositis. All patients had previously failed at least two conventional immunosuppressants and 108 out of 111 had a good response to JAK inhibitors, both in monotherapy and in combination: 2 patients with anti-MDA5 DM-ILD and poor prognostic factors died and 1 patient with refractory JDM suspended the therapy because of a recurrence of skin disease. Fifteen patients suffered from side effects, mainly viral and bacterial infections, and in 2 of the treatment with JAK inhibitors was stopped. A patient died because of newly onset metastatic lung cancer after clinical remission of DM at 12 months follow up. The daily dosage was variable, ranging for Tofacitinib from 5 to 20 mg, for Ruxolitinib from 5 mg to 30 mg and for Baricitinib from 4 mg to 12 mg.
Discussion. A growing amount of evidence is reporting the efficacy of JAK inhibitors in IIM, namely DM with severe extramuscular involvement, including rapidly progressive ILD. In our experience, we have employed Tofacitinib and Baricitinib in difficult-to-treat subjects, including a patient with lung carcinoma. Our small cohort, as well data coming from literature, have evidenced an overall good safety and efficacy of this class of drugs in IIM, but longitudinal, long-term, studies are needed, particularly in diseases other than DM.

P-105. Table I. Clinical and serological features of patients included in our case-based review.

		Tofacitinib	Ruxolitinib	Baricitinib
Patients (n=115)		69	34	12
Diagnosis and antibodies	DM	55 (30 MDA5, 1 Mi2, 5 TIF1 gamma, 3 NXP2)	7 (1 MDA5, 4 TIF1gamma, 1 SAE)	3 (1 MDA5, 1 Mi2)
	JDM	12 (3 MDA5, 1 Mi2)	27 (4 NXP2, 2 TIF1gamma, 1 MDA5)	8 (2 TIF1gamma, 1 NXP2, 1 MDA5)
	PM	1	0	0
	ASS	1 (JO1)	0	1 (JO1)
Daily dosage		from 5 mg to 20 mg	from 5 mg to 30 mg	from 4 mg to 12 mg
Previous conventional IS (≥2)		69	34	11
Outcome	Remission	67	33	12
	Death	2	0	0
	Side effects	9	4	2

ASS: anti-synthetase syndrome; DM: dermatomyositis; IS: immunosuppressants; JDM: juvenile dermatomyositis; PM: polymyositis.

P-106

ARTIFICIAL INTELLIGENCE IN INFLAMMATORY IDIOPATHIC MYOPATHIES

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Objective. To evaluate the response to treatment with intravenous (IVIg) and subcutaneous (SCIg) in our series of patients with Inflammatory idiopathic myopathies (IIM) by the means of Artificial intelligence (AI).
Background. Dermatomyositis (DM) and polymyositis (PM) are rare IIM with clinical, laboratory and radiological characteristics. Artificial intelligence (AI) represents computer processes capable of performing complex calculations and data analysis, with the least human intervention. The use of AI in medicine increased significantly in recent years, especially through machine learning (ML) which analyzes large information and accordingly makes decisions, and deep learning (DL) which uses artificial neural networks to analyze data and automatically learn.

Methods. In this study, we employed AI in the evaluation of the response to treatment with intravenous (IVIg) and subcutaneous (SCIg) in our series of patients with DM and PM. Diagnoses was based on EULAR/ACR criteria for IIM. The treatment response was evaluated employing the following: serum creatine kinase levels, muscle strength (MMT8 score), disease activity (MITAX score) and disability (HAQ-DI score). We evaluated all the above parameters, applying, with R, different supervised ML algorithms, including lasso, ridge, elastic net, classification and regression trees (CART) and random forest to estimate the most important predictors for a good response to IVIg and SCIg treatment.
Results and Conclusions. By the means of AI we have been able to identify the scores that best predict a good response to IVIg and SCIg treatment.

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SUCCESSFUL MANAGEMENT WITH TOFACITINIB IN ADULT AND JUVENILE DERMATOMYOSITIS

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Background. Dermatomyositis (DM) is a systemic, autoimmune disease affecting the skin, blood vessels, and proximal skeletal muscles of both adult and juvenile individuals. A subset of DM patients present with subclinical or resolved muscle involvement but continue to have skin disease. In these cases, first and second line treatments including glucocorticoids are sometimes insufficient for controlling the disease, necessitating escalation of treatment. Several recent studies have investigated the response of Tofacitinib, an oral Janus Kinase inhibitor approved for the treatment of rheumatoid arthritis, psoriatic arthritis and juvenile idiopathic arthritis, in DM patients and patients with inflammatory skin diseases.
Methods. Seven patients with DM without evidence of current muscle involvement and four patients with evidence began treatment with Tofacitinib 5 to 11 mg daily. They had failed or had adverse effects to first-and second-line immunosuppressive agents. Four of the patients had Juvenile DM (JDM). These patients were all started on 5 mg daily and all were increased to 5 mg twice daily. Their skin disease was measured by the Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI) activity score. Their medical records were reviewed after several visits. Throughout their treatment, patients were additionally monitored for the necessity for concomitant treatments and any adverse effects to Tofacitinib. Extra-cutaneous disease manifestations were also noted while monitoring for improvement in skin disease.
Results. Ten of eleven patients within the case series showed significant improvement of their cutaneous diseaseactivity, indicated by reduction of CDASI score by 7-16 points, over the first 6 months of treatment. Individual scores can be seen in the table provided. Two patients flared when Tofacitinib was tapered, over two and six months respectively (see Table I). However they both regained response to Tofacitinib when restarting this medicine. One patient required use of one dose of Intravenous Immunoglobulin Therapy (IVIG) because of a flare despite continued use of Tofacitinib at eight months. This patient also required concomitant use of Plaquenil. Another patient continued to require concomitant use of Methotrexate due to inflammatory arthritis. One patient required concomitant use of low dose oral Prednisone at 3 mg daily. One patient continued to require concomitant use of IVIG. This patient additionally required use of Colchicine for calcinosis. The patients that required additional treatment had extra-cutaneous manifestations of JDM/DM. A patient with JDM did not respond to Tofacitinib after 2 months and was taken off this medicine. No worsening muscle disease or adverse effects including cardiac events were noted with Tofacitinib use. Ten of eleven patients continue Tofacitinib for their myositis.
Conclusions. Tofacinitib is believed to play a role in the inhibition of IFN signaling pathways that are overactive in dermatomyositis. Ten of the eleven patients within this retrospective study showed significant improvement of cutaneous disease with Tofacitinib use. Other disease manifestations such as arthritis, myositis, and calcinosis may not respond as well as cutaneous disease and therefore further study of JAK inhibition in inflammatory myopathies is warranted.

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P-108

THERAPEUTIC AGENTS, COMBINATIONS AND RESPONSE IN ANTI-JO-1 NEGATIVE ANTISYNTHETASE SYNDROME

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Background. The antisynthetase syndrome is a type of immune-mediated myopathy defined by the presence of inflammatory myopathy and extramuscular findings including interstitial lung disease, "mechanic hands", inflammatory arthritis, and Raynaud phenomenon with an antibody directed against an aminoacyl-transfer RNA (tRNA) synthetase. Among these antibodies, the most frequent is anti-Jo, although antibodies against the following antigens have also been described: PL-12, PL-7, OJ, KS, EJ, Zo and Ha. Corticosteroids have traditionally been used as the first-line agent along other agents like methotrexate, cyclosporine, azathioprine, mycophenolate mofetil and rituximab. Add-on immunoglobulins has been shown to be effective and safe in steroid refractory or worsening episode. The purpose of this study was to examine the therapeutics used and clinical curse and response of this syndrome.
Methods. Retrospective descriptive study on 9 cases with anti-Jo negative antisynthetase syndrome were identified from databases at the Virgen del Rocio Hospital of Seville. As parameters of improvement, we used: absence of symptoms, muscle functional capacity, muscle enzymes, improvement of diffusion lung capacity (DLC) and forced vital capacity (FVC), together with absence of arthritis and no dermatological lesions. High resolution pulmonary CT scans were performed to monitor response in those patients with partial response or worsening.
Results. All patients received initial doses of glucocorticoids adjusted by 0.5-1mg/kg, with a sparing immunosuppressant according to initial involvement. Most of them started treatment with glucocorticoids and methotrexate (1) mycophenolate (2) and azathioprine (1), with general improvement of spirometric tests and functional class. Two patients have been treated with hydroxychloroquine to control joint symptoms. They are currently on corticosteroid lowering and one patient has been able to withdraw complete immunosuppressive treatment. Two of them who started immunosuppressive treatment (one with azathioprine and the other with methotrexate) required subsequent hospital admission for symptomatic control with boluses of methylprednisolone (0.5 g/kg), cyclophosphamide (750 mg) and immunoglobulins (2g/kg). Three patients required at the beginning complete treatment with immunoglobulins, methylprednisolone and cyclophosphamide due to severe involvement at debut (functional class IV, 6-minute test less than 400 m, pseudobulbar involvement, severe drop in DLCO in less than three months). In these patients, rituximab was used as maintenance immunosuppressive treatment at discharge every 6 months. Only one of the patients had hypogammaglobulinemia as a complication. All patients have shown analytical improvement of muscle enzymes and improvement of functional capacity. There has been progression in the high resolution CT in one of the patients with fibrosis pattern. No patient died during follow-up.
Conclusions. In the present descriptive study, we report the good clinical response of anti-JO-1 negative anti-synthetase syndrome to treatment with immunosuppressants. The strategy of "rescue therapy" with immunoglobulins and rituximab has been shown to be effective for functional recovery and limitation of muscle inflammatory activity in both acute and maintenance episodes, with few side effects and complications. Spirometric and inflammatory activity parameters are not well established in the literature, and it is necessary to agree on the activity data to be able to decide on treatment intensification or withdrawal. Further studies are needed to correlate clinical phenotypes and autoantibody expression with treatment response.

P-109

CONSUMER-DRIVEN EVALUATION OF ASSISTIVE TECHNOLOGY USAGE AND PERCEIVED VALUE IN PEOPLE WITH MYOSITIS IN AUSTRALIA

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Background. The Myositis Discovery Programme (MDP) based in Perth, Western Australia works closely with consumers to provide direction and guidance in their research endeavours. Together with the Myositis Association Australia, a

P-107. Table I.

Sex/ Age/ Ethnicity	Subtype duration to date	Previous Treatment	Concomitant Treatment with TOF*	TOF start	Date: Month/Year - CDASI Activity	Other Outcomes
M/ 58/ Caucasian	Amyopathic 9 years	AZA, HCQ, IVIG, MTX, MMF, Prednisone, RCI, RTX, TAC	HCQ - 7/19	4/19	4/19 – 12 7/19 – 5 12/19 – 4 10/20 – 2 7/21 – 2 11/21 – 2	
F/ 62/ Caucasian	Amyopathic 4 years	AZA, MTX, Prednisone, Colchicine	Prednisone MTX - 7/19	5/19	5/19 – 17 7/19 – 15 1/20 – 5 5/20 – 8 7/20 – 10 11//20 – 7 3/21 – 8 7/21 – 7 12/21 – 5	Pruritus improved Calcinosis persists Prednisone continued 3mg/d
F/ 39/ Caucasian	Amyopathic 10 years	AZA, HCQ, IVIG, MTX, MMF, Prednisone, RCI, TAC	IVIG - 1/20 MTX - 5/20 Prednisone - 11/20	6/19	6/19 – 15 9/19 – 8 1/20 – 5 5/20 – 4 3/21 – 3 8/21 – 3	Pruritus and CRP improved
F/ 49 African American	Classic 5 years	AZA, colchicine, HCQ, IVIG, MTX, MMF, pamidronate Prednisone, RCI, RTX, TAC	IVIG, Colchicine	6/19	6/19 – 22 8/19 – 8 11/19 – 7 2/20 – 7 5/20 – 7 7/20 – 7 11/20 – 4 3/21 – 4 9/21 – 4	Pruritus and calcinosis improved IVIG continued
F/ 71/ Caucasian	Amyopathic 4 years	AZA, HCQ, MMF, Prednisone		1/20	12/19 – 11 3/20 – 2 5/20 – 1 9/20 – 0 1/21 – 0 4/21 – 0 9/21 – 0 12/21 – 1	Stopped TOF → flare after 6 months off treatment → regained response
F/ 61/ Caucasian	Amyopathic 9 years	HCQ, IVIG, MTX, MMF, Prednisone, RTX, TAC		2/20	2/20 – 15 4/20 – 4 6/20 – 2 11/20 – 2 3/21 – 2 6/21 – 2 7/21 – 9 11/21 – 1	Stopped TOF → flare after 2 months off treatment → regained response
F/ 10/ Caucasian	Classic 6 years	AZA, HCQ, IVIG, LEF, MTX, MMF, Prednisone, TAC	HCQ IVIG - 10/20	4/20	4/20 – 16 6/20 – 0 8/20 – 1 11/20 – 6 12/20 – 2 1/21 – 0 4/21 - 0 5/21 – 0 6/21 – 0 10/21 – 0 2/22 – 0	Skin and muscle Flare 11/20 → regained response with IVIG → off IVIG 10/20
F/ 39 / Caucasian	Amyopathic 2 years	MTX, HCQ		6/20	6/20 – 17 7/20 – 4 8/20 – 3 12/20 – 1 3/21 – 0 8/21 – 0 11/21 – 0	
F/ 8/ Caucasian	Classic 5 years	AZA, HCQ, IVIG, MTX, MMF, Prednisone, RTX		8/20	8/20 – 14 10/20 - 14	No response, stopped TOF → switched to Abatacept
M/ 9/ Caucasian	Amyopathic 2.5 years	HCQ, MTX, Prednisone		10/20	10/20 – 16 1/21 – 11 4/21 – 7 6/21 – 5 10/21 - 4	
M/ 8 Hispanic	Classic 1.5 years	Prednisone	MTX (added for arthritis)	3/21	3/21 – 8 4/21 - 4 6/21 – 1 9/21 – 1 1/22 – 0	Significant improvement in arthritis

AZA: azathioprine; CDASI: Cutaneous Dermatomyositis Disease Area and Severity Index CRP: C-reactive protein; DC: discontinue; HCQ: hydroxychloroquine; IVIG: intravenous immunoglobulin; MTX: methotrexate; MMF: mycophenolate mofetil; RCI: repository-corticotropin injection; RTX: rituximab; TAC: tacrolimus; TOF: tofacitinib.
*Provided dates indication discontinuation date of concomitant treatment while the patient continued to take TOF.

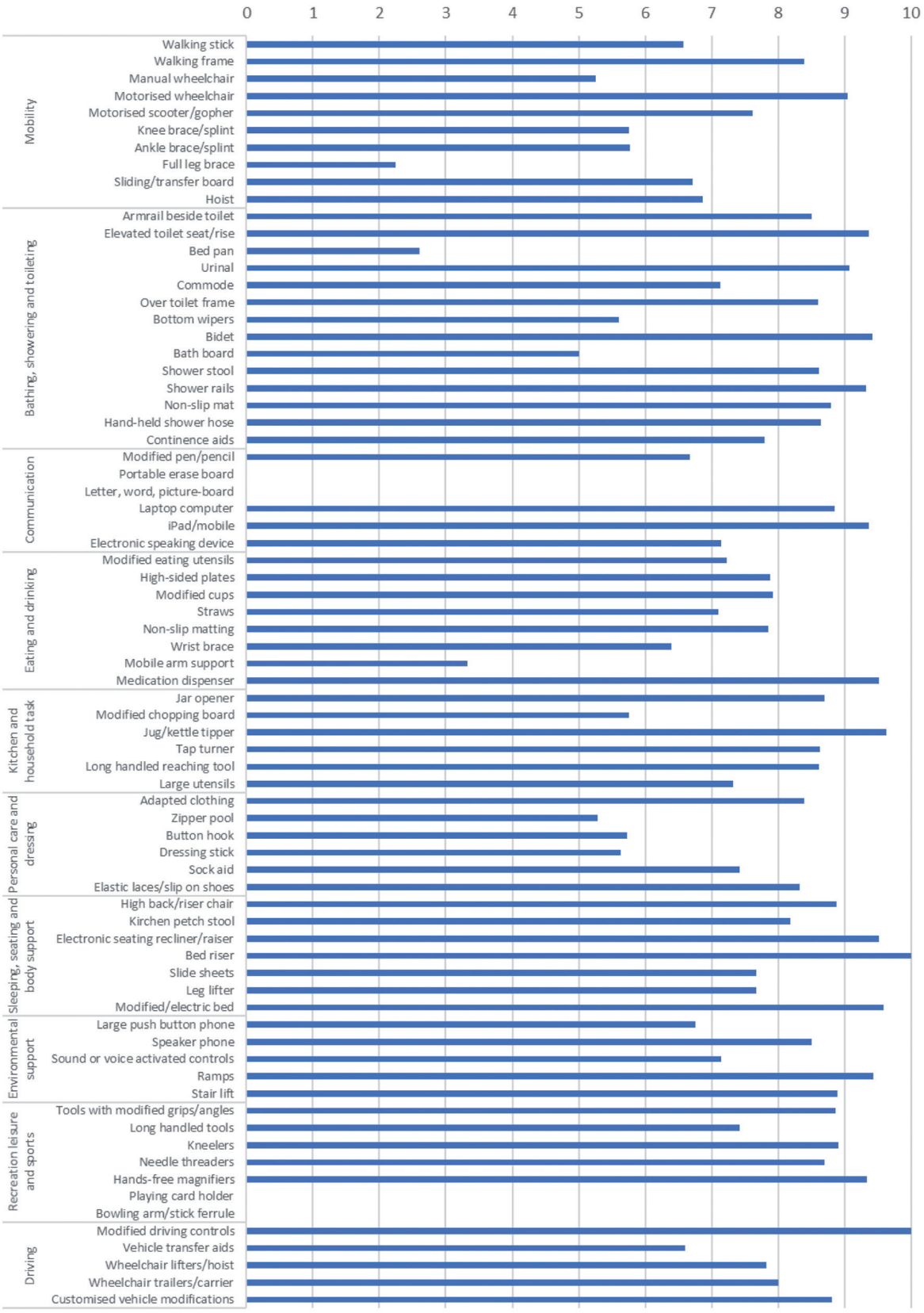
Myositis Research Consumer Panel was established. Comments from members of the Panel during meetings revealed that they felt they learn more about Assistive Technology (AT) from their peers than from health professionals. As a result of this discussion, a study was initiated to investigate usage and perceived value of AT used by people with myositis.

Methods. Based on literature review, therapist advice and input from the Myositis Research Consumer Panel, an online survey (Qualtrics) was designed to capture information regarding AT use and value, as well as information regarding demographics, health status and quality of life, including via validated questionnaires. Members of the Myositis Association Australia and patients of the MDP (Perth, Australia) were invited to participate. Participants were asked to rate the 'usefulness' of items of AT that they use and were asked to complete health status information via the Neuromuscular Symptom Score (NSS) as well as well-being status via the 'Patient Health Questionnaire (PHQ-9)' and 'Personal Wellbeing Index (PWI)'.

Results. 102 myositis patients completed the survey, with majority of respondents diagnosed with IBM (n=80). 100 participants owned at least one AT device with an average of 14 items owned. The most used assistive devices pertained to bathroom and mobility. Participants rated AT devices relating to environmental support, sleeping, seating and body support as most useful. There was a correlation between disease severity and numbers of devices used. Additionally, it was found that most people with myositis self-funded their own AT. It was hypothesised that items which aided mobility would be most valued, however this was not found to be the case, with items that help patients to retain their independence rather than simply provide physical assistance (*e.g.* smart phones, tablets, modified driving controls) rated most valuable.

Conclusions. As expected, AT device usage is high among people with myositis, particularly those with more severe or disabling disease. Most items were deemed to be of value, however, AT devices that support people with myositis to retain independence were found to be of higher value than AT devices that provide physical support alone.

Acknowledgements. We would like to thank Members of the Myositis Association Australia, Myositis Research Consumer Panel, and patients and supports of the MDP, Perth, Australia.



P-109. Fig. 1. Mean usefulness of AT devices.

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CLINICAL CHARACTERISTICS AND THERAPEUTIC RESPONSE OF PATIENTS WITH MYOSITIS TREATED WITH RITUXIMAB

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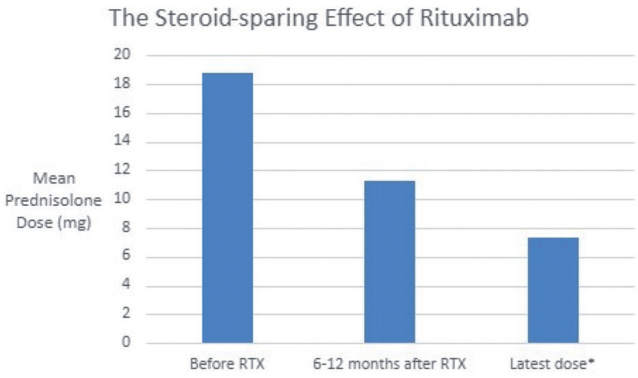
Background. Studies have reported safety and efficacy of the use of rituximab in patients with severe and refractory myositis. Eligibility for rituximab in the UK requires patients to fulfil EULAR/ACR classification criteria, have a myositis antibody, and have failed on two or more immunosuppressive or immunomodulatory drugs. We present results of an observational retrospective study describing the clinical characteristics, safety and steroid/IV Ig sparing effects in patients with myositis receiving treatment with rituximab.
Methods. Data were collected using the Salford Royal Hospital Electronic Patient Records system. A list of 33 patients from the MYOPROSP-MYOACT registry who received rituximab from 2013 to March 2021 was obtained. Patients were assessed at multiple timepoints: baseline and during follow-up at 3, 6, 12, 24 and 48 months since first rituximab infusion. Clinical characteristics as well as baseline and follow-up treatment changes, glucocorticoid doses and laboratory results at each visit were also recorded.
Results. Of 34 patients, 73% were female and the majority were Caucasian (88%). The mean age of onset of disease was 43 years, and mean age at rituximab treatment 49 years. The most prevalent disease subtype was dermatomyositis (32%), followed by anti-synthetase syndrome (29%), overlap syndrome (18%), polymyositis (12%), and immune mediated necrotising myopathy (9%). 94% of the patients had at least one myositis specific/associated autoantibody, the most common being anti-Jo-1 (26%) and/or anti-Ro (18%). Two of the patients were seronegative. The eligibility criteria were met by 94% of the cohort. Six to twelve months after the first rituximab cycle, there was an average 36% steroid dose reduction from 19 mg to 11 mg prednisolone and an overall 69% reduction since starting rituximab treatment. For courses received, 15 patients had at least three or more rituximab cycles, with a maximum of 9 cycles in one patient. A third of patients had converted from IV Ig to rituximab treatment with an estimated annual saving of £736,340. Allergic reactions and infections were the most common adverse events, mild in nature with no hospital admission required.
Conclusions. This retrospective study provides data suggesting that rituximab is a safe and effective treatment for patients with refractory myositis, with both steroid and IVIg sparing effects.



P-110. Fig. 1.

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'TIME IS MUSCLE': A DOUBLE-BLIND RANDOMIZED CLINICAL TRIAL OF INTRAVENOUS IMMUNOGLOBULIN AND PREDNISONE VERSUS PREDNISONE IN NEWLY DIAGNOSED MYOSITIS: THE STUDY DESIGN

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Background. Idiopathic inflammatory myopathies (IIM, also known as myositis), include dermatomyositis, anti-synthetase syndrome, overlap myositis and immune mediated necrotizing myopathy. The standard initial treatment is high dosed glucocorticoids, which results in relatively slow improvement of muscle strength. Early intensive treatment ('hit-early, hit-hard') may induce faster reduction of disease activity and prevent chronic disability due to disease damage. Compared to other immunomodulating compounds, intravenous immunoglobulin (IVIg) is more fast-acting, which could lead to an early and sustained suppression of the inflammatory process when administered together with glucocorticoids. Addition of IVIg may be promising in this regard: data from previous studies have shown that add-on IVIg improved symptoms and muscle strength in refractory myositis patients, and that monotherapy IVIg improved outcomes after nine weeks in about half of treatment naive patients. We hypothesize that early add-on IVIg leads to a greater clinical response after twelve weeks in patients with newly diagnosed myositis, in comparison to prednisone monotherapy. Secondary, we expect that early treatment with add-on IVIg leads to a shorter time to improvement and sustained positive effects on health-related quality of life, physical activity, fatigue and reduction of muscle MRI abnormalities on the longer term (26 and 52 weeks).
Methods. The Time Is Muscle trial is a phase-2 double-blind randomized controlled clinical trial. Recruitment of patients will be performed through the Dutch Myositis Network (DMN), a collaboration between myositis centres in the Netherlands. The Amsterdam UMC is major hub and serves as a tertiary referral centre for IIM. Based on 2.5-3 referrals for suspected myositis per month (ongoing ADAPT study), we expect to include 1-2 patients per month. Following a power analysis based on data of the IMMEDIATE study, we aim to include 48 patients with IIM. Participants will be treated with IVIg or placebo at baseline and after 4 and 8 weeks, in addition to standard therapy with prednisone. The first infusion will be administered within one week after diagnosis. The primary outcome is the Total Improvement Score (TIS) of the myositis response criteria after 12 weeks compared to baseline. At baseline, and after 4, 8, 12, 26 and 52 weeks, secondary outcomes will be assessed, including time to improvement, daily prednisone dosage, physical activity (accelerometer) and MRI muscle imaging parameters.
Discussion. Time Is Muscle study is a double-blind randomized controlled trial in early myositis aiming to provide evidence for an effect of IVIg in addition to standard treatment with prednisone in the first three months after diagnosis. The secondary outcomes will provide useful data for future trial designs in IIM. As of yet (February 2022) the inclusion rate is one per month (n=6) and we expect to conclude enrolment of patients in the first half of 2024. At the conference, the concept of the Dutch Myositis Network will be presented, in addition to the detailed study design.
Acknowledgements. Several authors of this publication are members of the Netherlands Neuromuscular Center (NL-NMD) and the European Reference Network for rare neuromuscular diseases ERN-EURO-NMD.

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TREATMENT OF ACTIVE IDIOPATHIC INFLAMMATORY MYOSITIS BY INHIBITING FCRN: PRE-REGISTRATION REPORT OF ALKIVIA, A PHASE 2/3 TRIAL WITH EFGARTIGIMOD

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Background. Idiopathic inflammatory myositis (IIM) is a heterogeneous group of diseases that includes subtypes with varying pathologies primarily targeting muscle and/or skin and other organs. In many subsets, there is a potential role of myositis-specific autoantibodies, most of which are immunoglobulin G (IgG) in the disease pathogenesis. The neonatal Fc receptor (FcRn) maintains constant levels of IgG in the serum by rescuing IgG antibodies from lysosomal degradation following uptake into cells. Efgartigimod is an engineered Fc fragment that inhibits FcRn function by outcompeting endogenous IgG binding, resulting in reduced IgG recycling and increased IgG degradation. ALKIVIA is a global Phase 2/3 randomized, double-blind, placebo-controlled trial of efgartigimod in patients with active IIM. The primary objective of ALKIVIA is to evaluate the efficacy and safety of efgartigimod PH20 subcutaneous (SC) treatment compared with placebo, in addition to standard-of-care immunomodulatory therapy, for the treatment of IIM.
Methods. Adults with a diagnosis of immune-mediated necrotizing myopa-

thy, dermatomyositis, or polymyositis (including antisynthetase syndrome) are eligible for participation in ALKIVIA. Eligible participants must be receiving a stable treatment dose of oral corticosteroids, and/or a single antimalarial or immunosuppressant. The trial includes an exploratory Phase 2 (90 participants) and a confirmatory Phase 3 stage (150 participants). In both stages, participants will be randomized in a 1:1 ratio to receive efgartigimod PH20 SC 1000 mg or matching placebo (with the same concentration of rHuPH20) weekly, added to standard care. These two stages will consist of independent patient cohorts, and the data from these cohorts will be analyzed independently. The Phase 2 stage will consist of a 24-week treatment period which is considered adequate for a proof-of-concept trial. It will assess efficacy and safety to determine futile subtypes as well as confirm the endpoints and sample size for the Phase 3. Once all participants have been randomized in the Phase 2 stage, enrolment for the confirmatory stage will begin; any adaptations to the protocol will be completed before the first participant completes the phase 3 screening. The Phase 3 stage will consist of a 52-week treatment period to assess the durability of response, considering the chronic nature of IIM and natural waxing and waning course of its subtypes. A glucocorticoid taper is allowed following week 24. At the end of the treatment period, participants who completed either stage may roll over into the open-label extension (OLE).
Results. The primary endpoint is total improvement score (TIS) at weeks 24 (Phase 2) and 52 (Phase 3) as assessed by the 2016 American College of Rheumatology/European League Against Rheumatism myositis response criteria. Key secondary endpoints include minimal and moderate response per the TIS and time to response. Several other secondary outcomes were chosen to assess how participants feel and function including muscle strength, muscle endurance, pain, and fatigue. Corticosteroid sparing effect will also be evaluated. Safety will be assessed by incidence and severity of adverse events.
Conclusions. ALKIVIA, utilizing an innovative basket trial and adaptive design, will help to identify which IIM subtypes are potentially IgG-driven by evaluating the efficacy and safety of efgartigimod PH20 SC and the benefits of FcRn blockade in the treatment of those subtypes.

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HIGH THROUGHPUT SCREENING TO IDENTIFY INHIBITORS OF THE TYPE I INTERFERON – MAJOR HISTOCOMPATIBILITY COMPLEX CLASS I PATHWAY IN SKELETAL MUSCLE: POSSIBLE THERAPEUTIC REPURPOSING FOR MYOSITIS

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Background. The standard of care for myositis patients includes treatment with steroids and immunosuppressive agents. However, these drugs are often not curative and have serious side-effects. We initiated a drug repurposing program to identify more targeted, less toxic therapeutics to treat these conditions. Although its cause is not fully understood, muscle from a subset of patients (particularly dermatomyositis) have an overabundance of the inflammatory cytokine type I interferon (IFN) and a down-stream product major histocompatibility complex (MHC) class I. Our goal was to identify inhibitors of this pathway as potential therapeutics for myositis. Type I IFN signaling is mediated by members of the Janus kinase family (JAK1, JAK2, JAK3, TYK2) through phosphorylation and activation of intracellular signaling pathways and transcription factors. There is growing recognition for the usefulness of treating autoimmune conditions like myositis with drugs called JAK inhibitors (jakinibs), but which is most safe and effective for myositis is unknown. Therefore, one of our aims was to identify which jakinibs were most potent at inhibiting type I IFN signaling in skeletal muscle.
Methods. We conducted quantitative high throughput screening of >25,000 compound titrations, including all approved drugs, through a series of cell-based assays to identify those that inhibit the IFN-beta stimulated expression of MHC class I in muscle precursor cells (myoblasts). The primary screen utilized CRISPR/Cas9 genome-engineered human myoblasts that contained a pro-luminescent reporter HiBit fused to the C-terminus of the endogenous HLA-B*08:01 MHC class I allele. Active compounds were counter-screened for cytotoxicity and validated by MCH class I immunofluorescence, western blot, and RT-qPCR.
Results. Active compounds generally fell into two major mechanisms: jakinibs and epigenetic/transcription factor modulators. The most potent actives were the TYK2 inhibitor deucravacitinib, JAK1/2 inhibitor upadacitinib, the hypoxia-inducible factor-1 inhibitor echinomycin, and histone deacetlyase inhibitors such as romidepsin.
Conclusions. These results are consistent with the compounds primary targets' JAK1/TYK2 that are known to mediate type I IFN signaling. Deucravacitinib was the most potent compound of the jakinibs, and literature shows it is highly selective for TYK2 due to its novel allosteric inhibition mechanism. An HDAC inhibitor givinostat is currently in clinical trials for Duchenne muscular dystrophy, where it has been shown to reduce inflammation, so may also be useful for other inflammatory myopathies. These active drugs warrant further evaluation in animal models and clinical trials to show their safety and efficacy in myositis.
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FROM BENCH TO BEDSIDE...AND BACK AGAIN: INTEGRATING RESEARCH AND CLINICAL CARE IN MYOSITIS

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Background. Idiopathic Inflammatory Myopathies (myositis) are a group of rare neuromuscular diseases. Conditions within this group include Dermatomyositis (DM), Necrotising Myositis (NAM), Polymyositis (PM), Overlap Myositis and the currently un-treatable Inclusion Body Myositis (IBM). It is well established that patients within research-active clinical environments have better outcomes and development of effective disease-modifying treatments is dependent on translational, patient-centered research.
Aim: Establishment of a translational research programme within specialist myositis outpatient clinics at Perron Institute for Neurological and Translational Science and Murdoch University (Perth, Australia).
Methods. Facilitated through a significant patient bequest towards myositis research, a laboratory and clinical research programme was founded in 2017 by Professor Merrilee Needham. Appointment of laboratory and clinical research leads supported new workflows where during clinic visits, patients meet with research nurses/coordinators and are provided the opportunity to take part in myositis research, including donating blood and urine samples that are taken directly to the on-site laboratories for analysis. Consented patients are also enrolled in the team's emerging observational Myositis Registry, and natural history data is collected via questionnaires and outcome measures through our team physiotherapist. At their clinic visit, patients are kept up to date with clinical trial opportunities and research news. For those actively taking part in clinical trials, research visits are often aligned with clinic appointments, increasing convenience and ease of participation. Within our laboratory programme, Lead Scientist Dr Jerome Coudert and his team are characterising the immune profiles, underlying pathways and mechanisms, genetic and metabolic changes of patients over time, as well as performing detailed analyses on blood, urine and muscle samples. A critical element of the research clinic model is keeping patients actively engaged with the research programme. Our patients are kept up to date with current and upcoming projects, advise us of what is important to study next, and are actively participating in project design and review. In recent years, our group has been complimented by an increasing number of higher degree students as well as medical students, across both the clinical and laboratory arms of the programme.
Results. At time of submission, we have over 400 active patients and disease-control participants, with over 2,000 samples collected and biobanked. Our ethical approvals support invitation of participants to take part in future studies based on genotype or phenotype of interest. Our programme has supported five Investigator-Initiated clinical trials over the last 3 years and four commercial clinical trials in myositis. Our highly collaborative approach sees growing national and international collaborative projects and grant applications. In 2020 we received a $1.8M grant from the Australian Government to lead an international, multi-site, Phase 3 trial of Sirolimus in IBM.
Conclusions. Research allows us to offer our patients hope and to partner with them on the journey to finding new treatments and improving quality of life. Our translational programme features a direct and bi-directional pipeline between laboratory and clinical research, built on a solid foundation of observational research projects designed to facilitate future research and treatment trials in myositis.

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RECOMBINANT HUMAN HYALURONIDASE-FACILITATED SUBCUTANEOUS IMMUNOGLOBULIN FOR IDIOPATHIC INFLAMMATORY MYOSITIS: A MULTICENTER OBSERVATIONAL STUDY

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Background. The spectrum of idiopathic inflammatory myositis (IIM) includes a heterogeneous group of diseases characterized by chronic inflammation of skeletal muscle, often associated with skin, joints, lungs, esophageal, gastrointestinal and cardiac involvement. Conventional treatment for IIM is based on glucocorticoids and immunosuppressants. Moreover, intravenous immunoglobulin (IVIg) has emerged as a promising steroid- and DMARD-sparing treatment for myositis (1). However, the long-term use of IVIg is complicated by the fact that the intravenous route requires in-hospital drug administration, which not only influences patients' quality of life, but is also associated with an increased risk of systemic adverse effects, difficulties in venous access over time, and high costs (2). On these bases, administration of subcutaneous Ig (SCIg) by a programmable pump has been considered as a possible alternative to IVIg. Recombinant human hyaluronidase-facilitated (hf)-SCIg is currently approved for the use in patients with primary immunodeficiency disorders, while its efficacy and safety in myositis disorders is limited (3). Objectives: This multicenter retrospective observational study is sought to evaluate the effectiveness and safety of recombinant human hf-SCIg in patients with IIM treated at different referral centers.
Methods. A multicenter, retrospective, cohort study was conducted on adult patients diagnosed with IIM according to the EULAR/ACR classification criteria (4) treated with recombinant human hf-SCIg according to routine clinical practice. The effectiveness of this treatment was assessed in terms of variations in the Medical Research Council (MRC) score, creatine kinase values, inflammatory parameters, and daily prednisolone dosage. Safety data were also collected.
Results. Twenty-three patients with IIM treated with hf-SCIg were included (16/23 females, 70%; median age at diagnosis of 61 years (IQR 43-65)). In most patients (22/23, 96%), IIM had been initially treated with high-dose corticosteroids (± synthetic or biologic DMARDs), and 20/23 patients (87%) had received previous IVIg treatment (in 12 for remission induction and in 8 for maintenance). Hf-SCIg were introduced after a median time of 2 years (1-4) from the diagnosis of IIM, mostly for remission maintenance (18/23). Hf-SCIg was started in combination with oral corticosteroids in 19/23 [83%, at a median dose of 5 mg/day (4-12.5)] and/or with traditional or biologic DMARDs (18/23, 78%). At time of hf-SCIg introduction, the median MRC score was 4 (3-4) and the median creatine kinase level was of 134 U/L (44-243). After 6 months of treatment, the median MRC score was 4 (3-5); no patient discontinued hf-SCIg, and only one experienced a mild adverse event.
Conclusions. Hf-SCIg seems effective to maintain remission in a high proportion of IIM patients while showing a good safety profile in the first 6 months of treatment.

P-115. Table I. Effectiveness and safety of hf-ScIG treatment in a cohort of 23 patients with myositis (6-month follow-up).

	hf-Sclg beginning	3 months	6 months
N patients with available follow-up data	23	20*	19*
MRC score§	4 (3-4)	4 (4-5)	4 (3-5)
Creatine kinase, U/L§	134 (44-243)	118 (77-308)	130 (84-222)
ESR, mm/h§	21 (15-28)	30 (25-43)	31 (23-39)
CRP, mg/dl§	0.2 (0.1-0.5)	0.3 (0.1-0.5)	0.4 (0.1-0.3)
Prednisolone dosage, mg/day§	5 (4-12.5)	7.5 (5-10)	5 (5-7.5)
Adverse events		NA	1 **

*None discontinued. **One infusion site reaction. §median value (IQR):
CRP: C reactive protein; ESR: erytrocyte sedimentation rate.

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RITUXIMAB IN THE TREATMENT OF IDIOPATHIC INFLAMMATORY MYOPATHIES WITH INTERSTITIAL LUNG DISEASE, LONG-TERM FOLLOW-UP

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Background. Interstitial lung disease (ILD) is the common internal organ manifestation of idiopathic inflammatory myopathies (IIM) that can severely affect the course and prognosis of the disease. Rituximab (RTX) has been used to treat IIM, including variants with ILD.
Objectives. To describe the course of disease in IIM patients with ILD, treated with RTX in long-term follow-up.
Methods. Our prospective study included 35 pts with IIM fulfilling Bohan and Peter criteria and having ILD. The mean age was 51.8±11.9 years, female-26 pts (74%); 24 (68.5%) with antisynthetase syndrome, 5 (14.3%) dermatomyositis (DM), 5 (14.3%) with a-Pm/Scl overlap myositis and 1 (2,9%) with a-SRP necrotizing myopathy were included. 25 (71,4%) patients had nonspecific interstitial pneumonia, 9 (25,7%) organizing pneumonia (OP) and 1 (2,9%) OP, transformed to diffuse alveolar damage. All pts had the standard examination including manual muscle testing (MMT), creatinkinase (CK) anti-Jo-1 antibodies (anti-Jo-1) assay; forced vital capacity (FVC) and carbon monoxide diffusion capacity (DLCO) evaluation as well as high-resolution computed tomography (HRCT) scanning of the chest were performed at baseline, and 36 and more months. The median disease duration was 3.2 [0.16-18] years, 21 (60%) of pts were positive for a-Jo-1 antibody. All pts received prednisolone at a mean dose of 24.3±13 mg/day, immunosupressants at inclusion received 25 (71%) pts: cyclophosphamide 18 , mycophenolate mofetil 6 and comdination 1; Rituximab (RTX) was administered in case of severe course of disease and intolerance or inadequate response to GC and other immunosuppressive drugs.
Results. The mean follow-up period after the first infusion of RTX was 47.2±11.9 months. Pts received 1-11 courses of RTX . The cumulative mean dose of RTX was 4.6 ±2.5g. MMT 8 increased from 135.8±13.5 to 148.75±3.5 (p=0.000001). CK level decreased ΔCK – 762 u/l(median 340; 25th% 9; 75th% 821). anti-Jo-1 decreased from 173.4±37 to 96.5±79 u/ml (p=0.00002), FVC increased from 82±22.6 to 96,9±22% (p=0.00011). DLCO increased from 51.4±15.2 to 60±77.8% (p=0.0001). The mean prednisone dose was reduced from 24.3±13 to 5.7±2.4 mg/day. 3 pts died: ILD progression was the cause of death in 1 case, 1 bacterial pneumonia and COVID19 pneumonia.
Conclusions. The results of this study confirm the positive effect of RTX in IIM patients with ILD (increase of muscle strength and improve lung function, decrease in anti-Jo-1 levels) and also its good steroid-sparing effect. RTX could be considered as an effective drug for the complex therapy of IIM patients with ILD when standard therapy is ineffective or impossible.

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LONG-TERM EFFICACY AND TOLERABILITY OF SUBCUTANEOUS IMMUNOGLOBULINS IN CHRONIC INFLAMMATORY MYOPATHIES: A MEAN 5-YEAR FOLLOW-UP IN 30 PATIENTS

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The use of subcutaneous immunoglobulin (SCIg) therapy in primary and secondary immunodeficiencies is well established. However, few studies investigated the feasibility and safety of SCIg in autoimmune diseases. We did a retrospective review to describe the real-life use of SCIg in chronic inflammatory myopathies, including polymyositis (PM), dermatomyositis (DM), inclusion body myositis (IBM), and other myositides.
Thirty cases were included (11 PM, 7 DM, 5 IBM, 7 other myositides). Patients were treated up for a mean (±SD) of 69.97±18.2 months (range: 37-115 months),

during which 21,220 infusions were documented, with a median of 681 SCIg infusions/patient. The majority of patients (83.3%) showed significant improvement in muscle strength score following SCIg infusions (69.3±11.2 at baseline vs 80.4±10.4 at last infusion; $p<0.05$). Significant improvement in muscle disability scale was observed in PM and DM (15.3±12.5 at baseline vs 6.5±7.2 at last infusion). SCIg significantly improved dysphagia in all IBM patients. Most patients expressed a preference for home infusion. Where available, quality of life data showed significant improvement in both physical and mental component summary score. Few mild adverse reactions were reported, including local skin reactions (8 cases), headaches, and chills. No severe adverse event was reported. These real-world results suggest that the use of high-dose SCIg is efficacious and well-tolerated for long-term treatment of patients with inflammatory myopathies. SCIg was a feasible alternative to IVIg in this population of myositis patients with insufficient response to previous therapies, difficult venous access, and/or with a preference for self-administration.

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LENABASUM REDUCES IFNΓ AND PIRF3 IN DERMATOMYOSITIS SKIN: BIOMARKER RESULTS FROM A DOUBLE-BLIND PHASE III INTERNATIONAL RANDOMIZED CONTROLLED TRIAL

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Dermatomyositis is an autoimmune skin disease with limited treatment options, and lenabasum is a cannabinoid type 2 receptor agonist with anti-inflammatory properties. Our previous work showed that IFNγ and IL31 are increased in DM skin vs. skin from healthy controls and lenabasum reduces type 1 interferon (IFN-1) and IL-31 production by DM PBMCs *in vitro*. Lenabasum 20 mg BID treatment improved CDASI activity (CDASI-A) scores vs. placebo at 1 year in an international, double-blind, randomized Phase 3 trial. Imaging mass cytometry was done on 66 total FFPE skin biopsies obtained at Baseline and Week 16 in that trial, testing expression of 12 intracellular biomarkers in 9 cell types and using a zero-based, linear mixed effects model and Spearman's correlation for statistical analyses. Subjects in both treatment groups had similar immune infiltrates in skin at Baseline except plasmacytoid dendritic cells were increased in placebo group ($p<0.05$). At Week 16, subjects treated with lenabasum 20 mg BID vs. placebo had a significant decrease in IFNγ ($p<0.05$) and phosphorylated-IRF3 (activated transcription factor for IFN-1) ($p<0.05$) expression. There was a trend towards decrease in IL-31 expression with lenabasum treatment ($p=0.08$). Absolute change in CDASI-A scores was positively correlated with a change in IL-31 staining (R=0.636, $p=0.026$). These results suggest clinical benefit of lenabasum on skin disease in DM may be mediated in part through reduction of IFNγ and pIRF3 (IFN-1 Type 1) expression.

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VIVACITY-MG: A PHASE 2, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE SAFETY, TOLERABILITY, EFFICACY, PHARMACOKINETICS, PHARMACODYNAMICS, AND IMMUNOGENICITY OF NIPOCALIMAB ADMINISTERED TO ADULTS WITH GENERALIZED MYASTHENIA GRAVIS

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Background. The objective of this study is to evaluate the safety, tolerability, efficacy, pharmacokinetics, pharmacodynamics, and immunogenicity of nipocalimab vs. placebo in patients with generalized myasthenia gravis (gMG) who have had an insufficient response to ongoing, standard-of-care therapy. Nipocalimab (M281) is a fully human, aglycosylated, effectorless IgG1 anti-FcRn monoclonal antibody that targets the IgG binding site on FcRn with high affinity, thereby interfering with the binding of IgG. IgG that is not bound to FcRn cannot be recycled and thus undergoes lysosomal degradation. This is expected to reduce serum levels of total IgG and pathogenic IgG autoantibodies that cause MG and ameliorate the disease.
Methods. 68 patients were randomized 1:1:1:1:1 to 4 treatment groups or a placebo group. To maintain study blinding, all patients received an intravenous infusion (either nipocalimab or placebo) every other week for a total of 5 infusions during the 8-week treatment period. After completion of the follow-up period, patients could enroll in a separate open-label extension study and receive treatment with nipocalimab.
Results. There were no discontinuations due to treatment-emergent adverse events (AEs), severe AEs, or related serious AEs with nipocalimab. The incidence of infections and headaches with nipocalimab were comparable to placebo. Nipocalimab was well-tolerated and achieved substantial, dose-dependent and rapid reductions in serum total IgG, including all IgG subtypes and anti-AChR autoantibodies.
Treatment with nipocalimab resulted in a robust and significantly greater mean improvement from baseline in MG activities of daily living (MG-ADL) scores across all continuous dosing arms vs. placebo at the end of the treatment period. A greater proportion of patients treated with nipocalimab exhibited rapid improvement (within two weeks of treatment) in MG-ADL across all 4 dosing arms vs. placebo. 51.9% of patients who received nipocalimab (all doses) reported a durable MG-ADL response vs. 15.4% of those who received placebo ($p=0.017$).
Conclusions. Nipocalimab was well-tolerated, safe, and efficacious in patients with gMG.
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Inclusion body myositis

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SPORADIC INCLUSION BODY MYOSITIS AFFECTS TYPE 1 AND TYPE 2 MYOFIBRES DIFFERENTLY IN TERMS OF MORPHOLOGY, REGENERATION AND INFLAMMATION

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Background. Sporadic inclusion body myositis (sIBM) is characterised by progressive muscle weakness, which is largely refractory to immunosuppressive treatment. The knowledge of sIBM concerning the differences related to fibre types, such as fibre size and fibre type distribution, are scarce. Further, the fibre type related distribution and content of satellite cells (SCs), myonuclei, macrophages, as well as capillaries are not described in the literature. As such, this study aimed to investigate fibre type differences in sIBM patients in terms of fibre size, SCs, myonuclei, macrophages and capillarisation.
Methods. Baseline muscle biopsies from sIBM patients (n=18) from a previous study (NCT02317094) were analysed for myofibre type differences on mCSA, SC content (resident and proliferating), myonuclei content (overall and centrally placed), macrophages (pro- (M1) and anti-inflammatory (M2), and capillarization using three-color immunofluorescence microscopy and computerised quantification.
Results. Type 1 (slow) fibre mCSA ($p<0.001$), overall myonuclei content (Six1+) ($p<0.001$) and myonuclear domain ($p=0.005$) were larger than in type 2 (fast) fibres. In contrast, type 2 resident SCs (Pax7+/Six1+) ($p<0.001$), centrally placed myonuclei (Six1+), M1 macrophages (CD68+/CD206-) ($p<0.002$), M2 macrophages (CD68+/CD206+) ($p=0.013$) and capillary content (CD31+) ($p<0.001$) was larger than in type 1. Only proliferating SCs (Pax7+/Ki67+) did not differ between fibre types ($p=0.68$).
Conclusions. The current study presents observations of abortive compensation of mCSA in type 1 myofibre, with increased size, but with the lack of parallel increase of myonuclei number and SCs activation. Type 2 fibre mCSA showed high levels of atrophy accompanied by higher numbers of resident SCs, mac-

rophages and capillary compared to type 1 fibres. These findings suggest that sIBM is targeting myofibres differently based on fibre type. More research is needed to clarify how disease duration and physical activity affects muscle based on fibre type in sIBM.

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TEMRA PATHOLOGY DISTINGUISHES INCLUSION BODY MYOSITIS FROM OTHER INFLAMMATORY IDIOPATHIC MYOPATHIES

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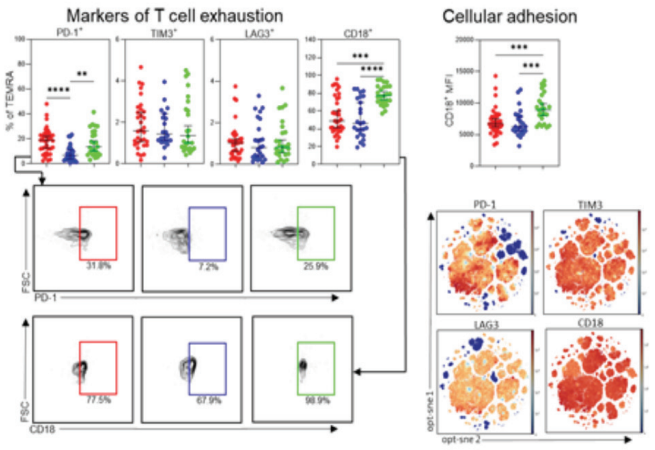
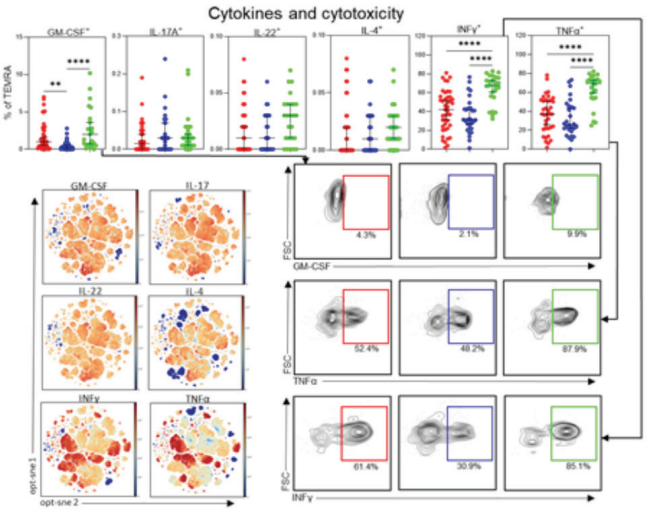
Background and aim. The immunological mechanisms underlying inflammatory idiopathic myopathies (IIM) remain enigmatic. Previous studies have suggested that perturbations of terminally differentiated effector memory T cells (TEMRAs) are present in inclusion body myositis (IBM). To better understand this T cell pathology, we employed a high-dimensional flow cytometry approach to compare the TEMRA subsets among the IIM spectrum. We decided to include three cohorts of IIM patients. We included dermatomyositis (DM) and anti-synthetase syndrome (ASyS) patients. We aimed to understand the specific changes to the TEMRA compartment in IBM in comparison to other IIM entities. Therefore, we used a high-dimensional flow cytometry approach to investigate TEMRAs from ASyS, DM and IBM patients.
Methods. We included a total of 41 ASyS, 20 DM and 28 IBM patients in our analysis. Peripheral mononuclear cells (PBMC) were isolated according to standard protocol. PBMCs were washed and resuspended in PBS/FBS/EDTA and analyzed by flow cytometry using a CytoFlex Flow Cytometer. Statistical Analysis was performed using GraphPad Prism 9.2 (GraphPad Software, Inc., San Diego, CA) and R 3.5.3 (R Foundation for Statistical Computing, Vienna, Austria). The local ethics committee (2016-053-f-S) approved the study.
Results. We acquired flow cytometric data on PBMCs from ASyS (n=41), DM (n=20) and IBM (n=28) patients. In essence, we observed that:
- PD-1+ TEMRA cells were decreased in DM as compared to ASyS and IBM.
- CD18 mediates T cell activation and adhesion. CD18+ TEMRA cells were markedly expanded in IBM and CD18 expression as measured by mean fluorescence intensity was increased.
- Fewer GM-CSF+ TEMRA cells were detected for DM as compared to other IIM.
- INFγ and TNF-α expressing TEMRAs were substantially expanded in IBM.

Conclusions. Our data corroborates the presence of highly differentiated, cytotoxic TEMRA cells in IBM and adds the potential for cellular adhesion and infiltration as evidenced by CD18 expression.



P-121. Fig. 1. A



P-121. Fig. 1 B.

P-122

NKG2D ORCHESTRATES NATURAL KILLER CELL ACTIVATION AND INVASION IN INCLUSION BODY MYOSITIS IN ASSOCIATION WITH ANTI-CN1A-ANTIBODY STATUS

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Background. Inclusion body myositis (IBM) is the most frequent idiopathic inflammatory myopathy (IIM) of old age. The pathophysiological framework of IBM remains enigmatic and calls for deeper immunological analysis. Interestingly, the anti-cytosolic 5´-nucleotidase 1A (cN1A) antibody is highly specific for IBM. Natural killer (NK) cells are at the interface of adaptive and innate immunity. Knowledge of NK cell patterns might improve our mechanistical understanding of IBM.
Methods. To extend our understanding of immunological alterations and dissect NK cell patterns in IBM, we compared signatures and distribution profiles of peripheral blood mononuclear cells (PBMCs) by multi-color flow cytometry (FC) in IBM patients (n=22) with a non-diseased, age- and sex-matched control cohort (NDC; n=22). Here, we investigated the NK cell receptor repertoire of CD56^{dim} NK cells shaping the cellular response to inflammatory stimuli. Cell surface expression of targets was quantified by measuring the mean fluorescence intensity (MFI) employing flow cytometry. Further, we compared peripheral CD56^{dim} NK cells between anti-cN-1A-ab positive and negative patients as well as NDC to investigate the pathogenic potential of anti-cN-1A-ab. Aiming to further dissect the cytolytic potential of the NK cell repertoire, we performed intracellular staining for serine proteases.
Results. We did not observe significant differences for B cells, CD4 and CD8 T cells, while NK cell subtypes were altered with a particular decrease of CD56^{dim} NK cells in IBM as compared to NDC. In contrast, CD56^{bright} NK cells displayed no meaningful changes. Comparisons of cell surface expression of a large panel of NK receptors revealed an increased mean fluorescence intensity of NKG2A$^+$ and NKG2D$^+$ on NK cells from IBM patients compared to NDC. While NKG2D$^+$ expression was increased on both total and CD56^{bright} NK cells, NKG2A$^+$ was overexpressed on total but not CD56^{bright} NK cells. Interestingly, reductions in peripheral CD56^{dim} NK cells were driven by anti-cN-1A-ab positive patients with a significant change as compared to NDC. Further investigation revealed that NKG2A$^+$ and NKG2D$^+$ expressions were associated with anti-cN-1A-ab serostatus. NKG2A$^+$ expression was increased on all NK cell subsets for anti-cN-1A-ab negative patients compared to NDC while anti-cN-1A-ab positive patients only displayed significance for CD56^{bright} NK cells. In contrast, NKG2D$^+$ expression was altered in respect to anti-cN-1A-ab serostatus for all NK cell subsets with a difference when comparing to NDC only observed for anti-cN-1A-ab positive patients. Investigating the cytolytic potential of the NK cell repertoire, granzyme B levels were sharply increased in CD56^{dim} NK cells comparing IBM with NDC, while other granzymes and perforin displayed no meaningful differences. Lastly, serostatus had no impact on granzyme A levels with no difference between anti-cN-1A-ab positive and negative patients observed.

Conclusions. We describe NK cell patterns in peripheral blood as well as muscle of IBM patients and dissect the prominent role of NKG2D for NK cell infiltration and activation. Understanding the mechanism by which NK cells initiate, propagate or modulate tissue specific consequences of IBM, might enable us to form a more conclusive concept of autoimmunity in IBM.

P-123

COMPARING HISTOPATHOLOGY, TRANSCRIPTOMIC AND PROTEOMIC PROFILES OF SPORADIC INCLUSION BODY MYOSITIS (SIBM) AND POLYMYOSITIS WITH MITOCHONDRIAL PATHOLOGY (PM-MITO): ARE WE MOVING TOWARDS SIBM-SPECTRUM DISEASE (IBM-SD)?

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Polymyositis with mitochondrial pathology (PM-Mito) has been described as a distinct form of idiopathic inflammatory myopathy (IIM) with marked mitochondrial pathology. Histopathologically, PM-Mito resembles 'polymyositis' but shows additional features of mitochondrial damage (*i.e.* COX/SDH-negative fibers). But unlike in sIBM, rimmed vacuoles are not observed in PM-Mito. Nevertheless, studies have described possible links between these two diseases. Up to 50% of patients initially diagnosed as PM-Mito may progress to sIBM. On the molecular level, similar patterns of mitochondrial DNA deletions have been detected in patients with PM-Mito and sIBM. Clinically, some response to immunosuppressive therapy has been described in PM-Mito as opposed to therapy-refractoriness in sIBM. It remains unclear to date if PM-Mito and sIBM are distinct disease entities or if they should rather be seen as pathophysiologically and clinically related diseases. We aimed to analyze and compare histological and molecular profiles of PM-Mito and sIBM on the RNA-and protein level with a focus on inflammation and T-cell dysfunction. Molecular findings were validated using specific immunostaining on muscle biopsy specimen derived from patients of both disease entities. Skeletal muscle biopsies and clinical data from 25 PM-Mito and 12 sIBM patients were available for analysis. We detected inflammatory infiltrates and morphological changes of similar appearance, but in strinkingly different quantities in both diseases. On the molecular level, we found an expression of interferon-gamma-induced molecule GBP6 and T-cell function-related KLRG1 in sIBM, but not in PM-Mito and normal controls. Additionally, we report the first proteomic data of PM-Mito biopsies, providing new insights into the pathophysiology of the disease including mitochondrial dysfunction. Clinically, about half of the PM-Mito patients progressed to sIBM with two re-biopsies obtained 5 years apart illustrating a gradual transition. Our data indicate that PM-Mito and sIBM may be part of an sIBM-spectrum disease (IBM-SD). The introduction of the IBM-SD concept could have a significant impact on the management of patients and the design of trials in the context of sIBM/PM-Mito in the future.

P-124

THE INCLUSION BODY MYOSITIS HEALTH-INDEX (IBM-HI): DEVELOPMENT OF A NOVEL, DISEASE SPECIFIC PATIENT-REPORTED OUTCOME MEASURE FOR IBM IN CLINICAL TRIALS

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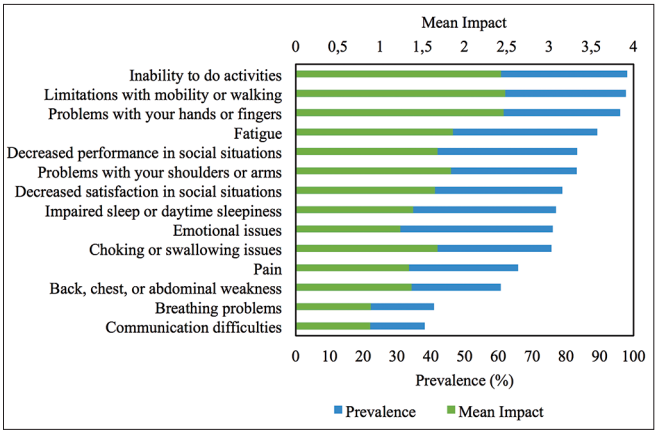
Objective. In response to the need for relevant therapies and improved clinical infrastructure in the Inclusion Body Myositis (IBM) scientific community, we have developed and validated the IBM-HI (Inclusion Body Myositis-Health Index) for use in IBM therapeutic trials and clinical monitoring.
Background. In preparation for upcoming clinical trials involving patients with IBM, there is a clear need for reliable, sensitive, and disease-specific patient reported outcome measures capable of detecting small, clinically relevant changes in therapeutic gain and/or disease progression over time. According to regulatory bodies, patient reported outcome measures are an effective mechanism to support drug-labeling claims.
Methods. We conducted qualitative interviews with individuals with IBM to identify potential symptoms of importance in IBM. Next, we conducted a cross-sectional study to determine the prevalence and importance of the symptoms identified through IBM interviews. We selected questions for the first version of the Inclusion Body Myositis-Health Index (IBM-HI) based on their high frequency and relative importance in the cross-sectional sample population as well as their ability to respond to therapeutic interventions. Instrument subscales, measuring granular areas of symptomatic health, were generated using factor analysis. We performed beta interviews with individuals with IBM and test-retest reliability assessments to optimize instrument clarity, usability, meaningfulness, responsiveness, and reliability. Known groups validity testing was used to demonstrate how the IBM-HI can differentiate between groups of patients with different levels of disease burden.
Results. Ten individuals with IBM participated in the initial qualitative interviews. A total of 569 individuals with IBM participated in the cross-sectional study which inquired about 216 individual symptoms represented by 14 distinct symptomatic themes (Figure 1). Results from the cross-sectional study were used to create the first version of the IBM-HI. The IBM-HI was beta tested with 15 individuals with IBM and was found to be comprehensive, easy to use, and highly relevant to participants. The reliability of the IBM-HI questions and subscales was determined using 21 participants with IBM. The final IBM-HI is comprised of 13 distinct subscales of IBM health that collectively measure how a patient feels and functions. Overall, validation testing found the IBM-HI and its subscales to be highly relevant, reliable, and capable of differentiating between patients with different levels of disease severity.
Conclusions. The IBM-HI provides researchers and clinicians with a reliable and sensitive mechanism to serially measure relevant changes in total health and 13 areas of symptomatic health during therapeutic trials involving patients with IBM.
Acknowledgements. We would like to thank the IBM patients who participated in this study as well as The Myositis Association who assisted with patient recruitment.



P-124. Fig. 1. IBM Prevalence and Mean Impact by Symptomatic Theme.

P-125

SELECTIVE DEPLETION OF KLRG1+ T CELLS IN A FIRST-IN-HUMAN CLINICAL TRIAL OF ABC008 IN INCLUSION BODY MYOSITIS (IBM)

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Background. Inclusion body myositis (IBM), a relentlessly progressive autoimmune skeletal muscle disease, has no effective available pharmacological therapy. A prominent feature of IBM on microscopy is $CD8^+$ highly cytotoxic T (Tc) cells invading non-necrotic myofibers (1, 2). These cells include T effector memory (TEM) and terminally differentiated T effector cells (TEMRA), known to be relatively resistant to apoptosis, and express markers including killer cell lectin-like receptor G1 (KLRG1) (3). ABC008, a first-in-class humanized, afucosylated monoclonal antibody (mAb) specific for KLRG1, was developed to selectively deplete these $CD8^+$ Tc cells while sparing other cell populations, *e.g.*, naïve, central memory, and regulatory T cells and B cells. ABC008 has been designed to treat diseases mediated by Tc cells such as IBM and T-cell large granular lymphocytic leukemia (T-LGLL). IBM overlaps clinically with T-LGLL (2)

and shares similar expansions of large granular lymphocytes, which also express KLRG1. We report here preliminary data from our ongoing first-in-human trial of ABC008 in IBM (NCT04659031).
Methods. In this open label, single ascending dose trial with 3+3 design evaluating ABC008 administered subcutaneously (SC), eligible participants must have clinicopathologically defined, clinically defined, or probable IBM according to the European Neuromuscular Centre 2011 research diagnostic criteria (3) and an IBM Functional Rating Scale (IBMFRS) score <38. Four dose cohorts are planned: ABC008 0.1, 0.5, 2.0, and 5.0 mg/kg. Pharmacodynamics (PD), pharmacokinetics (PK), safety, and disease severity assessments are performed predose (Day 0) and during the 6 month follow-up period.
Results. As of 12 February 2022, Cohorts 1 (C1) and 2 (C2) have received 0.1 and 0.5 mg/kg of ABC008 SC and completed 168 and 56 days of follow-up, respectively. Cohort 3 evaluating ABC008 2.0 mg/kg is enrolling. Across C1 and C2, mean baseline age is 65.7 years, IBM disease duration 6.8 years, and IBMFRS score 27.5. Maximum depletion of $CD8^+KLRG1^+$ cells in C1 and C2 ranged from 46-96% and 98-99%, respectively, with depletion evident within 24 hours (first time point assessed) (Figure). Recovery in C1 began at Day 84 with Day 168 depletion at 29-71%. Deep depletion was also present in other relevant pathogenic populations including $CD4^+KLRG1^+$, $CD8^+CD57^+$ (LGLs), CD8+ TEM, and $CD8^+$ TEMRA cells. Protective populations of immune cells were preserved, including B cells, regulatory T cells that protect against autoimmunity, and central memory T cells that protect against infection (Figure). ABC008 SC displays a long absorption phase and slow clearance properties typical of mAb therapies. No severe adverse events (AEs) or discontinuations due to AEs have been reported. One unrelated serious AE of fall with muscle tear occurred in a participant with a prior history of falls.
Conclusions. In study participants with IBM, single SC doses of 0.1 and 0.5 mg/kg of ABC008 resulted in dose dependent depletion of $CD8^+KLRG1^+$ cells, $CD8^+CD57^+$ LGLs, and other highly cytotoxic populations, while sparing protective populations of immune cells, without apparent safety signals. Additional cohort dosing is ongoing, and a multi-ascending dose phase of the study is planned.

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P-126

ANTI-CYTOSOLIC 5'-NUCLEOTIDASE 1A (CN1A) ANTIBODY IN DIAGNOSIS OF INCLUSION BODY MYOSITIS: AN ITALIAN REAL-LIFE CASE SERIES

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Background. Inclusion body myositis (IBM) is a rare, autoimmune, progressive myopathy typically affecting people older than 50 years old. It is more common in men and is characterized by a typical involvement of finger flexors and knee extensors. The clinical course, which is treacherous and inevitably progressive, due to the lack of effective drugs, may be complicated by the onset of dysphagia and, less commonly, dyspnea. Diagnosis can be made with the combination of clinical and laboratory exams, such as creatine-kinase elevation, but de facto still relies on muscle biopsy. Antibodies anti-cytosolic 5'-nucleotidase 1A (cN1A) have recently being proposed as reliable biomarkers for the diagnosis of IBM, but controversial evidence in terms of sensitivity (33-76%) and specificity (87-100%), as well as the low availability in the common clinical practice, strongly limits their use in the diagnostic work-up of IBM. In this regard, the aim of this study was to assess specificity of anti-cN1A in a cohort of patients who underwent myositis immunoblot in the suspicion of idiopathic inflammatory myopathies.
Methods. We retrospectively collected all patients who underwent myositis immunoblot (EUROLINE Test, Euroimmune, Lubeck, Germany) at University Hospital of Siena, Italy, from August 2020 to December 2021. The test provides qualitative in vitro determination of human autoantibodies of the immunoglobulin class IgG to 17 different antigens Mi-2α, Mi-2β, TIF1γ, MDA5, NXP2, SAE1, Ku, PM-Scl100, PM-Scl75, Jo-1, SRP, PL-7, PL-12, EJ, OJ, Ro-52 and cN-1A. Exclusion criterion was a previous diagnosis of IBM. For each patient, the following data were recorded: age, sex, definite diagnosis, date of symptoms onset, date of diagnosis, risk factors, clinical features, muscle biopsy, magnetic resonance imaging and EMG findings (when available), autoimmune profile and outcome.
Results. During the observational period, a total of 340 underwent myositis immunoblot and 21 (16 females, 5 males) were tested positive for anti-cN1A. The mean age was 53,4 years and they had diagnosis of: 6 seronegative arthritis (one with concomitant panuveitis), 3 polymyositis, 3 dermatomyositis, 2 IBM, 1 scleromyositis, 1 undifferentiated connective tissue disease, 1 miastenia gravis, 1 hypersensitivity pneumonia, 1 sarcoidosis, 1 metastatic pancreas carcinoma, while in the latter no definite diagnosis was made. ANA were positive in 8 patients (titer ranging from 1:160 to 1:640), while 6 of them displayed a concomitant positivity for CENP, RNA-POL III, anti-TPO (2 patients), anti-SSA and anti-SM (1 each).
Conclusions. To date, this is the first study which enrolls the largest cohort of anti-cN1patients without a previous diagnosis of IBM. Opposite of as previously reported, our study showed low specificity of cN1A in IBM diagnosis: 2 out of 21 patients had a definite diagnosis of such disease. Conversely, it should be remarked that 8 of them eventually displayed clinical and/or histological findings consistent with any IIM, while only one did not meet any precise diagnosis of any autoimmune diseases. Our findings, unitedly to the ones displaying a certain prevalence of anti-cN1A in several autoimmune diseases such as Sjogren's syndrome and systemic lupus erythematosus, does not confirm a good diagnostic accuracy of such antibody for IBM diagnosis, thus remarking the importance of muscle biopsy for a definite diagnosis. Conversely, the high incidence of autoimmune diseases in patients carrying anti-cN1A warrants an accurate and cautious diagnostic work-up.

P-127

IL-1B AND IFNΓ COMBINED INCREASE SARCOPLASMIC P62 PUNCTA SIZE BUT DO NOT INFLUENCE TDP-43 AGGREGATION IN HEALTHY MYOTUBES

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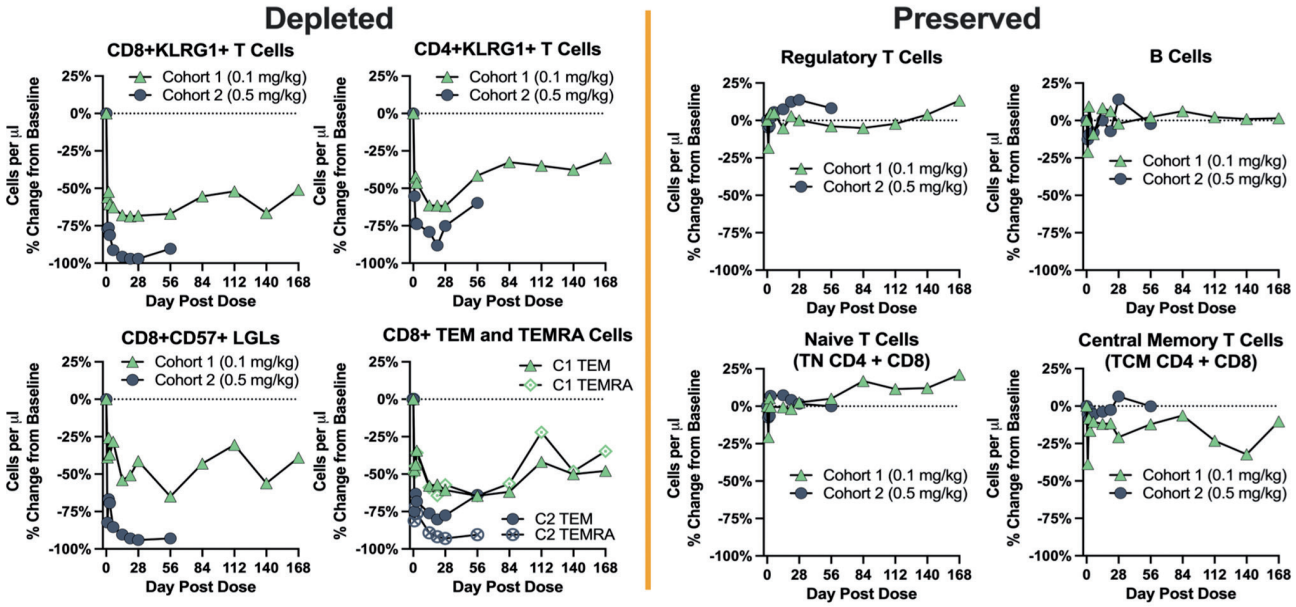
Background. Skeletal muscle of patients with sporadic inclusion body myositis (sIBM) presents with inflammation and muscle degeneration. $CD8^+$ T cells infiltrate into the endomysium and muscle fibres, and there is upregulated expression of inflammatory cytokines such as interferon γ (IFNγ). Further, sarcoplasmic accumulation of proteins such as TDP-43 and p62 is observed in affected sIBM muscle fibres. This project aims to explore the effect of inflammatory cytokines IFNγ and interleukin 1-β (IL-1β) on TDP-43 and p62 aggregation *in vitro*, building on previous work by others investigating the effect of these cytokines in sIBM pathology.
Methods. Primary human myogenic cells from 5-6 non-disease donors were differentiated for 7 days into myotubes. IL-1β (20 ng/mL) and IFNγ (750 ng/mL) alone or combined were added to myotubes for a further 2 days. Protein expression of TDP-43 and p62 was assessed using Western blotting. Sarcoplasmic TDP-43 aggregates and p62 puncta were assessed using image analysis for size, frequency relative to cell area, and co-localisation with each other. To investigate whether IL-1β and IFNγ treatment influences TDP-43 subcellular localisation, image analysis was used to classify TDP-43 as nuclear, sarcoplasmic, both nuclear and sarcoplasmic, or not expressed.
Results. Combined IL-1β and IFNγ treatment increased puncta size of p62 compared to control (0.49±0.13 μm^2 versus 0.28±0.06 μm^2), without affecting puncta frequency. There was an observed increase in total p62 protein when treating with IL-1β and IFNγ combined for all myogenic cell donors, however densitometry analysis was not significantly different compared to control. In contrast, treatment with either IL-1β or IFNγ alone did not alter p62 puncta size or frequency but both cytokines individually increased total p62 protein expression compared to control. The presence of TDP-43 sarcoplasmic aggregates was not affected by IL-1β or IFNγ treatment alone or combined. Furthermore, none of the cytokine treatments affected total TDP-43 protein expression, or size and frequency of TDP-43 sarcoplasmic aggregates. TDP-43 aggregates were not always found co-localised with p62 puncta and the percentage of co-localisation was not affected by any IL-1β or IFNγ treatment. The subcellular localisation of TDP-43 was not affected by IL-1β or IFNγ alone or combined and TDP-43 was frequently found localised to the sarcoplasm under control conditions.
Conclusions. Combined treatment of IL-1β and IFNγ was able to recapitulate p62 sarcoplasmic aggregation as seen in sIBM. As p62 is an adaptor for protein degradation pathways, this suggests a disruption of autophagic flux or the ubiquitin-proteasome system. An increase in p62 sarcoplasmic puncta size was not seen when the cytokines were used individually, suggesting a combined insult of multiple inflammatory mediators may be necessary to disrupt p62 processing. TDP-43 protein expression, aggregation or localisation was not affected by any IL-1β or IFNγ treatment, contrary to previously published in vitro and sIBM biopsy findings. These results suggest IL-1β and IFNγ do not influence TDP-43 aggregation or mislocalisation as seen in sIBM.
Acknowledgements. The authors would like to thank Cook MyoSite for their generous donation of human skeletal muscle derived cells. This project was supported by funding from the Medical Research Council (MRC).



P-125. Fig. 1. Study ABC008-IBM-101 key blood pharmacodynamic responses. Depleted blood populations included directly targeted KLRG1+ cells (both CD8+ and CD4+) and related populations of CD8+CD57+ large granular lymphocytes (LGLs), and CD8+ TEM and TEMRA cells. In contrast, preserved populations included anti-inflammatory regulatory T cells; B cells; naïve T cells (TN); and central memory T cells (TCM).

P-128

TRANSVERSOSPINALIS INVOLVEMENT IS SPECIFIC TO INCLUSION BODY MYOSITIS

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Background/objective. To clarify the sensitivity and specificity of selective involvement of transversospinalis (TS) in paraspinal muscles for a diagnosis of inclusion body myositis (IBM).
Methods. We retrospectively evaluated skeletal muscle CT images of 112 histologically-diagnosed IBM patients from 2006 to 2021 and 832 non-IBM patients including various neuromuscular diseases from 2016 to 2021.
Results. Selective fatty replacement of TS in paraspinal muscles was observed in 20% (22/112) of IBM patients, significantly higher than that of non-IBM patients (1.6%, 14/832, p<0.01). The sensitivity was 20%. The specificity was 98%; 97% when the control was limited to myositis other than IBM. Non-IBM patients with this finding included individuals with amyotrophic lateral sclerosis, myotonic dystrophy, and other idiopathic inflammatory myopathies.
Conclusions. Selective TS involvement yielded a high specificity despite a low sensitivity. It is one of the characteristic imaging features and can be a diagnostic clue for IBM.

P-129

CHALLENGES IN RARE DISEASES AND THE CASE FOR OPTIMISM IN IBM: AN MSG STUDY

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Background. Inclusion body myositis (IBM) is a progressive disabling muscle condition without any effective disease-modifying therapies. Sirolimus works by blocking the activity of effector T cells whilst preserving T regulatory cells, as well as inducing autophagy, thereby having effects on both the chronic inflammation and abnormal proteostasis that contribute to myocyte death in IBM. Sirolimus was recently trialled in 44 French IBM patients in a proof-of-concept monocentric controlled phase 2 study. While the primary outcome was not met, a number of secondary outcome measures suggested a positive impact on disease progression.
Methods. Optimism in IBM (NCT04789070; ANZCTR: ACTRN-12620001226998p) is a double-blind randomised controlled phase 3 trial investigating the potential effect of Sirolimus on stabilising or slowing disease progression in patients with IBM as measured by the IBM Functional Rating Scale (IBM-FRS). In this investigator-initiated trial, we will be comparing 2 mg Sirolimus vs Placebo, in a minimum of 140 participants across 14 trial sites in Australia, Europe, and the United States of America over 84 weeks. The primary outcome measure is the comparison between Sirolimus and placebo on the mean change in patient function from Baseline to Week 84 as assessed by the IBM-FRS. Secondary outcomes include changes from Baseline to Week 84 in the 6- and 2- minute walk test, modified Timed-up-and-go, a number of patient reported outcomes, manual and quantitative muscle tests, and measures to assess sirolimus safety and tolerability.
Results. This study is about to commence, but the prolonged set-up phase highlights the challenges in establishing a multi-centre trial across the world. In addition to securing funding, collaboration and coordination are both absolutely necessary in rare disease research. These require hard work, tenacity and dedication from clinicians, project managers and study co-ordinators, strong commitment of patients to be engaged at different stages and vigorous support from patient advocacy groups across the world. Moreover, awareness of IBM natural history, data-driven selection of robust outcome tools and appropriate design of patient inclusion and exclusion criteria are critically important to optimise the probability to detect a positive signal. Some of the key challenges include obtaining sufficient funding to fund placebo and pharmacy costs, to support site costs and for central data co-ordination and monitoring, in addition to the complex web of contracts that must be negotiated and agreed in different regulatory environments across the world. All these important challenges are surmountable but time-consuming.
Conclusions. Having a network of similarly-minded and driven clinicians with appropriate support staff across the world who care for cohorts of well phenotyped patients is a solid foundation for global clinical trials. Whilst in an ideal world, these centres would simply follow the same protocol and combine results, the reality of the costs and time involved in running clinical trials and the governance required to ensure these are carried out in a standardised manner across the world, means that significant challenges and prolonged starting timelines remain even in established clinical trial networks. We believe we have established rigorous processes that enhance team collaboration and coordination that are essential for the successful initiation and completion of our study – Optimism in IBM.
Acknowledgements. We acknowledge funding support by the National Health and Medical Research Council (NHMRC) Medical Research Future Fund (MRFF) of Australia, which is funding central trial coordination activities and support of the trial at seven Australian sites, and by The Myositis Association of America which is supporting USA sites. We are grateful to the Myositis Research Consumer Panel for their valuable involvement and for Pfizer for providing Sirolimus across the world to support this study. We are also thankful for the Muscle Study Group (MSG) and the International Myositis Assessment & Clinical Studies (IMACS) group for critically reviewing the protocol.

P-130

A DOUBLE-BLINDED PLACEBO-CONTROLLED CROSSOVER TRIAL TO ESTABLISH WHETHER TESTOSTERONE TREATMENT COMBINED WITH EXERCISE IMPROVES MUSCLE STRENGTH AND FUNCTION, AND QUALITY OF LIFE, IN MEN AFFECTED BY INCLUSION BODY MYOSITIS

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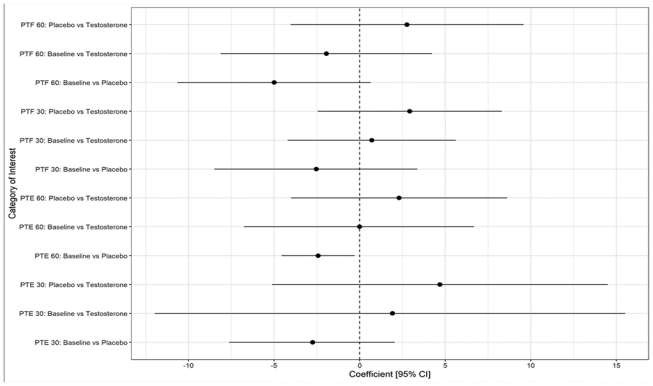
Background. Inclusion body myositis (IBM) is the most common acquired skeletal muscle disease associated with ageing and involves both an autoimmune attack on muscle fibres as well as muscle degeneration with protein deposition. There have been multiple studies showing a relationship between exercise and improved outcomes in IBM, however only one prior trial showed a modest benefit of Oxandrolone in IBM. No studies have explored a combination of the two. We hypothesised that a combination of exercise training and testosterone treatment would improve muscle strength and physical activity in males affected by IBM, more than exercise alone.
Methods. This pilot study adopted a double-blinded, placebo-controlled, crossover design to assess whether testosterone combined with a prescribed exercise program would improve measures of muscle strength, physical activity and quality of life in men affected by IBM, over exercise alone. Treatment (exercise and placebo) and placebo (exercise only) arms were 12 weeks in duration, with a two-week wash-out period between arms. Primary outcome was quadriceps strength, measured by isokinetic dynamometer (Humac Norm). Secondary outcomes included lean body mass, functional tests and Patient Reported Outcomes (PROs). Outcome measures were collected at baseline, Week 12 and Week 26. In response to participant feedback, a 12-month Open Label Extension (OLE) was offered, with outcome measures collected at new baseline, 6-months and 12-months.
Results. The primary outcome, quadriceps extension strength the placebo and treatment arms, was non-significant. The DEXA assessment of lean body mass and other functional tests were also non-significant between the placebo and treatment arms. There was a significant reduction of peak torque extension at 60 degrees during the placebo period (p=0.04). Within the SF-36 questionnaire, the domain of 'role limitations due to emotional problems' demonstrated higher scores during the testosterone arm when compared to the placebo arm (p=0.044). All other domains, as well as the IBM-FRS, were non-significant. Within the OLE, the 2- minute walk test regular and fast were significant at 6 months (p=0.03 and p=0.032 respectively) but not at 12 months. The most common adverse event reported was falls which were considered a complication of IBM rather than the study. Within the OLE, 3 of the 12 participants withdrew from the study due to adverse events related to rising prostate specific antigen and haematocrit.
Conclusions. In this study comparing exercise alone to exercise in combination of testosterone supplementation, we were unable to detect a significant effect of the treatment on muscle strength, function or quality of life. However, peak torque extension at 60 degrees worsened significantly during the exercise-only arm, which could indicate that testosterone conferred some stabilisation effect during the treatment period. Individuals on testosterone also felt that their daily activities were not as limited due to the emotional problems compared with placebo, perhaps indicating that testosterone contributes to improved mood and mental health. Individuals who participated in the OLE had improved walk tests at 6 months which then declined at 12 months. This warrants further investigation in future studies, where the benefit of testosterone on walking strength may decline after a prolonged period. Finally, we note that 12 men requested the OLE due to perceived positive effects and lack of adverse effects, so potentially the benefits of testosterone require a longer period of intervention to manifest than that applied during the crossover phase.
Acknowledgements. We would like to acknowledge the dedication of all our IBM patients, and especially those men and their partners who participated in this study.



P-130. Fig. 1.

P-131

CLINICAL FINDINGS OF A COHORT OF DEEP PHENOTYPED IBM PATIENTS

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Background. Inclusion body myositis (IBM) is a progressive myopathy with degenerative and inflammatory features on muscle biopsy, most commonly affecting individuals over the age of 50. The current IBM diagnostic criteria for clinicopathological defined IBM requires specific clinical, laboratory, and pathological features. While antibody to cytosolic 5'-nucleotidase 1A (cN1A) has been proposed as a helpful tool in the diagnosis of IBM, it is not included in the diagnostic criteria. Objective: We performed a retrospective review of a cohort of 17 well-characterized patients with IBM to examine this cohort's clinical features.
Methods. All patients were evaluated in the Neuromuscular Clinic at the McGovern Medical School at the University of Texas Health Sciences Center. The patients underwent an extensive evaluation by a neuromuscular specialist, including detailed clinical examination, muscle biopsy, and laboratory studies.
Results. Eight females and nine males with an average age at symptom onset of 56.6 years (range 35 to 74 years) were included in this study. The average age at the time of diagnosis was 60.7 years (range 43 to 77 years). The median time between symptom onset to diagnosis was 6.2 years (range 1 to 19 years). The average highest creatine kinase level was 728 U/L (range 118 to 3256 U/L). Anti-cN1A antibody was detected in eleven patients. The anti-cN1A antibody status in one patient and myositis specific antibody (MSA) and myositis associated antibody (MAA) status in five patients were unknown. In twelve patients, no MSA and MAA were detected. Four patients with anti-cN1A antibodies did not have finger flexor weakness at presentation. Most cN1A seropositive patients (8/11) did not have more severe knee extension than hip flexion weakness, and few (4/11) cN1A seropositive patients showed finger flexor weakness. On the muscle biopsy, most cN1A seropositive patients (7/11) showed many muscle fibers devoid of cytochrome C oxidase (COX) activity, and many (6/11) had rimmed vacuoles. Most cN1A seronegative patients (4/5) showed few to several muscle fibers devoid of COX activity. Increased p62 reactive aggregates were present in six cN1A seropositive patients and unknown in five patients.
Discussion. Similar to previous studies, p62 aggregates, COX-negative fibers, and anti-cN1A antibodies were present in most patients with IBM in our cohort. Among our patients, knee extension weakness was a less reliable feature than hip flexor weakness, with ten patients (8 cN1A seropositive) not clinically manifesting with preferential involvement of the quadriceps muscle. Our findings suggest that the finger flexor and knee extension weakness may not be present early in the IBM disease course. Although IBM patients invariably develop these clinical features, the requirement for these examination findings to fulfill the most recent criteria for clinic-pathologically defined IBM may result in a delay in diagnosis and hinder patient recruitment for clinical trials.

P-132

FLOW CYTOMETRY AND SORTING OF SINGLE ANTIBODY SECRETING CELLS FROM FROZEN MUSCLE TISSUE

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Background. Idiopathic inflammatory myopathies (IIM) – dermatomyositis (DM), polymyositis, and inclusion body myositis - are poorly understood autoimmune muscle disorders. Isolation of relevant immune cell populations is made difficult by most protocols requiring fresh tissue.
Methods. Our objective was to develop an approach to obtain intact antibody secreting cells from clinical samples of cryopreserved muscle biopsies. Recent publications described the ability to isolate intact cells from frozen biopsies of human lupus nephritis and rheumatoid arthritis (1, 2). These relied on collect-

ing material in HypoThermosol FRS (HT), followed by freezing using CryoStor CS10 (CS) medium (both STEMCELL Technologies, Cambridge, MA) – a method not currently used in clinical practice. The authors achieved non-inferior results compared to fresh tissue. We integrated the above approach with published methods of preparing non-human primate muscle (3, 4). Using deidentified human tonsils, we independently tested tissue processing, freezing, and storage methods. Paired 1 cm3 tonsil samples were subjected to collection media [HT or normal saline (NS)], freezing method [CS or liquid nitrogen-cooled isopentane (IP)], and digestion protocols. Flow cytometry was used to identify major antibody secreting cell subsets. Stored clinical DM and IBM samples were subjected to the final validated protocol and CD138+ cells were sorted into 96-well plates. PCR was then performed to confirm expression of heavy and light chain as well as PRDM1 and Bcl6 to probe cell lineage.

Results. We recovered similar proportions of $CD19^+$ cells and downstream $CD27^+IgD$-, $CD138^+$, and $CD38^+$ cell subsets by flow cytometry from tonsil collected with NS (Fig. 1A). Quantitation of our data showed that IP freezing was non-inferior to CS with statistically greater recovery of $CD19^+$ (p=0.002) and $CD138^+$ (p<0.001) cells compared to fresh tissue (Fig. 1B). IP freezing outperformed CS conditions for $CD19^+$ (p=0.001) and $CD27^+IgD$- cells (p=0.002). Substitution of HT for NS did not alter results (data not shown). Applying the digestion protocol to 6 frozen patient biopsies (3 DM, 3 IBM) showed similar proportions of live $CD19^+$ B cells and downstream populations (Fig. 1C and D). All samples had recoverable cells despite an average sample age of 6.5 years. A quantitative comparison revealed no statistically significant differences in isolated cell populations between DM and IBM (Fig. 1E). When subjected to PCR, all examined cells expressed similar levels of PDRM1 and Bcl6 and produced immunoglobulin heavy and light chains.

Conclusions. By making it feasible to use stored samples of frozen muscle tissue, the diagnosis and histology of which are known, our approach serves to make a large impact on human translational research of myositis. A major benefit is that the derived muscle digestion protocol does not require specialized collection or freezing media and is compatible with standard clinical samples. We plan to use this approach in the study of antibody repertoire and in situ immune response in IIM.

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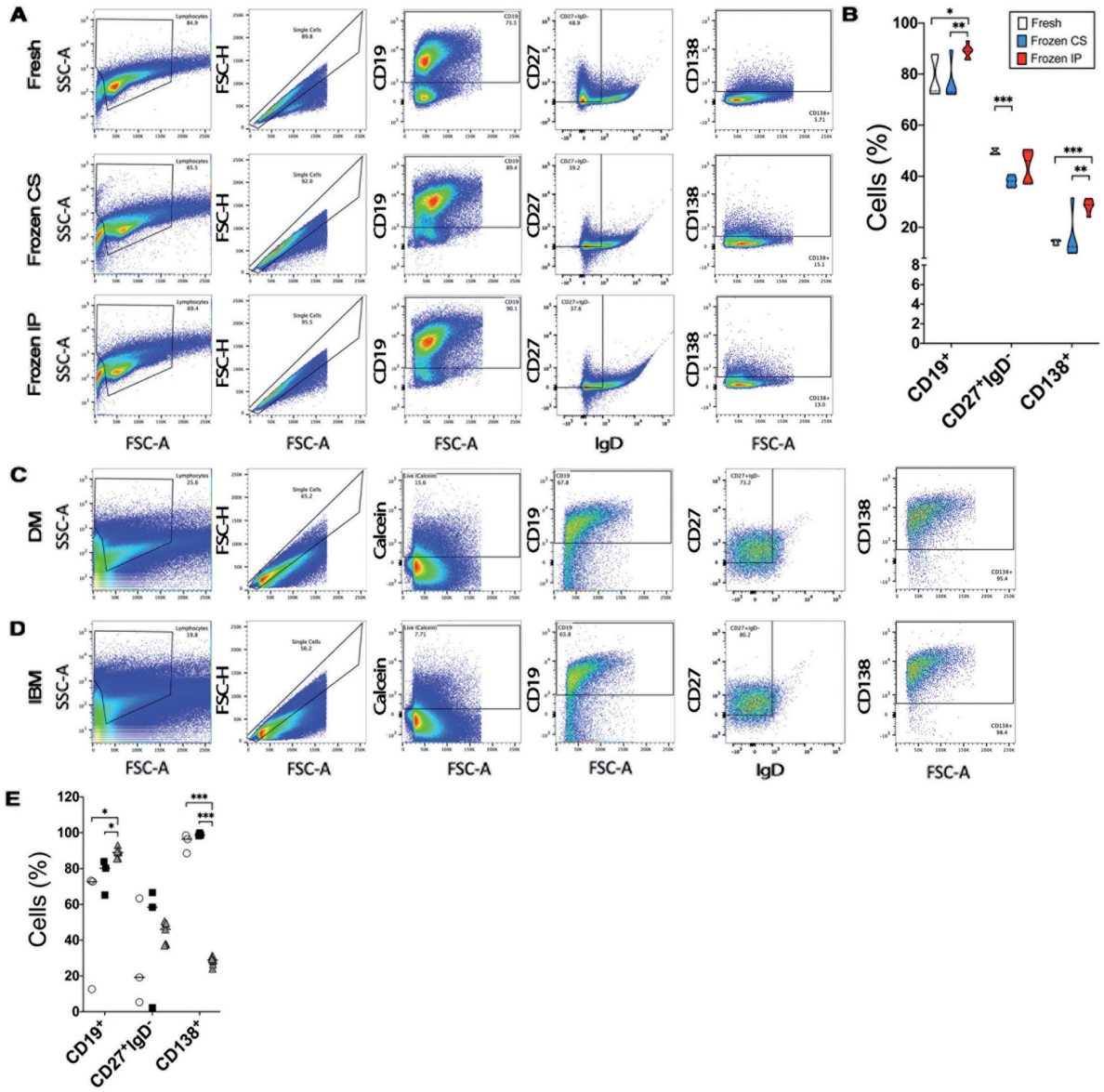

P-132. Fig. 1.

P-133

PHENOTYPICAL AND CLINICAL INDICATIONS OF A LYMPHOPROLIFERATIVE DISORDER OF CD8+ T CELL LARGE GRANULAR LYMPHOCYTES AMONG INCLUSION BODY MYOSITIS PATIENTS

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Background. Inclusion body myositis (IBM) is an autoimmune disease characterised by intense muscle infiltration by CD8+ T lymphocytes with a predominant terminally differentiated effector (TEMRA) phenotype. Recently, IBM was found to be often associated with a lymphoproliferative disorder of CD8+ T cells known as T cell Large Granular Lymphocytes (T-LGL). T-LGLs represent a spectrum of conditions that range from a lymphoproliferation in response to antigenic stimulation "reactive" to an aggressive leukemia. The incidence of expanded T-LGLs among IBM patients (between 40-60%) suggests that these cells play a distinct, yet unknown role in the pathology of this disease. This study aims to determine the T-LGL phenotypical characteristics and TCR clonal diversity and investigates the clinical implications of T-LGLs in IBM.
Methods. Blood samples collected from 85 IBM patients and an aged-matched group of 56 healthy donors were analysed using flow cytometry for phenotype characterisation. CD8+ T cells isolated from PBMCs collected in each donor group were separated into CD57+ (T-LGL) and CD57- (internal control) and sequenced to determine TCR repertoire diversity in both cell type. Multi-variate analysis of biological and clinical data at the time of sample collection, such as aid-assisted mobility, was used to investigate the impact of T-LGL in disease severity.
Results. 33/85 (39%) of IBM patients and 6/56 (10.7%) of healthy controls (HC) exhibited an elevated number of T-LGLs in blood. Immunophenotyping of the TCRαβCD8+ T-LGL population revealed aberrant expression of surface molecules such as decreased CD5 and increased CD57+, CD56+, and KLRG1+ that are commonly displayed by the natural killer cell lineage. Longitudinal analysis of thirteen T-LGL+ patients showed that this expanded cell population persists over time (average time elapsed between samples=1.5 years). Comparison of the proportion of T-LGL within the CD8 T cell population between muscle and blood samples showed that they preferentially accumulate within the muscle (blood: mean= 41.1%±11.7% vs Muscle mean= 70.1%±12.8%). Blood T-LGLs isolated from 6 IBM and 2 HC donors and submitted to bulk TCR-analysis consistently exhibited polyclonal characteristics, with diverse TCRβ VDJ segment-usage and CDR3 repertoire. Clinically, an increased proportion of IBM T-LGL positive patients required more-assisted mobility aids compared to T-LGL negative patients, even though both groups had experienced IBM symptoms for similar durations (T-LGL+ median=12 years vs T-LGL- median=11 years, *p*-value=0.99)
Conclusions. Our results demonstrate that a CD8+ T-LGLs lymphoproliferative disorder is more prevalent in IBM patients than in healthy individuals. These cells display a late-differentiated phenotype, characterised by reduced TCR-associated co-receptors and high expression of innate lymphocyte-related surface co-receptors and adhesion molecules, suggesting that these cells may be submitted to TCR-independent regulation. In contrast with previous findings, we found that the peripheral CD8+ T-LGL expansion is polyclonal suggesting their expansion is reactive in nature, yet capable of persisting for years. Nonetheless, the presence of expanded CD8+ T-LGL is associated with increased disease severity in IBM. Further investigations into the clonal diversity of muscle-infiltrating T-LGLs should be evaluated to determine if their expansion is antigen-driven or due to bystander activation.

P-134

HIGH-RESOLUTION HLA GENOTYPING REFINES GENETIC ASSOCIATIONS WITH INCLUSION BODY MYOSITIS AND REVEALS ALLELE OF INCREASED RISK OF NT5C1A ANTIBODY PRODUCTION

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Objectives. Inclusion body myositis (IBM) is a progressive inflammatory and degenerative disease of the skeletal muscles that affects individuals over the age of 45 and leads to a gradual loss of mobility. It has been widely reported that a subgroup of 33 to 72% of IBM patients produce self-reactive antibodies that bind cytosolic 5'-nucleotidase 1A (NT5C1A) within the muscles and possibly exacerbate the disease severity. A genetic association between immune-related genes with IBM has been described. This study aimed to deepen our knowledge about the human leukocyte antigen (HLA) genes that alter the risk to develop IBM and to investigate whether specific HLA alleles may contribute to the occurrence of NT5C1A-directed antibodies.
Methods. In this study, we used Illumina next-generation sequencing to resolve the high resolution HLA haplotype of 102 Caucasian IBM patients from the Western Australian cohort. We then compared the frequency and carriage of the identified alleles within the IBM cohort to reference databases of Caucasian cohorts. We additionally compared the HLA allele carriage within the genotypes of anti-NT5C1A-positive and-negative patients within our IBM cohort.
Results. Our results confirmed the previously identified association risk of the 8.1 MHC ancestral haplotype with IBM. We also lifted ambiguities and clarified the identity of the risk-associated alleles that have been previously reported at a lower level of resolution. Additionally, we identified previously unreported risk allele associations with IBM. Furthermore, our analysis validated previously reported protective HLA alleles, and also revealed reduced carriage frequency of additional alleles, suggesting their protective role in the disease. Lastly, our study revealed two alleles, which carriage are associated with anti-NT5C1A antibody production.
Conclusions. Our findings refine and expand on the knowledge of the HLA genetic background of IBM. Stratifying patients based on their HLA genotype provides a genetic basis for new therapeutic intervention strategies early in the disease process to slow down symptom development.

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EFFICACY OF RAPAMYCIN IN A XENOGRAFT MODEL OF INCLUSION BODY MYOSITIS

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Background. We have developed a novel mouse model of sporadic inclusion body myositis (IBM) in which patient-derived muscle biopsy tissue is implanted into immunocompromised mice (Britson *et al*., Sci Transl Med. 2022). The xenografts recapitulate the key features of the disease including endomysial inflammation, protein aggregates, and rimmed vacuoles. Rapamycin (Sirolimus) is an FDA approved drug used as an immunosuppressant in organ transplant recipients. In a single center pilot study in IBM patients, rapamycin improved secondary endpoints including 6-min walking distance and thigh fat fraction measured by quantitative MRI, though it did not show efficacy in its primary outcome measure of knee extension strength (Benveniste *et al*., Lancet Rheumatol. 2021). Rapamycin may show efficacy via its effect in stimulation of autophagy or via immunosuppression. Currently, rapamycin is planned for an international phase III clinical trial in IBM.
Methods. Muscle biopsy samples were obtained from a 67-year-old woman who was diagnosed with clinico-pathologically defined IBM and a 50-year-old woman who showed mild hip flexor weakness but had normal muscle histology for use as control. Xenografts were performed on 14 nod-Rag1[null]IL2rγ[null] (NRG) mice lacking the ability to generate mature B cells, T cells, and innate lymphoid cells, including natural killer cells (7 IBM and 7 control). After the xenografts had fully matured (3 months), four mice in each group were fed encapsulated rapamycin (14 mg/kg food) for 3 months, and xenografts were harvested for analysis. Three mice with IBM and control xenografts were administered placebo (eudragit). Frozen sections of the xenografts were analysed by histochemistry and immunohistochemistry in a blinded manner.
Results. IBM xenografts exhibited MHC-I up-regulation of the muscle fibers and endomysial inflammatory infiltrates of CD3+ T cell while control xenografts did not show these features. Rimmed vacuoles were observed in an IBM xenograft, while p62-positive aggregates were present in all the IBM xenografts and two of seven control xenografts. All the rapamycin fed mice showed marked elevation of serum rapamycin levels after 3 months (42.1±4.6 ng/mL) whereas levels were undetectable in mice fed placebo (<2.0 ng/mL). Among the IBM xenografts, rapamycin treated xenografts showed fewer CD8+ T cells compared with the placebo group (441±173 cells/mm2 (rapamycin group), 1148±261 cells/mm2 (placebo group), p =0.02) while there was no significant difference in the number of CD4+ T cells between rapamycin treated xenografts and the placebo group (967±284 cells/mm2 (rapamycin group), 980±50 cells/mm2 (placebo group), p=0.94). There was no significant difference between the two groups regarding myofiber density or the presence of p62-positive aggregates.
Conclusions. In this small pilot study in xenografts from a single IBM patient and control, rapamycin reduced the number of endomysial CD8+ T cells without altering the number of CD4+ T cells, suggesting one potential mechanism by which rapamycin may show efficacy in IBM by depletion of cytotoxic T cells. Studies of xenografts from three additional IBM patients and controls, including longer treatment with rapamycin (5-6 months), are ongoing.

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IMMUNOREGULATORY EFFECTS TESTOSTERONE SUPPLEMENTATION COMBINED WITH EXERCISE TRAINING IN IBM PATIENTS: A DOUBLE-BLINDED RCT IN WESTERN AUSTRALIA

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Background. Sporadic Inclusion body myositis (IBM) is an inflammatory disease that affects skeletal muscles in individuals over the age of 45. It leads to progressive muscle wasting and progressive disability and loss of independence for patients. Histologically, inflammation is characterised by myofibers displaying upregulated expression of major histocompatibility complex (MHC) class I molecules and invasion by immune cells comprising abundant $CD8^+$ T cells. There is currently no cure, and regular exercise is the only recommended treatment recognised to be effective at limiting muscle inflammation and hindering the disease progression. In healthy men, physical exercise along with administration of testosterone was shown to increase skeletal muscle mass and performance in an additive fashion. Previous studies report that androgens are anti-inflammatory, inhibiting CD4+ T cell differentiation into inflammatory Th1 cells and promoting regulatory T cells. We hypothesised that combining testosterone supplementation with exercise training will reduce the level of autoimmune inflammation better than exercise alone, in men affected by IBM.
Methodology. We conducted a double-blind, placebo-controlled, cross-over randomised controlled trial (RCT) in fourteen men with IBM, to assess whether a period of exercise training using a personalised regime combined with topical application of testosterone, reduced the inflammatory immune response associated with this disease over and above just exercise alone. To assess the intervention efficacy, we analysed the phenotype of immune cells in the blood by flow cytometry, and measured the serum cytokine and chemokine content by Luminex immunoassay.
Results. The testosterone supplementation resulted only in a significant reduction of eosinophil numbers. However, we found additional immunoregulatory effects of the exercise training program over study that were testosterone-independent, including altered proportions of subsets within monocytes, T and B cells, and reduced circulating concentration of several pro-inflammatory cytokines such as IL-12, IL-17, TNF-alpha, MIP-1beta and sICAM-1.
Conclusions. Overall, our findings indicate that regular exercise training impacts the immune response in IBM and provides anti-inflammatory benefits to IBM patients; concomitant testosterone supplementation over a 12-week period provided essentially no anti-inflammatory effect over exercise alone. This work further emphasizes that maintaining a regular level of exercise helps in controlling inflammation in IBM, and also possibly, the pace of progression of the disease toward severe stages. We cannot exclude that incorporating testosterone supplementation to exercise training may provide a synergistic anti-inflammatory in IBM, but the optimal duration of intervention and the stage of disease progression when the intervention provides most benefits will need to be further characterised and refined to achieve optimal outcomes.

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PHENOTYPIC ANALYSIS OF MYOBLASTS FROM INCLUSION BODY MYOSITIS PATIENTS

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Background. In a mouse xenograft model of sporadic inclusion body myositis (IBM) depleted of T cells with anti-CD3 (OKT3), myofiber regeneration occurs normally, but myofibers retain degenerative pathologic features such as rimmed vacuoles and loss of TDP-43 function (Britson *et al*., Sci Transl Med, 2022). These findings have led us to hypothesize that newly regenerated myoblasts are genetically or epigenetically programmed to develop cell-autonomous pathology. Indeed, prior studies have suggested that cultured IBM myoblasts undergo premature senescence (Morosetti et al, Neurobiology of Aging, 2010). The goal of this study is to use transcriptomic, epigenomic, and in vitro culture methods to characterize regenerating myoblasts from IBM patient muscle biopsies compared with controls in order to better understand IBM pathogenesis.
Methods. Muscle biopsy samples were obtained from patients who were diagnosed with IBM or other myopathies. Biopsy samples were treated with collagenase solution and either directly plated for cell culture or labelled with myoblast markers including CD56 and CD82 for isolation using flow cytometry. DNA or RNA were isolated from sorted myoblasts for ATAC-seq or RNA-seq, respectively. In parallel, dissociated muscle cells were allowed to proliferate before myoblast isolation via flow cytometry and cultured in media containing DMEM, FBS, and for differentiation into myotubes. Myotubes were stained for p62, TDP-43, and myosin heavy chain to investigate myotube maturation and degenerative phenotypes. Myotubes were also stained for beta-galactosidase to investigate senescence.
Results. IBM myoblasts proliferate at a much slower rate and generated fewer differentiated myotubes compared to non-IBM muscle. IBM myotubes show signs of senescence by use of beta-galactosidase staining compared to those from non-IBM controls. Direct cell isolation from biopsies provided approximately 15,000 $CD56^+CD82^+$ myoblasts which create suitable libraries for epigenomic and transcriptomic profiling.
Conclusions. Myoblasts can be directly isolated from human IBM muscle biopsies for multiomic analyses and differentiation into myotubes. However, cultured myoblasts from IBM patients proliferate at much slower rates and undergo early senescence compared with non-IBM controls, in agreement with prior studies (Morosetti et al., Neurobiology of Aging, 2010). Since these findings seem to contradict our observations of robust myofiber regeneration in the xenograft model, we are now comparing transcriptomic and epigenomic profiling of myoblasts cultured in vitro from those culture in the mouse xenograft *in vivo*.
Acknowledgements. T.E. Lloyd has received support from NIH (R01-AR076390), Orphan Disease Center at Penn Million Dollar Bike Ride Pilot Grant, Muscular Dystrophy Association (630399), and Peter and Carmen Lucia Buck Foundation.

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CELL TYPE-SPECIFIC TRANSCRIPTOMIC TRAJECTORIES UNDERLYING DISEASE PROGRESSION IN INCLUSION BODY MYOSITIS

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Background. Inclusion body myositis is a chronic, treatment-refractory and slowly progressing inflammatory muscle disease. The unknown molecular and cell type-specific disease mechanisms prevent the development of targeted precision therapies to halt progression and limit inflammation.
Methods. We utilized single-nucleus and spatial RNA-sequencing in combination with multiplex RNA and Protein tissue mapping to decode the muscle and immune cell and subtype diversity as well as identify molecular drivers of disease progression in inclusion body myositis.
Results. By cell type-specific sequencing and spatial validation, we could decode the wide diversity of innate and adaptive immune cell subtypes and disentangle homeostatic and reactive muscle cell subtypes according to their fiber type specificity. Further, we were able to generate transcriptomic damage trajectories of reactive muscle fibers relative to the surrounding inflammatory infiltrate and tissue microenvironment. Specifically, we found that certain muscle fiber subtypes were more vulnerable than others and followed distinct damage trajectories linked to specific cell stress pathways.
Conclusions. Single-cell and spatial sequencing tools in combination with multiplex imaging assays are highly suitable to decode the full breadth of cell

type diversity in inclusion body myositis. These techniques help identify so far unknown dysregulated damage pathways and pave the way toward cell type-specific targeted therapeutic interventions.
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ROLE OF THE CGAS/STING PATHWAY IN INCLUSION BODY MYOSITIS

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Background. Muscle fibers in sporadic inclusion body myositis (IBM) are pathologically characterized by rimmed vacuoles, cytoplasmic aggregates of TAR-DNA binding protein-43 (TDP-43) DNA/RNA-binding protein, mitochondrial defects, and invasion of $CD8^+$ T cells. Although IBM is considered an autoimmune inflammatory myopathy, pathophysiologic overlap with neurodegenerative diseases including our recent studies in a mouse xenograft model (Britson, KA *et al*., Sci Transl Med, 2022) suggests the existence of additional muscle cell/fiber-derived pathology. An *in vitro* model of amyotrophic lateral sclerosis (ALS) demonstrated that TDP-43 can trigger release of mitochondrial DNA (mt-DNA) into the cytoplasm, with subsequent activation of the pro-inflammatory response induced by the cyclic GMP-AMP synthase (cGAS)/stimulator of interferon response CGAMP interactor 1 (STING1) pathway (Yu, CH *et al*., Cell, 2020). Given the shared TDP-43 pathology in both ALS and IBM we sought to investigate the potential link between the cytoplasmic aggregation of TDP-43, mitochondrial pathology, and the role of cGAS/STING1 pathway in IBM.
Methods. Muscle biopsies were obtained from male and female IBM patients, and from control neurogenic atrophy and normal subjects. Specimens were cryosectioned and prepared for histochemistry, immunofluorescence (IF), and extraction of total RNA and DNA for qPCR analysis.
Results. Preliminary analysis by IF showed increased levels of STING1+ fibers in IBM muscle when compared with neurogenic atrophy and normal controls. However, IF analysis of cGAS level did not show any difference between IBM samples vs. control samples. qPCR analysis showed marked increased expression of both STING1 and cGAS in IBM muscle compared to normal muscle and disease controls. IBM samples also displayed cytosolic accumulation of TDP-43, mitochondrial DNA deletions, and sarcolemmal accumulation of the nucleotide-binding oligomerization domain-like receptor (NLR) family pyrin domain containing 3 (NLRP3), evidence of activation of the inflammasome. Inflammasome activation was confirmed by marked upregulation of gene expression of the inflammasome multiprotein complex, NLRP3, Caspase-1 (CASP1), and ASC (PYCARD) in IBM muscle. The induction of the cGAS/STING1 and inflammasome in IBM muscle is correlated with an increased expression of genes for key inflammatory cytokines, including interleukins 1β (IL1B) and 18 (IL18), interferon-β1 (IFNB1), and tumor necrosis factor-α (TNF).
Conclusions. IBM muscle shows signs of mitochondrial DNA damage coupled with the activation of the cGAS/STING1 pathway. This correlates with activation of the inflammasome system and the putative release of inflammatory cytokines from myofibers. Our results suggest a possible role for inhibitors of the cGAS/STING1 and inflammasome pathways in the treatment of IBM. Additional studies are needed to better understand whether myofibers or the immune cells are the source of the high level of expression of the inflammatory cytokines.
Acknowledgements. C.I. is supported by the Myositis Association (90097118). T.E.L is supported by fundings from the NIH (R01-NS082563 and R01-AR076390), Orphan Disease Center Million Dollar Bike Ride Pilot Grant, and Muscular Dystrophy Association (630399). T.E.L. and R.H.R. are supported by the Peter and Carmen Lucia Buck Foundation.

P-140

SYSTEMATIC REVIEW OF TENDON TRANSFERS IN INCLUSION BODY MYOSITIS TO IMPROVE HAND FUNCTION

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Background. Hand dysfunction in inclusion body myositis (IBM) leads to marked impairment in quality of life (QOL) and function. Our objective is to systematically assess the potential for tendon transfer surgery to improve hand function in IBM patients.
Methods. The data sources were the databases of PubMed, CINAHL, and MEDLINE were searched from inception to December 2021 for studies of inclusion body myositis and tendon transfers. Two investigators independently selected studies. Standardized data abstraction was used to extract surgical technique and measures of hand function. The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRIMSA) reporting guideline was followed. The main outcome was improvement in hand function (e.g. patient reported outcome measures (PROMs), range of motion, pinch/grip strength, muscle grade). Recorded information included indications and tendon transfer techniques with post-operative protocol.
Results. Three case reports were analyzed. Indications for tendon transfer in all 3 cases involved grip/pinch strength limitations that affected QOL. All patients had improvement in gross hand function for at least 2 years. In all three patients, wrist extensors were used to reconstruct finger flexors. Specific transfers included: (1) brachioradialis (BR) to FDP and extensor carpi radialis longus (ECRL) to FPL transfers, (2) BR to FPL and ECRL to FDP, and (3) ECRL to FPL and extensor carpi ulnaris to FDP. Post-operatively, patients were immobilized for 4 weeks prior to starting hand therapy. Standardized measures of hand function or QOL were not reported.
Conclusions. In this systematic review, evidence is limited to case reports regarding the utility of tendon transfers in improving hand functions in IBM. However, tendon transfers are commonly used in orthopedics to treat muscle-tendon unit dysfunction and may provide a viable treatment option for some IBM patients. Given the limited amount of standardized data, we propose a surgical trial (using a modified Burkhalter transfer with end-to-side coaptation using a Pulvertaft weave) with systematic assessment of hand function with a hand exam, pinch and grip dynamometry, and PROMs as well as early mobilization at 2 weeks for hand rehabilitation.

P-141

IN-PATIENT COMORBIDITIES IN INCLUSION BODY MYOSITIS COMPARED TO OTHER INFLAMMATORY MYOSITIS: A NATIONAL INPATIENT SAMPLE-BASED STUDY

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Background. Inclusion body myositis (IBM) is a progressive and debilitating disease with muscle inflammation and atrophy. IBM has a distinct pattern of muscle atrophy and weakness compared to other inflammatory myopathies (IIMs), but other comorbidities in IBM have received limited attention. In this study, we examined inpatient comorbidities in IBM compared to other IIMs by assessing in-hospital complications.
Methods. We identified patients with a primary diagnosis of IBM or other idiopathic inflammatory myopathies (IIM) (dermatomyositis (DM) and polymyositis (PM)) from the National Inpatient Sample from 2012 to 2018. We then compared the rate of various comorbidities during their hospital admission between the IBM and other IIM (DM and PM) cohorts.
Results. There were 18,819 admissions for patients with either IBM or other IIM. IBM patients were older (72.9±10.7 years, vs. 59.3±18.4 years for IIM $p<0.001$), predominantly men (65.0% vs. 31.2% for IIM $p<0.001$) and White Caucasians (82.5% vs. 58.4% for IIM, $p<0.001$). IBM patients had more frequent atrial fibrillation (16.8% vs. 11.3%, $p<0.001$), aspiration pneumonia (14.3% vs. 3.6% in IIM, $p<0.001$) and fall (10.7% vs. 4.1% in IIM, $p<0.001$). IBM was a risk factor for aspiration pneumonia (Odds Ratio (OR) 3.0) or a PEG tube placement (OR 2.9), fall (OR 2.1) when compared to other IIM and adjusted for age and gender.
Conclusions. IBM patients are at higher risk for complications of atrial fibrillation, dysphagia, and falls as compared to other IIM patients. More extensive population-based studies are warranted to better understand the impact of these comorbidities in patients with IBM.

P-142

INCLUSION BODY MYOSITIS-ON-A-CHIP

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Background. Inclusion body myositis (IBM) is characterized by progressive muscle weakness due to muscle atrophy, fatty infiltration and sarcomeric weakness of individual muscle fibers. IBM is caused by a complex and only partially understood interplay between muscle inflammation, degeneration and impaired proteostasis, which results in the accumulation of proteins in rimmed vacuoles in muscle. Antibodies against cytosolic 5'-nucleotidase (anti-cN-1A) are present in 30-60% of IBM patients and have been associated with a more severe phenotype and increased mortality rates. Our understanding of the role of anti-cN-1A in the pathophysiology of IBM remains limited. In this project, we investigate the effect of anti-cN-1A antibodies on muscle contractility, autophagy, and viability/survival using a muscle-on-a-chip model, a state-of-the-art technology that allows disease modeling in terminally differentiated striated contractile muscle fibers.
Methods. Myogenic progenitor cells, derived from healthy control induced pluripotent stem cells (iPSCs), are grown in a 3D culture system. This results in multinucleated 3D muscle fiber bundles that are able to contract and generate strength. Anti-cN-1A antibodies isolated from IBM patient sera were added during differentiation.
Results. Muscle-on-a-chip models were successfully generated. Addition of anti-cN-1A antibodies revealed no changes in the amount of strength generated, nor of autophagy markers such as p62/SQSMT1 and LC3B. Fluorescent staining for p62 also showed no aggregate formation or indication of rimmed vacuoles in 3D muscle bundles. Next, we will perform knockdown of cN-1A using shRNAs or induce amyloid-β protein accumulation often found in patients with IBM by transgenic overexpression. Finally, we will generate human iPSC-derived myogenic progenitors using skin biopsies of patients with IBM to include the genetic background in this disease model.
Conclusion. Novel models for disease may improve our understanding of the pathophysiology of IBM and provide tools to develop treatment.
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P-142-1

CHARACTERIZATION OF CYTOSOLIC 5'-NUCLEOTIDASE 1A ACCUMULATION IN CULTURED HUMAN CELL LINES

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Background. IBM (inclusion body myositis) is a progressive autoimmune disease affecting skeletal muscles, which is defined by asymmetrical muscle weakness affecting knee extensors, finger flexors and frequently also facial, bulbar axial muscles. IBM is associated with rimmed vacuoles and protein accumulation in inclusion bodies, but the etiology has yet to be determined. Frequently, IBM patients produce autoantibodies directed against cN1A (cytosolic 5'-nucleotidase 1A). cN1A is involved in nucleotide metabolism, where it hydrolyses adenosine monophosphate to adenosine. It is most highly expressed in muscle tissue. As for the etiology of IBM, the origin of these autoantibodies still has to be determined. Other enzymes involved in nucleotide metabolism (CTPS1 and IMPDH2) were shown to form distinct intracellular structures, termed rods and rings, under specific conditions. In chronic hepatitis C virus-infected patients, autoantibodies directed against IMPDH2 rods and rings were found. Our initial analyses showed that cN1A also accumulates in rods and rings-like structures. Here, we further characterized these intracellular accumulations and present an experimental strategy to investigate the composition of cN1A-containing rods and rings.
Methods. Various human cell lines were used to analyze endogenous cN1A expression: HEp-2, HeLa, FlpIn T-Rex HEK293, T-Rex HeLa cells, C25 human myoblasts and LHCN-M2 human immortalized myoblasts. For the overexpression of cN1A, HEp-2 cells were transfected with EGFP-C3-cN1A. cN1A expression was detected in cell lysates using immunoblotting and in whole cells using immunofluorescence microscopy. Proteins involved in cN1A aggregation will be identified using APEX proximity labelling. The peroxidase APEX2 catalyses the conjugation of biotin-phenol to tyrosine side chains of proteins. The expression of APEX2 creates a contour map of biotinylated proteins with a radius of 10-20 nm. Expressing the APEX2-cN1A fusion protein provides information of proteins that are in close proximity to cN1A. The biotinylated proteins in cell lysates are detected by western blotting.
Results. In cultured human cell lines (HEp-2, HeLa, T-Rex HeLa and FlpIn T-Rex HEK293), the expression of cN1A was not detectable or very low. In cells which showed low cN1A expression, Hep-2 and T-Rex HeLa, cN1A was diffusely distributed in the cytosol. Also, in cultured myoblasts cN1A expression was undetectable. However, during differentiation of myoblasts into myotubes cN1A expression was observed. Overexpression of EGFP-cN1A in HEp-2 cells showed filamentous cytoplasmic structures in the perinuclear region. These cN1A filaments appeared to be dynamic; small filaments migrate towards each other and fuse into larger filaments, reminiscent of rods and rings. Immunofluorescence experiments showed that cN1A filaments do not colocalize with CTPS1 and IMPDH2 rods and rings. To be able to apply proximity labelling, the fused cN1A-APEX2 protein was successfully expressed in HEK293 cells. Moreover, cN1A-APEX2 resulted in a distinct biotinylated protein pattern compared to other APEX2 fusion proteins on western blots.
Conclusions. cN1A is only poorly expressed in cultured human cells, except for myotubes. Ectopic cN1A expression in cultured cells show dynamic aggregations in the perinuclear region. These large cN1A aggregations are very similar to rods and rings. APEX proximity labelling allows the identification of macromolecules colocalizing with cN1A-containing intracellular accumulations.
Acknowledgements. This work was supported in part by the Prinses Beatrix Spierfonds and by AFM-Telethon.

Repairing damage

P-143

ASSESSMENT OF QUALITY AND RELIABILITY OF YOUTUBE VIDEOS FOR PATIENT AND PHYSICIAN EDUCATION ON INFLAMMATORY MYOSITIS

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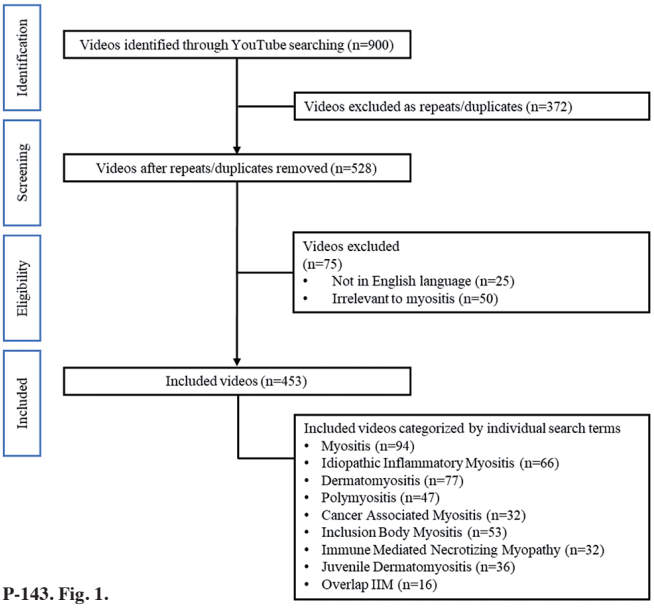
Background. Nowadays 80% of internet users access health information online, with YouTube being the second most popular search website worldwide. This study was undertaken to assess the reliability and quality of videos pertaining to myositis on YouTube and identify lacunae in information material on the platform.
Objectives. This study aims to assess the quality and profile of myositis information videos on YouTube, and to compare and delineate attributes of useful and not useful videos using standard metrics.
Methods. A thorough search was carried out on YouTube using 9 search terms related to myositis. The inclusion criteria were primary English content related to myositis, acceptable audio-video quality, and multi-part videos to be considered as one, while duplicates and advertisements were excluded. The videos were classified as useful, not useful or misleading, and patient experiences (Figure 1). Reliability of the videos was determined using the 5-point modified DISCERN (mDISCERN) criteria and quality by the 5-point Global Quality Scale (GQS) and 4-point JAMA scoring system. Score-based usefulness was defined as mDISCERN >4 or GQS >4 or JAMA >3. All values are in median and IQR.
Results. Of 453 analyzed videos 74% and 2% provided useful and not useful information respectively. 24% were patient experiences, and 324 (71%) were intended specifically for patients while 313 (69%) were for healthcare providers and students. Nearly one-thirds (n=143) reported information related to treatment of myositis. Noteworthily, useful and not useful videos had similar views count. However, number of likes and daily viewership were higher for useful videos (p=0.024, p=0.046). Nearly half (47%) of useful videos were by professional medical societies/patient support groups while not useful ones were often by nonmedical media (38%). Useful videos had higher mDISCERN reliability scores [4(3-4) vs 2(1-3), p<0.001] and better quality on GQS [4.5 (3.5-5) vs 1 (1-2.8), p<0.001] and JAMA [3 (3-4) vs 2.25 (2-3), p=0.004]. Physician predicted usefulness was discordant with score-based usefulness (κ=0.129). However, GQS score emerged significant (p=0.008) for predicting video usefulness in multivariate analysis (Table I).
Conclusion. The majority of English YouTube videos on myositis provide useful information for patients, largely related to treatment of myositis. However, the dynamic nature of YouTube could potentially change this equation in the

future and physicians should correct any misinformation identified in face-to-face meetings or teleconsultations. High quality useful videos, often predicted by validated scores and produced by professional medical societies should be promoted as the first-line of content consumed.



P-143. Fig. 1.

P-143. Table I.

Factors predicting usefulness of video in binary logistic regression

Variable	B coefficient	S.E.	Exp (B) and 95% CI	*p* value
Intended audience				
Anyone/General public	-5.45	2.586	0.004 (0.0-0.68)	0.035
Average GQS	-2.86	1.076	0.05 (0.007-0.47)	0.008

GQS: Global Quality Scale. Exp (B) is odd's ratio, $p<0.05$ is significant.

Other

P-144

PAIN PROFILE AND OPIOID MEDICATION USE IN MYOSITIS

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Background. Pain is commonly reported in patients with myositis, yet the prevalence and management of pain in myositis are unknown. Pain is an understudied and underappreciated aspect of myositis. This study assesses the presence of pain in the subtypes of myositis as well the frequency of opioid and non-opioid pain medication use.
Methods. A survey was developed and distributed by Myositis Support and Understanding, a patient-led advocacy organization, to members of its group. Multivariate logistic regression analysis and chi-square tests were performed.
Results. A total of 468 participants completed the survey. 423 participants (dermatomyositis n=183, polymyositis n=109, and inclusion body myositis n=131) were included, based on reported diagnosis, for final analysis. 91.5% of myositis patients reported current or past pain with 99% attributing their pain to myositis. There was a lower likelihood of pain in patients age over 60 years (OR 0.2, 95%CI:0.1-0.6, p=0.003). The percentage of patients reporting pain was statistically different based on myositis type (DM 97.2%, IBM 80.9%, and PM 94.5%, p<0.001) with a higher likelihood of pain in DM compared to IBM (OR 3.7, 95%CI:1.3-10.2, p=0.011). There was a lower likelihood of pain in patients age over 60 years (OR 0.2, 95%CI:0.1-0.6, p=0.003). Of the 387 participants reporting pain, 335 reported using pain medications (69% prescribed opioids). Male sex, age over 60 years, and myositis subtype were not associated with the likelihood of non-opioid use.
Conclusion. Pain is a commonly reported symptom in myositis with variable treatment strategies, including opioid medications. This study highlights the importance of addressing pain as part of myositis treatment as well as the need for future studies understanding treatment effectiveness.
Acknowledgments. We thank Myositis Support and Understanding as well as the myositis patients and caregivers who contributed to this work.

P-144. Table I. Demographic, pain profile and pain medications by myositis type

	All Patients N=423	Dermato-myositis N (% of total) =183 (43.3)	Inclusion-Body Myositis N (% of total) =131 (31.0)	Polymyositis N (% of total) =109 (25.7)	*p*-value
Demographic Information					
Age [N (%)]					**p<0.001**
20-30 years	12 (2.8)	5 (2.7)	0 (0)	7 (6.4)	
30-40 years	43 (10.2)	30 (16.4)	0 (0)	13 (11.9)	
40-50 years	75 (17.7)	47 (25.7)	7 (5.3)	21 (19.3)	
50-60 years	110 (26.0)	58 (31.7)	20 (15.3)	32 (29.4)	
60-70 years	109 (25.8)	35 (19.1)	49 (37.4)	25 (22.9)	
70-80 years	63 (14.9)	8 (4.4)	44 (33.6)	11 (10.1)	
>80 years	11 (2.6)	0 (0)	11 (8.4)	0 (0)	
Male [N (%)]	107 (25.4)	17 (9.4)	70 (53.4)	20 (18.4)	**p<0.001**
Time since myositis diagnosis [N (%)]					p=0.176
<1 year	60 (14.2)	31 (16.9)	16 (12.2)	13 (11.9)	
1-5 years	169 (40.0)	73 (39.9)	52 (39.7)	44 (40.4)	
5-10 years	94 (22.2)	39 (21.3)	37 (28.2)	18 (16.5)	
10-15 years	50 (11.8)	18 (9.8)	14 (10.7)	18 (16.5)	
15-20 years	29 (6.9)	10 (5.5)	11 (8.4)	8 (7.3)	
20-25 years	7 (1.6)	4 (2.2)	0 (0)	3 (2.8)	
>25 years	13 (3.3)	8 (4.4)	1 (0.8)	5 (4.6)	
Pain Profile					
Current or past pain [N (%)]	387 (91.5)	178 (97.2)	106 (80.9)	103 (94.5)	**p<0.001**
Pain secondary to myositis [N (% of patients with pain)]	383 (99.0)	178 (100)	103 (97.2)	102 (99.0)	p=0.074
Pain Medications					
Any pain medication [N (% of patients with pain)]	335 (86.6)	152 (85.4)	88 (83.0)	95 (92.2)	p=0.122
Non-opioid pain medication [N (% of patients taking pain medication)]	311 (92.8)	147 (96.7)	82 (93.2)	82 (86.3)	p=0.445
Opioid pain medication [N (% of patients taking pain medication)]	231 (69.0)	104 (68.4)	55 (62.5)	72 (75.8)	p=0.051

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NUTRITIONAL ASSESSMENT, BODY COMPOSITION AND PHASE ANGLE IN JUVENILE DERMATOMYOSITIS PATIENTS

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Background. Bad food consumption can contribute to promoting adipogenesis, an increased risk of obesity, and other cardiometabolic and chronic diseases. This study aimed to assess body composition (BC) using Bioelectrical impedance and food intake in juvenile dermatomyositis (JDM) patients. Possible associations between BC and physical activity, disease activity/cumulative damage, and health-related quality of life parameters were also evaluated.
Methods. This was a cross-sectional study with 30 consecutive JDM patients and 24 healthy volunteers of both sexes followed at our Pediatric Rheumatology Unit. Anthropometric and dietary data, physical activity, and bioelectrical impedance were performed. Clinical and therapeutic data were collected from medical records. Data were analyzed using MedCalc Statistical Software.
Results. Current age (11.8±4.0 vs. 10.7±3.1 years; p=0.249) and sex (18 Female (F): 12 Male (M) vs.14 F:10 M; p=0.924) were similar in JDM patients and healthy controls. Median of JDM disease duration was 3.3 (0.21-16.6) years and 10/30 (33.3%) had active disease (Disease Activity Score-DAS≥3). In JDM patients two parameters of body composition (body fat and lean mass) were positively correlated with disease duration (rs=+0.629, p<0.0001 and rs=+0.716, p<0.0001, respectively) and phase angle (PhA) (rs =+0.400, p=0.029 and rs=+0.619, p<0.0001, respectively). In contrast, body fat and lean mass demonstrated a negative correlation with Childhood Health Assessment Questionnaire (CHAQ) parameter (rs=-0.545, p=0.002 and rs= -0.616, p<0.0001, respectively) and with JDM scores: DAS total (rs=-0.463, p=0.010 and rs=-0.566, p=0.001, respectively) and DAS-muscular (rs=-0.483, p=0.007 and rs=-0.476, p=0.008, respectively). High and comparable percentages of inadequacy in fiber consumption were found in JDM patients and

controls (71% vs. 53.3%, 0.577) but just 30% of patients had an adequate intake of antioxidant selenium compared to 62.5% of controls (p=0.027). JDM patients with PhA ≥5.5 presented higher lean mass when compared to patients with PhA <5.5 (p=0.001).
Conclusion. We demonstrated that bioelectrical impedance can be an auxiliary exam in the medical and nutritional follow-up of JDM patients since it seems to impact functional ability. These findings may assist professionals to advise JDM patients about the importance of physical activity to preserve lean mass and eat healthily.
Acknowledgments. We thank Ulysses Doria Filho for having performed the statistics of this study. Also the Division of Nutrition of Children and Adolescents' Institute for providing bioimpedance equipment and work support.

P-146

HIGH FATIGUE SCORES IN PATIENTS WITH IDIOPATHIC INFLAMMATORY MYOPATHIES: A MULTIGROUP COMPARATIVE STUDY FROM THE COVAD E-SURVEY

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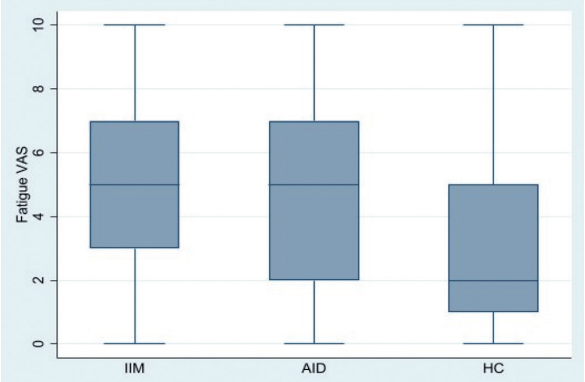
Background. Idiopathic inflammatory myopathies (IIM) are a rare, multisystem, heterogeneous disease, and contribute to a high psychological burden. The patients' perception of physical health, deteriorating independence and social and environmental relationships may not always be a direct function of disease activity. To face with these aspects, several worldwide specialized organization have recommended the use of patient reported outcome measures (PROMs) both in clinical trials and observational studies to highlight patient's perception of the disease. Unfortunately, data on fatigue scores in IIM is limited. We compared fatigue VAS scores in patients with IIM, autoimmune diseases (AIDs) and healthy controls (HCs) and triangulated them with PROMIS physical function in a large international cohort made up of answers from the e-survey regarding the COVID-19 Vaccination in Autoimmune Diseases (COVAD) study.
Methods. Data of 16327 respondents was extracted from the COVAD database on August 31th 2021. VAS fatigue scores were compared between AID, HC and IIM using univariate followed by multivariate analysis after adjusting for baseline differences. We further performed a propensity score matched analysis on 1827 subjects after adjusting for age, gender and ethnicity. The Kruskal-Wallis test was used for continuous variables and chi-square test for categorical variables, and Bonferroni's correction was applied for the post hoc analyses considering IIMs as a reference group.
Results. We analyzed answers from 6988 patients, with a mean age of 43.8 years (SD 16.2). The overall percentage of female was 72% and the population ethnicity was mainly composed of White (55.1%), followed by Asian (24.6%), and Hispanic (13.8%). The overall fatigue VAS was 3.6 mm (SD 2.7). IIMs VAS was 4.8 mm (SD 2.6), AIDs 4.5 mm (SD 2.6), and HC 2.8 mm (SD 2.6) (p<0,001). VAS fatigue scores of IIMs were comparable with AIDs (p 0.084), albeit significantly higher than the HCs (p<0,001). Notably, fatigue VAS was lower in IIMs than AIDs in two distinct subsets: inactive disease as defined by the patient's perception and the "excellent" general health condition group, where IIMs had worse scores (p<0,05). Interestingly, fatigue VAS was comparable in active disease defined by physician assessment, patient perception, based on general functional status, or when defined by steroid dose being prescribed. Notably, after propensity matched analysis of patients adjusting for gender, age and ethnicity (1.827 answers, *i.e.* 609 subjects per group, p=1) the differences disappeared and IIMs and AIDs had comparable fatigue levels across all levels of disease activity, although the fatigue discrepancies with HCs were substantially confirmed. After application of a multivariate linear regression analysis we found that lower fatigue VAS scores were related to HC (p<0,001), male gender (p<0,001), Asian and Hispanic ethnicities (p<0,001 and 0,003).
Conclusions. Our study confirms that there is a higher prevalence of fatigue in all the AIDs patients, with comparable VAS scores between IIMs and other AIDs. We can also read our data commenting that females and/or Caucasians patients suffer a higher impact of this manifestation of chronic autoimmune diseases upon their lives. This is why these subjects, to our judgement, should be carefully evaluated during outpatients visits and to whom we should spend some extra time to discuss health related issues and how to improve them.



P-146. Fig. 1. Graph: distribution of Fatigue VAS scores in the three population evaluated. IIM idiopathic inflammatory myositis; AID autoimmune diseases; HC healthy controls; *p<0.05.

P-147

OUTCOMES OF PREGNANCY IN WOMEN WITH IDIOPATHIC INFLAMMATORY MYOPATHIES IN AFRICA: A SYSTEMATIC REVIEW

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Background. This is the first systematic review on outcomes of pregnancy in women with idiopathic inflammatory myopathies (IIMs) in Africa.
Methods. PubMed, EMBASE and African Journals Online were searched for relevant studies published up to March 4, 2021. Data were pooled narratively.
Results. We included 4 case reports and 2 case series reporting a total of 18 singleton post-IIM pregnancies and 10 singleton pre-IIM pregnancies in 12 women aged 26-42 years at conception. Among women with ethnicity data, 6 were Black Africans, 1 Black Caribbean and 1 North African. Specified IIM subtypes were overlap myositis (n=4), dermatomyositis (n=4) and immune-mediated necrotizing myopathy (n=2). Pre-IIM pregnancies ended with 2 adverse outcomes including a medical termination (for unspecified cause) and a stillbirth. Ten post-IIM pregnancies had unfavourable outcomes including premature delivery (n=4), cesarean section (n=3), medical termination for unspecified causes (n=3), offspring small for gestational age (n=2), neonatal death (n=2), maternal pulmonary infection (n=1), stillbirth (n=1) and neonatal lupus (n=1).
Conclusion. Maternal and offspring outcomes of pre-and post-IIM pregnancies are poorly characterized in Africa. This issue needs to be further studied in a prospective multicenter African registry.

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EPIDEMIOLOGY OF IDIOPATHIC INFLAMMATORY MYOPATHIES IN AFRICA: A CONTEMPORARY SYSTEMATIC REVIEW

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Background. This is the first systematic review on the epidemiology of idiopathic inflammatory myopathies (IIMs) in Africa.
Methods. We queried PubMed, EMBASE and African Journals Online to select relevant studies published up to December 30, 2020. Data were pooled narratively. The review was registered with PROSPERO, CRD42020186781.
Results. We included 39 studies reporting 683 cases (71.7% adults) of IIMs. The incidence of dermatomyositis (DM) was estimated at about 7.5/million person-years and 1.2/million person-years, and that of polymyositis (PM) at 8.8/million person-years. The prevalence of IIMs was estimated at 11.49/1,00,000, and that of the PM subtype at 11/100,000 persons. Mean age at diagnosis ranged from 7.9

to 57.2 years, and 50% to 100% of patients were females. Main adult-onset IIM subtypes were DM (21%-93%) and PM (12%-79%), and juvenile DM (5.8%-9%) was the commonest childhood-onset IIM. Skeletal muscle involvement (56%-100%) was the commonest disease feature, and oesophagus the most commonly affected internal organ (6%-65.2%). The commonest myositis-specific antibodies were anti-Jo1/histidyl tRNA synthethase (7%-100%) and anti-Mi2 (17%-45%). Early mortality was high (7.8%-45%), main death causes being infections, cancers and organ damage in respiratory and cardiovascular domains.
Conclusion. The epidemiology of IIMs in Africa appears to be similar to that in other regions of the world, except for the age at onset of adult IIMs which is likely much younger in Africans. Further high-quality studies are needed from Africa.

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VITAMIN D AND THE GENE EXPRESSION OF ITS RECEPTOR (VDR) IN SKELETAL MUSCLE PLAY A ROLE IN DISEASE MANIFESTATION AND PHYSICAL FITNESS OF PATIENTS WITH MYOSITIS

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Background. Idiopathic inflammatory myopathies (IIM) are chronic inflammatory disorders characterised, apart from extramuscular manifestations, by symmetrical progressive muscle weakness that may persist even after pharmacological suppression of inflammation, suggesting a significant involvement of nonimmune mechanisms. Low levels of vitamin D have been associated with several autoimmune diseases. Vitamin D is essential for the maintenance of skeletal muscle, and mounting evidence supports its relation to muscle damage, regeneration, and energy metabolism. The aim was to analyse vitamin D and its receptor in muscle tissue of IIM patients, and to associate it with muscle health parameters.
Methods. A total of 46 IIM patients (40 females, 6 males; mean age 56.7±12.4; disease duration 6.5±6.0 years; dermatomyositis (21), polymyositis (18), necrotizing myopathy (7)) and 67 healthy controls (HC) (56 females, 11 males; mean age 50.9±14.7) were recruited. In total, 27 IIM patients participated in a 24-week intervention combining activities-of-daily-life, resistance and stability training [Špiritović M, *et al*. *Arthritis Res Ther.* 2021]. Muscle biopsies from m. vastus lateralis (by Bergström needle) were obtained from 7 IIM patients before/after the 24-week training program, and from 13 control IIM patients, and 21 HC. Primary muscle cell cultures were established from these samples. Disease-associated parameters were evaluated by MYOACT/MITAX, MDI, VAS, HAQ, MMT8, FI-2 and CK, myoglobin, LD, ALT, AST, and CRP levels. Myostatin, as a myokine involved in muscle atrophy, was determined from serum samples by ELISA. Circulating concentrations of 25(OH) vitamin D (calcidiol) and active 1,25(OH) vitamin D (calcitriol) were measured by routine biochemistry techniques. Gene expression of vitamin D receptor (VDR) and 25-hydroxyvitamin D 1-alpha-hydroxylase (CYP27B1), an enzyme catalysing calcidiol conversion to hormonally active calcitriol, was determined by real-time PCR in muscle tissue and primary muscle cell cultures. Data are presented as mean ± standard deviation.
Results. Decreased levels of active 1,25(OH)D were observed in IIM patients compared to HC (125.0±45.4 vs. 164.7±49.2 pmol/l; $p<0.0001$). No difference was found for 25(OH)D. The 24-week training program did not have an effect on 25(OH)D or 1,25(OH)D serum levels. 25(OH)D was significantly associated with CRP (r=-0.322, $p=0.040$), MITAX (r=-0.380, $p=0.021$) and HAQ (r=-0.370, $p=0.017$) in IIM patients, even after correction for BMI, gluccocorticoid (GC) and vitamin D daily supplementation dose. After 24 weeks of exercise, active 1,25(OH)D was positively associated with MMT8 (r=0.866, $p<0.0001$), FI2 (r=0.608, $p=0.013$) and HAQ (r=-0.537, $p=0.032$) (corrected for BMI, GC and vit.D supplementation). Numerically higher gene expression of VDR and CYP27B1 was found in muscle tissue and primary muscle cells in IIM compared to HC. After the 24-week training, gene expression of both VDR and CYP27B1 in primary muscle cells decreased ($p=0.031$ and $p=0.078$, respectively). Associations of VDR gene expression in muscle tissue with MMT8 (IIM: r=-0.559, $p=0.013$), serum myoglobin (IIM: r=0.510, $p=0.026$; HC: r=0.473, $p=0.035$), myostatin (IIM: r=-0.519, $p=0.023$; HC: r=0.586, $p=0.005$), and CK (HC: r=0.484, $p=0.031$) were observed. CYP27B1 gene expression in the muscle was also associated with MMT8 (IIM: r=-0.555, $p=0.011$), serum myoglobin (HC: r=0.501, $p=0.024$), and VDR gene expression in muscle (IIM: r=0.561, $p=0.012$; HC: r=0.632, $p=0.002$).
Conclusion. Decrease of the biologically active form of vitamin D in circulation suggests an impairment of its metabolism in IIM. Vitamin D serum levels and gene expression of its receptor and activating enzyme in muscle tissue associate with disease activity and muscle function parameters indicating an important role of vitamin D in physical fitness and disease manifestations in IIM patients.
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ENDOCRINE RISK FACTORS FOR OSTEOPOROSIS IN MYOSITIS: A PILOT COHORT STUDY

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Background. Hypogonadism occurs in 6% of middle-aged men and is more frequently observed in older and obese men with a poor health status. Hypogonadism can lead to osteoporosis, which is a risk factor for bone fractures and, thus, adds to an impaired mobility and reduced quality of life. Patients with impaired mobility due to neuromuscular diseases are at risk of severe falls with the risk for bone fractures, particularly in the presence of osteoporosis. It is known that some hereditary myopathies like myotonic dystrophy type 1 are associated with hypogonadism. However, little evidence is available for hypogonadism in myositis, a muscle disease that mostly affects middle aged patients. Thus the aim of the study was to assess frequency and extent of hypogonadism and osteoporosis in patients with myositis.
Methods. We conducted a cohort study at the Neuromuscular center in Göttingen. Male patients with myositis including inclusion body myositis (IBM), dermatomyositis (DM), polymyositis (PM), antisynthetase syndrome (ASS), necrotizing myopathy (NM) and unspecific myositis (UM) were invited to take part in the study. Each patient had to answer three questionaries regarding the risk for hypogonadism, risk for osteoporosis and quality of life. Every patient received a full clinical examination as well as a laboratory screening tests for hypogonadism. Patients with abnormal laboratory findings were subsequently seen by endocrinologists and subsequent visits and treatment offers were made depending on the outcome.
Results. 15 patients with IBM and 15 patients with other myositis subsets (DM=3, PM=3, NM=5, UM=3, ASS=1) participated in the study. The average age of the patients with IBM was 67.4 years and the average age of the patients with other myositis was 55.9 years. In both groups, pathological laboratory tests regarding hypogonadism were found in 26.7%. In half of these patients, further diagnostic by the endocrinologists was initiated. A “decline in energy” was reported by two thirds of the patients with IBM and in 73.3% in other myositis subsets. An erectile dysfunction was reported in a little less than half of the patients. A loss of libido was mentioned in half of the patients. In addition to the hypogonadism studied here, the use of current or recent cortisone (26.7% in IBM; 66.7% in other myositis) and gastroprotective drugs (53.3% in IBM and other myositis) appeared relevant in myositis patients regarding an increased risk of osteoporosis. Particularly in IBM patients, a significant reduction in walking distance was reported with less than 100m in 60% of patients. Falls in the last few months were reported by two-thirds of patients at risk of bone fractures.
Conclusion. Patients with myositis are at higher risk for osteoporosis and seem to be at higher risk for hypogonadism. The disease itself as well as a hypogonadism can lead to typical symptoms of hypogonadism, like a decrease of energy, muscle strength and loss of libido. The impaired walking distance and increased tendency to fall, especially in IBM patients, underscores the relevance of assessing the risk for osteoporosis. Hypogonadism and osteoporosis should be specifically addressed in patients with myositis. Further studies are required to solidify our findings and to identify myositis patients at risk for osteoporosis and hypogonadism.
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THYROID DISORDERS ASSESSMENT: AN UNMET NEED IN PATIENTS WITH IDIOPATHIC INFLAMMATORY MYOPATHIES?

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Background. Thyroid diseases (TD) might compromise health status of patients, in particular owing to their possible impact on cardiovascular risk, bone mineral density (BMD) and muscle function. The prevalences of Hashimoto thyroiditis (HT), multinodular goiter (MNG) and Graves' disease (GD) in general population correspond respectively to about 12%, 10% and 1.3%; it is well known HT represents a risk factor for the development of thyroid papillary cancer (TPC). Idiopathic inflammatory myopathies (IIMs) are rare systemic autoimmune disorders, with a pleiotropic clinical picture. TD are a known comorbidity of patients with connective tissue diseases; in particular, they might increase the risk of osteoporosis (OP) and fragility fractures (FF) in patients with SLE (1). A recent study described the association between IIMs and both hyper- and hypothyroidism (1). To evaluate the prevalence of TD in a monocentric cohort of patients with IIMs, we explored possible correlations with serology, organ involvement and comorbidities.
Methods. We retrospectively analyzed medical records of consecutive patients diagnosed with IIM according the EULAR/ACR 2017 criteria and regularly followed at our specialistic outpatient Myositis Clinic from January 2018 to December 2021. We collected data about demography, subset and duration of disease, organ involvement, serology, thyroid dysfunction and other comorbidities. As TD, we took into account the occurrence of HT, MNG and GD. Intergroups comparisons were assessed by using Chi-square, t-test and ANOVA. P values <0.05 were considered significant.
Results. The clinical charts of 151 patients were examined: 101 (66,9%) were female, the mean age was 65,1±14,0 years and the mean disease duration was 8,5±6,5 years. Clinical diagnosis were the following: 69 (45.7%) polymyositis, 59 (39.1%) dermatomyositis, 11 (7.3%) clinically amyopathic dermatomyositis, 10 (6.6%) inclusion body myositis, 2 (1.3%) juvenile dermatomyositis. Seventy-five patients (49.7%) had a TD; in particular, 39/151 (25.8%) had MNG, 34/151 (22.6%) had HT and 2/151 (1.3%) GD. The presence of a TD was significantly related with esophagus' involvement (p=0.037), Raynaud's phenomenon (RP) (p=0.045), sicca syndrome (SiS) (p<0,001), OP (p<0,001) and cataract (p=0,017). In particular, HT and MNG occurrence was respectively associated with a higher risk of OP (p<0,001) and of sicca syndrome (p<0,001). Interestingly, TD were significantly less frequent in patients with anti-Mi2beta autoantibodies (p=0,003) and anti-Jo1 autoantibodies (p=0,026). No further significant correlations emerged.
Conclusion. Our study showed nearly half of our IIMs patients had a TD, with a prevalence of both MNG and HT significantly higher than in general population; besides, owing to the retrospective nature of our study, these data could be underestimated. In addition to correlating with RP and SiS, TD showed a significant association with esophagus involvement; this result should be confirmed and clarified with future analyses. Moreover, in our cohort, TD were confirmed as a risk factor for a compromised BMD; in particular, HT was significantly associated with the occurrence of OP. Further studies are needed to corroborated our data in other cohorts of IIM patients and to explore if TD represent a risk factor for FF also in IIM; finally, since HT is a risk factor for TPC, an evaluation of its occurrence in our cohort should be designed. However, our data seem sufficient to underline the need to regularly screen IIM patients for thyroid function, aiming at optimizing their quality of care, both for activity and damage domains of their autoimmune disease.

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DETERMINANTS OF PATIENT REPORTED GLOBAL DISEASE ACTIVITY IN ADULT INFLAMMATORY MYOPATHY

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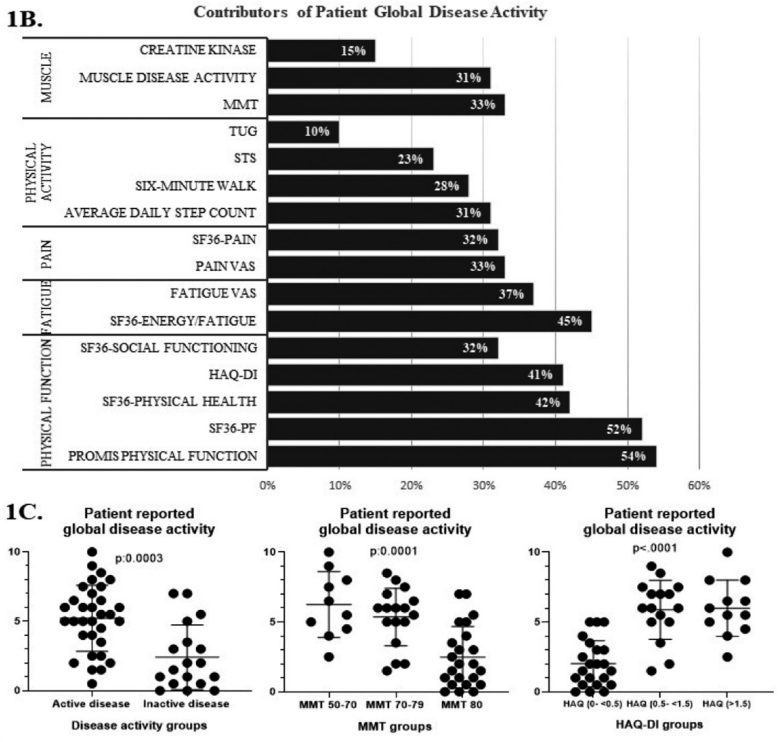
Introduction. Patient reported global disease activity (ptGD) is one of the two patient-reported outcome measures in myositis core set measures used in the 2016 ACR/EULAR criteria for minimal, moderate and major response in adult idiopathic inflammatory myopathies (IIM). Assessment of disease activity in systemic autoimmune diseases can be affected by several measures. Understanding the determinants of ptGD is important in the assessment of the patients to be able to best address patients' needs. Disagreements between physician and patient assessment of disease activity may negatively impact shared decision making leading to patient dissatisfaction and prevent physicians from providing patient-centric care. In this study, we examined the determinants of ptGD, and rates and causes of discordance between ptGD and physician global disease activity (MDGD) in patients with IIM.

1A.

Other measures at baseline	PtGD *Rho*	MDGD *Rho*
Disease Activity		
Cutaneous disease activity	-0.02	0.14
Pulmonary disease activity	0.08	0.19
Extramuscular global disease activity	0.17	0.58
Muscle disease activity	0.58	0.74
MDGD/ptGD	0.53	0.53
Creatine kinase	0.36	0.29
Muscle Strength		
MMT score	-0.62	-0.66
Physical Function Forms		
HAQ-DI Score	0.66	0.65
PROMIS T Score	-0.75	-0.69
SF36-Physical Functioning	-0.72	-0.65
Pain		
Pain VAS	0.58	0.37
SF36-Pain	-0.57	-0.59
Fatigue		
Fatigue VAS	0.61	0.44
SF36-Energy/Fatigue	-0.67	-0.53
Quality of Life		
SF36-Role limitation due to physical health	-0.61	-0.53
SF36-Role limitation due to emotional problems	-0.23	-0.25
SF36-Emotional well-being	-0.38	-0.18
SF36-Social functioning	-0.60	-0.44
SF36-General health	-0.52	-0.47
Physical Function Tests		
Sit-to-stand test	-0.46	-0.39
Timed up-and-go test	0.44	0.32
Six-min walk test	-0.56	-0.55
Physical Activity		
Actigraph average daily step count	-0.60	-0.41



P-152. Fig. 1. Correlations between patient-reported global disease activity PtGD, physician-reported global diseae activity (MDGD), and other myositis outcome measures (1A): percent contributions of muscle disease, physical activity, pain, fatigue and physical function measures to ptGD (1B): and distribution of ptGD across different clinical groups (1C).

Methods. Adult patients with IIM who were consecutively seen at the University of Pittsburgh Myositis Center were enrolled in the study. PtGD/MDGD are rated on a 10-cm visual analog scale from 0 (no disease activity) to 10 (extremely severe disease activity) by asking patients/physicians to assess the disease activity by considering all involved organ systems. Patients report their disease activity on the day of the assessment, whereas physicians rate the disease activity over the past 4-weeks. The following myositis outcome measures were assessed: ptGD, MDGD, manual muscle testing (MMT), HAQ-DI, creatine kinase (CK), fatigue and pain VAS, PROMIS physical function 20, SF-36, sit-to-stand (STS), timed up-and-go (TUG), six-minute walk test (6MWD), and Actigraph® average daily step count. Spearman correlation was used for cross sectional correlations between ptGD and the other outcome measures. Measures with strong-moderate correlations with ptGD were used as independent variables in a linear regression model to determine the contribution of each measure to ptGD (R2). The intergroup differences of ptGD were evaluated among MMT groups (50-70, 71-79, 80), HAQ-DI groups (<0.6, 0.6-1.6, >1.6), and active vs inactive disease groups (physician reported binary categorical assessment). Concordance of ptGD and MDGD was defined as being within 3 points of each other based on published literature, and difference between active vs inactive disease (2.8)(discordance if ≥3 points of each other).

Results. Fifty probable or definite (2017 ACR/EULAR Classification Criteria) myositis patients [60% females; mean age 51.6 (±14.9); 24 DM, 6 PM, 9 NM and 11 anti-synthetase syndrome] were enrolled. PtGD was significantly different between physician-defined active and inactive disease, MMT groups and HAQ-DI groups (Figure 1). PtGD correlated strongly with muscle disease activity, MDGD, MMT, HAQ-DI, PROMIS physical function, pain VAS, fatigue VAS, SF36 physical function, health, fatigue, social functioning and pain subdomains, 6MWD and average daily step count (r=0.57-0.75), and moderately with STS, TUG and CK levels (r=0.36-0.46). Physical function measures contributed to ptGD the most (32-54%), followed by measures of fatigue, pain, physical activity and muscle disease (Figure 2). PtGD was discordant with MDGD in 30% of the patients of which ptGD was higher than MDGD in 66%. Pain (33% vs 10%), fatigue (37% vs 15%) and energy levels (45% vs 26%) contributed more to ptGD than MDGD. The patients who had discordantly high ptGD had significantly higher levels of pain (median VAS 4 vs 1), fatigue (median VAS 5.5 vs 4.2), and more limitations in physical function (HAQ-DI 1 vs 0.3).

Conclusion. In this study, the main determinants of ptGD were physical function, fatigue and pain. One third of myositis patients had discordant ptGD and MDGD measures with two-thirds having a higher ptGD than MDGD. Pain, fatigue and energy levels were important driving factors of the differences observed in the patient vs. physician assessment of myositis disease activity.

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VALIDATION OF THE 2016 ACR/EULAR MYOSITIS IMPROVEMENT CRITERIA IN ADULT DERMATOMYOSITIS AND POLYMYOSITIS CLINICAL TRIALS AND CONSENSUS PROFILES

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Background. Idiopathic inflammatory myopathies are heterogenous systemic autoimmune diseases which characteristically affect skeletal muscle and other target organs. The ACR/EULAR myositis response criteria (MRC) were developed as a composite continuous measure (Total Improvement Score (TIS)) using absolute percent changes (abs%) in 6 differentially weighted core set measures (CSM), providing improvement categories (minimal, moderate, major) based on pre-specified thresholds. As the MRC do not specifically require improvement in strength and function, it is unclear whether patients can achieve response without improvement in strength, a concern to regulatory agencies. Only 2 CSMs are patient reported measures (PRO) (Health Assessment Questionnaire (HAQ) and Patient Global Disease Activity (PTGA)); thus, reflection of PRO in the TIS is uncertain. It is also unclear whether patients can achieve response per the criteria with worsening in any CSMs. In this study, we aimed to assess the contribution of each CSM to TIS, frequency of strength vs. extramuscular global activity (EMGA) improvement, representation of PRO in the TIS, and frequency of worsening in CSMs across MRC categories.

Methods. Data from adult DM/PM patients enrolled in the Rituximab in Myositis (n=147), Etanercept in DM (n=14), and Abatacept Treatment in PM/DM

P-153. Table I. Frequency and Distribution of Patients, Median TIS, Improving and Worsening CSMs, and CSM Contribution to TIS by the TIS Categories for Combined Adult Trial and Consensus Profile Data.

	Total Improvement Score Categories			
	No improvement	**Minimal improvement**	**Moderate improvement**	**Major improvement**
N (%)	151 (36.7%)	101 (24.5%)	102 (24.8%)	58 (14.1%)
Median TIS (IQR)	7.5 (2.5 – 12.5)	27.5* (22.5 - 32.5)	47.5*† (42.5 - 52.5)	70*†‡ (65 - 77.5)
Median Number of CSM Improved (Range)	2 (0 - 3)	3* (1 - 5)	5*† (3 - 6)	6*†‡ (4 - 6)
Median Number of CSM Worsened (Range)	2 (0 - 6)	1 (0 - 4)	0 (0 - 3)	0 (0 - 2)
Median Absolute Percent Change in each CSM [IQR]				
MMT	0 [(-4) – 3]	5* [1 – 9]	10*† [6 – 15]	20*†‡ [16 – 25]
MDGA	0 [(-7) – 4]	9* [3 – 15]	19.5*† [12 – 27]	30*†‡ [21 – 42]
EMGA	-2 [(-8.5) - 0]	5* [0 – 13]	13*† [6 – 20]	21*†‡ [12 – 33]
PTGA	-2 [(-12) – 7]	9* [(-3) – 21]	21*† [6 – 35]	37.5*†‡ [29 – 49]
HAQ	0 [(-8) – 4]	4* [0 - 13]	11* [0 – 21]	29*†‡ [17 – 42]
Muscle Enzyme	1 [(-8) – 8]	6* [(-1) – 18]	14.5 *† [2 – 36]	39 *†‡ [11 – 86]
Median Percent Contribution of each CSM to TIS [IQR]				
MMT (32.5% expected contribution)	0§ [0 - 57.1]	33.3 [0 – 47.2]	25 [20 - 42.1]	32.2 [28.6 - 36.7]
MDGA (20% expected contribution)	0§ [0 – 20]	23.1§ [0 - 33.3]	30.4§ [17.7 – 35]	23.8§ [21.2 - 26.7]
EMGA (20% expected contribution)	0§ [0 – 20]	0 [0 – 30]	17.7 [13.6 - 27.3]	17.9§ [12.5 - 20.8]
PTGA (10% expected contribution)	0§ [0 – 14.3]	7.1 [0 - 22.2]	10.5 [5 - 15.8]	10.6§ [9.1 - 13.3]
HAQ (10% expected contribution)	0§ [0 – 10]	0 [0 – 21.4]	10.8 [0 – 15]	10.7§ [9.4 - 12.5]
Muscle Enzyme (7.5% expected contribution)	7.5§ [0 – 25]	6.7 [0 - 18.2]	6.3 [0 - 14.3]	8.7 [4.2 - 10.3]
Physician Rated Change Categories from the RIM trial (N (%))				
No Improvement or Worsened (n=46)	31 (67.4%)	9 (19.6%)	5 (10.9%)	1 (2.2%)
Slight Improvement (n=45)	3 (6.7%)	22 (48.9%)	17 (37.8%)	3 (6.7%)
Moderate Improvement (n=46)	1 (2.2%)	6 (13%)	23 (50%)	16 (34.8%)
Marked Improvement (n=10)	0 (0%)	1 (10%)	3 (30%)	6 (60%)

Abbreviations: CSM: core set measure; IQR: Interquartile range; TIS: Total improvement score; MMT: Manual Muscle Testing; MDGA: Physician Global Disease Activity; EMGA: Extramuscular Global Disease Activity; PTGA: Patient global disease Activity; HAQ: Health assessment questionnaire; Muscle enzyme: Most abdormal enzyme; RIM: Rituximab in Myositis Trial.

Improvement categories: No Improvement: 0 ≤Total Improvement Score ≤20: Minimal Improvement: 20 ≤ Total Improvement Score <40; Moderate Improvement. 40 ≤Total Improvement Score <60; and Major Improvement: 60 ≤Total Improvement Score.

A CSM was considered improving (or worsening) if Abs% change was >5% (<-5% for worsening) for all CSMs except for Manual Muscle Testing (MMT), which was considered improving if the Abs% change is >2% (<-2% for worsening) per points assigned in the TIS.

Expected contribution was based on (CSM maximum TIS point contribution/100).

*Statistically significant difference from the No Improvement category. A *p*-value <0.008 is considered significant.

†Statistically significant difference from the Minimal Improvement category. A Bonferroni adjusted *p*-value <0.008 is considered significant.

‡Statistically significant difference from the Moderate Improvement category. A Bonferroni adjusted *p*-value <0.008 is considered significant.

§Statistically significant difference from the expected contribution (Sign Test). A Bonferroni adjusted *p*-value <0.005 is considered significant.

(n=19) trials, and consensus profiles from natural history and open-label treatment studies (n=232) were included. The TIS and number of improving/worsening CSMs by MRC category were examined. Abs% change of each CSM was computed as ((final - baseline value)/CSM range)*100. Frequency of improvement with muscle-related CSMs (MMT, HAQ, and/or muscle enzyme (CK)), without muscle-related CSMs (EMGA) and PRO (HAQ and PTGA) was calculated. Wilcoxon test with Bonferroni adjusted p-value was performed for comparison among MRC categories. Regression analysis of the TIS was performed to assess contribution of each CSM. Observed % contribution of each CSM to TIS was calculated as: (CSM Improvement Score/TIS)*100. Sign test was performed to compare the observed vs expected contribution of each CSM. Physician rated assessment of change were compared to MRC categories.

Results. Of 412 adults with DM/PM, there were 36.7%, 24.5%, 24.8%, and 14.1% with no, minimal, moderate, and major improvement by MRC, respectively (Table). A significant increase in the number of improving CSMs by each MRC category was noted. Patients with no-minimal improvement had a median of 1-2 CSM worsening, whereas patients with moderate-major improvement had a median of zero CSM worsening. Patients who had no improvement by MRC had minimal change in individual CSMs. As the level of improvement increased from minimal to major, the Abs% change in all CSMs significantly increased (Table). In minimal-moderate improvement, only MDGA contributed significantly more than expected, and other CSM contributed as expected. The change in each CSM significantly contributed to the TIS except muscle enzyme. Of the patients with at least minimal improvement, 83% had improvement in MMT and 95% had improvement in muscle related measures (MMT, HAQ, or CK). Conversely, only 13% had improvement in EMGA without improvement in MMT, and only 4% had improvement in EMGA without improvement in muscle related measures. Of the patients with at least minimal improvement, 84% had improvement in PTGA or HAQ. In general, most physician-rated assessment of change was in agreement with the TIS categories.

Conclusion. This study demonstrated that each CSM significantly contributes to the TIS except muscle enzyme. The majority of DM/PM patients who improve by the MRC show improvement in muscle disease, while it is uncommon to meet MRC improvement without improvement in muscle disease. The MRC categories often reflect improvement in PRO, and infrequently show worsening in any CSMs. The ACR-EULAR MRC are robust and perform consistently across multiple studies.

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RELIABILITY AND VALIDITY OF PROMIS PAIN INTERFERENCE, FATIGUE, AND PHYSICAL FUNCTION AS PATIENT REPORTED OUTCOME MEASURES IN ADULT IDIOPATHIC INFLAMMATORY MYOPATHIES: INTERNATIONAL STUDY FROM THE OMERACT MYOSITIS WORKING GROUP

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Background. Over the past decade, the OMERACT Myositis Working Group (MWG) conducted several focus groups and international consensus studies with adult idiopathic inflammatory myopathy (IIM) patients, and identified pain, fatigue and physical activity (later operationalized as physical function based on focus groups) as the most important domains to assess. There is a lack of reliable and valid patient-reported outcome measures (PROMs) assessing these domains that are also available in multiple languages. A systematic literature review and discussions with patient research partners resulted in identification of three Patient Reported Outcome Information System (PROMIS) scales assessing pain interference (6a v1.0), fatigue (7a v1.0) and physical function (8b v2.0) as candidate PROMs. The objective of this study was to evaluate the construct validity and test-retest reliability of the PROMIS pain interference, fatigue, and physical function forms in adult IIM.

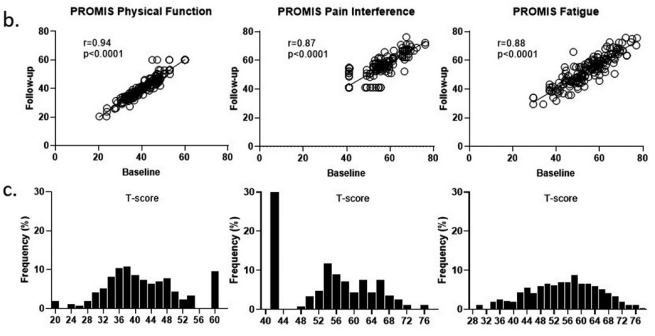
Methods. PROMs were deployed to adult IIM patients (excluding inclusion body myositis) from the OMERACT MWG international clinic sites (Australia, Canada, the Netherlands, South Korea, Sweden, UK, USA). For construct validity, data was analyzed from the OMERACT MWG 2019 Survey of Content Validity and Feasibility and 2021 Survey of Construct Validity and Reliability. In addition to the three candidate PROMs, Functional Assessment of Chronic Illness Therapy-Fatigue, Pain Disability Index, International Physical Activity Questionnaire, Myositis Activities Profile, numeric pain rating scale, PROMIS anxiety (4a v1.0), depression, sleep disturbance, and social participation were obtained. For construct validity, a total of 14 a priori hypotheses were generated based on consensus (>75% agreement by MWG members). Pearson correlation was calculated to assess the correlations between instruments for each hypothesis. For test-retest reliability, PROMIS instruments were administered at time zero and 7 days later with numeric pain rating scale as anchor. Test-retest reliability was assessed using both Pearson correlation and intra-class correlation coefficient (ICC) (considered strong if ICC or r >0.75). Internal consistency was assessed using Cronbach-α (considered good if ≥0.8, and excellent if ≥0.9). Floor and ceiling effects were determined based on histograms of each instrument.

Results. Of 368 participants who received a survey link, 161 (44%) completed ≥1 PROM and 263 completed test-retest questionnaire. Average age of participants was 60 (SD 11) with 73% female: 80% were from USA (n=129), followed by Australia (n=8, 5%), the UK (n=7, 4%), Canada (n=5, 3%), the Netherlands (n=2, 1%), and Sweden (n=2, 1%). For construct validity, 11 out of 14 a priori hypotheses were met supporting construct validity of the three PROMIS instruments (3/5 for pain interference, 4/4 for fatigue, and 4/5 for physical function) (Figure). Test-retest reliability was strong for all three PROMIS instruments with ICCs (95%CI) of 0.93 (0.91-0.95) for pain interference, 0.94 (0.91-0.95) for fatigue, and 0.97 (0.96-0.98) for physical function. All three PROMIS instruments demonstrated good/excellent internal consistency with Cronbach-α ranging from 0.89 to 0.97. None of the measures demonstrated any ceiling or floor effects with the exception of a significant ceiling effect in the pain interference scale (31%).

Conclusions. This study provides reliability and validity evidence for application of the PROMIS pain interference (6a v1.0), fatigue (7a v1.0), and physical function (8b v2.0) instruments in a large international cohort of adult patients with IIM. Internal consistency of these instruments was good to excellent. Both fatigue and physical function instruments did not show any ceiling or floor effect supporting their ability to capture the full spectrum of constructs. However, significant ceiling effect noted in the pain interference instrument raises concern about its use in patients with minimal/no pain. Further longitudinal studies to assess the responsiveness of these measures are currently ongoing in multiple countries.

a.

	Instruments	n	*A priori* hypothesis-expected correlation	% Agreement of Members	Pearson's r	Hypothesis confirmed
PROMIS Pain Interference	PROMIS Sleep Disturbance (4a v1)	263	Moderate	93%	0.35	Yes
	Pain Intensity Numeric Scale	263	Mod-High	100%	0.87	Yes
	Sex	N/A	Low	57%	Dropped	N/A
	Age	65	Low	93%	-0.18	Yes
	Pain Disability Index	100	High	100%	0.63	No
PROMIS Fatigue	PROMIS Anxiety (4a v1.0)	263	Moderate	93%	0.58	Yes
	PROMIS Sleep Disturbance (4a v1)	263	Moderate	100%	0.54	Yes
	Sex	68	Low	100%	0.17	Yes
	Age	68	Low	100%	-0.18	Yes
PROMIS Physical Function	PROMIS Depression (4a v1)	263	Moderate	93%	-0.49	Yes
	Sex	78	Low	100%	-0.01	Yes
	Age	78	Low	100%	-0.11	Yes
	International Physical Activity Questionnaire	100	Moderate	86%	-0.13	No
	Myositis Activities Profile	100	Moderate	86%	0.77	Yes



P-154. Fig. 1. Correlation between PROMIS instruments (pain interference, fatigue, physical function), and other measures for construct validity assessment (a), scatter plots of baseline and follow-up results of the PROMIS instruments (b), and histograms of the PROMIS instruments at baseline.

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MUSCLE BIOPSY PRACTICES IN THE EVALUATION OF MYOPATHIC DISEASE: A SYSTEMATIC LITERATURE REVIEW

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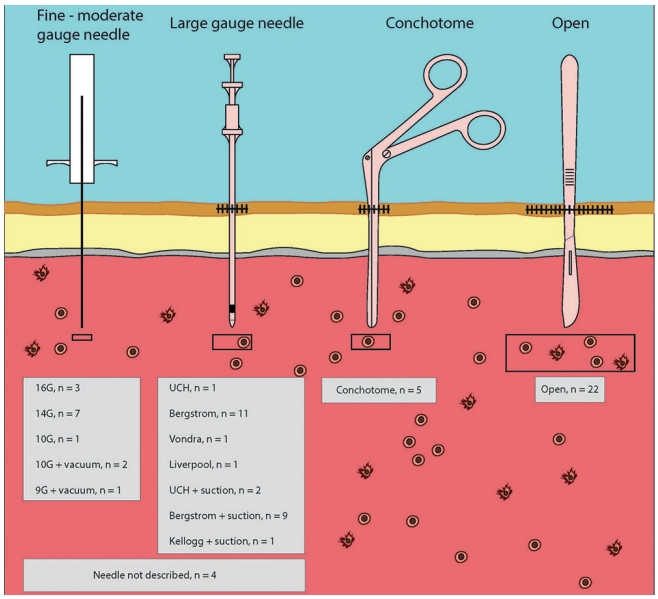
Background. Muscle biopsy is an important tool in the evaluation of myopathic disease and is often considered the gold standard for diagnosis. A wide variety of muscle biopsy techniques are practiced worldwide however the relative performance of these methods is poorly defined.
Methods. We performed a search of Medline and EMBASE from January 1970-July 2021 using keywords related to muscle biopsy. All English language studies that described the muscle biopsy technique with information regarding sample size, complications or diagnostic yield were included. Two authors (LR, JD) independently assessed the eligibility of full text articles and performed data extraction. Narrative summaries were used to present data due to the heterogeneity of included studies.
Results. The search identified 5521 references, of which 64 were included. Twenty-two studies reported open surgical biopsies, 10 reported fine needle biopsies (14-16G), four reported moderate-gauge biopsies (9-10G), 26 reported large-gauge needle biopsies (> 9G) and five reported conchotome biopsies. Seven studies directly compared two different biopsy techniques. Surgical biopsies were commonly performed under general anaesthesia (7/12, 58%) in operating theatres. Conversely, needle and conchotome biopsies were performed under local anaesthesia (40/42, 95%), commonly in outpatient or bedside settings. Only two needle studies reported use of general anaesthesia in selected patients and five reported select use of sedation, generally for paediatric patients only. Total sample weight was lowest in fine needle and moderate-gauge biopsies without vacuum (4.2-55mg, n=5) compared with moderate-gauge biopsies with vacuum (190-400mg, n=2), large-gauge needle biopsies (37-233mg, n=14) or the conchotome approach (23-1000mg, n=3). Use of suction during large-gauge needle biopsy significantly increased the sample size in one comparative study. The rate of inadequate sampling for histological analysis was 0-5% for surgical biopsies (n=10 studies, 1,294 biopsies), 0-8.3% for large-gauge needles (n=17 studies,16,342 biopsies), 0-8% for moderate-gauge biopsies (n=3, n=242 biopsies), 0–15% for fine needle biopsies (n=7 studies, 591 biopsies) and 0-3% for conchotome biopsies (n=4 studies, 1330 biopsies). Complications were infrequent, with haematoma or bleeding being rarely observed in all biopsy types. Syncope or presyncope (0.2%-1.4%, four studies) and pain at biopsy site (0.03-2.4%, nine studies) were reported in needle or conchotome biopsy studies whereas malignant hyperthermia (1.1%, one study), vascular injury (0.6%, one study) and keloid scarring (3.1%, one study) were reported complications in surgical biopsy studies.
Conclusions. Needle and conchotome muscle biopsies are safe, are typically performed under local anaesthesia or light sedation and can be performed at the bedside or in ambulatory care settings. The sample yield was higher using large-gauge needles and the conchotome method compared with fine needle biopsies, which is reflected in the higher rates of inadequate sampling observed in the latter. The application of vacuum or suction increases sample yield following needle biopsy. Needle and conchotome methods of muscle sampling are a satisfactory alternative to surgical biopsy.



P-155. Fig. 1.

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ARE THERE CLINICAL AND PROGNOSTIC DIFFERENCES BETWEEN MEN AND WOMEN IN INFLAMMATORY MYOPATHIES? ANALYSIS OF A HISTORICAL MULTICENTER COHORT

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Objectives. To analyze the clinical characteristics and severity of disease of patients diagnosed with idiopathic inflammatory myopathy (IIM), and to compare differences between men and women.
Methods. Retrospective, multicenter and observational study of consecutive patients with IIM from the REMICAM cohort (registry of patients with inflammatory myopathy of the community of Madrid). The patients were diagnosed between January 1980 and December 2014, all fullfiling Bohan and Peter classification criteria. Data was extracted from medical records and telephone visits in cases of loss of follow-up. IIM were classified as idiopathic polymyositis (PM), idiopathic dermatomyositis (DM), overlap myositis (OM), and cancer-associated myopathies (CAM). Juvenile myopathies and inclusion body myositis were excluded. Comorbidity, including cardiovascular risk factors (arterial hypertension, diabetes mellitus, dyslipidemia and active smoking), chronic obstructive pulmonary disease (COPD), and ischemic heart disease were studied. Severity factors including death, severe infections and duration of steroid treatment were analyzed. Factors associated with death were analyzed in a multivariate study and were adjusted by age, time of duration of disease and cancer. Survival was studied with Cox regression analysis.
Results. We included 381 patients (25% males, age at diagnosis of 49±17 years, disease duration of 9.8±8.4 years). Comparing clinical subgroups, there was a greater difference in classification subgroups between women and men in OM (86 vs. 14%, respectively) and DM (80 vs. 20%, respectively) and a smaller difference in CAM (54 vs. 46%, respectively). Age at diagnosis was similar between men and women (51±16 vs. 48±17 respectively; p=0.13), although men had a shorter time of duration of the disease (6.6±7.5 vs. 10.8 ±8.4 respectively, p<0.01). In bivariate analysis (Table I), men had a higher mortality, more active smoking, more COPD and more cancer than women, although less arterial hypertension. There were no differences regarding severe infections or prolonged steroid treatment. In multivariate analysis adjusted by age, time of duration of disease and cancer, mortality was similar between men and women (OR 1.4; 95% CI 0.7-2.5; p=0.31).
Conclusions. In the REMICAM registry with 381 patients with IIM, men had a higher mortality compared to women, and presented higher active smoking, COPD and cancer. No differences were observed in the main manifestations of the disease, severe infections or the need for prolonged steroid treatment. The worse survival in men could be explained by factors other than gender.

P-156. Table I. Bivariate analysis.

	Men n (%)	Women n (%)	p	OR	CI 95%
Cardiovascular risk factors	64 (68)	184 (64)	0,51	1,2	0,7-1,9
Arterial hypertension	25 (28)	111 (39)	0,05	**1,7**	**1,1-2,8**
Diabetes mellitus	14 (16)	42 (15)	0,88	1,1	0,6-2,0
Dyslipidemia	33 (37)	111 (39)	0,65	1,1	0,7-1,8
Active smoking	32 (41)	31 (17)	<0,01	**3,5**	**2,0-6,4**
Ischemic heart disease	11 (12)	16 (6)	0,04	2,3	1,0-5,2
COPD	20 (22)	6 (2)	<0,01	**13,1**	**5,1-33,8**
Systemic manifestations	43 (47)	110 (40)	0,23	1,3	0,8-2,2
Arthritis	61 (65)	196 (68)	0,54	1,2	0,7-1,9
Skin manifestations	52 (55)	177 (72)	0,28	1,3	0,8-2,1
Cardiac manifestations	22 (23)	66 (23)	0,94	1,0	0,6-1,8
ILD	31 (33)	105 (37)	0,57	1,2	0,7-1,9
Cancer	29 (31)	40 (14)	<0,01	**2,8**	**1,6-4,8**
Exitus	38 (44)	71 (29)	0,01	**2,1**	**1,3-3,2**
Steroid treatment (months)	61 ± 74	90 ± 89	<0,01	1,0	1,0-1,0
Severe infections	32 (36)	76 (27)	0,12	1,5	0,9-2,5

COPD: Chronic obstructive pulmonary disease, ILD: interstitial lung disease.

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PREDICTORS OF MUSCLE INVOLVEMENT IN PORTUGUESE PATIENTS WITH MIXED CONNECTIVE TISSUE DISEASE

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Background. Mixed connective tissue disease (MCTD) is a rare heterogeneous disease, characterized by overlapping features of classic connective tissue diseases. Myositis may be present in up to two-thirds of patients with MCTD and it is included in all diagnostic criteria available. Although some possible associations have been reported, to the best of our knowledge, no independent predictors of MCTD-related myositis have been described. We aimed to identify clinical and laboratorial predictors for muscular involvement in a cohort of Portuguese patients with MCTD.

Methods. Multicentre retrospective cohort study including adult-onset patients with a clinical diagnosis of MCTD and fulfilling at least one of the following diagnostic criteria: Sharp, Kasukawa, Alarcón-Segovia or Kahn criteria. Myositis was defined as proximal muscle weakness, creatine kinase elevation, electromyography (EMG) suggestive changes or a positive muscular biopsy. Univariate analysis was performed using Chi-Square, Fischer's Exact Test and MannWhitney Test, as appropriate. Multivariate analysis was performed using binary logistic regression modelling. The linearity of the continuous variables concerning the logit of the dependent variable was assessed via the Box-Tidwell procedure. Cases with missing information and outliers were excluded from the multivariate analysis to fulfil all assumptions necessary to assure the validity of the regression.

Results. A total of 98 patients were included, 43 (44.3%) of whom had muscular involvement at any time of the disease course. Concerning patients with MCTD-related myositis, the mean age at diagnosis was 34.8±12.5 years and the mean disease duration of 4.1±4.9 years. The majority of patients were female (90.7%) and of European ancestry (66.7%). EMG was performed in 24 patients, of whom 10 (41.7%) had a myopathic pattern. Seventeen patients were submitted to a muscular biopsy, of whom 8 (47.1%) had histological myositis features. Capillaroscopy was performed in 24 patients and 12 (50%) had a scleroderma pattern. African ancestry and leukopenia were positively associated with myositis at disease onset. Furthermore, fever at the onset of disease, younger age at diagnosis and shorter disease duration were positively associated with the occurrence of myositis at any phase of the disease. The multivariate analyses predicting myositis at diagnosis included 54 patients and at any time of the disease included 90 patients. These models explained 37.8% and 26.9% (Nagelkerke R2) of the variance in myositis and correctly classified 79.6% and 73.3% of all cases, respectively. African ancestry (OR 8.39, 95%CI: 1.43-49.37, p=0.019), leukopenia (OR 6.24, 95%CI: 1.32-29.48, p=0.021) and younger age at diagnosis (OR 1.07/year, 95%CI: 1.01-1.14, p=0.035) were identified as independent predictors of myositis at diagnosis. Fever (OR 6.51, 95%CI: 1.23-34.37, p=0.027) was an independent predictor of muscular involvement at any time of the disease in MCDT patients.

Conclusions. African ancestry, leukopenia and younger age at diagnosis are independent predictors of myositis at presentation in MCTD patients, while fever is an independent predictor of myositis at any time of the disease. While evaluating patients with MCTD, these predictive factors should be considered.

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VALIDATION OF THE 2018 EUROPEAN NEUROMUSCULAR CENTRE (ENMC)CLASSIFICATION CRITERIA OF DERMATOMYOSITIS AND COMPARISON WITH 2017AMERICAN COLLEGE OF RHEUMATOLOGY/EUROPEAN LEAGUE AGAINST RHEUMATISM (ACR/EULAR) AND BOHAN & PETER CRITERIA

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Backgrounds. In 2018, ENMC formulated a new classification criteria for dermatomyositis (ENMC-DM), which recommends classifying DM based on clinical, pathological features and myositis-specific antibodies (MSAs). There is no study about the validation of ENMC-DM criteria in the DM cohort. we aim to verify the applicability of the ENMC-DM new classification criteria, compare it with the previous classification criteria, assess the diagnostic performance and consistency of each criteria, and observe the characteristics of DM classified by the new criteria in our cohort.

Methods. The demographic, clinical characteristics, pathological and laboratory data of IIM patients in the Rheumatology and Immunology Department of China-Japan Friendship Hospital from May 2008 to October 2020 were retrospectively collected. DM was reclassified according to Bohan & Peter criteria (B&P), 2017ACR/EULAR criteria and 2018 ENMC-DM criteria. The diagnostic performance of each criterion was evaluated according to sensitivity, specificity, and negative-positive predictive value. Cohen's kappa coefficient was used to analyze the agreement among the criteria.

Results. A total of 1370 adult IIM patients were included. Among them, 857 cases were diagnosed as DM by physician, and 913 cases, 693 cases and 671 cases of DM were classified by B&P, ACR/EULAR and ENMC-DM criteria, respectively. The specificity of the three criteria was 69%, 86% and 91%, and the sensitivity was 88%, 72% and 73%, respectively, and the agreement with the physician's diagnosis was moderate (κ=0.58, 0.55 and 0.60). The sensitivity of each criterion with muscle biopsy was higher than that without muscle biopsy (94% vs. 78%, 75% vs. 68%, 73% vs. 61%), and the specificity was slightly lower than that without muscle biopsy time (65% vs. 79%, 86% vs. 87%, 88% vs. 92%). The sensitivity and specificity of the new ENMC-DM criteria were higher with MSAs than that without MSAs (73% vs. 43% and 91% vs. 83%), and were highest in the presence of both muscle biopsy and MSAs (97% and 76%). Myasthenia, myalgia, Gordon's papules, Gordon's sign, Heliotrope rash, V-type rash, CK levels, anti-MDA5 and anti-TIF1γ distributions were significantly different in DM patients classified by the three criteria (χ^2=208.4, 9.1, 10.2, 13.1, 29.4, 10.1, 17.2, 49.8, 11.2, p<0.01). The incidence of muscle weakness was highest in DM patients classified by ACR/EULAR criteria (100%). The incidence of Gordon's papules, Gordon's sign, Heliotrope rash and the positive rate of MSA were the highest in DM patients classified by the ENMC-DM criteria (99.7%, 72.1%, 83.5%, 82.7%, p<0.01). Among them, Gordon's sign, positive rash, proximal muscle weakness, and elevated CK levels were the most obvious in anti-MDA5, anti-SAE, anti-NXP2, and anti-Mi-2 positive DM, respectively. Muscle biopsy mainly showed perifascicular atrophy and perivascular lymphocytes infiltration.

Conclusion. The 2018 ENMC-DM new criteria are clinic-pathologically oriented and include subgroups defined by MSAs in the classification, which improves sensitivity and specificity. It has potential as a clinical classification criterion for DM in the future.

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CLINICAL FEATURES AND OUTCOMES OF MYOCARDITIS IN IDIOPATHIC INFLAMMATORY MYOPATHIES: A RETROSPECTIVE STUDY

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Background. Myocarditis in idiopathic inflammatory myopathies (IIM) is poorly understood, with large knowledge gaps regarding the associated clinical phenotype and outcomes. We sought to describe the demographics, clinical features, autoantibodies, and mortality of IIM patients with myocarditis.

Methods. We performed a retrospective study of all adult IIM patients (meeting Bohan and Peter criteria) enrolled in the Johns Hopkins Myositis Center research registry with myocarditis diagnosed any time after IIM onset. Myocarditis diagnoses were first identified using ICD-9/10 codes then adjudicated by a rheumatologist and cardiologist using 2013 European Society of Cardiology diagnostic criteria, with a myocarditis expert serving as a final adjudicator for any disagreements. Clinical variables, demographics, autoantibodies, and outcomes were collected via retrospective chart review and database queries. Descriptive statistics and the Kaplan-Meier method were used for analysis.

Results. We identified 31 patients in our myositis registry from 2004-2021 with an ICD-9/10 code of myocarditis, of whom 15 were adjudicated to have myocarditis. Reasons for exclusion included: myocarditis criteria not met (n=12), sarcoidosis (n=2), myositis criteria not met (n=1), and insufficient records (n=1). Clinical features of IIM patients with confirmed myocarditis are shown in Table 1. Median age at IIM diagnosis was 49 years (IQR 35-57 years) and myocarditis diagnosis was 56 years (IQR 36-65 years), with the median duration between IIM diagnosis and myocarditis 3 years (IQR 2-9 years). Most patients were female (n=9, 60%) and black (n=11, 73%). IIM subtypes included anti-synthetase syndrome (n=8), immune-mediated necrotizing myopathy (n=3), polymyositis (n=1), inclusion body myositis (n=1), and scleroderma/myositis overlap (n=2). The most common autoantibodies were anti-Jo1 (n=3) and anti-PL12 (n=3). Two-thirds of patients (n=10) had active myositis at time of myocarditis diagnosis documented by the treating physician, defined as elevated creatine kinase and/or muscle weakness. Most patients were symptomatic at myocarditis diagnosis (n=13), with a heterogenous initial presentation: subacute/chronic (>3 months) worsening of dyspnea (n=5), acute chest pain (n=3), new onset dyspnea (n=2), palpitation and/or unexplained arrhythmia and/or syncope (n=2), and cardiogenic shock (n=1). Almost all required hospitalization (n=14, 87%) at time of myocarditis diagnosis, of whom half were in the intensive care unit (cardiogenic shock, n=2; cardiac arrest, n=1; high flow oxygen, n=2; hemodynamic monitoring for hypotension not requiring pressors, n=1; post-left heart catherization monitoring, n=1). At time of myocarditis diagnosis, 69% (n=11) had reductions in left ventricular ejection fraction (LVEF) <50%; 6 had severely reduced LVEF <35% and 4 subsequently received implantable cardioverter defibrillators. Most patients (n=13, 87%) received intensification of baseline immunosuppression after myocarditis diagnosis, typically with prednisone (n=8) and/or addition of Rituximab (n=5). All patients received a combination of heart failure medications at the discretion of their cardiologist. Despite this, 40% (n=6) expired within a median time of 6.3 years (range 2.6-20.8) from IIM diagnosis and 2.5 years (range 1.1-6.3 years) from myocarditis diagnosis. The 7-year overall survival rate from IIM diagnosis was 67% and 7-year overall survival from myocarditis diagnosis was 38%.

Conclusion. Myocarditis was diagnosed most often in patients with the anti-synthetase syndrome, immune-mediated necrotizing myopathy, and scleroderma overlap patients. Clinical presentations in this select cohort were severe and heterogeneous, with poor outcomes despite intensification of immunosuppression. However, this study was limited by its small sample size, selection bias (*i.e.* patients are not routinely screened for cardiac manifestations), and retrospective nature. Larger prospective studies are needed to validate these results and to determine which high-risk patients may benefit from cardiac screening for earlier intervention.

P-159. Table I. Clinical features of IIM patients with myocarditis (n=15).

Variable		
Demographics		
Age at IIM diagnosis (median [IQR], years)	49	(35-57)
Age at myocarditis diagnosis (median [IQR], years)	56	(36-65)
Duration between IIM diagnosis and myocarditis (median [IQR], years)	3	(2-9)
Sex, n (%) female	9	(60)
Race		
White, n (%)	3	(20)
Black, n (%)	11	(73)
Asian, n (%)	1	(7)
IIM Clinical Features		
IIM Diagnosis		
Dermatomyositis	0	
Polymyositis	1	(7)
Immune-mediated necrotizing myositis	3	(0.2)
Anti-synthetase syndrome	8	(53)
Inclusion body myositis	1	(7)
Scleroderma/myositis overlap	2	(13)
Concomitant autoimmune diseases (n=9/15)		
Rheumatoid arthritis	6	(40)
Scleroderma	3	(20)
SLE	1	(7)
Sjogren's	3	(20)
Clinical characteristics, n (%) (ever)		
Myalgia	4	(27)
Proximal muscle weakness	7	(47)
Raynaud's phenomenon	6	(40)
Polyarthralgia	6	(40)
Interstitial lung disease	7	(47)
Dysphagia	2	(13)
Antibodies, n (%)		
Anti-Jo1	4	(33)
Anti-PL12	3	(20)
Anti-SRP	2	(13)
Anti-mitochondrial	3	(20)
Anti-Ro52	5	(33)
RNA polymerase III	1	(7)
Scl-70 (topoisomerase)	1	(7)
Unidentified band	1	(7)
Labs, median (IQR)		
Highest CK (U/L)	1,295	(844-3024)
Highest aldolase (U/L)	21	(15-29)
Highest troponin I (ng/ml)	0.25	(0.23-0.46)
Highest proBNP level (pg/ml)	4,519	(2006-15,101)
Myocarditis diagnostic criteria met		
Clinical symptoms	14/15	(93)
Elevated troponin	9/15	(60)
New left ventricular function abnormality	11/15	(73)
Tissue characterization by cardiac MRI	7/13	(54)
Endomyocardial biopsy	4/6	(67)
Baseline immunosuppressive or immunomodulatory treatment, n (%)†		
Azathioprine	1	(7)
Cyclophosphamide	1	(7)
Hydroxychloroquine	1	(7)
IVIG	4	(27)
Methotrexate	2	(13)
Mycophenolate mofetil	3	(20)
Prednisone	10	(67)
Tocilizumab	1	(7)
None	2	(13)
Change in immunosuppressive treatment after myocarditis diagnosis, n (%)		
No change	2	(13)
Increase prednisone	8	(53)
Add Rituximab	5	(33)
Add IVIG	2	(13)
Add azathioprine	1	(7)
Add methotrexate	1	(7)
Add mycophenolate mofetil	1	(7)

*All patients had myositis antibodies checked (12 via EuroImmun; 3 via Oklahoma Medical Research Foundation). No patients with anti-EJ, anti-Ku, anti-MDA-5, anti-NXP2, anti-OJ, anti-PM7, anti-PM100, anti-PM75, anti-SAE, anti-TIF1, and anti-HGMCR. Patient with IBM tested negative for anti-NT5C1A. Missing data for anti-mitochondrial antibodies in 6 patients, anti-Ro-52 in 2 patients, anti-Scl-70 antibodies in 2 patients, RNA polymerase III in 3 patients.

†Not mutually exclusive as patients could be on combination therapy.

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THE EFFECT OF A 24-WEEK TRAINING ON THE PRODUCTION OF MYOKINES IN PATIENTS WITH IDIOPATHIC INFLAMMATORY MYOPATHIES

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Background. Endurance exercise has beneficial effects on muscle mass and function in patients with idiopathic inflammatory myopathies (IIM). Muscle contraction during exercise is a major stimulus for the release of myokines that are supposed to take part in the beneficial adaptation to exercise. The aim of this study was to investigate the effect of 24-week training on the production of myokines in patients with IIM.

Methods. Our study included 27 patients with established IIM who participated in a 24-week supervised training focused on activities of daily living, muscle strengthening, and stability and 26 age/gender/BMI-matched healthy controls (HC). 20 IIM patients and 21 HC underwent a vastus lateralis muscle biopsy. Isolated skeletal muscle cells obtained from 7 IIM patients before and after 24-week exercise and from 9 HC were cultured and differentiated into myotubes. Serum and culture media levels of myokines (myostatin, activin A, follistatin, follistatin like 3, IL-6, IL-17, tumor necrosis factor, and vascular endothelial growth factor) were analyzed with ELISA and the multiplex immunoassay. RT-PCR was used to assess myokine gene expression in muscle tissue and cultured myotubes. Data are presented as medians [interquartile ranges].

Results. According to the manual muscle test-8 and the functional index-2, 24-week training significantly improved muscle strength (from 56 [49-65] to 72 [65–76], $p<0.001$) and endurance (from 26 [11–46] to 76 [57–93], $p<0.001$) in patients with IIM. Compared to HC, IIM patients had significantly lower baseline serum myostatin (MSTN) levels (2947 [2216-3790] vs 1918 [1227-2822] pg/ml, $p<0.01$), and non-significantly (NS) higher activin A (262 [223-335] vs 311 [208-419] pg/ml, NS) and follistatin (FST; 1120[876-1672] vs 1448 [1171-1989] pg/ml, NS) levels. After 24 weeks of exercise, a significant ($p<0.05$) increase in serum MSTN concentration by an average of 14% and a significant ($p<0.05$) decrease in FST concentration by an average of 17% was observed in IIM patients. At baseline, myotubes derived from IIM patients released more MSTN (0.47 [0.16-1.01] vs 0.29 [0.14-0.34] pg/µg protein, $p=0.04$) and activin A (43 [17-61] vs 24 [15-43] pg/µg protein, NS) into the medium than myotubes from HC. Similarly, MSTN gene expression was significantly higher in the muscle (11 [4-14] vs 13 [6-35] AU, $p<0.05$) and myotubes (1.2 [0.7–1.9] vs 1.9 [1.7–2.8] AU, $p<0.05$) from IIM patients than from their healthy counterparts. Myotubes obtained from IIM patients after 24-week training secreted 4 times less activin A ($p<0.01$), 2 times more FST ($p=0.03$), and 2 times less follistatin like 3 protein ($p<0.05$) than myotubes derived from IIM patients before training. There was no difference in secretion of IL-6, IL-17, tumor necrosis factor (TNF), and vascular endothelial growth factor (VEGF) into the culture media between muscle cells derived from IIM patients and HC. However, after 24-week exercise, IIM myotubes significantly reduced the release of IL-6 (from 13 [8-18] to 7 [5-11] pg/µg protein, $p<0.05$), IL-17 (from 16 [12-25] to 2 [0-5] pg/mg protein, $p=0.03$), TNF (from 30 [20-41] to 9 [0-14] pg/mg protein, $p=0.02$) and VEGF (from 4823 [3826-6171] to 1578 [907-2652] pg/mg protein, $p<0.01$).

Conclusion. In conclusion, 24-week training resulted in an increase of myostatin and a decrease of follistatin in the serum of IIM patients. Cultured IIM muscle cells responded to training with increased follistatin and decreased activin A and follistatin like 3 protein release into the media, together with reduced production of muscle related cytokines. Remodeling of muscle myokine synthesis and release could be one of the mechanisms by which physical activity improves muscle strength and endurance in patients with IIM.

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INAUGURAL DROPPED HEAD SYNDROME AND CAMPTOCORMIA IN INFLAMMATORY MYOPATHIES

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Background. Inflammatory myopathies (IMs) are a heterogeneous group of diseases that can affect muscles, skin, lungs, heart, and joints. Increased knowledge about histopathological features, clinical manifestations and auto-antibodies have allowed further novel classification of IMs. Today, the main IMs subgroups are: dermatomyositis (DM), inclusion body myositis (IBM), immune-mediated necrotizing myopathies (IMNM), overlap myositis (OM) and immune-checkpoint inhibitor-related myositis (ICIrm). Axial muscle involvement is atypical and poorly described in the course of IMs. It results either in a "Dropped Head Syndrome (DHS)" characterized by a marked weakness of the neck extensors, or in a camptocormia (CC), characterized by thoracolumbar paraspinal muscles weakness, causing major disability. This atypical presentation may delay the diagnosis of myositis. This study aimed to describe IMs revealed by DHS and/or CC and their clinical, biological and histopathological characteristics as well as the treatments and outcomes.

Methods. A historical cohort was designed using the register MYOLYON which includes all IMs followed at the University Hospital of Lyon (France) between 2000 and 2021. All patients with histologically-proven IMs diagnosis and revealed by DHS and/or CC were included, after exclusion of alternative diagnosis. Clinical, biological, immunological, and histopathological data as well as outcomes and treatments were collected through a standardized form. The study was approved by the local research ethics committee.

Results. Twenty-two patients presented inaugural axial muscular weakness. Median age at diagnosis was 67.0 years [53.0-75.3], 77.3% (n=17/22) of patients were female and median length of follow-up was 6.50 years [3.75-11.0]. Ten patients (45.4%) had distal muscle involvement and the axial involvement was apportioned as follow: DHS only (n=6, 27.3%), CC only (n=2, 9.09%), and both (n=14, 63.6%). IMs diagnosis included: DM (n=4, 18.2%), IBM (n=7, 31.8%), OM (n=8, 36.7%), ICIrm (n=2, 9.09%) and one patient with myositis and anti-Hu antibodies (Figure 1). Dysphagia concerned 12/22 patients (54.5%). Extra muscular symptoms included skin lesions (n=12/22), interstitial lung disease (n=8/22), arthralgia (n=5/22), and Raynaud's syndrome (n=9/22). All but two IBM patients were treated; 17 patients (77.3%) received steroids, 16 (59.1%) were treated with conventional treatments, 77.3% (n=17/22) of the patients had a refractory disease and required a second-line therapy. Two DM patients had plasma exchanges or cyclophosphamide. All IBM patients had a refractory disease without improvement under treatment. After analysis, 2 groups of patients were distinguishable according to the age at first symptoms and to the type of muscle axial involvement (*e.g*, DHS and/or CC). Before the age of 70 (n=13/22), axial involvement was diffuse (DHS and CC) , and the 2 most common diagnoses were DM (30.8%, n=4) and OM (53.8%, n=7). After 70 years of age (n=9/22), axial involvement was selective (DHS or CC); and diagnosis were IBM and ICIrm (Figure 1).

Conclusions. While IM diagnosis is challenging in the presence of inaugural axial involvement, these results highlight the subset of IM to be considered according to the age at first symptoms and the type of axial involvement (*e.g.*, DHS and/or CC).

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SENSITIVITY AND SPECIFICITY OF THE EULAR/ACR CLASSIFICATION CRITERIA FOR MYOSITIS IN A COHORT OF NEUROMUSCULAR PATIENTS IN GERMANY

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Background. The EULAR/ACR criteria for the classification of idiopathic inflammatory myopathies were developed in 2017 by an international and multidisciplinary collaboration to improve the diagnosis of inflammatory myopathies. The criteria can be used to classify suspected myositis cases into "definite," "probable," and "possible," as well as into the subtypes dermatomyositis (DM), juvenile myositis (JM), polymyositis (PM) and inclusion body myositis (IBM).
The aim of this study was to provide "real-world" data for the ACR/EULAR classification criteria for myositis by applying the criteria to a monocentric cohort of myositis patients at the University Medical Center Göttingen, Germany. As additional control cohort, patients with muscular dystrophies from the same center were included in the assessment.
Methods. In this retrospective study, data from 354 patients with neuromuscular diseases treated at the University Medical Center Göttingen were included and informed consent was obtained. Sensitivity and specificity of the classification criteria were tested in 270 myositis patients with established diagnosis PM, DM, IBM, (immune mediated) necrotizing myopathy (NM), or unspecified myositis (UM). 84 patients with genetically confirmed hereditary myopathies were included, among them myotonic dystrophy type 1 and 2 (DM1/2), facioscapulohumeral muscular dystrophy (FSHD), Duchenne (DMD)- and Becker muscular dystrophy (BMD) and others. The clinical records of all subjects were assessed for all parameters required for applying the EULAR/ACR classification criteria. The cohort of myositis patients was also used to compare the ACR/EULAR criteria with other established myositis classification including those from Rose, Amato, Dalakas, Targoff, Troyanov, and Hoogendijk.
Results. In the myositis cohort, the EULAR/ACR classification criteria showed high sensitivity for the diagnosis of DM (90.9%), PM (89.7%) and IBM (85.7%). Patients with NM were mainly classified as PM (88.9%), and unspecified myositis syndromes were also mostly classified as PM (63.6%). Of the 84 patients with confirmed hereditary myopathy, 29% of patients with DM1, 48% of patients with DM2, 28% of patients with FSHD, 0% of patients with BMD, and 9% of patients with DMD (one female carrier) were misclassified as having either "possible", "probable" or "definite" myositis, translating to an overall specificity of 64.3% for separating hereditary from inflammatory myopathies using the EULAR/ACR classification criteria.
Conclusion. Assessment of the EULAR/ACR classification criteria using our patient cohort revealed a reliable sensitivity for the diagnosis of DM, PM and IBM. The diagnosis of myositis can be compromised in cases with atypical clinical or histological findings. By nature of the classification system, the 2017 EULAR/ACR criteria fall short of discriminating the more recently established myositis subforms NM and anti-synthetase syndrome. For the differentiation between inflammatory and hereditary myopathies, the rather low specificity of the classification criteria reflects the diagnostic challenges in daily practice, particularly in diseases that may present with similar symptoms as myositis such as DM2 or FSHD.
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DIRECT AND INDIRECT COSTS ASSOCIATED WITH THE MANAGEMENT OF DERMATOMYOSITIS AND POLYMYOSITIS IN ADULT PATIENTS

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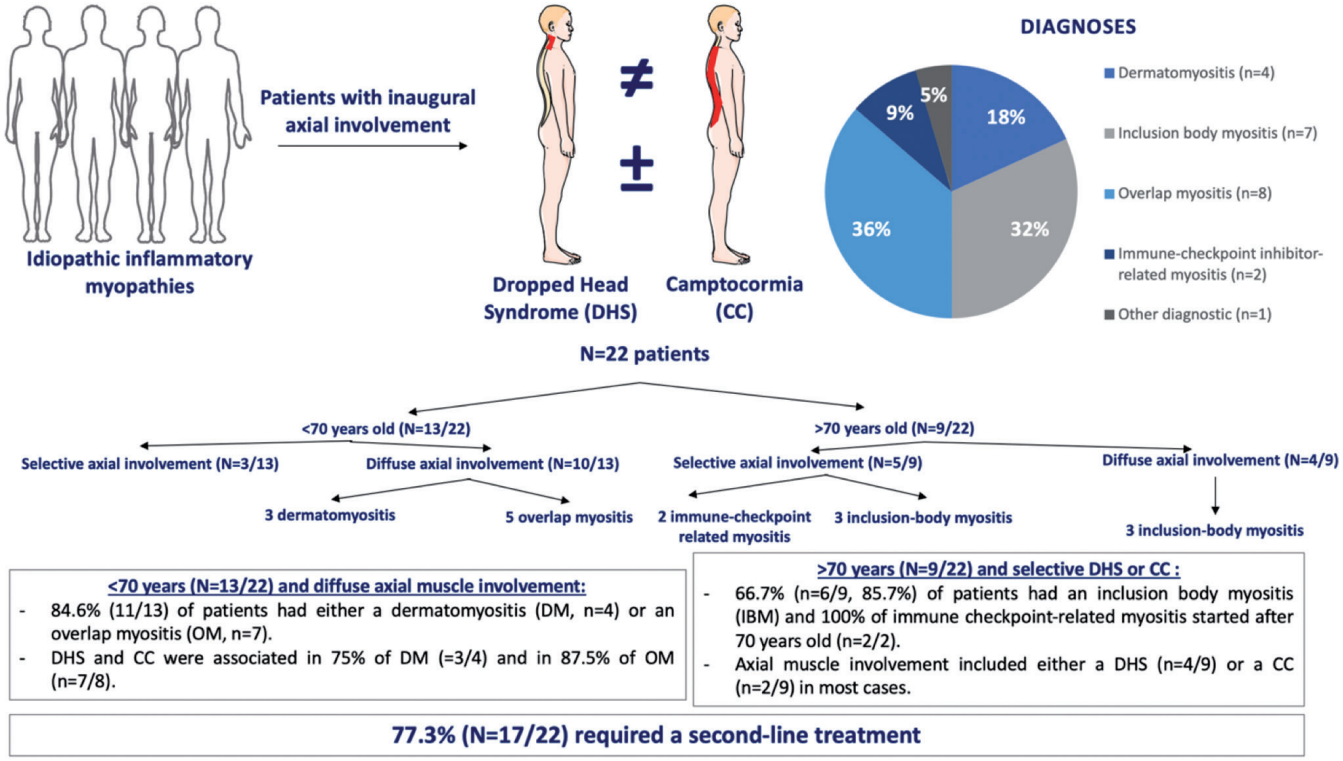
Background. Dermatomyositis (DM) and polymyositis (PM) are rare autoimmune inflammatory myopathies characterized by muscle weakness and multiple extra-muscular manifestations that have a detrimental impact on patients' lives.



P-161. Fig. 1.

DM and PM require complex management that may lead to high costs and healthcare resource utilization (HCU), but the true economic impact on healthcare systems is not well understood. The goal of our study was to systematically review and summarize evidence on economic burden of DM and PM in adult patients.
Methods. A systematic literature review (SLR) was conducted in MEDLINE and Embase databases to identify studies in children and adults with DM and PM, published in the English language between Jan 1, 2011, and Apr 28, 2021. Studies enrolling at least 10 patients were included, irrespective of country or region. Each eligible article was independently reviewed by two reviewers. The title and study abstracts were reviewed to assess eligibility for full-text review. The topics of interest were clinical, humanistic, and economic burden of disease, current management, and unmet needs in DM and PM. The current abstract summarizes data on direct and indirect costs and HCU in adults with DM and PM.
Results. From 2,967 non-duplicated publications retrieved from medical databases, 2,574 records were excluded at title and abstract screening and 185 records were excluded during full-text review. Searching reference lists of relevant studies yielded 8 additional papers. In addition, 13 conference abstracts were identified in the conference proceedings searches. A total of 222 studies (229 publications) were finally included in data abstraction. Sixteen studies reported economic burden data: 12 studies from the US and 2 studies each from Canada and Sweden. Most studies were retrospective analyses or large nationwide claims or electronic medical record (EMR) databases or patient registries. DM and PM were associated with substantial costs and HCU in both outpatient and inpatient settings in the US. Compared to age-gender and comorbidity matched controls without DM and PM, adult patients with DM and PM had a significantly higher HCU (emergency department visits, inpatient visits, rheumatologists, neurologists, physical therapy care and other visits). Over half of these visits were directly related to DM and PM. In the inpatient setting, patients with DM and PM required 1.7 to 1.9-day longer length of stay (LOS) ($p<0.05$) and significantly more specialized tests and procedures compared to patients without DM and PM. In the US, total weighted 2014-inflation adjusted cost of hospitalization of DM adults was estimated at 168 million USD with mean cost of care being 53% higher than in inpatients without DM ($p<0.0001$). Mean total hospitalization charged to payers was 55,774 USD per hospitalization, which was 13,351 USD higher compared to non-DM and PM inpatients. DM comorbidities were associated with a considerable excess cost. Serious infections and related complications in DM increased mean annual hospitalization cost by 13,815 USD and prolonged mean LOS by 5 days, relative to DM adults hospitalized without serious infection. A Canadian study suggested that total cost of healthcare services in DM and PM may equal or exceed rheumatoid arthritis and systemic sclerosis (mean cost per patient: 4,099 CAD vs 3,395 CAD and 3,249 CAD, respectively). On average, adult DM and PM patients had 2 days more of work loss per year than matched controls without DM or PM ($p<0.001$). Productivity loss was associated with disease flare frequency. One third of patients perceived their ability to work as poor according to the total score in the Work Ability Index. Twenty-one percent of patients (median disease duration of 14.2 years) had permanent inability to work for at least 2 years.
Conclusion. Current management of DM and PM has incurred substantial consumption of healthcare resources and costs to the healthcare systems. The significant economic burden despite currently available treatments suggests that there is a high unmet need for a more effective therapy for DM and PM.

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POOR QUALITY OF LIFE AND SUBSTANTIAL DISABILITY IN ADULT PATIENTS WITH DERMATOMYOSITIS AND POLYMYOSITIS

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Background. Dermatomyositis (DM) and polymyositis (PM) are rare autoimmune inflammatory myopathies characterized by muscle weakness and multiple extra-muscular manifestations that have a detrimental impact on patients' lives. The current evidence focuses on the clinical outcome of the disease, and little is known about true impact of DM and PM on patient's health-related quality of life (HRQoL). The goal of our study was to systematically review and summarize evidence on humanistic burden of disease in adults with DM and PM.
Methods. A systematic literature review (SLR) was conducted in MEDLINE and Embase databases to identify studies in children and adults with DM and PM, published in the English language between Jan 1, 2011, and Apr 28, 2021. Studies enrolling at least 10 patients were included, irrespective of country or region. Each eligible article was independently reviewed by two reviewers. The title and study abstracts were reviewed to assess eligibility for full-text review. The topics of interest were clinical, humanistic, and economic burden of disease, as well as the current management and unmet needs in DM and PM. The current abstract summarizes data on humanistic burden of DM and PM in adult patients.
Results. From 2,967 non-duplicated publications retrieved from medical databases, 2,574 records were excluded at title and abstract screening and 185 records did not meet study selection criteria at full-text review. Searching reference lists of relevant studies yielded 8 additional papers. In addition, 13 conference abstracts were identified in the conference proceedings searches. A total of 222 studies (229 publications) were included in data abstraction. Sixteen studies reported data on HRQoL, daily functioning or disability-related outcomes in adults with DM and PM. Identified studies were conducted in the US (7 studies), Europe (6 studies), Brazil (2 studies) or enrolled patients from multiple countries worldwide (1 study). Adults with DM had significantly worse HRQoL measured by Skindex-29 questionnaire compared to multiple other skin disorders, such as cutaneous T-cell lymphoma, rosacea, and vitiligo. Similarly, DM and PM patients reported significantly worse HRQoL across multiple domains of the 36-Item Short Form Survey (SF-36) than matched healthy controls/general population and controls with chronic non-skin conditions (*e.g.*, type 2 diabetes, hypertension, clinical depression). Multiple studies demonstrated disability and progressive loss of independence in patients with DM and PM. Muscle symptoms significantly affected physical domain of the SF-36 while reduced grip force was shown to significantly affect DM and PM patients' ability to perform domestic activities measured by Myositis Activity Profile (MAP) ($p<0.05$). Furthermore, patients reported that their disease interfered with leisure time activities and ability to move and work. Between 27% and 48% of patients depended on caregivers for gripping and opening things, running errands, shopping, and other daily activities, and up to 38% of them required walking aids or other facilitating devices. Patients with DM suffered more frequently from clinically significant fatigue measured by SF-36 vitality domain than healthy controls ($p<0.01$). Extreme fatigue/exhaustion, pain and trouble climbing stairs were frequently reported by DM and PM patients and showed increased tendency with disease flares (17-67% in patients with no flare vs 70-87% in those with at least 4 flares/past year, $p<0.05$).
Conclusion. Patients with DM and PM suffer from a high level of disability and poor HRQoL across multiple domains of life, including the physical, psychological, and social role functioning. There is a high unmet need for a therapy that can improve HRQoL in patients with DM and PM.

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COMORBIDITIES AND LONG-TERM OUTCOMES IN ADULT PATIENTS WITH DERMATOMYOSITIS AND POLYMYOSITIS

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Background. Dermatomyositis (DM) and polymyositis (PM) are rare autoimmune inflammatory myopathies characterized by muscle weakness and multiple extra-muscular manifestations that have detrimental impact on patients' lives. Despite various therapies used in clinical practice, a large proportion of patients do not to achieve sustainable remission. There is a need to better understand long-term outcomes and comorbidities in patients with DM and PM. The aim of this work was to systematically review and summarize evidence on clinical burden of disease in adults with DM and PM.
Methods. A systematic literature review (SLR) was conducted in MEDLINE and Embase databases to identify studies in children and adults with DM and PM, published in the English language between Jan 1, 2011, and Apr 28, 2021. Studies evaluating 10 or more patients were included, irrespective of country or region. Each eligible article was independently reviewed by two reviewers. The title and study abstracts were reviewed to assess eligibility for full-text review. The topics of interest were clinical, humanistic, and economic burden of disease, as well as the current management and unmet needs in DM and PM. The current abstract summarizes data on the long-term disease outcomes and comorbidities in adults with DM and PM.
Results. From 2,967 non-duplicated publications retrieved from medical databases, 2,574 records were excluded at title and abstract screening and 185 records did not meet study selection criteria at full-text review. Searching reference lists of relevant studies yielded 8 additional papers. In addition, 13 conference abstracts were identified in the conference proceedings searches. A total of 222 studies (229 publications) were included in data abstraction. There were 88 studies with data on the long-term disease outcomes and comorbidities in adult DM and PM patients. These studies enrolled patients from all regions worldwide, mostly from Asian countries (33 studies) and USA (20 studies), followed by Europe (18 studies). The remaining studies were conducted in individual countries in Latin America, Middle East countries, Africa, and Australia. Patients with DM and PM had poor long-term outcomes with 34-67% of them failing to achieve

remission of symptoms during up to 5 years of follow-up. Seventy-three percent of patients reported at least one disease flare in the past year that manifested as muscle weakness, difficulties in reaching over head, muscle-related pain, extreme fatigue, and other symptoms. Long-term prognosis was generally poor, with 5-year and 10-year survival rates ranging from 70% to 95% and 56% to 84%, respectively. The main causes of death were pulmonary and cardiovascular related events, malignancies, and infections, which were also the most common comorbidities reported in DM and PM. Multiple studies have shown significantly increased risk of serious cardiovascular disorders such as venous thromboembolism, acute myocardial infarction, and heart disorders in patients with DM and PM, compared to controls from the general population without DM and PM. Both DM and PM patients suffered from comorbid malignancies (5-29%), with multiple studies suggesting increased risk compared to the general population (standardized incidence ratio 2.17 to 14.2). Infections were reported in 19% to 42% of patients and often led to hospitalizations and increased in-patient mortality. Patients with DM and PM had significantly increased risk of opportunistic infections including but not limited to herpes zoster, Pneumocystis Jirovecii pneumonia, and fungal infections, which were 1.2- to 7-times more common in DM and PM than in the general population or controls without DM and PM. Long-term treatment with corticosteroids was the major factor contributing to increased risk of opportunistic infections.
Conclusion. DM and PM are associated with poor long-term outcomes. Patients are often hospitalized or die due to underlying comorbidities such as cardiovascular disorders, malignancies, and infections. There is a high unmet need for a therapy that can improve the long-term disease outcomes in DM and PM.

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A NEW DIAGNOSIS OF MYASTHENIA GRAVIS DURING THE FOLLOW UP OF ANTI-PHOSPHOLIPID SYNDROME

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Background. The association between anti-phospholipid syndrome (APS) and myasthenia gravis (MG) is barely described, whereas in literature there are multiple examples of systemic lupus erythematosus (SLE) and MG, in most of which MG precedes SLE.
Methods. We describe a case of a paediatric-onset lupus-like autoimmune disease who developed MG during follow-up.
Results. When 7-years-old, the young patient presented the first symptoms characterized by petechiae and bruising on lower limbs and severe thrombocytopenia. The identification of antiplatelet antibodies and bone marrow biopsy contributed to the diagnosis of immune thrombocytopenia. Other laboratory findings detected antinuclear antibodies, triple positive antiphospholipid profile, anti-dsDNA, low C3 and C4, supporting an APS-SLE disease. After an initial treatment with high dose IVIg and prednisone (0.6 mg/kg/die with slow tapering) an optimum platelet level was achieved. In the following years, she continued outpatient follow-up. To prevent APS-SLE manifestations the only therapy was hydroxychloroquine 200mg/day. At the age of 16-years-old she developed mild anaemia with positive direct Coombs's test, solved with a short-course corticosteroids.
Four years later, she presented rhinolalia, bilateral Bell's phenomenon, and lid closure deficit. Serum acetylcholine receptor antibody (AChRAb) was positive and MG with thymic hyperplasia was diagnosed. Therapy with pyridostigmine and low dose prednisone (10mg/die) was introduced with good control of neurological symptoms. Hydroxychloroquine was suspended, introducing low-dose aspirin, due to the thrombotic risk.
Conclusion. The association between APS/ SLE with MG is complex and several pathogenic mechanisms were proposed. In APS/ SLE patients presenting with muscle strength deficiency and fatigue, MG should be excluded.

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MUSCLE INVOLVEMENT IN SYSTEMIC SCLEROSIS: REVISITING THE CLASSIFICATION IN LIGHT OF AUTOMATED MORPHOMETRY

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Background. Systemic Sclerosis (SSc) is a multisystemic autoimmune disease characterized by interstitial fibrosis and microangiopathy. Muscular involvement in the diffuse form can reach up to 81%, depending on the diagnostic criteria. We have previously shown that SSc patients with muscular involvement may be classified in two main types: 'SSc myositis', which is characterized by inflammation and myonecrosis; and 'SSc myopathy', characterized by fibrosis, microangiopathy and atrophy of type II muscle fibers. A recent retrospective analysis of muscle biopsies findings from 18 SSc patients showed that 12/18 had a histopathological pattern corresponding to minimal myositis with capillary pathology (MMCP) and 6/18 that of other overlap myositis (Siegert E et al, 2021). Fibrosis and microangiopathy are the main lesions found in SSc and are of a great clinical and prognostic importance. In order to better determine the prognosis impact of muscle involvement, we developed an automated morphometrical approach to quantify SSc-related muscular changes.
Methods. A retrospective study was performed on 81 deltoid muscle biopsies, 66 SSc patients and 15 control patients. Muscle biopsies were retrospectively analyzed and patients stratified according to histopathological profile. Sections were next stained for fibrosis (Picrosirius red), fibers size and endothelial cells (CD31/PECAM). FIJI program and home-made algorithms were used for quantifying these features.
Results. The 66 SSc patients were classified as following: SSc myopathy (52%), myositis (30%) and necrotizing autoimmune myopathy (NAM; 18%) features. Fibrosis: SSc samples showed a significantly higher percentage of total connective tissue area (CTA) (31% vs 23%, p=0.03), especially myopathy patients (p=0.017). Endomysial CTA represented larger heterogeneity compared to controls that had similar endomysial CTA (p=0.047). The significant increase of CTA in both the whole muscle and endomysial regions indicates an active process of fibrotic connective tissue deposition. Microangiopathy: The endomysial capillaries were fewer in number (p=0.029) and occupied a larger area (p<0.001), compared to the controls. The myositis type associated with endomysial capillaries size and number changes (p<0.001 and <0.01, respectively), while the two other types had only significantly enlarged capillaries (p=0.02 and 0.003, respectively). This indicates that all types have an ongoing microangiopathy. Fiber morphology: the cross-sectional surface area (CSA) of type II myofibers in all types was significantly reduced compared to the controls (41% vs 50.5%, p<0.001). Generally, SSc patients muscles had a significant reduction in the number of type II fibers having the normal CSA (p=0.01). Therefore, we established the atrophy scores for all fibers and found that the myositis group was the most affected with an average atrophy score of 5.9. Whatever the type, we observed a notable variation in the quantified parameters, ranging from normal parameters to severely affected muscles. These parameters associated between them, a severely affected patient having more CTA, and a more critical microangiopathy and type II fiber atrophy.
Conclusions. From our results, it appears that fibrosis, microangiopathy and type II fibers atrophy constitute the hallmarks of muscle changes specifically induced by SSc, which may associate or not with myositis or NAM. Combining the quantified histological features with clinical parameters will help to more accurately stratify patients and more appropriately tailor the therapeutic strategy.

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PATIENTS WITH IDIOPATHIC INFLAMMATORY MYOPATHIES WHO REPORT LOW LEVELS OF PHYSICAL ACTIVITY REPORT HIGHER LEVELS OF ANXIETY AND DEPRESSION - A CROSS-SECTIONAL STUDY OF SELF-REPORTED DATA

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Background. Having inflammatory diseases, such as rheumatoid arthritis (RA) or systemic lupus erythematosus (SLE), is linked with a reduced level of physical activity compared to normative population. Further, patients with these diseases are often not physically active on a health-enhancing level. It is also common that patients with RA and SLE suffer from anxiety and/or depression. Being physically active on a health-enhancing level can help reduce anxiety and depression as

well as other co-morbidities. A majority of patients at the Karolinska University Hospital visit a physical therapist to receive individualized exercise programs and information about PA with regular follow-up visits. The aim of this study is to assess levels of self-reported physical activity (PA), depression and anxiety amongst adult patients with idiopathic inflammatory myopathies (IIM). A further aim is to evaluate differences in anxiety/depression in relation to levels of PA as well as to analyze relationships between PA and anxiety/depression.

Methods. All patients with IIM visiting the Rheumatology clinic at Karolinska University Hospital in Solna between February 2019 and January 2022 where asked to participate. Those who have not visited the clinic during this time have been invited to participate by completing the questionnaires at home and posting them back to the clinic. The International Physical Activity Questionnaire – short form (IPAQ) and the screening instrument Hospital Anxiety and Depression Scale (HADS) were used. HADS is scored in two sub-scales, one for depression (HADS-D) and one for anxiety (HADS-A). Max score is 21 and ≥8 is cut-off for probable depression or anxiety. IPAQ-results was scored as low PA, (not reaching moderate/high criteria), moderate PA, (≥ 600 MET-minutes/week) and high PA, (≥1500 vigorous or 3000 moderate MET-minutes/week). Questionnaires were distributed by the myositis team nurse during visits at the clinic, or by mail. Spearman's rho was used for correlation analysis. Kruskal-Wallis with Bonferroni correction was used to analyze group differences.

Results. A total of 117 patients have answered the questionnaires so far, with 74 females and 43 males. Low PA was reported by 23 (20%) patients, moderate PA by 53 (45%) and high PA by 41 (35%). Patients with low PA scored significantly higher on HADS-A compared to patients with moderate and high PA, p=0.03 and p=0.002, respectively (Fig. 1, red color). Patients with low PA also scored significantly higher on HADS-D compared to high PA, p=0.016, but not compared to moderate PA, p=0.16 (Fig. 1, blue color). The correlation between PA and anxiety was rs=-0.29 CI (-0.46; -0.12) and between PA and depression, rs=-0.25 CI (-0.42; -0.06).

Conclusions. A majority of the patients reported moderate or high PA. Patients reporting low PA score significantly higher anxiety than those reporting moderate or high PA. Further, patients reporting low PA score significantly higher depression compared to those reporting high PA. However, levels of PA show low correlation to depression and anxiety. This is cross-sectional, preliminary and self-reported data. It seems that our sample reported higher PA compared to previously reported of individuals with RA and SLE. We hypothesize that regular and frequent information about and support to get started and continue with PA has contributed. Longitudinal studies with objective measures are needed to confirm our results and enable causal analysis. Data collection proceeds during 2022.

Acknowledgements. To participating patients.

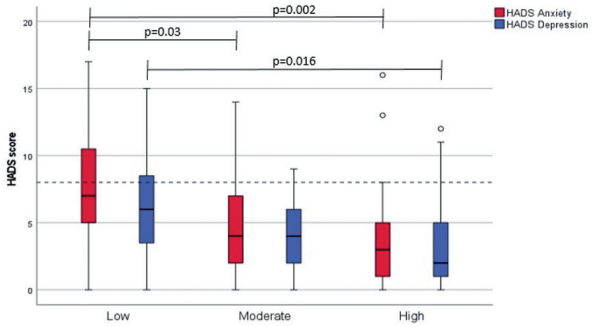

Figure 1. IPAQ

Level of physical activity (PA) based on IPAQ-questionnaire. HADS score ≥8 (dashed line) means probable anxiety or depressive disorder.

P-168. Fig. 1.

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THE PATTERN OF MAJOR HISTOCOMPATIBILITY COMPLEX CLASS I EXPRESSION IN MUSCLE BIOPSIES FROM PATIENTS WITH DIFFERENT TYPES OF MYOSITIS AND OTHER NEUROMUSCULAR DISORDERS

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Objectives. Immunostaining for major histocompatibility complex (MHC) class I is used by many pathologists to distinguish between inflammatory and non-inflammatory myopathies. The aim of this study was to analyze the patterns and prevalence of MHC class I immunostaining in a large number biopsies from patients with different types of myopathies and neurogenic disorders.

Methods. All patients with a muscle biopsy immunostained for MHC class I at the Johns Hopkins Neuromuscular Pathology Laboratory from 2013 to 2017 were included (n=357). The prevalence and pattern of MHC class I immunostaining were compared between patients with histologically normal muscle biopsies (n=31), inflammatory myopathies (n=170), other myopathies (n=60), and neurogenic disorders (n=96).

Results. Major histocompatibility complex class I immunostaining was absent in histologically normal biopsies but present in biopsies from those with dermatomyositis (DM; 98%), sporadic inclusion body myositis (IBM; 100%), immune-mediated necrotizing myopathy (IMNM; 100%), polymyositis (77%), non-inflammatory myopathies (all <32%), and neurogenic disorders (30%). A focal staining pattern was associated with IMNM. A global pattern of MHC class I staining was more prevalent in sIBM. A perifascicular pattern of immunostaining was significantly more common in dermatomyositis. Among the 18 DM patients without perifascicular atrophy, 50% had MHC class I staining in a perifascicular pattern.

Conclusion. Major histocompatibility complex class I immunostaining is useful to differentiate inflammatory myopathies from non-inflammatory myopathies. DM was associated with a perifascicular pattern even in half of those patients without perifascicular atrophy. IMNM and sIBM were associated with focal and global patterns of MHC class I staining, respectively. There were no differences in the prevalence of sarcoplasmic versus sarcolemmal patterns of MHC class I staining between the different types of myositis.

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EFFECTS OF CONVENTIONAL REHABILITATIVE AND AEROBIC TRAINING IN PATIENTS WITH IDIOPATHIC INFLAMMATORY MYOPATHY

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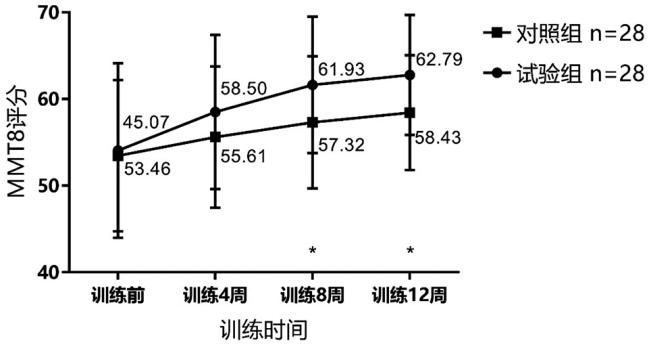
Background/Objective. Idiopathic inflammatory myopathies (IIMs) are a group of chronic autoimmune diseases mainly involving the muscular tissue. Physical therapy has recently become major means of intervention to help IIM patients regain muscle strength and the physical capacity in addition to conventional medications. This research is to investigate the efficacy of conventional rehabilitation alone and conventional rehabilitation combined with aerobic training on muscle strength and function, health condition, and quality of life for patients with stable idiopathic inflammatory myopathy.

Methods. This is a historical retrospective cohort study, in which the medical records of IIM patients who received the combination of conventional rehabilitative therapy and aerobic training (combined training group, CTG), from February 2015 to December 2017 were reviewed. IIM patients who received conventional therapy alone were matched based on their age, gender, and disease activity as the control group (CG). Manual Muscle Testing (MMT8) was the primary outcome, and Myositis Functional Index (FI-2), Health Assessment Questionnaire (HAQ), and Short Form 36 (SF-36) scores at 12 weeks during training were the secondary outcomes.

Results. 56 patients were included in this analysis: 28 in CTG, 28 in CG. Patients in both groups had improved MMT8, FI-2, HAQ, and SF-36 scores after

12 weeks' physical therapy. There was a significantly higher score of MMT8 and HAQ in CTG than CG at the 12th week. FI-2 scores were significantly higher in the CTG in 4 items (P<0.05) of hip flexion, step test, heel lift, and toe lift. SF-36 scores of the CTG were also higher than CG in 5 items (p<0.05) of physical functioning, general health, vitality, social functioning, and mental health.
Conclusions. Physical exercise training including conventional rehabilitation and aerobic training improved muscle function, health condition, and quality of life. Conventional rehabilitative training combined with aerobic training achieved better improvement compared with conventional rehabilitation training alone.
Acknowledgements. We acknowledge all patients included in this research.



P-170. Fig. 1.

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REFINING RHEUMATOID ARTHRITIS AND MYOSITIS OVERLAP: A MULTICENTRIC FRENCH CASE-SERIES

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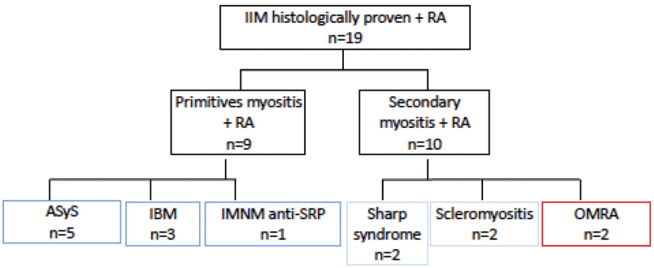
Background. Myosistis can be separated into primitives (such as dematomyositis, anti-synthetase syndrome (ASyS), inclusion bodie myositis (IBM) and immune mediated necrotizing myopathy (IMNM)) or secondary when associated with a systemic disorder (such as lupus, sharp syndrome or sclerodermia). Association between rheumatoid arthritis and myositis remains poorly described despite the fact that arthritis is a frequent symptom of myositis, notably for ASyS.
Objective. Aim of the study was to analyze a case-series of patients presenting histologically proven myositis and rheumatoid arthritis to refine RM definition.
Methods. Through a multicentric French case-series of patients diagnosed with rheumatoid arthritis and idiopathic inflammatory myopathy (IIM). Inclusion criteria were: histologically proven myositis and RA based on the ACR/EULAR criteria. Medical records were analyzed and characteristics, clinical, investigational data were collected through a standardized forms. Treatment and outcomes were also collected. Patients were classified as primitive myositis (or secondary myositis
Results. Nineteen patients were included. Nine patients were considered as primitive myositis (ASyS (n=5), IBM (n=3) et IMNM (n=1), while 10 patients were considered as secondary myositis: Sharp syndrome (n=2), scleromyositis (n=2) and a subgroup composed of patients who did not fulfilled well-defined myositis criteria. The latter patients were classified as overlap myositis with RA (OMRA). For OMRA patients, the RA preceded the myositis in all cases. Patients presented proximal muscular impairment, predominant in lower limbs and had frequent erosive polyarthritis (60%) and with positive anti-citrullinated protein antibodies (83%), and rheumatoid factor (100%). OMRA patients displayed rare extra musculo-articular lesions: Raynaud's phenomenon (16.7%) and interstitial lung disease (16.7%). OMRA muscle biopsy analysis identified positive major histocompatibility complex class I myofiber overexpression and endomysial inflammatory infiltrates composed of T cells (n=6/6) and B cells (n=3/6). Histological pattern was not responding to criteria for other known myositis subgroup (no capillary dropout for DM, nor perifascicular specificity in muscle damage for ASyS of DM, nor rimmed vacuoles or aggregates within myofibers for IBM, nor myofibers necrosis of IMNM). OMRA patients required all first and second line of treatment, and during follow-up, patients presented recover under RA and myositis care. For these 6 cases of OMRA, no patients were receiving anti TNF therapy at time of myositis diagnosis.
Conclusion. OMRA appear as a particular entity with specific muscle biopsy findings. This work proposes new criteria of diagnosis for the myositis and RA overlapping. OMRA could correspond to the old definition of rheumatoid myositis after discarding the newly defined IIM such as ASyS, or Sharp syndrome, which in turn may be associated with RA.



P-171. Fig. 1. Flowchart that illustrates the classification of patients with myositis histologically proven and Rheumatid Arthritis (RA).
ASyS: anti synthetase syndrom; IBM: inclusion body myositis; IMNM: immune mediated necrotizing myopathy; OMRA: overlap myositis with RA.

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DIAGNOSTIC ACCURACY OF ELECTROMYOGRAM FOR MYOSITIS

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Background. The skeletal muscle biopsy is the gold standard for idiopathic inflammatory myopathies (IIM) diagnosis. Myositis specific antibodies are diagnostic biomarkers for IIM but are present in only 60-70% of cases. Another non-invasive procedure: the electromyogram (EMG) maybe useful for IIM diagnosis but its diagnostic accuracy has been poorly investigated. We aim to define the sensitivity, the specificity, and the positive and negative predictive values of EMG for IIM diagnosis.
Methods. We conducted a single-center retrospective study between January 2018 and October 2020. We selected all consecutive patients referred to the neuropathology department for a suspicion of IIM. Patients were enrolled if an EMG was performed in our department before the muscle biopsy. Patients were diagnosed as IIM based on myopathological finding. Patients were subclassified into dermatomyositis (DM), anti-synthetase syndrome (ASyS), overlap myositis (OM), immune mediated necrotizing myopathy (IMNM), Inclusion body myositis (IBM) and immune checkpoint inhibitor induced myositis (ICI) based on ENMC criteria.
Results. Two hundred and thirty-one patients were screened and 182 patients were included. Patients were 57.8±15.8 years and 62.6% were female. EMG was described as myogenic in 74.1% of cases. Patients were diagnosed as IIM in 86.2% of cases. The sensitivity was 82.2%, and the specificity was 76%. The positive likelihood ratio was 3.4. The positive predictive value was 95.6% and the negative predictive value 40.4%. The presence of EMG abnormality was highly dependent on the IIM subgroup. The sensitivity was high in DM (90%), ASyS (93.8%) and IMNM (95%). The sensitivity also high in sIBM (85.2%) and in OM (85.1%) but low in ICI myositis (29.4%). Univariate analysis showed that factors associated with a false negative EMG (patients; n=28) were the use of corticosteroids prior to EMG (21.7% vs 46.4% p=0.01) and the absence of myositis specific antibody (68% vs. 88.9% p=0.03).
Conclusion. EMG was sensitive and specific for IIM diagnosis but its accuracy decreases with the use corticosteroids.

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RISK OF CARDIOVASCULAR EVENTS AND SUBCLINICAL ATHEROSCLEROSIS IN MYOSITIS PATIENTS COMPARED TO HEALTHY CONTROLS: PRELIMINARY DATA FROM A SINGLE-CENTER CROSS-SECTIONAL STUDY

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Background. Idiopathic inflammatory myopathies (IIM) are associated with systemic inflammation, limited mobility, and glucocorticoid (GC) therapy, which can negatively impact metabolic disorders, atherogenesis, and increase the cardiovascular (CV) risk. This study aimed to evaluate CV risk in IIM patients in comparison with healthy controls (HC) and explore its associations with disease-specific features.

Methods. 39 patients with IIM (32 females; mean age 56; mean disease duration 4.8 years; dermatomyositis 16, polymyositis 7, immune-mediated necrotizing myopathy 8, antisynthetase syndrome 8) and 39 age-/sex-matched HC (32 females, mean age 56) were included. Subjects with a history of CV disease (angina pectoris, myocardial infarction, cerebrovascular, and peripheral arterial vascular events) were excluded in both groups. Disease activity, damage, and muscle involvement (Manual Muscle Testing (MMT)-8, Myositis Intention to Treat Activity Index (MITAX), Myositis Damage Index (MDI)) were assessed. Comorbidities and current treatment were recorded. All participants underwent examinations of carotid intima-media thickness (CIMT), pulse wave velocity (PWV), ankle-brachial index (ABI), and body composition (densitometry: iDXA Lunar, bioelectric impedance: BIA2000-M). The risk of fatal CV events was evaluated by the Systematic COronary Risk Evaluation (SCORE and SCORE2, charts for the European population; modified mSCORE according to the 2015 EULAR recommendation for inflammatory arthropathies - only in IIM patients).

Results. In IIM, disease activity and damage were predominantly mild (MITAX 0.13, MDI 0.05). Compared to HC, there was no significant difference in the prevalence of traditional risk factors in IIM. Only PWV was significantly increased in IIM compared to HC (p=0.015). No other significant difference was observed between the IIM and HC regarding the CV examinations (CIMT, ABI, carotid plaques) and calculated SCORE and SCORE2 (p>0.05 for all). In IIM, age and mean arterial pressure were the most significant parameters that correlated positively with SCORE, SCORE2, and mSCORE; arterial hypertension was significantly associated with a higher SCORE, carotid plaque count/thickness, and PWV. Lipid profile parameters, body composition, and disease activity were significantly associated with CIMT and carotid plaques (p<0.05 for all). Antihypertensive treatment was associated with an increase in carotid plaque count (p=0.020) and higher (favorable) ABI (p=0.004), while hypolipidemic treatment was associated with an increase in carotid plaque count/thickness (p=0.009, p=0.008). Diabetes was associated with lower (worse) ABI values (p=0.034), and prediabetes with a higher carotid plaque count (p=0.036) and thickness (p=0.011), and a worse ultrasound examination related CV risk (p=0.006). Anti-Jo-1 positivity was associated with a lower (better) CIMT and lower SCORE (p<0.05 for all). There were no significant associations between clinical manifestations, immunosuppressive treatment, and GC cumulative dose. However, exposure time to GC therapy was significantly associated with the carotid plaques count (p<0.001) and the carotid plaque thickness (p=0.003). In multivariate analysis, the age of the patients was the most significant factor affecting most of the parameters analyzed (SCORE and its modifications, PVW, CIMT, and the total count of carotid plaques). Other significant predictors were total cholesterol and atherogenic index of plasma (for ABI), mean arterial pressure (for PWV), and disease duration (for the total count of carotid plaques).

Conclusions. No significant differences in CV risk factors between IIM patients and HC were observed. In IIM, CV risk was associated with age, disease duration, duration of glucocorticoid therapy, lipid profile, and body composition, but not with clinical manifestations and disease activity.

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LIPID PROFILE IN PATIENTS WITH IDIOPATHIC INFLAMMATORY MYOPATHIES COMPARED TO HEALTHY POPULATION AND ITS ASSOCIATION WITH DISEASE-RELATED FEATURES

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Background. Systemic inflammation, limited mobility, and glucocorticoid treatment in idiopathic inflammatory myopathies (IIM) can have a negative impact on intermediate metabolic pathways, especially on lipid metabolism. The aim of this study was to evaluate the differences in the lipid profile of IIM patients in comparison with healthy controls (HC) and explore the associations with disease-related features.

Methods. 133 patients with IIM (106 females; mean age 60.3; disease duration 2.2 years; dermatomyositis (DM) 45 / polymyositis (PM) 25 / immune-mediated necrotizing myositis (IMNM) 46, antisynthetase syndrome (ASS) 17) and 133 age-/sex-matched HC (106 females, mean age 60.2) were included. Patients with IIM fulfilled the 2017 EULAR/ACR classification criteria for adult IIM. Levels of selected parameters of lipid metabolism were measured in sera after 8 hours of fasting. In IIM patients, disease activity, damage, and muscle involvement [Myositis Intention to Treat Activity Index (MITAX), Myositis Damage Index (MDI), Manual Muscle Testing (MMT)-8,]) were assessed. Comorbidities and current treatment were recorded. Data are presented as median.

Results. In IIM, disease activity and damage were predominantly mild (MITAX 0.11, MDI 0.05, MMT-8 62). Compared to HC, IIM patients had increased levels of total cholesterol (TC), low-density lipoprotein (LDL), non-high-density lipoprotein (non-HDL), apoprotein-B (apo-B), triglycerides (TG), and increased atherogenic index of plasma (AI) (p<0.05 for all). All of these parameters are negative cardiovascular (CV) risk predictors. These changes were most evident in IMNM and DM patients, whereas there were minimal differences in lipid profile in PM and ASS patients compared to HC. ASS appeared to have only significantly increased TG levels (p=0.007), while in PM, there was only a trend to higher TG levels (p=0.07) compared to HC. The positive cardiovascular risk predictors, such as HDL and apo-A, were significantly lower only in DM and IMNM (p<0.001 for HDL in both DM and IMNM; p=0.014 for apoA in IMNM). There were significant differences in lipid profile within the IIM group (p<0.02 for all), whereas IMNM demonstrated the most unfavorable changes in terms of increased negative CV risk predictors. In IIM, the negative CV risk predictors of lipid profile (TC, TG, LDL, apo-B, and non-HDL) correlated negatively with disease duration (p<0.001 for all) and positively with prednisolone equivalent dose and age (p<0.05 for all). HDL and apo-A negatively correlated with systemic inflammation; apo-A was also negatively associated with creatine kinase and C-reactive protein levels. AI, TG, non-HDL, and apo-B were positively associated with body mass index (p<0.05 for all).

Conclusions. We have observed significant alterations in serum lipid parameters in our IIM patients compared to healthy age-/sex-matched individuals. Differences were also found among the four subsets of IIM. These alterations were associated with several measures of disease activity, and the current dose of corticosteroids.

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NUTRITIONAL STATUS IN PATIENTS WITH IDIOPATHIC INFLAMMATORY MYOPATHIES COMPARED TO HEALTHY POPULATION AND ITS ASSOCIATION WITH DISEASE-RELATED FEATURES

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Background. Systemic inflammation, involvement of the gastrointestinal tract, and glucocorticoid treatment in idiopathic inflammatory myopathies (IIM) can have a negative impact on nutrition and intermediate metabolic pathways. The aim of this study was to evaluate the differences in the nutrition status of IIM

patients in comparison with healthy controls (HC) and explore the associations with disease-specific features.
Methods. 133 patients with IIM (106 females; mean age 60.3; disease duration 2.2 years; dermatomyositis (DM) 45 / polymyositis (PM) 25 / immune-mediated necrotizing myositis (IMNM) 46, antisynthetase syndrome (ASS) 17) and 133 age-/sex-matched HC (106 females, mean age 60.2) were included. Patients with IIM fulfilled the 2017 EULAR/ACR classification criteria for adult IIM. Levels of selected nutrition parameters were measured in sera after 8 hours of fasting. In IIM patients, disease activity, damage, and muscle involvement [Myositis Intention to Treat Activity Index (MITAX), Myositis Damage Index (MDI), Manual Muscle Testing (MMT)-8,]) were assessed. Comorbidities and current treatment were recorded. Data are presented as median.
Results. In IIM, disease activity and damage were predominantly mild (MITAX 0.11, MDI 0.05, MMT-8 62). Compared to HC, IIM patients had significantly decreased levels of total protein, albumin and prealbumin, transferrin, and minerals (Fe, Zn) (p<0.005 for all). Although levels of 1,25-OH-vitamin D (biologically active form, calcitriol) were significantly decreased in IIM compared to HC (p<0.001), levels of total vitamin D (calcidiol) were comparable. Orosomucoid and lactate dehydrogenase (LDH), as the potential disease activity markers and vitamin B12, were significantly higher (p<0.001 for both) in IIM. IIM patients had higher thyroid function (increased free thyroxin (p=0.01), but a trend to lower thyrotropin (TSH; p=0.06) and levels of insulin and C-peptide (p<0.001 for both) compared to HC. On the other hand, cholinesterase levels (a marker of synthetic liver function) were decreased in IIM (p<0.05). Complement C4 was significantly lower in IIM (p<0.05), whereas complement C3 had a trend to be higher in IIM (p=0.09) than in HC. Comparison of the four disease subsets within the IIM group showed significant differences in levels of proteins (total protein, albumin), vitamin D (calcidiol and calcitriol), and LDH. The most unfavorable changes were observed in IMNM patients (<0.05). In IIM, total protein and albumin levels correlated negatively with age, MITAX, creatine kinase (CK) and LDH levels, and current dose of glucocorticoids (GK), but positively with disease duration and MMT-8. In contrast, prealbumin correlated negatively with disease duration, MDI, and CRP but positively with the current dose of GK. Orosomucoid, the acute phase reactant, was associated positively with CRP, ESR, the current dose of GK, and BMI. Vitamin D levels (calcidiol and calcitriol) were associated positively with disease duration and damage (MDI) but negatively with markers of muscular damage (myoglobin, CK, LDH), BMI, and the current dose of GK. Increased levels of insulin and C-peptide were associated with higher BMI and the current dose of GK, while insulin correlated negatively with age. Thyroxin was negatively associated with MMT-8 but positively with myoglobin and LDH, whereas TSH was positively associated with CRP and muscular damage markers. Complement C4 levels correlated positively with muscular damage markers, age, and BMI but negatively with disease duration. Complement C3 was positively associated with BMI and CRP but negatively with MITAX. Higher cholinesterase levels were associated with longer disease duration and lower MITAX and dose of GK (p<0.05 for all).
Conclusions. We have observed significant alterations in markers of nutritional status in our IIM patients compared to healthy age-/sex-matched individuals. Differences were also found among the four subtypes of IIM. These alterations were associated with laboratory parameters of disease activity and the current dose of corticosteroids.
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THE ROLE OF IMACS CORE SET MEASURES TO ROUTINELY EVALUATE THE QUALITY OF LIFE OF IDIOPATHIC INFLAMMATORY MYOPATHIES PATIENTS IN CLINICAL PRACTICE

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Background. Idiopathic Inflammatory Myopathies (IIMs) are rare, multisystemic and complex diseases, often impacting on patients' quality of life (QoL). Patient Reported Outcomes (PROs) assess the overall health status of patients, particularly for emotional and functional domains. In clinical practice, the administration of PROs might have some limitations, because they tend to be time-consuming and sometimes difficult to be filled in by patients. The International Myositis Assessment & Clinical Studies Group Disease Activity Core Set Measures (IMACS-CSM) are a tool created to specifically assess disease activity and QoL in IIMs.
Objectives. To evaluate the ability of IMACS-CSM in assessing IIMs patients' QoL in comparison with both generic and IIMs specific PROs.
Methods. Consecutive adult patients with an established diagnosis of IIM (2017 EULAR/ACR criteria) followed at our Myositis Clinic were enrolled and evaluated during scheduled follow-up visits. Demographic and clinical data (age, sex, disease subset and duration, organ involvement) were collected. IMACS-CSM [Physician Global Activity (PhGA), Patient Global Activity (PGA), 8-items Manual Muscle Testing (MMT8), Health Assessment Questionnaire (HAQ), CPK values, Myositis Disease Activity Assessment Tool (MDAAT)] were used to evaluate both disease activity and QoL. Patients' perspective was evaluated also by administration of PROs not included in the IMACS-CSM: Short-Form 36 Items Health Survey (SF-36), Functional Assessment of Chronic Illness Therapy Fatigue Subscale (FACIT-F), Myositis Activity Profile (MAP), MD Anderson Dysphagia Inventory (MDADI). Results were expressed as mean±SD for continuous variables and as percentage for categorical variables. Intergroup comparisons were assessed by using Chi-square, t-test and ANOVA. Pearson coefficient was used to analyse the correlations between IMACS-CSM variables and the other PROs. P values <0.05 were considered significant.
Results. Sixty patients (65% female, mean age 59.9±13.5 years, mean disease duration 7.7±6.1 years), 37 (61.7%) with polymyositis, 20 (33.3%) with dermatomyositis and 3 (5%) with inclusion body myositis, were enrolled. Among IMACS-CSM, the mean HAQ and PGA scores were significantly worse in case of muscle (p=0.017) and oesophageal involvement (p=0.017), respectively; as expected, MMT8 score was associated with muscle involvement (p=0.017); MDAAT score was instead associated with oesophageal dysfunction (p<0.001). No associations were found between IMACS-CSM and others clinical and demographic parameters. FACIT-F correlated positively with MMT8 (r 0.432, p=0.001) and negatively with PhGA, PGA, HAQ and MDAAT (all r <-0.404 and p≤0.002 except for PhGA with r=-0.338 and p=0.016). SF-36 domains correlated positively with MMT8 (all r >0.259, p≤0.05) and negatively with PGA (all r <-0.393, p≤0.001), HAQ (all r <-0.422, p≤0.001) and MDAAT (all r <-0.276, p≤0.05). Opposite correlations were found for MAP domains: MMT8 all r <-0.297, p≤0.05; PGA all r >0.326, p≤0.05; HAQ all r >0.483, p≤0.001; MDAAT all r >0.268, p≤0.05. Similarly, MDADI scores correlated negatively with MMT8 (r <-0.363, p=0.005) and positively with PGA, HAQ and MDAAT (all r >0.318, p≤0.015). Notably, no correlations emerged between these PROs and CPK values.
Conclusion. Even if IMACS-CSM offer a partial evaluation of patients' perspective, our data show how not only HAQ and PGA, but also PhGA, MMT8 and MDAAT (expressing rheumatologist's point of view) seem to adequately reflect overall health status of IIMs patients, thus giving to clinicians a reliable assessment of their QoL. Therefore, the core set should be routinely used in clinical practice during every outpatient visit, while more accurate and complex PROs might be administered at larger time intervals or during disease flares, to optimize IMACS-CSM's analysis.

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A PROSPECTIVE DIAGNOSTIC ACCURACY STUDY OF MULTIMODALITY TESTING IN PATIENTS SUSPECTED OF A TREATABLE IIM: THE ADAPT STUDY PROTOCOL

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Background. Idiopathic inflammatory myopathies (IIMs) are a group of heterogeneous auto-immune disorders characterised by subacute onset and progressive proximal muscle weakness which are frequently part of a multisystem auto-immune disorder. The clinical symptoms and signs differ widely between patients at disease onset and reaching a correct diagnosis in a timely manner can be challenging. There is no gold standard for the diagnosis of IIM. Diagnostic modalities include serum creatine kinase (sCK) activity, muscle imaging (magnetic resonance imaging (MRI) or ultrasound (US)), electromyography (EMG), myositis auto-antibody testing and muscle biopsy. Several diagnostic criteria have been developed for IIMs, varying in reported sensitivity and specificity. We hypothesize that an evidence-based diagnostic strategy, using fewer and preferably the least invasive diagnostic modalities, can achieve the accuracy of a complete panel of diagnostic tests, including MRI, US, EMG, myositis-specific auto-antibody testing and muscle biopsy.
Methods. The OptimizAtion of Diagnostic Accuracy in idioPathic inflammaTory myopathies (ADAPT) study is a prospective diagnostic accuracy study with an over-complete study design in IIM patients, excluding inclusion body myositis (IBM). All consenting participants undergo standardized history taking, physi-

cal examination, standard laboratory testing (including sCK), muscle imaging by whole body muscle MRI and muscle US, EMG, myositis auto-antibody testing, and muscle biopsy. One-hundred patients suspected of a treatable idiopathic inflammatory myopathy will be included. To be eligible, symmetrical proximal muscle weakness causing a functional limitation that justifies treatment with high dose glucocorticoids, with an onset of symptoms ≤24 months before inclusion should be present. A reference diagnosis will be assigned by an expert panel using all clinical information and all results of all ancillary tests available, including 6 months follow-up. Several predefined diagnostic strategies will be compared against the reference diagnosis to find the optimal diagnostic strategy. In addition, the patient burden of the ancillary investigations will be assessed and compared between the diagnostic modalities.

Discussion. Although the individual diagnostic accuracy of some of the previous mentioned diagnostic modalities have been studied before, to the best of our knowledge, no previous study has examined a complete diagnostic panel for myositis. Our prospective study enables the evaluation of the diagnostic accuracy of individual items and procedures and of the incremental value of multi-test diagnostic strategies, and the assessment of the burden of each diagnostic test. At the conference we will present an interim-analysis of the first 50 patients in terms of the patient burden related to the different ancillary investigations.

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CLINICAL CHARACTERISTIC DEFINING ANTISYNTHETASE SYNDROME: RESULTS FROM THE UNIVARIATE ANALYSIS ON THE CLASS PROJECT'S DATASET

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Background. The CLASS project (Classification criteria for antisynthetase syndrome project) is aimed at developing and validating classification criteria for antisynthetase syndrome (ASSD). The project consists of a data-driven and an expert-driven part. We here report the preliminary results of the data-driven part, i.e. the univariate analysis for each variable included in the dataset.

Methods. The initial feasibility survey was evaluated from 175 centers across the world, with each of which has in turn submitted the project to the local IRB. Each center was requested to include retrospective or prospectively collected data about patients diagnosed as ASSD (cases) or as other mimickers of ASSD such as myositis or other systemic autoimmune diseases or patients with ILD, arthritis, rashes etc (controls). In addition, if feasible, centers were requested to send serum samples on the cases and controls, so that myositis specific antibodies can be evaluated in central research lab. The data inclusion started on August 2020 and ended in April 2021. The records were then evaluated for the presence of all the requested variables (key variables) and the diagnosis of case or control was verified by 4 Rheumatologists of the working group (RA, LC, GZ and SFK). The records with lacking data were excluded from the analysis and reported to the center that included them through queries. The univariate analysis of each key variable for diagnosis of ASSD was then conducted by a statistician (DR) using the software R foundation for statistical analysis (Vienna, Austria). The relevance of each variable in discriminating ASSD from controls was calculated through odds ratio (OR) and p values.

Results. The total number of records included was 3647 (1715 cases, 1915 controls, 20 missing) from 92 centers and 350 investigators from all over the world. After quality controls, the number of records included was 1996 (836 cases, 1160 controls). In addition, 1200 sera samples of both cases and controls are being evaluated for myositis specific antibodies (MSA) using radio-active immunoprecipitation method. The cases included 460 patients with anti Jo-1 (57.3%), 123 with anti PL7 (17.8%), 120 with anti PL12 (17.4%), 61 with anti-EJ (9.3%) and 27 with anti-OJ (4.2%) autoantibodies as reported locally. The controls included were dermatomyositis (27.6%), systemic sclerosis (11.2%), RA (10.4%), polymyositis (9.6%), IPAF (8.4%), scleromyositis (3.7%), IMNM (3.3%) and other connective tissue diseases (11%). Arthritis, myositis and interstitial lung disease (ILD) were more common in ASSD than controls (arthritis 60% vs 42.7%, OR 2 $p<0.001$; ILD 85% vs 37%, OR 9.7, $p<0.001$; myositis 68.8% vs 53.7%, OR 1.9 $p<0.001$), as well as mechanic's hands/hiker's feet (43% vs 7.5%, OR 9, $p<0.001$), and Raynaud's phenomenon (36.3% vs 29.4%, OR 1.37, $p=0.001$). Interestingly, also cytoplasmic ANA resulted more commonly present in ASSD than controls (32.7% vs 11.3%, OR 3.79, $p<0.001$) whereas Gottron's papules and heliotrope rash were more common in controls than in cases (16% vs 21%, OR 0.7, p 0.006 and 11.3% vs 20%, OR 0.51, $p<0.001$ respectively). More results are available in Table I.

Conclusion. These preliminary data showed that ASSD displays some peculiar clinical characteristics that differentiate it from other systemic autoimmune diseases. Obviously, more analysis is going to be conducted on the whole dataset once that the queries will be completed and all MSA analysis completed in central research lab. Moreover, more specific subsets of cases and controlled will be considered in future analysis, such as the subset of ASSD defined by ARS positivity through immunoprecipitation. All these results will then be integrated in a multivariate analysis, compared to the results obtained in the data-driven part of the project and finally validated on an independent cohort. This huge effort will hopefully lead to a reliable and valid set of classification criteria for ASSD which will also be applicable and useful in common clinical practice.

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P-178. Table I. Results of univariate analysis for key variables of antisynthetase syndrome.

Variable	Prevalence cases (total n=863)	Prevalence controls (tot n=1160)	OR	*p*-value
Joint inflammatory disease	489 (59.9%)	489 (42.7%)	2	<0.001
Arthrithis	101 (12.4%)	145 (12.7%)	1.393	0.023
Arthralgias	388 (47.5%)	344 (30%)	2.256	<0.001
Symmetric polyarthritis (bilateral and > 4 joints)	318 (41.3%)	313 (27.6%)	1.845	<0.001
Muscle disease	562 (68.6%)	625 (54.2%)	1.851	<0.001
Muscle weakness	405 (52.5%)	549 (48.7%)	1.164	0.105
Diffuse myalgias	338 (43.5%)	398 (35.2%)	1.416	<0.001
Muscle enzyme elevation related to muscle disease	422 (53.3%)	479 (42.7%)	1.531	<0.001
EMG positive	173 (34.5%)	317 (35.4%)	0.963	0.75
MRI positive	105 (26.5%)	177 (24.3%)	1.123	0.416
Muscle Biopsy positive	138 (33.8%)	249 (30.9%)	1.145	0.294
Lung disease	707 (85.1%)	424 (36.9%)	9.749	<0.001
HRCT findings Consistent with ILD	669 (82%)	399 (34.8%)	9.51	<0.001
Ground-glass	523 (64.1%)	262 (22.8%)	6.029	<0.001
Reticulations	357 (43.8%)	243 (21.2%)	2.893	<0.001
Honeycomb	84 (10.3%)	76 (6.6%)	1.617	0.004
Traction bronchiectasis	237 (29%)	147 (12.8%)	2.785	<0.001
Other	154 (18.9%)	88 (7.7%)	2.799	<0.001
UIP	80 (9.8%)	73 (6.4%)	1.599	0.005
NSIP	428 (52.5%)	231 (20.1%)	4.374	<0.001
OP	148 (18.1%)	50 (4.4%)	4.861	<0.001
DAD	3 (0.4%)	4 (0.3%)	1.054	0.945
LIP	3 (0.4%)	8 (0.7%)	0.525	0.343
Other	35 (4.3%)	37 (3.2%)	1.344	0.218
Skin disease				
Mechanic's hands / hiker's feet	344 (42.6%)	84 (7.5%)	9.091	<0.001
Gottron papules	130 (16%)	240 (21%)	0.718	0.006
heliotrope rash	92 (11.3%)	227 (19.9%)	0.514	<0.001
V-sign	67 (8.3%)	172 (15.2%)	0.506	<0.001
Palmar papules	6 (0.7%)	27 (2.4%)	0.306	0.009
Puffy hands	85 (10.5%)	150 (13.4%)	0.758	0.055
Skin thickening/cutaneous sclerosis	67 (8.3%)	153 (13.6%)	0.575	<0.001
Fingertip/digital pits or ulcers (from ischemia)	27 (3.3%)	67 (5.9%)	0.552	0.011
Other types of cutaneous ulcerations	13 (1.6%)	65 (5.8%)	0.266	<0.001
Raynaud phenomenon	295 (36.3%)	338 (29.4%)	1.368	0.001
Pulmonary hypertension (PH)	77 (9.5%)	47 (4.1%)	2.443	<0.001
Group 1, primary pulmonary artery hypertension (due to connective tissue disease, PAH)	20 (2.6%)	29 (2.7%)	1.053	0.86
Group 3, secondary pulmonary hypertension (due to ILD)	51 (6.7%)	12 (1.1%)	6.491	<0.001
Serology				
ANA	534 (66.2%)	753 (68.3%)	0.909	0.334
Positive cytoplasmic ANA pattern	225 (32.7%)	108 (11.3%)	3.794	<0.001
Anti-Ro52	356 (51.4%)	207 (24.6%)	3.235	<0.001

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PRELIMINARY STEPS FOR MULTICRITERIA DECISION ANALYSIS PROCESS IN THE DEVELOPMENT OF CLASSIFICATION CRITERIA FOR ANTISYNTHETASE SYNDROME: THE USE OF 1000MINDS FOR THE CLASS PROJECT.

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Background. The CLASS project (Classification criteria for antisynthetase syndrome project) is aimed at developing and validating classification criteria for antisynthetase syndrome (ASSD). The project consists of a data-driven and an expert-driven part. We here report the preliminary results of the expert driven part, based on the multicriteria decision analysis performed on 1000Minds© software, previously applied in the development of classification criteria of several rheumatic diseases including systemic sclerosis and systemic lupus erythematosus (1, 2).

Methods. A broad list of variables was obtained through a systematic literature review on ASSD definitions (3). A Delphi consensus involving 19 experts of ASSD from various regions of the world (12 rheumatologists, 3 pulmonologists, 2 neurologists and 2 dermatologists) was then performed for item reduction. The resulting candidate criteria were used to create 20 clinical vignettes. Using the 1000minds software, the 19 experts ranked the vignettes according to the likelihood of ASSD diagnosis (ranking survey). In a virtual meeting, the experts discussed the results of the survey and agreed on the key variables and possible responses for consideration of ASSD classification. Finally, experts re-ranked the vignettes and answered if they would treat the case as anti-synthetase syndrome based on given information. This was followed by consensus of the case ranking based on median scores and on final list of key variable and response.

Results. The initial list encompassed 359 variables, then reduced to 109 after the Delphi consensus. These variables were used for drafting 20 clinical vignettes, each one describing a case of ASSD or of one of its mimickers. The ranking-survey highlighted a poor inter-rater reliability in ranking the vignettes in five degrees of likelihood for ASSD (κ=0.12, 95%CI 0.06-0.17). During the meeting the summary results of the ranking were revealed to all the participants and each expert explained the reasons for their choices. The re-ranking process improved the inter-rater reliability to fair-moderate agreement (κ=0.4, 95%CI 0.26-0.52). Figure 1 graphically reports the variability in the ranking and the improvement of the agreement after the meeting. More importantly, the exercise encouraged the experts to systematically focus on the most important clinical characteristics of ASSD, thus allowing a further refinement of the initial list of variables, which were further reduced to 11 domains and 42 variables. Consensus was reached on the domains, variables and their responses through follow up Delphi process and is going to be used for development of an expert consensus driven candidate for ASSD classification.

Conclusion. The multicriteria decision analysis is a valuable process to develop better decision-making tools using expert opinion and consensus. It has already proved as a suitable approach to develop classification criteria for different medical conditions and is aimed at removing the "noise" in expert's judgments, intended as the natural variability among subjects in making decisions. Our survey revealed that this "noise" is present even when the decision makers share the same background of knowledge and scientific interests. On the other hand, sharing individual views and a systematic approach in decision making revealed helpful in reducing this noise, as proved by the results of the re-ranking survey. On the other hand, the whole exercise highlighted once more, the huge variability in diagnosing ASSD and pointed out the need of shared classification criteria for this disease.

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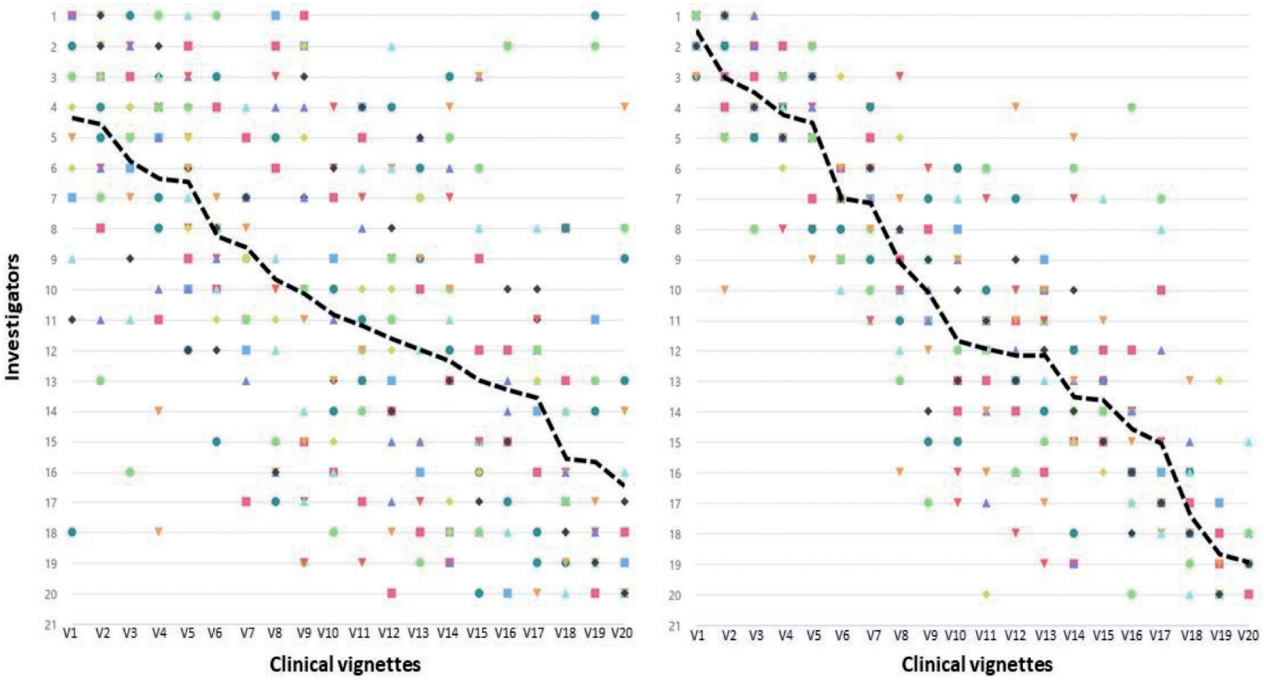

P-179. Fig. 1. Ranking distribution before (left) and after (right) the meeting. The black dashed line represents the ranking mean, each colored form represent one investigator.

P-180

PSYCHIATRIC COMORBIDITIES ASSESSMENT: AN UNMET NEED IN PATIENTS WITH IDIOPATHIC INFLAMMATORY MYOPATHIES?

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Background. Idiopathic Inflammatory Myopathies (IIMs) are rare and complex chronic diseases, with a strong impact on patients' Quality of Life (QoL) in terms of both physical and emotional functioning. Despite its key role in daily life, patients' emotional status could be difficult to be investigated by physicians. As known, patients with chronic conditions are at higher risk of anxiety and depression, but data about their prevalence in IIMs are still limited. The Hospital Anxiety and Depression Scale (HADS) is a validated questionnaire to evaluate the presence and severity of both anxiety (HADS-A) and depression (HADS-D) in patients.
Objectives. To determine the prevalence of anxiety and depression in a monocentric cohort of IIMs patients and to evaluate possible correlations with clinical features, disease activity and parameters of QoL.
Methods. Consecutive adult patients with a diagnosis of IIM (2017 EULAR/ACR criteria) were recruited during a scheduled follow-up visit. Demographic and clinical features were recorded (sex, age, disease subset and duration, organ involvement, comorbidities). IIM disease activity was evaluated following International Myositis Assessment & Clinical Studies Group Disease Activity Core Set Measures. To detect anxiety and depression status, HADS was administered to patients, who were also asked to fill in Short-Form 36 Items Health Survey (SF-36). For both HADS-A and -D subscales, patients were classified as at risk for scores ≥8 (borderline for scores 8-10, high risk if ≥11). Results were reported as mean±SD for continuous variables and as percentage for categorical variables. Intergroup comparisons were assessed by using Chi-square, t-test and ANOVA. Pearson coefficient was used to analyse the correlations between variables. P values <0.05 were considered significant.
Results. Fifty-three patients (72% female; mean age 64.8±12.0 years; mean disease duration 7.4±6.2 years) were enrolled. Twenty (37.7%) showed increased anxiety scores (mean 11.35, min. 8 – max. 17): 10 (50%) borderline and 10 (50%) high risk. Twenty (37.7%) had an increased depression score (mean 11.75, min. 8 – max. 19): 6 (30%) borderline and 14 (70%) high risk. If abnormal scores of both HADS-A and -D were found in 15 patients (28.3%), 17 patients (32.1%) were at high risk of at least one of the conditions. Sex, age, disease subset and duration did not seem to influence patients' emotional status. Apart from an association between Raynaud's Phenomenon occurrence and higher HADS-A scores (p=0.045), no significant correlations with organ involvements emerged. A strong association was found between fibromyalgia and higher HADS-A and -D scores (p=0.006 both). Patients with elevated anxiety levels presented significantly higher scores of Patient Global Assessment (PGA, p=0.002) and Health Assessment Questionnaire (HAQ, p=0.007) and significantly lower scores of Manual Muscle Testing (MMT8, p=0.004). HADS-D scores were similarly associated with PGA (p=0.001), HAQ (p<0.0001) and MMT8 (p=0.001). The presence of anxiety and depression was associated with lower scores in all SF-36 domains (all $p\leq0.016$ for HADS-A and all $p\leq0.006$ for HADS-D). Moreover, a correlation was found among SF-36 scores and PGA (all r <-0.516, p<0.01), HAQ (all r <-0.541, p<0.01) and MMT8 values (all r >0.299, p<0.05).
Conclusion. These results show nearly 40% of our cohort was at risk of anxiety or depression; almost 30% were at risk of developing both conditions together and quite one third was at high risk to develop at least one of them. As expected, these conditions were favoured from a concomitant fibromyalgia. Moreover, a compromised QoL and a functional limitation, as evaluated by PGA, HAQ and MMT8, in agreement with SF-36 domains, were significant risk factors for their occurrence. Therefore, our data, although preliminary, underline the need of a more comprehensive evaluation of IIMs patients, who should be screened for psychiatric comorbidities and, in case of high risk, referred to a specialist evaluation, in the perspective of improving their quality of care.

P-181

IFN-I DEPENDENT IMPAIRMENT OF MUSCLE STEM CELL PROLIFERATION IN DERMATOMYOSITIS

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** contributed equally*

Background. Dermatomyositis (DM) is an acquired inflammatory myopathy, occurring during child and adulthood, and characterized by muscle weakness, as well as pulmonary and skin lesions. Myositis specific autoantibodies are frequently found in DM sera and skeletal muscle analysis identify myofiber damage and sustained inflammation. In normal muscle, damaged myofibers are replaced by adult muscle stem cells (MuSCs) that activate, proliferate and implement the myogenesis program to build new functional myofibers.
Methods. MuSCs derived from 8 DM adult patients (5 severe form and 3 mild form, established from histological evaluation), from 3 juvenile DM patients and from normal muscle were used to analyze their proliferation and differentiation in vitro.
Results. DM-derived MuSCs exhibited strongly reduced proliferating capacities as compared with healthy MuSCs. This led to alteration of the subsequent steps of the myogenesis program and poor myotube formation. DM-MuSCs were enriched in beta-galactosidase positive senescent cells. Type I interferon (IFN-I) being the main cytokine implicated in DM pathogenesis, gain and loss of function experiments were performed. Treating healthy MuSCs with IFN-I led to a decreased proliferation as observed in DM-derived cells. Inversely, treating DM-derived MuSCs with either an inhibitor of the JAK-STAT pathway downstream IFN-I (ruxolitinib) or a blocking antibody against IFN-I receptor rescued DM-MuSC proliferation up to the control values.
Conclusion. These results show that in DM muscle, sustained IFN-I signaling prevents MuSC expansion, leading to poor myogenesis and muscle repair deficit, which in turn may participate to the persistent muscle weakness observed in severe DM patients.

P-182

FURTHER DELINEATION OF THE IDIOPATHIC EOSINOPHILIC MYOSITIS, A CLINICAL-PATHOLOGICAL ANALYSIS OF A CASES SERIES

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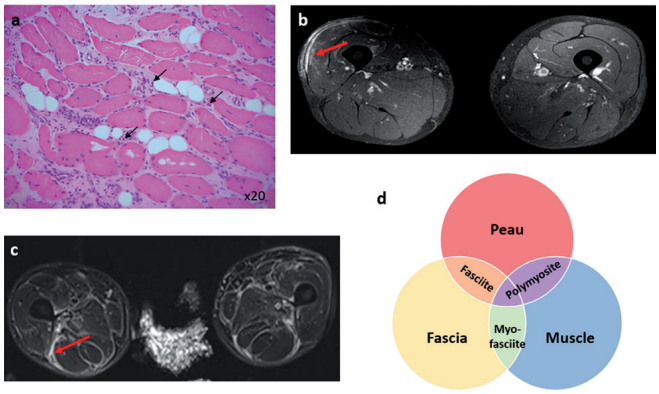
Background. Idiopathic inflammatory myopathies (IIM) are rare acquired muscle disorders, mainly defined by inflammatory infiltrates within the muscle. These inflammatory infiltrates are composed of various inflammatory cells such as lymphocytes and macrophages. The role of eosinophils in IIM is poorly defined. Eosinophilic myositis belongs to IIM and is defined by an infiltrate of eosinophils within the muscle. To date, no consensus exists for the definition of such diagnosis. Clinical or pathological characterization as well as specificities of the care for these patients remain based on several case reports. This retrospective study aims to further characterize eosinophilic myositis based on clinical and histological features.
Methods. In this French multicenter retrospective case series, patients included had muscle biopsy and diagnosis of eosinophilic myositis between 2000 and 2022. Inclusion criteria were diagnosis of myositis proven histologically associated with muscular eosinophilic infiltration (Figure 1a). Diagnosis was considered after exclusion of alternative diagnosis. Demographic, clinical, laboratory, and histological data, as well as treatment and outcome were recorded for each patient.
Results. 20 cases of eosinophilic myositis were included in the analysis. Median

age was 58.5 [39.0-70.0] years; there were 13 males and 7 females. Muscle impairment was focal (15%, n=3) or diffuse (85%, n=17). Muscle investigations objectified abnormalities: muscle weakness (20%, n=4), creatine kinase elevation (20%, n=4), myogenic aspects on electromyography (58%, n=7/12), muscular inflammation on MRI (25%, n=3/12). Extra muscular involvements were either implicating skin (skin induration (70%, n=14), skin edema (35%, n=7) or fascia (identified on magnetic resonance imaging 67%, n=8/12). Blood eosinophilia was present for 14 (70%) patients. After analysis of the overall records, easily distinguishable subgroups were delineated: focal versus diffuse myositis. Focal eosinophilic myositis represented a limited and benign form. Within the diffuse muscle impairment, two different subgroups were delineated: diffuse eosinophilic myositis (n=9) and eosinophilic myofasciitis (n=8). Identified criteria for diffuse eosinophilic myositis were: diffuse major histocompatibility complex overexpression and inflammatory infiltration into muscle associated with objective diffuse muscle impairment (motor deficit (44%, n=4/9) and/or creatine kinase elevation (33%, n=3/9), and/or myogenic aspects on electromyography (75%, n=6/8) and/or myositis identification on magnetic resonance imaging (33%, n=4/6, Figure 1b)). Identified criteria for eosinophilic myofasciitis were major histocompatibility complex overexpression and inflammatory infiltration into muscle, associated with fascia inflammatory infiltrates (38%, n=3) and/or fasciitis identification on magnetic resonance imaging (100%, n=4, Figure 1c), and absence of objective muscle impairment on clinical or biological/morphological/electrophysiological investigations. Clinical evolution of focal eosinophilic myositis was favorable (100%, n=3), without relapse, even in the absence of treatment. In contrast, all patients with diffuse eosinophilic myositis or eosinophilic myofasciitis required the use of corticosteroids, frequently associated with an additional immunosuppressive therapy (33%, n=3/9 and 88%, n=7/8 respectively), and relapses or second-line therapy were not rare (50%, n=4/8 and 25%, n=2, respectively).

Conclusions. The present study allowed to further characterize eosinophilic myositis disease, with the proposition of a new clinical-pathological delineation of eosinophilic myositis subgroups. One subgroup presents a focal pattern, and is easily distinguishable; the two others may correspond to a clinical continuum with eosinophilic induced disturbances, involving from muscle to fascia and skin (figure 1d).



P-182. Fig. 1. (a) Histopathological findings. Eosinophil infiltration: eosinophils can be observed as part of inflammatory cells (arrows) (H&E x20). (b) Magnetic resonance imaging of thighs showing inflammatory lesions (arrows) with high-intensity signals on the T2-weighted image in vastus intermedius and lateralis muscles. (c) Magnetic resonance imaging of thighs showing inflammatory lesions (arrows) with high-intensity signals on the T2-weighted image in fascia. (d) Clinical continuum with eosinophilic induced disturbances, involving from muscle to fascia and skin.

P-183

REUMA.PT/MYOSITIS – THE PORTUGUESE REGISTRY OF INFLAMMATORY MYOPATHIES

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**These authors share first co-authorship*

Background. The idiopathic inflammatory myopathies (IIM) module of the Rheumatic Diseases Portuguese Register (Reuma.pt/Myositis) is a tool used to systematically evaluate IIM patients. Our objective was to clinically characterise the Reuma.pt/Myositis cohort.

Methods. Multicentre open cohort study, including IIM patients registered in Reuma.pt up to January 2022. Data collected included demographic, clinical, and treatment data and patient-reported outcomes. Data were presented as frequencies and median (interquartile range) for categorical and continuous variables, respectively.

Results. 280 patients were included, 71.4% female, 89.4% Caucasian, with a median age at diagnosis and disease duration of 48.9 (33.6-59.3) and 5.3 (3.0-9.8) years, respectively. Patients were classified as having definite (N=57/118, 48.3%; N=35/224, 15.6%), likely (N=23/118, 19.5%; N=50/224, 22.3%), or possible (N=2/118, 1.7%; N=46/224, 20.5%) IIM by 2017 EULAR/ACR and Bohan-Peter criteria, respectively. Disease subtypes included dermatomyositis (DM, N=122/280, 43.6%), polymyositis (N=59/280, 21.1%), myositis in overlap syndromes (N=41/280, 14.6%), clinically amyopathic DM (N=17/280, 6.1%), nonspecific myositis (N=13/280, 4.6%), mixed connective tissue disease (N=12/280, 4.3%), immune-mediated necrotizing myositis (N=9/280, 3.2%), and inclusion bodies myopathy (N=7/280, 2.5%). Over the course of the disease, the most common symptoms were proximal muscle weakness (N=180/215, 83.7%), arthralgia (N=127/249, 52.9%), fatigue (N=47/127, 37.0%), Raynaud's phenomenon (N=76/234, 32.5%), and dysphagia (N=33/121, 27.3%), and the most common clinical signs were Gottron's sign (N=75/184, 40.8%), heliotrope rash (N=101/252, 40.1%), Gottron's papules (N=93/237, 39.2%), and arthritis (N=38/98, 38.8%). Organ involvement included lung (N=78/230, 33.9%), oesophageal (N=40/221, 18.1%), and heart (N=11/229, 4.8%) involvements. Most patients expressed myositis-specific (MSA, N=158/242, 65.3%) and/or myositis-associated (MAA, 112/242, 46.3%) antibodies. The most frequent antibodies were anti-SSA/SSB (N=70/231, 30.3%), anti-Jo1 (N=56/236, 23.7%), and anti-Mi2 (N=31/212, 14.6%). Most patients had a myopathic pattern on electromyogram (N=101/138, 73.2%), muscle oedema in magnetic resonance (N=33/62, 53.2%), and high CK (N=154/200, 55.0%) and aldolase levels (N=74/135, 54.8%) at diagnosis, with median highest CK levels of 1308 (518-3172) mg/dL and aldolase of 42 (12-121) mg/dL. Neoplasia was found in 11/127 patients (8.7%), most commonly breast (N=3/11, 27.3%), non-melanoma skin (N=2/11, 18.2%), and colorectal (N=2/11, 18.2%) cancer (Table 1). Most patients with cancer-associated myositis had DM (N=8/11, 72.7%) and expressed MSA (N=6/11) and/or MAA (N=3/11). The most used drugs over the course of disease were glucocorticoids (N=201/280, 71.8%), methotrexate (N=117/280, 41.8%), hydroxychloroquine (N=87/280, 31.1%), azathioprine (N=85/280, 30.4%), mycophenolate mofetil (N=56/280, 20.0%), intravenous immunoglobulin (N=55/280, 19.6%), and rituximab (N=45/280, 16.1%). At the last follow-up, there was a median MMT8 of 150 (142-150), modified DAS skin of 0 (0-1), global VAS of 10 (0-50) mm, and HAQ of 0.125 (0.000-1.125).

Conclusions. Reuma.pt/Myositis adequately captures the main features of inflammatory myopathies' patients, depicting in this first report a heterogeneous population, with frequent muscle, joint, skin and lung involvements. Of interest, most patients reached low disease activity at the last follow-up appointment.

P-183. Table I. Autoantibodies in cancer-associated myositis

Cancer	IIM	Autoantibodies
Breast	DM (3)	Mi2, SRP (+ SSA/SSB), Pm/Scl
Skin (non-melanoma)	Clinically amyopathic DM, PM	Jo1, SAE1 (+SSA/SSB)
Colorectal	DM (2)	Mi2 (2)
Kidney	DM	-
Lung	DM	-
Lymphoma	Inclusion bodies myopathy	-
Unknown	DM	-

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POLYMYOSITIS IS A RARE CLINICAL SUBTYPE OF IDIOPATHIC INFLAMMATORY MYOPATHIES WITH FAVORABLE PROGNOSIS

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Background. Idiopathic inflammatory myopathies (IIM) are a group of heterogenous autoimmune diseases characterised by inflammatory infiltration of skeletal muscle. Bohan&Peter criterion in 1975 classified IIM into polymyositis (PM) and dermatomyositis (DM). In 1991, Dalakas proposed muscle biopsy of PM is featured by endomysial inflammatory infiltration consisting of CD8+ T cells which invade non-necrotic muscle fibers expressing the MHC-1 antigen. With the finding of different myositis-specific antibodies (MSAs) and deep understanding of muscle pathology, several subtypes of IIM were strictly defined, such as DM, immune-mediated necrotic myopathy(IMNM) and sporadic inclusion body myositis(sIBM). Some experts considered definite PM is rare in the real world, and it should be an excluded diagnosis. However, how to strictly define PM, and the true incidence and characters of PM are undetermined.
Methods. Patients diagnosed as IIM according to the 2017 EULAR/ACR criteria who hospitalized in the department of rheumatology of China-Japan Friendship Hospital from 2014 to 2021 were involved in the study. We created a new diagnosed flowchart of definite polymyositis(dPM). The clinical features and prognosis of dPM were analyzed.
Results. Six patients are diagnosed as dPM, accounting for 0.79% (6/755) of previously diagnosed IIM with muscle biopsy, and 3.8%(6/159) of original PM. ASS and IMNM patients were the most to be misdiagnosed. The dPM patients manifested with muscle weakness mainly, mild CK elevation, and less frequent myalgia compared with MSA- IMNM and NSM. One patient developed ILD. Two of them overlapped other CTD. CD8/MHC-1 complex is the typical pathological feature. All of the dPM patients achieved remission after a two-year follow up.
Conclusion. Polymyositis is a rare clinical subtype of idiopathic inflammatory myopathies but a with favorable prognosis. A detailed clinical and serological data, comprehensive screening of myositis-specific antibodies and CD8/MHC-1 complex expression in muscle biopsy are critical for dPM diagnosis.
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AN UNUSUAL CASE OF A RECURRENT BRONCHOPNEUMONIA

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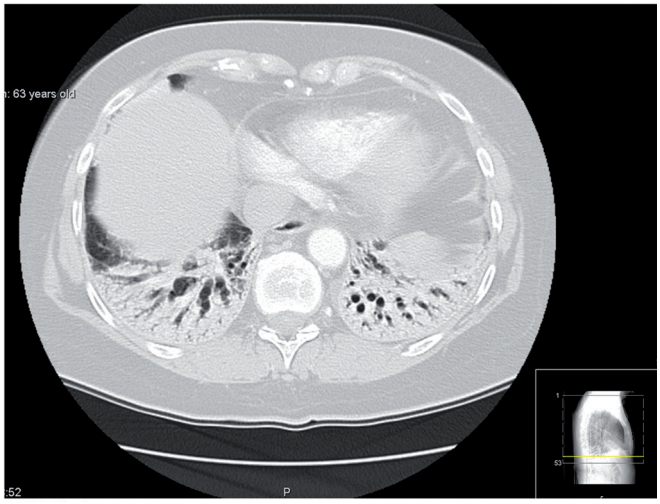
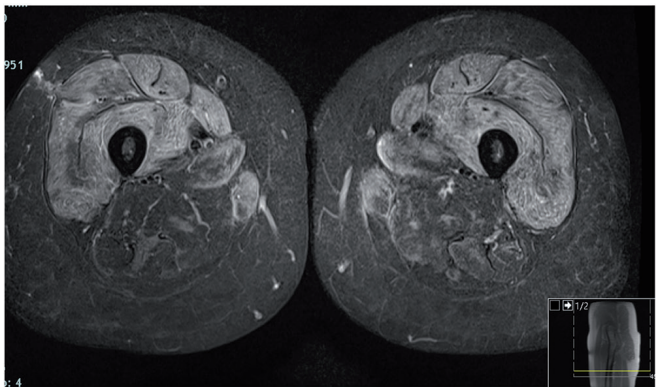
Background. Anti-synthetase syndrome (ASS) is a rare chronic autoimmune disorder characterized by varying degrees of interstitial lung disease, myositis, arthropathy, fever, Raynaud's phenomenon, and mechanic's hands. It is characterised by antibodies against aminoacyl transfer ribo-nucleic acid (RNA) synthetase; of which anti Jo-1 are the largest group. The lung is the most common extra-muscular organ involved in ASS and it may be affected in the absence of muscular involvement. Interstitial lung disease is the most common lung manifestation and has been reported in about 90% of patients with anti-synthetase autoantibodies. There have only been a few documented cases of organising pneumonia in ASS. We however present a case of a 63-year-old lady who presented with organising pneumonia as the first manifestation of ASS.
Case presentation. A 63-year-old lady admitted with dry cough and worsening shortness of breath into the medical admission unit. She had been started on steroids by her GP for suspected Polymyalgia Rheumatica (PMR) 12 months before the current presentation, but she had tapered and stopped the steroids couple of months prior to this presentation. The only other notable past medical history was hypothyroidism, treated with levothyroxine. Clinical examination revealed coarse crepitations in both lung bases. Elevated inflammatory markers were noted on the blood tests and CXR was reported as bilateral bronchopneumonia. She was started on IV antibiotics for bronchopneumonia, symptoms improved after couple of days, and she was discharged. She was however re-admitted 8-weeks later with fever, confusion, and dry cough. She also had lethargy and stiffness which was still ongoing since previous admission. Clinical examination revealed bilateral crepitations and blood gases showed she had Type 1 respiratory failure. She was started on Non-Invasive Ventilation (NIV), steroids and antibiotics. Sputum culture yielded no growth. Atypical pneumonia and tuberculosis tests were negative. High-resolution computed tomography (HRCT) of the chest showed bilateral consolidation with air bronchograms involving left lower and right middle lobe associated with subtle interstitial septal thickening. The second admission prompted the clinician to look for reasons for unresolved pneumonia and a thorough clinical examination revealed proximal muscle weakness raising the possibility of inflammatory myopathy which was later confirmed by raised Creatinine Kinase (CK – 1888), MRI thigh muscles showing muscle oedema as well as positive anti-nuclear antibody (ANA – 8.7), Anti-Jo-1 and Anti Ro. Muscle biopsy showed Idiopathic Inflammatory Myopathy (IIM) with necrosis and frequent regenerating fibres. A diagnosis of Organising Pneumonia secondary to Anti tRNA synthetase syndrome was made and she was started on high dose intravenous (IV) methyl prednisolone and 6 pulses of IV cyclophosphamide at 2 weekly intervals. Symptoms improved within few weeks of starting the treatment. She was also started on maintenance therapy with mycophenolate 1.5gm bd and steroid was gradually tapered and stopped. The muscle power improved, and the follow-up HRCT showed significant improvement with interval subtotal resolution of bi-basal bronchiectasis related consolidation.
Lung function tests also showed steady improvement even after 5-years of follow up (FEV1 increased from 1.93 to 2.17L, FEV1/FVC increased from 78.3 to 80%).
Conclusion. The incidence of Anti Jo-1 positivity ranges from 1.2 to 2.5 per million and the average age of diagnosis is 50-years. Many features of SS may evolve over time making a clear diagnosis difficult at the outset of the disease. The joint and muscle symptoms as well as raised CRP may be wrongly diagnosed as PMR and treated inadequately with oral steroids like in this case. Acute presentation with organising pneumonia can mimic a simple community acquired pneumonia and a high index of suspicion is needed to diagnose this rare condition as early diagnosis and prompt initiation of appropriate treatment in cases of ASS is key to improving prognosis in these patients.
Acknowledgements. Dr Srinivas Boddu (Consultant radiologist).



P-185. Fig. 1.



P-185. Fig. 2

P-186

IMACS ICERS GUIDANCE FOR QUALITY CLINICAL TRIAL DESIGN OF EXERCISE IN IDIOPATHIC INFLAMMATORY MYOPATHIES (IIMS)

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On behalf of the International Myositis Assessment and Clinical Studies Group's (IMACS) Inter-disciplinary Collaborative on Exercise and Rehabilitation Studies (IMACS ICERS)
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Background. IMACS-ICERS, a global clinical research community of 47 members is dedicated to education and worldwide awareness, education and research in muscle, myositis and exercise. Quality standards in clinical trial design, implementation and reporting are essential and crucial in rare heterogeneous diseases such as the IIMs. IMACS ICERS undertook an iterative series of investigations into the evaluation of all published data on exercise interventions in IIMs up through April 30, 2020 to survey the current state of quality design, implementation and reporting with the goal of strengthening and unifying IIM research endeavors. The aim is to develop a quality checklist for future exercise trials.
Methods. Rolling systematic reviews were conducted between May 2016 to April 2020 with additional PubMed searches (Table I). A total of 37 articles were reviewed for content and quality by 47 project members of equally valued expertise in myositis, 15 Patient research partners (PRP) and 34 IIM-dedicated clinicians, representing 17 countries and 6 continents. Members were divided in 7 teams, 1 JDM, 1 IBM, and 5 DM/PM/ASyS/IMNM) teams each reviewing 4 to 7 articles. Team leaders were trained in nominal group strategy and in techniques for moderating mixed experience groups that included scripted language to foster equitable communication and ease amongst team members and to elicit content nomination. PRPs were supported and supervised in separate sessions. Data was collected through purpose-designed analysis templates used throughout the tri-phase analyses to facilitate systematic examination of elements. Each team member analyzed each article separately, followed by systematic team discussions and then reviewed by the entire assembly at plenary meetings. The following aspects were reviewed: Trial design, intervention characteristics, implementation, myositis and exercise related cohort characteristics, outcomes and assessment measures, analytic methods, results interpretation and reporting as to statistically significant changes versus clinically relevant changes, patients' perspective regarding feasibility/relevance of exercise programs and outcomes/assessments, and detection of bias.
Results. The resulting guidance on design and implementation of exercise studies in IIMs presented by IMACS ICERS are presented, without member dissension, as essential components of future studies and are itemized under:
- Pre-Study Procedures.
- Overall Study Design.
- Intervention Characteristics.
- Outcomes and Outcome Measures.
- Analysis.
- Results as to statistically significant changes/Clinically relevant changes.
- Patients' perspective on feasibility and relevance of exercise programs and outcomes/outcome measures.
- Detection of bias.

This investigation produced the IMACS-ICERS Checklist, an dual purpose instrument that supports IIM exercise trial design and also used to assess the quality of IIM exercise studies.
Conclusion. We report the process and results identifying major areas of design, implementation and reporting essential for consistency and quality across IIM exercise studies. Patient experts are crucial to assessing feasibility of IIM exercise clinical trial design. IMACS ICERS Checklist is an instrument to support, and assess the quality of, design and implementation of exercise studies in IIMs. IMACS-ICERS Checklist is anticipated to be generalizable for exercise studies generally. Future IMACS-ICERS projects forthwith include consensus guidelines on safety of exercise for individuals with IIM.
Acknowledgements. To IMACS Scientific Research Committee and IMACS coordinator Dr Lisa Rider.

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Databases	Medline (Ovid), Web of Science Core Collection (Clarivate), Embase (Elsevier), Cochrane (Wiley), Cinahl (Ebsco)
Major search terms	Exercise/ or Exercise Test/ or Exercise Movement Techniques/ or Fitness Centers/ or Gardening/ or Mobility Limitation/ or Muscle Strength/ or Physical Endurance/ or Physical Exertion/ or Physical Fitness/ or "Physical Education and Training"/ or Postural Balance/ or Recreation/ or Sedentary Lifestyle/ or Sports/
Inclusion criteria	Human studies including all ages, including PM/DM/ASyS/IMNM/IBM/JDM, and ≥ 3 participants, languages; English, Spanish, German, Swedish, Danish, Norwegian.
Exclusion criteria	Animal studies, hereditary IBM, other languages
Search results	Records identified through data base search (n=1370) Records after duplicates removed that were screened (n= 885) Records excluded (n=825) Full-text articles assessed for eligibility (n = 64) Full-text articles excluded, with reasons (n = 28) Review (n=15) Not human (n=1) Validation of exercise tolerance test (n=4) Case report with < 3 participants (n=9) Studies included in qualitative synthesis (n = 36) Criteria yielded 36 articles of which 11 were randomized controlled trials (RCTs), and 25 were open-label studies. 24 articles related to DM/PM (including ASyS and IMNM), 7 to IBM and 5 to JDM. One additional study on IBM was identified after April 30, 2020.

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DISCORDANCE BETWEEN PATIENT AND PHYSICIAN PERCEPTION OF DISEASE ACTIVITY AMONG PATIENTS WITH IDIOPATHIC INFLAMMATORY MYOPATHY: A REPORT FROM THE COVAD STUDY

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Objectives. To assess the disparity between patient and physician perception of disease activity among patients with idiopathic inflammatory myopathy (IIM) and to assess the potential contributors of reported disease activity from the COVAD study.
Methods. Data were collected from the international cross-sectional internet-based survey, which is part of the COVAD protocol. The survey consisted of 37 items, translated into 18 languages. Physician perception of disease activity was defined as affirmative answer on joint swelling or active rash or worsened muscle weakness and/or daily prednisolone dose ≥10mg. Patient perception of disease activity was dichotomised form a 5-point Likert scale. Discordant and concordant pairs between patient and physician definition of disease activity were noted. Data on fatigue, pain (both visual analogue scales, VAS-10) and physical function (PROMIS-10a short form v2.0, composite score) were also extracted. Association were analysed using the Phi statistic and multivariate generalised linear modelling (GLM) on the entire set and on individual myositis category.
Results. Total 1217 responses were available for analysis (Antisynthetase syndrome 12.2%, inclusion body myositis (IBM) 26.7%, dermatomyositis (DM) 31%, polymyositis (PM) 12.5%, overlap myositis (OM) 12.5%, necrotising myositis (NAM) 5.1%). Overall, 744 responses were concordant and 472 responses were discordant. Internal consistency of the PROMIS, pain VAS and fatigue scales were high (intra-class corelation, ICC>0.9 in all three). Overall agreement between patient and physician's responses were moderate concordant (Phi=0.23, $p<0.001$). In the disease subgroups, Phi scores were poorest in the IBM, OM and NAM subgroups (phi=0.12, $p=0.03$; phi=0.11, $p=0.17$ and phi=0.001, $p=0.99$ respectively). Significant differences between the concordant and discordant groups were observed in the subgroups DM in terms of composite PROMIS (21.5±9.5, vs 19.5±7.3, $p=0.032$) and OM (26.2±9.7, vs 22.5±8.7, $p=0.017$). In the multivariate GLM, in the DM subgroup, higher score in the PROMIS composite was associated with increased chance to belong to concordant group (OR1.03, 95% CI: 1.01-1.05, $p=0.012$) and inverse association with age (OR

0.98, 95% CI: 0.97-0.99, p=0.03). In the OM subgroup as well, higher score in the PROMIS composite was associated with increased chance to belong to concordant group (OR1.04, 95% CI: 1.01-1.06, p=0.012). Pain VAS and fatigue were not significantly different between the concordant and discordant groups.
Conclusion. Better tools are required to identify or define disease activity for disease subcategories of IBM, OM and NAM. Composite PROMIS score can be used in the DM and OM disease categories to better identify domains that are not touched upon by the patient's and physician's perception of disease activity.

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SOCIOECONOMIC IMPACT ON TIME TO DIAGNOSIS FOR IDIOPATHIC INFLAMMATORY MYOPATHIES

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Background. Idiopathic inflammatory myopathies are a set of rare diseases that require complex evaluation and management. As such, socioeconomic disparities may impact time to diagnosis and outcomes. In this study, we aimed to investigate the impact of median household income and race on time to myositis diagnosis and normalization of creatine kinase (CK).
Methods. We queried the electronic medical record of an academic center including the teaching hospital and the county public hospital for salient demographic and clinical data of patients diagnosed with myositis (polymyositis, dermatomyositis, inclusion body myositis, other inflammatory or immune-mediated myositis) from 2011 to 2021. Median household income was determined by zip code data. The primary outcomes were the impact of household income and race on: a) time to diagnosis, defined by time between initial elevated CK and documentation of diagnosis, and b) time until CK normalization, defined by time between initial CK elevation and normalization. These were analyzed using Cox regression models. Secondary outcomes included the frequency of Magnetic Resonance Imaging (MRI) femur and muscle biopsy testing using logistic regression analyses.
Results. There were 1850 patients included in the study, of which 65.49% were female. The median household income was $55,149. 73.43% of patients were White, 22.62% were Black, 19.50% were Hispanic, 3.21% were Asian, and 0.74% were of other races and ethnicities. For every $10,000 increase in median household income, there was no significant change in the time between first elevated CK and diagnosis (p=0.07). For every $10,000 increase in median household income, there was a 10.55% increase in the expected time between the first elevated CK and subsequent CK normalization (p=0.002). There was no significant difference between race for the time until diagnosis or CK normalization. Furthermore, there were no significant differences in the probability of MRI femur (p=0.91) or muscle biopsy being ordered (p=0.98) based on income. Relative to White patients, the probability of MRI femur being ordered was 2.50 times greater in Black patients (p=0.006). The probability of muscle biopsy being performed was 3.00 times greater for Hispanic patients (p=0.009).
Conclusion. These findings suggest an unexpected proportional relationship between median household income and improvement of CK. Secondary workup was more likely to be performed in Black and Hispanic patients. Further investigation into the etiology of these differences is warranted.

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DEVELOPMENT OF A PRELIMINARY SCREENING ALGORITHM TO DETECT SYSTEMIC SCLEROSIS-RELATED MYOPATHY

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Objective. The reported prevalence of muscle involvement in systemic sclerosis (SSc) varies widely from 5.6-96%, reflecting the heterogeneous spectrum of muscle involvement, ranging from non-specific myopathic changes to idiopathic inflammatory myopathies such as polymyositis. It may also be under-recognised due to the lack of a standardised approach to detection. Yet early diagnosis of inflammatory myopathy is essential to guide immunosuppressive therapy to minimise irreversible loss of muscle power and function. We sought to develop a preliminary algorithm for screening for SSc-muscle involvement and to determine the prevalence of biopsy-proven inflammatory myopathy in patients with SSc.
Methods. Consecutive patients with SSc, according to the 1980 American College of Rheumatology (ACR) or LeRoy and Medsger criteria, enrolled in the Australian Scleroderma Cohort Study (ASCS) since 2007, were assessed annually for features of myopathy: proximal muscle weakness and elevated creatine kinase (CK). No specific guidelines for further investigation were followed. In a subset of patients from a single ASCS centre, if proximal weakness and/or elevated CK were present, myositis immunoblot and/or magnetic resonance imaging (MRI) of upper or lower limbs for increased T2 signal or fatty infiltration and atrophy were performed. Positive findings prompted a muscle biopsy. Features of patients with and without histopathological features of inflammation on biopsy were compared.
Results. Among 1443 patients in the ASCS, 260/1832 (18.5%) patients had muscle weakness and 203/1282 (15.8%) had an elevated CK at least once during follow up. 26/1253 (2.1%) patients had biopsy-proven myopathy. Among the subset of 434 patients assessed by the screening algorithm, 117/425 (27.5%) had proximal weakness, 80/421 (19%) had an elevated CK and 42/423 (9.9%) had a muscle biopsy based on muscle weakness and/or elevated CK (n=48) or presence of myositis-specific or myositis-associated autoantibodies on immunoblot (n=10) or abnormalities on muscle MRI (n=8). All 42 biopsies were abnormal, with inflammatory myopathy (polymyositis, 11; dermatomyositis, 5; inclusion body myositis, 3; necrotising, 5; other, 4) confirmed in 28/42 (66.7%) and non-specific features of myopathy reported in 14/42 (33.3%). Among the patients undergoing muscle biopsy, the prevalence of the diffuse cutaneous subtype of SSc and levels of CK were significantly higher in those with inflammatory compared with non-inflammatory myopathy. All patients with inflammatory changes on biopsy received immunosuppressive treatment, with improvement in muscle power in all cases.
Conclusion. Annual application of a preliminary screening algorithm including myositis immunoblot and MRI muscle scan identified biopsy-proven muscle involvement in 9.9% of patients with SSc. Furthermore, the detection of inflammatory myopathy was increased by approximately four and a half fold to 6.7% of patients compared with 1.4% in unscreened patients, thus opening avenues for timely treatment and highlighting that muscle involvement in SSc is frequently under-recognised.

Patients' abstracts

Pat-1

MYOSITIS ASSOCIATION AUSTRALIA (MAA)

Christine Lowe, Anita Chalmers Oam
Myositis Association Australia, Sydney, Australia

Introduction The poster presents an established patient organisation formed in 2003, with 430+ members across the country. Association.
President: Christine Lowe, mail@myositis.org.au patient group general aims.
- Providing a network of support for people with IIM (idiopathic inflammatory myopathies).
- Raising awareness of IIM among the public, patients, family/friends, carers, and health professionals, including general practitioners, rheumatologists, neurologists, and allied health. about MAA is a patient group run by volunteers who have Myositis.

Our primary goal is to help people with Myositis connect, share their experiences and learn practical ways to manage their condition. We also work to raise awareness of Myositis and support relevant research. short-term goals.
- Organising member events including regular support meet-ups and triennial conferences and • Providing a patient newsletter with research updates, general news, members' stories, disability aid recommendations.
- Myositis awareness month activities (see below).
- Fundraising for relevant medical research.
- Maintaining website with disease information, patient stories, health tips, events, research news and support contacts.
- Personalised support for advanced ailing patients.

Engage in awareness building on global Rare Diseases Day may is myositis awareness month Planning for 2022 events is underway to include:
- Patient gatherings (in-person & online) with presentations by health experts.
- Publicity campaign (TV, radio and print media) to raise awareness.
- Dissemination of patient information brochures to neurologists, rheumatologists and dermatologists.
- Allocating funds to support appropriate research. cooperation with local organisations.

We partner with Rare Voices Australia (national peak body for Australians living with a rare disease), hospitals, other patient organisations, health care professionals and pharmaceutical companies. Consumer Panel: 18 members volunteer to serve on a consumer panel established as a joint venture with the Myositis Discovery Programme, led by Prof Merrilee Needham (Perth, WA), Consumer and Community Involvement Program and our Association.
The panel has:
- Given feedback on content and timing of research communications.
- Reviewed and provided input to grant proposals.
- Reviewed documents for Sirolimus/Rapamycin drug trial.
- Participated in an assistive technology survey.
- Undertaken patient-driven studies of daily patient & carer priorities, diet and knee braces.
- Advocated to the Health Minister to support trial funding.

The relationship between researchers and the consumer panel is very positive and productive. All patients actively engaged on the panel find the experience inspiring, respectful and encouraging. international cooperation and participation in international projects. Our Association is actively engaged in the World Myositis Coalition (which represents the support groups of TMA, Myositis Canada, Cure IBM, CURE JDM, Myositis Australia). We also have links with GCOM, iMyos, and IMACS. We keep our members informed on Myositis research updates and communicate when studies with local trial sites recruit participants.

Recent international projects our members have participated in:
- Phase 1 clinical trial by the Perron Institute in Western Australia, as part of a global study testing a new IBM treatment drug, ABC008.
- Clinical trial and an extension study sponsored by Novartis on drug BYM338 (bimagrumab) for IBM.
- Phase 3 clinical trial Sirolimus for IBM: A global research team led by The University of Notre Dame Australia School of Medicine's Prof Merrilee Needham, in collaboration with Perron Institute, Fiona Stanley Hospital and Murdoch University.

Conclusion: The current average time to diagnosis is 5 years. Health professionals play a critical role in diagnosing this rare and progressive muscle disease. The earlier a patient is diagnosed, the better their potential health outcomes. It's why we ran a recent publicity campaign targeting health professionals. It reached approx.100,000 people with 5 detailed articles published in the magazines of various health professional associations.
Campaign tagline: Muscle weakness? It could be Myositis.

Pat-2

CZECH MYOSITIS WORKING GROUP

Olga Drápalová
Czech League against Reumatism, Czech Republic

Introduction. The poster entitled the Czech Myositis Working Group presents a relatively young patient organization, which was established in 2020 and operates under the umbrella of the Czech League against Rheumatism. Chair of the group: Olga Drápalová, olga.drapalova@revmaliga.cz, https://www.revmaliga.cz/klub/myozitida/
General aims of the patient group:
- Associates patients with IIM (idiopathic inflammatory myopathies),
- Raises awareness of IIM among public, patients, their families/informal carers and also professionals such as rheumatologists, pulmonologists, neurologists, physiotherapists, occupational therapists, etc.

Services, information:
The group provides members the opportunity to get together with others in their area and share concerns, friendship, and ideas. It also offers education, support and advocacy in the form of individual consultations, regular online meetings, online webinars, poster, brochures - Living with myositis, we train with myositis. The Czech myositis working group focuses on public recognition of the rare disease - myositis, encourage an atmosphere of communication and compassion among members.
Short-term goals:
- Support for patients with myositis and increasing the number of group members,
- Myositis awareness month events (myositis webinar, myositis television broadcast, campaign),
- Individual meetings of group members,
- Members' rehabilitation stay,
- Members training in the field of information technology,
- Participation in the EULAR Edgar Stene Price essay competition.

MAY IS MYOSITIS AWARENESS MONTH
May is considered the month of myositis awareness. The main goal of the organized activities is to help spread awareness and educate patients, the general public and the healthcare sector about myositis.
Cooperation with local organisations and professional society:
We cooperate with the Institute of Rheumatology in Prague, the Czech Rheumatological Society, local hospitals, patient organizations, health care professionals and pharmaceutical companies.
International cooperation and participation in international projects: The rich international cooperation that developed during the short operation of the group is evidenced by its involvement in many international projects. We work with myositis associations from different countries, various medical societies, universities and pharmaceutical companies: International Myositis Assessment and Clinical Studies Group, International Myositis Society, Pulmonary Fibrosis Foundation, Boehringer Ingelheim and Ashoka. We also take part in various surveys and campaigns:
- International project Consensus Evidence-based Guidelines on Exercise and Rehabilitation, the International Myositis Assessment and Clinical Studies (IMACS) Group, in particular the IMACS Special Rehabilitation and Exercise Interest Group.
- International project Patient Partners sharing perspectives of exercise and therapy, IMACS.
- International project Social Entrepreneurship for Innovations in Health, Boehringer Ingelheim Corporate Center GmbH, suported by Ashoka.
- Pulmonary fibrosis patient podcast, Rare disease day patient campaign, in collaboration with patient organisations in Eastern Europe, Boehringer Ingelheim International GmbH.
- International projet Patient Perspective in Living with Manifestations of Connective Tissue Diseases, Tulane University.
- EULAR Edgar Stene Prize essay competition - this year, the prize for the best essay in the national round of the competition travelled to the Myositis group and advanced to the international round.

Conclusion. It is quite common for patients with myositis to wait for a long time and visit many doctors - practitioners and specialists before they receive the correct diagnosis and appropriate treatment. During this waiting, there is often significant damage to patients' tissues, not to mention the worries and stress that patients and their family's experience. Therefore, I would like to end our poster with the idea, the fulfilment of which would contribute to the early diagnosis and treatment of a rare disease.
Motto: Early diagnosis and successful treatment for all patients with myositis.

Pat-3

GERMAN PATIENT SUPPORT GROUP FOR MYOSITIS "DIAGNOSEGRUPPE MYOSITIS" (DG MYOSITIS)

Silke Schlüter
Diagnosegruppe Myositis in der DGM, Bad Salzuflen, Germany

Introduction. The German patient support group for myositis "Diagnosegruppe Myositis" (DG Myositis) was established in 2012 as "Aktion Myositis" by prof. Dr. Jens Schmidt, Dr. Martin Taylor, and Sigrun Matthiesen and joined 2014 the German Society for Neuromuscular Diseases (Deutsche Gesellschaft für Muskelkranke – DGM). Since this merging of the groups, the new name Diagnosegruppe Myositis was coined. The DGM has over 9300 members. 344 members are registered with myositis. The activities of the group are planned and implemented by nine myositis-patients, two relatives and one myositis specialist as medical advisor. A close cooperation exists with the German myositis network MYOSITIS NETZ. Its website contains an area for patients, which is maintained by the DG Myositis.
Chair. Silke Schlüter
Contact email: silke.schlueter@dgm.org
website: www.dgm.org/diagnosegruppe/myositis
Our mission:
As German patient support group, we represent the interests of those affected and their relatives. We want to: a) promote and support research projects, b) establish a network of patients, relatives, physicians, scientists, and other caregivers, c) educate patients, physicians, and other care givers, d) help establish diagnostic criteria, e) improve access to information for patients and relatives, f) strengthen the exchange between those affected, g) help for those in fear of the disease burden, h) inform and educate the public about this disease and its burden, i) establish and support patient registries.
Our daily activities:
An important goal is to support patients with myositis and their relatives. We provide support over the phone or email. We offer a monthly online discussion group for myositis patients to connect with each other. An online myositis discussion group for relatives is scheduled every two months. We provide information about our activities via social media like Facebook and Instagram and via the DGM and MYOSITIS NETZ websites. We regularly send out our Myositis newsletter and publish myositis news in the "Muskelreport" (newspaper of the DGM).
Our special projects:
- Organize symposia & "information days" with topics for one specific disease
- Support research projects.
- Funding the Myositis Trainee Award "Myositis-Nachwuchs-Forschungspreis"
- Meetings with experts from various clinics.
- Sending press releases about myositis to various journals.
- Conduct a myositis charity run.
- Design and distribution of an explanatory video on myositis.
- Design and dissemination of myositis podcasts on topics related to myositis

Our activities with national and international myositis groups/organizations:
- Participate in national and international myositis meetings.
- Networking & collaboration with national and international myositis networks, myositis support groups and myositis patient groups.
- Associated with MYOSITIS NETZ, iMyoS, TMA.
- Contribution to the international project: Consensus Evidence-based Guidelines on Exercise & Rehabilitation, the International Myositis Assessment and Clinical Studies (IMACS) Group, in particular the IMACS Rehabilitation & Exercise Special Interest Group.

How do we reach our aims?
To be able to help patients and their relatives, the group members receive regular training. The training topics include various topics such as how to manage a conversation, research in myositis, medication in myositis etc. Our regular meetings offer opportunities to share experiences in coping with myositis. Many projects are facilitated through funding from health insurance companies and donations.
Conclusion. Myositis is a rare disease and diagnosis is often difficult and lengthy. We are committed to provide the best possible support to affected individuals and their families on the road to a diagnosis and in living with myositis, because **our slogan is:**
MYOSITIS – Ohne Muskeln GEHT es nicht! = MYOSITIS – Nothing GOES without muscles!

Pat-4

DUTCH MYOSITIS WORKING GROUP (DMWG)

Ingrid de Groot
Spierziekten Nederland (Dutch patient association for neuromuscular disease)

Introduction. *The poster of the Dutch Myositis Working Group (DMWG) aims to inform people about her goals, activities and ambitions. The group is run by seven patients, representing all types of myositis, supported by Spierziekten Nederland, the umbrella patient organization for neuromuscular disorders in The Netherlands and 4 myositis specialists as medical advisors.*
Chair: Ingrid de Groot. Contact email: myositis@spierziekten.nl
Goals and ambitions of the Dutch myositis working group:
- In collaboration with medical advisors to provide information about IIM (idiopathic inflammatory myopathies) or myositis to newly diagnosed patients and their families: IIM types, symptoms, diagnosis, (new) treatment options, prognosis, inform them about the myositis expertise centres etc.
- To connect and support people with all types of IIM: dermatomyositis (DM), polymyositis (PM), Anti Synthetase Syndrome (ASyS), immune mediated necrotizing myopathy (IMNM), juvenile dermatomyositis (JDM), overlap myositis.
- To raise awareness of myositis among the public, health care professionals and researchers, pharmaceutical companies?
- To collaborate with clinicians, researchers and funds on a national and international level with the aim to improve (clinical) care and research.
- To stimulate and participate in the development and conducting of clinical trials.
- To collaborate with myositis working groups and patient organisations abroad.
- To represent the patient perspective within in the Myositis Network Netherlands and (inter)national myositis study groups.
- Patient advocacy.

Activities and services:
- In person or online meetings aiming to offer moral support and an opportunity to share experiences, concerns etc. or just to socialize. Three times a year we organize separate meetings for people with IBM, for people with other IIM and for caregivers.
- Website updates on treatment, guidelines, (inter)national research, activities and actualities (e.g. Covid situation).
- Supply patients with brochures for GP/ family doctor, physiotherapist etc.
- Online (secured) platform for members.
- Annual patient conference with diagnosis specific scientific programs.
- Monthly newsletters: these are personalized which means they contain mainly news on the receivers type of IIM (e.g. IBM or ASyS) and information on general topics concerning all people with IIM or neuromuscular disorder.
- In person meetings and / or online webinars on general topics e.g. living with a chronic condition, work, pain, fatigue.
- Annual meetings with medical advisors: the working group pays a visit to all medical advisors in their respective hospitals.
- Representation at (inter)national conferences.
- Representation in projects such as guidelines development.
- Collaboration in (inter)national studies leading to enrolling Dutch patients, researchers and clinicians in multi-centre studies, (co-) authorships in publications and to presentations during conferences (Treat NMD, IMACS, MNN).
- To advise and recommend on research proposals from patient perspective.
- To advise decision makers on continuation of expert centres from patient perspective.

Collaborations:
- Myositis Network Netherlands: patient representation on the board.
- OMERACT (Outcome Measures in Rheumatology): Patient Research Partner of the Myositis Working Group.
- IMACS (International Myositis Assessment and Clinical Studies Group): steering committee member of Exercise & Rehabilitation Group, led by Helene Alexanderson, ass.prof PhD, RPT).
- ENMC (European Neuromuscular Centre): patient representation in myositis workshops.
- EULAR (European League against Rheumatism): member of PARE and Patient Research Partner.
- GCOM.
- ERN – NMD (European Reference Network for Neuromuscular Diseases): member of NMD working group led by em. prof. dr. Marianne de Visser.
- Patient organizations for people living with myositis .

"We are in this together"
Since myositis is a (very) rare disease, the 'myositis community' is a small one although we're happy to say that it is expanding quite rapidly. Through our intensive involvement in several national and international studies and research projects we now have close contacts with many myositis experts across the globe, which makes it easier to keep up with actualities and developments concerning research, treatment etc. and to disseminate this knowledge to our members. This helps us to inform, support and advocate for the Dutch people living with myositis and their families and at the same time it offers opportunities to give

something back: by sharing with the research community and clinicians our experiential knowledge of the consequences of myositis on everyday life. That way we can contribute to more meaningful research. We can only go forward if we do this together!

That is why we are very ambitious in our efforts to contribute to myositis research. Here we list our collaborative efforts:

- In 2019 the *Myositis Network Netherlands* of clinicians and researchers with expertise in IIM was established in which the DMWG is representing the patient perspective by a member on the board.
- In *OMERACT Myositis Working Group* a member of the DMWG is one of the two Patient Research Partners and as such an equal partner of this study aiming to define a set of core patient reported domains with regard to the quality of life and respective instruments for use in IIM. The involvement of the DMWG has led to the opportunity for Dutch patients to participate in Delphi surveys and to an opportunity for Dutch myositis clinics to collaborate in the longitudinal study that emerged from this.
- The *IMACS* network is an important part of our international network. One of our DMWG members is member of the Executive Committee of the Exercise & Rehabilitation Group and as such can facilitate for Dutch patients to become involved in the current study with the ultimate objective to develop recommendations for exercise in all types of IIM.
- Members of the DMWG participated in several *ENMC* workshops on IIM as patient representatives and will continue to do so in the future.
- Through a PARE membership in *EULAR* and membership of the study group of 'collaborative research' the DMWG hopes to raise awareness of myositis within the influential EULAR community and to speak up on behalf of the patients in Europe living with IIM.
- One of our members is member of the *GCOM* committee responsible for the patient program of GCOM and shares the ambitions of this GCOM committee to increase the involvement of patients in this very important IIM conference.
- One DMWG member joined the ERN- Neuromuscular Disease group and as such represents the people with IIM living throughout Europe.
- DMWG has ambitions to empower people living with IIM and to connect with them, crossing borders by doing so. We have close and amicable relationships with patient organisations in Australia, Czech Republic, Germany, Sweden, UK and USA.
- Empowering patients is one of our goals and we accomplished this for instance in Sweden. On invitation by prof. dr. Ingrid Lundberg our chair visited the Karolinska Institute, spent a week with their myositis team and in return was one of the speakers on the annual patient meeting and helped the Swedish patients establish their own myositis working group.

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WORKING GROUP FOR MYOSITIS WITHIN THE SWEDISH RHEUMATISM ASSOCIATION

Anneli Dihkan, Shagun Kumar
The Swedish Rheumatism Association, Stockholm, Sweden

The Swedish Rheumatism Association, our umbrella Organization:
In Sweden, there are approximately one million people with different rheumatic diseases, and about 1400 of them have a myositis diagnosis. In addition to several local associations, there are 3 nationwide diagnostic groups for systemic inflammatory diseases: Working group for systemic lupus erythematosus (SLE), Working group for Systemic Sclerosis and Working group for Myositis.
Goals and vision:
We form opinion and influence politicians and decision-makers at all levels in issues that are important to us, such as access to rapid care and opportunities for rehabilitation.
Knowledge and Education:
We educate:

- Representatives who can share knowledge based on their own experience and to provide support and help for people living with rheumatic disease.
- Volunteers for patient schools.
- Patient Research Partners since 2008.

Research and fundings: :

- We are the single largest private funder of Swedish rheumatology research.
- Patient Research Partners should become obvious members in research projects.

Working group for Myositis was established in 2020 and most of our activities have been on-line. The number of members is growing as we spread out the information. We will continue with our on-line events and together with our experts arrange our first patient conference in 2022.
We are a member of the Swedish Rare Disease Association and European Network ERN ReCONNET. We have now three Patient Research Partners with myositis and we will continue to participate in international research projects, such as IMACS, Rehabilitation & exercise SIG.
Our mission is to give support to myositis patients and their families, share knowledge of their disease, facilitate meeting with others with the same diagnosis for an exchange of experiences or just for fun.
Our goals are to:

- Inform through newsletters, patient meetings, website and webcasts.
- Arrange lectures by myositis experts.
- Arrange annual patient conference.
- Raise awareness for the disease in society and inform healthcare professionals within primary care units.
- Contribute to that all patients receives equally good care all over the country.
- Inform about research results, ongoing studies and update information on new treatments and drugs.
- Contribute to that all newly diagnosed patients have access to patient education and written information material about myositis..
- Contribute for opportunities for rehabilitation, such as training in warm water pools and access to rehabilitation facilities in warm climate.
- Collaborate with the Youth organization of the Swedish Rheumatism Association for Juvenile Dermatomyositis and provide support for parents, children and adolescents.
- Collaborate with the myositis organizations in other countries.

Our Webinars: The experts who have shared their knowledge on our webinars are: Ingrid Lundberg, Professor; Maryam Dastmalchi, MD, Rheumatologist; Helene Alexanderson, PhD, Associate professor, PT; Malin Regardt, PhD, OT; Balsam Hanna, Specialist Rheumatology; Dag Leonard, MD, Rheumatologist; Antonella Notarnicola, MD, Rheumatologist; Fabricio Espinosa, Rheumatologist, PhD candidate; Kristofer Andreasson, PT, PhD candidate; Jonatan Sjögren, OT; Lars Nordelv, CBT Therapist, also a patient; Helena Andersson, MD, Rheumatologist; Hanna Brauner, PhD, Dermatologist.
Among the topics our webinars have covered so far are: Diagnostic criteria of myositis, new research findings, existing treatments and ongoing studies, Physical activity and its effects on depression, safety of high-intensity interval training, Occupational therapy, Patient Reported Outcomes, Myositis Associated Antibodies and how to deal with anxiety, cardiac involvement and osteoporosis in myositis, clinical findings and treatments for Antisynthetase syndrome skin involvement in Dermatomyositis, Covid-19 and vaccination.

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THE MYOSITIS ASSOCIATION

Chrissy M. Thornton
The Myositis Association, Columbia, MD, USA

Introduction. The poster presents an almost 30 year old international patient advocacy organization, established in 1993 and operated independently in the United States of America
Executive Director: Chrissy M. Thornton, chrissy@myositis.org,
https://www.myositis.org/the-myositis-association-announces-chrissy-thornton-as-executive-director/
General aims of the patient group: To improve the lives of persons affected by myositis, fund innovative research and increase myositis awareness and advocacy
Services, information: The aim of TMA's programs and services is to provide information, support, advocacy, and research for those concerned about myositis.
Education:
The Myositis Association's *International Annual Patient Conference* and brings together myositis patients with health professionals who specialize in myositis and related fields. This event features a panel of medical experts and sessions on treatments, promising research, coping strategies, exercise techniques, and more.
The Myositis Awareness Month Virtual Summit (May) creates broader community awareness, direct our members to TMA offerings and resources, educate around patient and disease advocacy, share clinical insights, and build a stronger and more connected myositis community.
TMA Publications (both in print and electronic) present information on diagnosis, treatments, research news, and other relevant topics that help patients and caregivers learn what they need to address their individual health care concerns.
Research:
The Myositis Association recognizes that the myositis patient's best hope for a cure lies in research. TMA offers a research fellowship program to attract and encourage post-doctoral trainees (PhD and MD) and young physicians to pursue

careers in the field of myositis research. TMA also funds research grants to initiate innovative pilot projects that will support larger funding opportunities.
Since 2002, The Myositis Association has funded research (over $7.5 million) designed to understand the underlying causes and natural progression of myositis, develop better treatments and more effective therapies, and ultimately to create a cure.
Support:
TMA's **Support Groups** offer members the chance to share their feelings and discuss their concerns with people in similar situations. These groups (offered in person and virtually) encourage an atmosphere of communication and compassion.
TMA supports **Affinity Group** meeting circles with outreach efforts targeted toward supporting and extending our organization's reach into new communities.The term affinity group is used as a bringing together of people who have commonality. Affinity groups are for individuals who identify as members of the group and can speak to the experience of being a part of the group from an "I" perspective.
Advocacy:
Public recognition of myositis, increased research funding, greater access to care, and better coverage and reimbursement for treatments; TMA gives our community tools and guidance to make a difference.
Core areas of focus:
- Increasing targeted clinical studies and research projects.
- Supporting the development of additional approved treatment protocols .
- Increasing disease management options for patients.
- Improving access to care.
- Increasing Healthcare Provider education.
- Amplifying patient voices.
- Addressing health equity.
- Creating increased community awareness.
- Addressing quality of life issues for patients.

The Myositis Association's Medical Advisory Board (MAB) is now made up of 22 of the world's most respected myositis researchers, scientists, and clinicians. These medical professionals are nominated and elected to serve on this distinguished board by their medical colleagues, because they are committed to making life better for those who live with myositis diseases.
Members of the MAB donate their time to TMA and serve by, offering monthly Ask The Doc webinar sessions, reviewing research funding proposals and drafts of the newly revised Myositis 101: Your Guide to Understanding Myositis. MAB members also help raise awareness of this rare disease among their medical colleagues by presenting lectures to medical students and grand rounds talks with medical trainees such as residents and research fellows.
These committed professionals also serve as the foundation of TMA's Annual Patient Conference, offering a wide variety of informative talks and answering questions from attendees about living with myositis diseases.
FUN FIT FLEX is The Myositis Association's new national signature fundraising campaign. Piloted in four US cities in 2021, and hosted virtually internationally, this community awareness event - a non-competitive fun walk, and a festival of fitness demonstrations and activities, nutrition and wellness components, and family fun, is dedicated to improving the lives of people affected by myositis. Funds raised through Fun Fit Flex will help support patient programs, enhance professional education efforts, and propel critical research for cures.
In 2022, we will launch this interactive community awareness event in six local communities across the country where an estimated more than 40,000 dedicated participants will work to raise funds to continue our critical work. Participate as an individual or gather your friends, family, and co-workers to form a team – build awareness, fundraise, and come out and enjoy!
Patient & family advisory council (PFAC)
The Myositis Association believes the voice of our patients and family members can be a powerful tool in improving and focusing the work of our organization.
PFAC objectives:
- To ensure patients and their families are at the center of everything we do at TMA.
- To provide patients and family members with the platform to share their stories and to help improve care for all patients.

World myositis coalition:
Knowing the immense responsibility myositis patient advocacy organizations carry in ensuring the lives of myositis patients are supported with education, advocacy, resources, and our work toward a cure, The Myositis Association launched the **World Myositis Coalition**. The objective is to promote partnership and collaborative work with other myositis focused patient advocacy organizations. The collective of organizations represents individuals living with myositis globally and strives to identify areas of collaborative opportunity for our organizations to give a voice to the patients, caregivers, care partners, and loved ones within our rare disease community.
Conclusion. The mission of The Myositis Association is to improve the lives of persons affected by myositis, fund innovative research, and increase myositis awareness and advocacy. Our programs and services provide much needed information, support, advocacy, and research for the myositis community.
Our dedicated staff keeps our operations, resources, and services alive and well for our members. They answer more than 25,000 emails, phone calls and letters each year, and more than 20,000 newsletters are mailed annually.
A Board of Directors oversees the work of the organization. Our current board of directors is made up of both myositis patients, care partners, and professionals. Our Medical Advisory Board, made up of myositis experts and doctors, is influential in compiling, presenting and reviewing TMA resources for members.
Motto: …the world's voice on myositis.

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MYOSITIS SUPPORT AND UNDERSTANDING (MSU)

Lynn Wilson, Jerry Williams, Manuel Lubinus
MSU-USA, Lincoln, DE, USA

Introduction. Myositis Support and Understanding Association (MSU) is a patient-centered, all-volunteer, USA-based nonprofit organization Empowering the Myositis Community through education, support, awareness, advocacy, access to research, and need-based financial assistance.
Founded in 2015 by Jerry Williams who fought for over 3 years for a true diagnosis (polymyositis but has since changed to dermatomyositis), MSU was created after identifying an unmet need for patient-focused programs and services and support for those living with Inflammatory myopathies.
MSU Mission. Our mission is to improve the lives of and empower those fighting myositis through education, support, awareness, advocacy, and access to research.
Myositis Community Resources
We are a patient-centered organization that provides:
- Independent, interactive online platforms that educate and connect patients, caregivers, and family members with each other and with healthcare professionals wherever they are.
- Educational resources for patients, families, and the healthcare community.
- Need-based financial support for medical-related expenses. (food & rent, home remodeling, medical visits, clinical trials etc.)
- Advocacy, bringing the Patient-voice to all levels of policymakers, FDA, industry, and other medical services.
- Innovations in research and treatments through clinical trial matching, FDA listening sessions, industry, and Academic partnering.

Research at MSU:
Our Research Philosophy: Patients are the experts in their disease and their data and experiences drive research. We keep the patient front and center in every collaboration with industry, corporate partners, academia, and other organizations. We will be intentional in our partnerships and research funding based on how impact the overall patient population.
Current Research Approach:
- Prioritizing patient-centered research initiatives that will benefit the quality of life of the myositis patient, among those:
  - Crowdsourcing of patients' needs/wants by myositis type to capture the voice of the patient.
  - The burden of care research that addresses gaps in myositis care management.
- Providing research grants through MSU or affiliate partners for studies that impact near term functional diagnostic and treatment improvements.
  - Novel clinical initiatives to prolong function in myositis patients.
  - International MSA standardization for diagnosis and treatment of myositis.
- Partnering with academia, industry, and government agencies to understand disease evolution and subtype response to advance research in drug treatment and improved clinical trial design.

Conclusion. MSU's achievements are driven by a commitment to diversity and inclusion of all patients with myositis. All of these activities will help MSU to further fulfil its vision which is to aim to "create a world where patients, caregivers, and providers have better knowledge, support, and understanding of myositis." We work to build programs and relationships to further this vision, making our work more inclusive and equitable for all myositis patients and care partners.

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