5th Global Conference on Myositis (GCOM)

March 13-16, 2024
Pittsburgh (PA), USA

Abstracts

Pathogenesis of Inflammatory Myopathies: Transcriptomic Analyses

O-1

CHARACTERIZATION OF A MOUSE MODEL FOR JO-1, PL-7 AND PL-12 ASSOCIATED ANTI-SYNTHETASE SYNDROME

Derya Cengiz[1], Corinna Preusse[2], Stefanie Lichtenberg[1], Kathrin Koch-Hoelsken[1], Vincent G. Umathum[3,4], Alexander Herrmann[1], Anne Schaenzer[3], Sven G. Meuth[1], Werner Stenzel[2], Tobias Ruck[1]
[1]Department of Neurology, Medical Faculty, Heinrich Heine University Duesseldorf, 40225 Duesseldorf, Germany; [2]Department of Neuropathology, Charité-University Medicine Berlin, Bonhoefferweg 3, 10117, Berlin, Germany; [3]Institute of Neuropathology, Justus Liebig University Giessen, 35392, Giessen, Germany; [4]Institute of Pathology and Molecular Pathology, German Armed Force Hospital Ulm, 89081 Ulm, Germany

Background. Anti-synthetase syndrome (ASyS) is an autoimmune condition, characterized by the presence of autoantibodies directed against an aminoacyl-tRNA synthetase (anti-ARS). Patients present clinical symptoms such as myositis, interstitial lung disease, Raynaud's phenomenon, and arthritis. Anti-Jo-1, anti-PL-7 and anti-PL-12 are the most frequent anti-ARS. However, their role in ASyS pathogenesis remains incompletely understood. Therefore, robust animal models are essential to gain a detailed insight into the underlying pathophysiology. Aiming to characterize these pathophysiological features, we established and studied a mouse model for Jo-1, PL-7 and PL-12 associated ASyS. **Methods.** ASyS was induced in NOD.Idd3/5 mice by injection of 200 μg Jo-1, PL-7 or PL-12 recombinant protein emulsified in Complete Freund's Adjuvant (CFA) in combination with OX86. Controls received CFA and Phosphate Buffered Saline only. Muscle strength was assessed by rotarod tests and the effects on the peripheral immune system were investigated by flow cytometry in spleen and lymph nodes. Morphological characteristics of skeletal muscle and lung tissue of immunized mice and the tissue infiltrating immune cells were validated using histology and immunohistochemistry. **Results.** Immunization of mice led to clinical symptoms including muscle weakness and demonstrated variations in the immune cell response between the ARS subtypes. Histological analysis of skeletal muscle tissues showed infiltration by immune cells in the epimysium, spreading into the adjacent perifascicular area with progressing disease. Analysis of lung specimens by immunohistological staining demonstrated peribronchial accentuated accumulation of lymphocyte aggregates. **Conclusion.** We present a mouse model, which recapitulates features of the human phenotype of ASyS, to study the molecular pathogenesis and provide new insights into the pathomechanisms.

O-2

TISSUE INFLAMMATION DRIVES SEVERE MITOCHONDRIAL DYSFUNCTION IN A MOUSE MODEL OF IFNγ-DEPENDENT MYOSITIS

Olivier Boyer[1,2]
[1]Inserm U1234 Research Laboratory, Pathophysiology, Autoimmunity and Immunotherapy, Faculty of Health - University of Rouen Normandy; [2]Department of Immunology and Biotherapies Rouen University Hospital, Normandy, France

Background. Inflammatory myopathies are autoimmune muscle disorders with unmet medical needs. ICOS pathway invalidation in NOD mice has resulted in a switch of autoimmunity from diabetes towards myositis. Our muscle proteome and transcriptome analyses have suggested that mitochondrial defects accompany inflammation in muscle of Icos$^{-/-}$ NOD mice. To establish the link between inflammation, oxidative stress and mitochondrial dysfunction in myositis and evaluate anti-inflammatory and antioxidant treatments.
Methods. Muscle spatial transcriptome analysis (Nanostring's GeoMx) was performed after segmentation with desmin and CD45. Mitochondrial function was evaluated by COX, SDH and NADH-TR histoenzymology and ex vivoassay of oxidative phosphorylation. Mitochondrial morphology was visualized by electron microscopy. Reactive oxygen species (ROS) were measured by electron paramagnetic resonance. N-acetylcysteine or IFNγ blocking antibodies were administered to Icos$^{-/-}$ NOD mice. In humans, transcriptome was performed on dermatomyositis muscle and IFN-treated myotubes. **Results.** Icos$^{-/-}$ NOD mice exhibited reduced muscle strength and muscle histopathological features including macrophage and IFNγ-secreting CD4 T cell infiltration. Elevated ROS indicated muscle oxidative stress. Spatial transcriptomics revealed under-expression of genes coding for the skeletal muscle contraction machinery. Similarly, genes expression of key mitochondrial metabolic processes, mitochondrial dynamics and structure stability was strongly reduced. Decrease was exacerbated in myofibers directly adjacent to large immune clusters. Histoenzymology, *ex vivo* oxidative phosphorylation assessment and electron microscopy confirmed severe mitochondrial defects in Icos$^{-/-}$ NOD myofibers. Both n-acetyl cysteine and anti-IFNγ therapies significantly ameliorated mitochondrial alterations, oxidative stress and clinical signs of myositis. Consistently, downregulation of mitochondrial gene signatures was observed in muscle from patients with dermatomyositis and IFN-treated normal myotubes. **Conclusion.** Our data revealed a link between tissue IFNγ-mediated inflammation and mitochondrial defects that can be attenuated by anti-inflammatory or antioxidant therapy, shedding new light on myositis pathogenesis and suggesting possible new therapeutic targets.

Genetic/Environmental

O-3

INCIDENT CASE OF MYOSITIS DURING POST-COVID-19 PERIOD: AN MULTICENTRIC ECOLOGICAL STUDY ON IMMUNOBIOLOGICAL AND MEDICO-ADMINISTRATIVE DATABASES

Dylan Vellas[1,3,19], Sandrine Pinto[2], Antoine Rozes[3], Yann De Rycke[3], Sylvain Dubucquoi[4], Cécile Bordes[5], Thierry Vincent[6], Nicole Fabien[7], Frédéric Coutant[8], Daniela Lakomy[9], Benoit Nespola[10], Nathalie Bardin[11], Fabienne Jouen[12], Pascale Ghillani[13], Chantal Dumestre-Perard[14], Pascale Nicaise[15], Pascale Chrétien[16], Claire Goulvestre[17], Anne-Emmanuelle Berger[18], Olivier Benveniste[19], Florence Tubach[*3], Yves Allenbach[*19]
*contributed equally.
[1]Department of Internal Medicine, University Hospital, Saint-Etienne, France; [2]Institut Pierre Louis d'epidemiologie, Sorbonne University, INSERM UMR-S 1136, Paris, France; [3]Département Biostatistique Santé Publique et Information Médicale, Centre de Pharmacoépidémiologie (Cephepi), CIC-1901, Sorbonne Université, Faculté de médecine Sorbonne Université, AP-HP, Hôpital Pitié-Salpêtrière, Paris, France; [4]Inserm, U1286-INFINITE: Institute for Translational Research in Inflammation, CHU de Lille, université de Lille, Lille, France; [5]Immunology Laboratory Department, Bordeaux University Hospital, France; [6]Immunology Laboratory, Department of Immunology, Saint-Eloi Hospital, CHRU Montpellier, France; [7]Department of immunology University claude bernard Lyon; [8]Immunogenomics and Inflammation Research Team, University of Lyon, Edouard Herriot Hospital, Lyon, France; Immunology Department, Lyon-Sud Hospital, Hospices Civils de Lyon, Pierre-Bénite, France; [9]Biochemistry Laboratory Department ; Dijon University Hospital, France; [10]Immunology Laboratory Department, Strasbourg University Hospital, France; [11]Biogénopôle, CHU La Timone, Assistance Publique-Hôpitaux de Marseille (AP-HM), Marseille, France; [12]Normandie Université, INSERM U1234, FOCIS Center of Excellence PAn'THER, Rouen, France; [13]Assistance Publique-Hôpitaux de Paris (AP-HP), Hôpital Pitié-Salpêtrière, Immunology Laboratory Department, Paris, France; [14]Immunology Laboratory Department, Pôle de Biologie, CHU Grenoble Alpes; [15]Department of Immunology, Bichat Hospital, Paris, France; [16]Immunology Laboratory Department, Hopital Bicetre, Le Kremlin-Bicetre, France; [17]Department of Immunology, Hôpital Cochin, APHP Centre, Paris, France; [18]Immunology Lab, University Hospital, Saint-Etienne, France; [19]Department of Internal Medicine, Sorbonne University, AP-HP, INSERM UMRS 974, Pitié-Salpêtrière Hospital, Paris, France

Background. Inflammatory idiopathic myositis (IIMs) represent severe, rare, and heterogeneous diseases. Beside muscular damages, pulmonary involvement is frequent (40%). Type 1 and 2 interferon (IFN) pathways intervene within IIM pathophysiology, notably during dermatomyositis. Genetic determinants partially explain IIM occurrence. Environmental factors seem to have an important role but remain poorly studied. The impact of respiratory infections is discussed. Indeed, a seasonality has been proven for incident cases of anti-MDA5 dermatomyositis. Moreover, there are similarities between immunological response during viral infections and myositis. The 2020 SARS-CoV-2 outbreak causing the COVID-19 pandemic enabled the study of the impact of a viral respiratory epidemic on the evolution of new IIM cases. **Methods.** An ecological study by time series was undertaken within two complementary databases: the National Health Data System (Système National des Données de Santé - SNDS) and a biological database

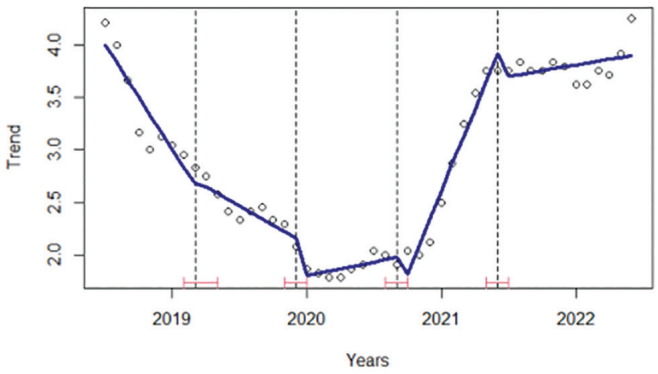


Fig. 1. Breakpoint identification in positive anti-MDA5 time series

including detection test results of Myositis-specific antibodies (MSAs). SNDS is a national medico-administrative database comprised of more than 61 million people. Incident IIM and chondrocalcinosis control cases were defined by ICD-10 codes of hospital stays, from 01/01/2012 to 06/30/2022. Immunological laboratories shared MSAs detection test results from 01/01/2018 to 12/31/2022. In case of iterative dosages, only the first one was considered. A time series was conceived for IIM incident cases and positive immunological tests. Each time series was decomposed within trend, seasonality, and noise. Breakpoint dates with their 95% confidence intervals were identified by a dedicated algorithm. **Results.** SNDS included 11,705 incident cases of IIM with major monthly variations (min: 57 cases/month – max: 126 cases/month). Patients were mostly females (59%) and 41% were aged between 60 and 80 years old. Nine breakpoints were identified corresponding to 3 peaks. Two were identified in 01/2014 and 08/2016, happening during the following 18 months of two main flu epidemics. An increase of monthly incident cases during the COVID-19 pandemic was identified for men only during the period of 10/2020. Control cases' analysis did not identify post-COVID-19 peaks but highlighted variations of health system use. During our study period, a total of 417,082 MSA dosages were analyzed in 14 centers with a 0.58% positivity. A progressive increase of positive MSA dosages reached a peak in 05/2021. This result was carried by dermatomyositis-related MSAs (maximum in 06/2021) anti-MDA5, anti-TIF1 gamma, and anti-SAE1.
Conclusion. This ecological study cannot define causality. Analysis of two complementary databases shows convergent results suggesting an impact of respiratory viral infections on dermatomyositis triggering.

O-4

TRANSCRIPTOMIC PROFILES IN MUSCLE BIOPSIES FROM SYSTEMIC SCLEROSIS PATIENTS WITH DIFFERENT AUTOANTIBODIES

Maria Casal-Dominguez[1,2], Jose Milisenda[1,3,4], Iago Pinal-Fernandez[1,2], Katherine Pak[1], Sandra Munoz-Braceras[1], Jiram Torres-Ruiz[1], Stefania Del Orso[1], Faiza Naz[1], Gustavo Gutierrez-Cruz[1], Shamima Islam[1], Yaiza Duque-Jaimez[3], Ana Matas-Garcia[3,4,5], Francesc J. Garcia-Garcia[3,4,5], Mariona Guitart-Mampel[3,4,5], Gloria Garrabou[3,4,5], Ernesto Trallero-Araguas[6,7], Brian Walitt[8], Lisa Christopher-Stine[2,9], Thomas E. Lloyd[2], Alfredo Guillen-del-Castillo[6], Carmen Pilar Simean-Aznar[6], Josep Maria Grau[3,4,5], Albert Selva-O'Callaghan[6,7], Andrew L. Mammen[1,2,9]
[1]Muscle Disease Unit, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD, USA; [2]Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, USA: [3]Muscle Research Unit, Internal Medicine Service, Hospital Clinic, Barcelona, Spain; [4]Barcelona University, Barcelona, Spain, [5]CIBERER, Barcelona, Spain; [6]Systemic Autoimmune Disease Unit, Vall d'Hebron Institute of Research, Barcelona, Spain; [7]Autonomous University of Barcelona, Barcelona, Spain; [8]National Institute of Nursing Research, National Institutes of Health, Bethesda, MD, USA; [9]Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Background. The inflammatory myopathies (IM) include dermatomyositis (DM), antisynthetase syndrome (AS), immune-mediated necrotizing myopathy (IMNM), inclusion body myositis (IBM), and overlap myositis (OM), in which IM exists in the context of another rheumatologic disease, such as systemic sclerosis (SSc). The objective of this study was to define the transcriptomic profiles of muscle tissue from patients with OM-SSc and to compare these with the transcriptomic profiles of muscle tissue from patients with other types of IM as well as healthy volunteers. **Methods.** Bulk RNA sequencing was performed on 201 muscle biopsies obtained from (a) OM-SSc patients with defined SSc autoantibodies recognizing PMScl (n=19), Scl70 (n=11), or centromeric autoantigens(n=6), (b) patients with DM, AS, IMNM, IBM (total n=132), and (c) 33 healthy volunteers. **Results.** In muscle biopsies from patients with OM-SSc, there was upregulation of genes associated with type I interferon (IFN) signaling (ISG15, MX1), type II IFN signaling (GBP2, PSMB8, IFI30), muscle regeneration (NCAM1, MYH3, MYH8, MYOD, MYOG, PAX7), immunoglobulin production (IGH1, IGH2, IGH3, IGHM, IGHA2), and specific types of immune cells (CD3E, CD4, CD8B, CD14, CD68, CD19, and CD20). The upregulation of these genes was more pronounced in biopsies from patients with OM-SSc who had anti-PMScl autoantibodies compared to those with other SSc autoantibodies. Specifically, the upregulation of type I IFN-associated genes in biopsies from patients with anti-PmScl was intermediate, resembling that observed in biopsies from patients with AS, while type II IFN-associated upregulation was high and comparable in biopsies from patients with AS and IBM. Conversely, structural muscle genes such as MYH1, MYH2, ACTA, and TTN, were downregulated in patients with all types of autoantibody-defined OM-SSc. **Conclusion.** Muscle tissue from patients with OM-SSc exhibit significant upregulation of interferon type I and II signaling, immunoglobulin production, muscle regeneration-related genes, and immune cell markers. Notably, these gene expression changes are more pronounced in muscles from patients with SSc who had anti-PMScl autoantibodies compared to those with anti-Scl70 and anti-centromere autoantibodies. These findings contribute to our understanding of the molecular mechanisms underlying SSc and provide insights into potential therapeutic targets.

Inclusion Body Myositis

O-5

IN VITRO PHENOTYPES OF MYOBLASTS OBTAINED FROM PATIENTS WITH INCLUSION BODY MYOSITIS

Andrew B. Wilson[1], Carlo Serra[1,2], Chiseko Ikenaga[1], Thomas E. Lloyd[1,2]
[1]Johns Hopkins University School of Medicine, Baltimore MD, USA; [2]Baylor College of Medicine, Houston TX, USA

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 to better understand IBM pathogenesis. **Methods.** Muscle biopsy samples were obtained from patients who were diagnosed with IBM or other diseases, 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. RNA was isolated from sorted myoblasts for bulk RNA sequencing. In parallel, dissociated muscle cells were allowed to proliferate before myoblast isolation via flow cytometry and then differentiated into myotubes. Myotubes were stained for TDP-43, gH2AX, $p16^{INK4A}$, and myosin heavy chain to investigate myotube maturation and degenerative phenotypes (n=4 per group). Myotubes were also stained for beta-galactosidase to investigate senescence. Nuclei were isolated from these myotubes for 10X Genomics transcriptomic and epigenetic profiling. **Results.** IBM myoblasts proliferate at a slower rate and generated fewer differentiated myotubes compared to non-IBM muscle. IBM myotubes show increased beta-galactosidase staining, suggesting senescence. IBM myotubes also show evidence of cryptic exon incorporation and loss of nuclear TDP-43. RNA sequencing data from both bulk and 10X sequencing show upregulated degenerative and immunological pathways in IBM myoblasts and myotubes compared with controls.

Conclusion. 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. In the absences of immune cells, IBM myotubes show signs of degenerative pathology in vitro including the loss of nuclear TDP-43 and cryptic exon incorporation. This data suggests that cell-autonomous epigenetic alterations in myofiber progenitor cells may drive IBM pathology.

References

1. BRITSON KA, LING JP, BRAUNSTEIN KE *et al*.: Loss of TDP-43 function and rimmed vacuoles persist after T cell depletion in a xenograft model of sporadic inclusion body myositis. *Sci Transl Med* 2022; 14(628): eabi9196. https://doi.org/10.1126/scitranslmed.abi9196.
2. MOROSETTI R, BROCCOLINI A, SANCRICCA C *et al*.: Increased aging in primary muscle cultures of sporadic inclusion-body myositis. *Neurobiol Aging* 2010; 31(7): 1205-14.

O-6

EFFICACY OF RAPAMYCIN AND SODIUM PHENYLBUTYRATE IN A XENOGRAFT MODEL OF INCLUSION BODY MYOSITIS

Chiseko Ikenaga[1], Andrew Wilson[1], Nicole Reed[1], Thomas E. Lloyd[1,2,3]
[1]Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA; [2]Solomon H. Snyder Department of Neuroscience, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA; [3]Department of Neurology, Baylor College of Medicine, Houston, Texas, USA

Background. Inclusion body myositis (IBM) is an idiopathic inflammatory myopathy that affects adults over 50 years of age without effective treatment. Rapamycin is an immunosuppressant for organ transplant recipients and may diminish protein aggregation by inducing autophagy. In a single-center pilot study of patients with IBM, rapamycin improved secondary endpoints including a 6-minute walking distance though it did not show efficacy in its primary outcome measure of knee extension strength (Benveniste *et al*., Lancet Rheumatol 2020). Sodium phenylbutyrate is another drug that may show efficacy in the treatment of patients with IBM by preventing misfolded protein aggregation as a chemical chaperone. We aimed to determine the efficacy of rapamycin and sodium phenylbutyrate on the muscle of patients with IBM using a xenograft model. **Methods.** We enrolled 94 mice with xenografts from the muscle of 8 IBM patients and 5 controls and fed them with either encapsulated rapamycin or placebo for 3 months or 6 months. The concentration of rapamycin in the whole blood was determined using mass spectrometry at the Johns Hopkins Medical Laboratory. We also enrolled 20 mice with 30 xenografts from the muscle of 1 IBM patient and 1 control and let them drink either sodium phenylbutyrate containing water or just water for 3 months or 6 months. One xenograft was implanted into the right leg of a mouse except for a control in the sodium phenylbutyrate trial whose xenografts were transplanted in both legs of a mouse. Harvested xenografts were analyzed by both histochemistry and immunohistochemistry for p62, TDP-43, p16, MHC-1, CD3, CD4, CD8, CD20, CD68, and CD138. **Results.** Seventy-six mice completed the treatment with either encapsulated rapamycin or placebo. The concentration of rapamycin in whole blood was 39.5±11.2 ng/ml with a 3-month treatment of rapamycin and that with a 6-month treatment was 43.6±8.8 ng/ml. Control xenografts did not show any rimmed vacuoles or abnormal protein aggregates while these pathologies were observed in xenografts derived from patients with IBM. The fiber fraction of xenografts that were treated with placebo for 6 months was correlated with that of an original muscle biopsy ($R^2 = 0.66$). The 3-month rapamycin treatment decreased fibers with rimmed vacuoles (p=0.04) while rapamycin did not decrease inflammatory infiltrates and fibrosis in the xenografts from patients with IBM. All 20 mice completed the treatment with either sodium phenylbutyrate containing water or just water, but the sodium phenylbutyrate treatment did not improve the pathology of xenografts from IBM patients. **Conclusion.** Three months of rapamycin treatment was effective in decreasing rimmed vacuoles of xenografts from IBM patients. Xenografts recapitulate the pathology of the original muscle biopsy well, and they can be utilized for personalized medicine in IBM.

Advances in Therapeutic Development

O-7

CLUSTERING ANALYSIS OF IMMUNE CELL SUBTYPES AND CLINICAL PHENOTYPES IN IDIOPATHIC INFLAMMATORY MYOPATHY

Xiaoyan Xing, Wanxing Mo, Yuhui Li, Jing He
Department of Rheumatology and Immunology, Peking University People's Hospital, Beijing, China

Background. Immune cell profiling plays a pivotal role in the pathogenesis of idiopathic inflammatory myopathy (IIM). Characterizing immune cell subtypes, such as $CD4^+$ T cells, $CD8^+$ T cells, $CD19^+$ B cells, natural killer (NK) cells, is essential for understanding the immunopathogenesis and treatment of these disorders. Immune cells contribute to aberrant immune responses, impacting disease progression. This nuanced understanding forms the basis for investigating targeted interventions to modulate specific immune cell populations and improve outcomes in patients with IIM. **Methods.** Data from 223 patients in a retrospective cohort of IIM at Peking University People's Hospital from 2012 to 2023 were analyzed. Cluster heatmap and t-distributed Stochastic Neighborhood Embedding (t-SNE) were employed using patient-reported outcomes, encompassing total lymphocyte count, $CD3^+$ T cells, $CD4^+$ T cells, $CD8^+$ T cells, $CD19^+$ B cells, and NK cells. Elbow method was used to select the optimal number of clusters and described each cluster according to clinical and laboratory differences (mean and proportions). The therapeutic effects of tofacitinib and low-dose Interleukin-2 were evaluated in conjunction with this analysis. **Results.** Based on immune cell subpopulations, these patients are categorized into five groups. Group 1 shows elevated proportions of $CD4^+$ T cells and Naïve Th cells, with a higher incidence of V-sign, subcutaneous calcification, and myocardial involvement. Group 2 patients exhibit a lower proportion of $CD3^+$ T cells, a higher $CD19^+$ B cell ratio, and an increased occurrence of Gottron's sign, periungual erythema, and rapidly progressive interstitial lung disease (RP-ILD) compared to other groups. Group 3 patients have a higher proportion of CLA+ Treg cells, often presenting with mechanic's hands, arthritis, and ILD. Group 4 patients have higher proportions of $CD8^+$ T cells and TNF-α^+ $CD4^+$ T cells, with a higher prevalence of immune-mediated necrotizing myopathy. Group 5 patients have higher proportions of NK cells, and overall, exhibit milder symptoms. Regarding treatment, groups 1, 3, and 4 show positive responses to tofacitinib, while some patients in groups 2 and 5 demonstrate poor response to tofacitinib treatment. Moreover, some patients in groups 1 and 3 exhibit a poor response to low-dose interleukin-2, while patients in groups 2, 4, and 5 respond well to low-dose interleukin-2 treatment. **Conclusion.** Immune cell subpopulation clustering analysis in IIM patients reveals distinctive features associated with diverse clinical manifestations. Each patient group exhibits varying responses to different treatment strategies, providing valuable insights for guiding the management and prognosis of IIM.

O-8

THROMBOEMBOLIC RISK ASSOCIATED WITH INTRAVENOUS IMMUNE GLOBULIN USE IN PATIENTS WITH IDIOPATHIC INFLAMMATORY MYOPATHY: A NATIONAL DATABASE STUDY

Rohan Mehta[1], Michael Putman[1], Didem Saygin[2]
[1]Medical College of Wisconsin, Milwaukee, Wisconsin, USA; [2]Department of Medicine, Division of Rheumatology and Clinical Immunology, University of Pittsburgh, Pittsburgh, PA, USA

Background. Intravenous immune globulin (IVIG) recently received regulatory approval for the treatment of dermatomyositis, one of the idiopathic inflammatory myopathies (IIM). The pivotal randomized trial informing approval observed 6 thrombotic adverse events among patients exposed to IVIG, which included both venous thromboembolism (VTE) and arterial thromboembolism (ATE). The objective of this study is to determine the real-world incidence of ATE and VTE among adults who received IVIG for IIM and other indications. **Methods.** Patients from TriNetX, a large federated health records data-

base, were included if they received ≥1 IVIG administrations. ATE and VTE were identified using ICD-9-CM/ICD-10-CM codes and patients were characterized as IIM if they received two codes separated by 30 days within 3 years of the first IVIG administration. Patients could contribute multiple IVIG exposure intervals, which could be 1 to 7 days long, depending on how many consecutive IVIG administrations a patient received. Risk periods were defined for each patient for each IVIG interval as follows: ATE (the first day of IVIG exposure to two days after the last day of IVIG exposure), VTE (the first day of IVIG exposure to thirteen days after the last day of IVIG exposure), and control (14 days after the last day of the IVIG exposure to 31 days after the first day of IVIG exposure). Unadjusted incident rate ratios (IRR) were calculated. **Results.** This project included 71,245 IVIg administrations to 10,058 patients, 513 of whom (5.1%) were categorized as IIM. The majority of IIM patients were female (70.8%) and white (59.1%). Among non-myositis patients there were 94 VTE and 65 ATE (Table I). During exposure and control periods, the incidence of VTE among non-myositis IVIG users was 39.4 and 23.4 per 1,000 person years, respectively (unadjusted IRR 1.68, 95% CI 1.10-2.56) and the incidence of ATE was 97.9 and 30.3 per 1,000 person years, respectively (unadjusted IRR 3.23, 95% CI 1.92-5.43). Among myositis patients there were 6 cases of VTE and 3 cases of ATE. During exposure and control periods, the incidence of VTE among myositis IVIG users was 6.5 and 38.2 per 1,000 person-years, respectively (unadjusted IRR 0.17, CI 0.02-1.46) and the incidence of ATE was 0.0 and 22.9 per 1,000 person-years, respectively (unadjusted IRR unable to be calculated given no events in exposed group). Prespecified adjusted analysis could not be conducted given a low rate of events. **Conclusion.** In this study, the risk of ATE and VTE among patients exposed to IVIG was low. For patients without myositis, the rate of ATE and VTE was elevated after exposure to IVIG. For patients with myositis, the incidence of ATE and VTE was too low for meaningful comparisons to be made. Ongoing surveillance studies using randomized designs should be conducted to corroborate these findings.

Table I. Incidence and incident rate ratios for venous and arterial thromboembolism among IVIG users with and without myositis.

Group	Outcome	Exposure period	Events	Follow-up Time	Unadjusted incident rate ratio IRR (95% CI)
Non-Myositis Cohort (n = 10,058)	Venous Thromboembolism	Control	34	1,450 person years	1.68 (1.10-2.56)
		IVIG-Exposure	60	1,524 person years	
	Arterial Thromboembolism	Control	44	1,450 person years	3.23 (1.92-5.43)
		IVIG-Exposure	21	214 person years	
Myositis Cohort (n = 1,677)	Venous Thromboembolism	Control	5	131 person years	0.17 (0.02-1.46)
		IVIG-Exposure	1	153 person years	
	Arterial Thromboembolism	Control	3	131 person years	NA
		IVIG-Exposure	0	31 person years	

Juvenile Myositis: Promising Avenues for New Therapies

O-9

INTERFERON-DRIVEN DYNAMICS: DISEASE TRAJECTORIES AND *IN VITRO* INSIGHTS IN JUVENILE DERMATOMYOSITIS

Saskia R. Veldkamp[1], Maud Reugebrink[1], Elsbeth Noppers[2], Butsabong Lerkvaleekul[2], Ellen J.H. Schatorjé[3], Wineke Armbrust[4], Sylvia S.M. Kamphuis[5], Petra C.E. Hissink Muller[6], J. Merlijn van den Berg[7], Judith Wienke[1], Brian M Feldman[8], Julia Drylewicz[1], Annet van Royen-Kerkhof[2*], Femke van Wijk[1*], Marc H.A. Jansen[2*]

*contributed equally.

[1]Center for Translational Immunology, University Medical Center Utrecht, Utrecht, Netherlands; [2]Paediatric Rheumatology and Immunology, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, Netherlands; [3]Paediatric Rheumatology, Amalia Children's Hospital, Radboud University Medical Centre Nijmegen, Nijmegen, Netherlands; [4]Paediatric Rheumatology and Immunology, Beatrix Children's Hospital, University Medical Center Groningen, Groningen, Netherlands; [5]Paediatric Rheumatology, Sophia Children's Hospital, Erasmus University Medical Centre, Rotterdam, Netherlands; [6]Paediatric Rheumatology, Willem Alexander Children's Hospital, Leiden University Medical Centre, Leiden, Netherlands; [7]Paediatric Immunology, Rheumatology and Infectious Diseases, Emma Children's Hospital, Amsterdam University Medical Centers, Amsterdam, Netherlands; [8]Division of Rheumatology, The Hospital for Sick Children, Child Health Evaluative Sciences, The Hospital for Sick Children Research Institute, and Departments of Pediatrics and Institute of Health Policy Management & Evaluation, University of Toronto, Toronto, Ontario, Canada

Background. Juvenile dermatomyositis (JDM) is a chronic inflammatory disease characterized by a heterogeneous disease course and a dysregulated interferon (IFN) pathway. Our aims were (1) to identify IFN-related biomarkers that can predict disease course and (2) to develop an in vitro model to study inhibition of IFN-mediated responses. **Methods.** For aim 1, latent class mixed effects models (LCMM) were employed to identify disease trajectories using longitudinal data from 81 JDM patients, including clinical scores (PGA, aCAT, CMAS) and IFN-related serum biomarkers Galectin-9 and CXCL10. For aim 2, we stimulated healthy donor (HD) PBMCs in vitro for 18h with IFN-α, -β, or -γ and measured Siglec-1 expression on monocytes using flow cytometry. Pre-incubation for 1h with JAK-inhibitors ruxolitinib, baricitinib, tofacitinib, filgotinib, or deucravacitinib or an anti-IFNα/βR2 blocking antibody was performed to study their inhibitory effect on Siglec-1 induction. In addition, Siglec-1 was measured after treatment of HD PBMCs with plasma of treatment-naïve JDM patients or HDs, with or without deucravacitinib, baricitinib and the anti-IFNα/βR2 blocking antibody. **Results.** Three distinct disease trajectories emerged based on PGA scores: class 1 (69%) steadily declined and stayed low, class 2 (20%) showed a decline followed by an increase at 20 months of follow-up (FU), and class 3 (11%) maintained high scores. During FU, class 3 had significantly higher aCAT scores than class 1. Calcinosis occurred in 5%, 25% and 33% of class 1, 2 and 3, respectively. Two distinct classes based on CXCL10 levels could be identified. CXCL10 levels in class 1 (83%) steadily declined and remained low, while class 2 (17%) initially declined but increased again around 20 months. Notably, all 3 patients in class 2 with available CXCL10 measurements after 25 months FU, flared at 29, 32 and 45 months FU, respectively. In vitro, Siglec-1 expression was induced by IFNα and IFNβ, and minimally by IFNγ. This induction could be inhibited by filgotinib, tofacitinib, baricitinib, anti-IFNα/βR2 blockade, and deucravacitinib, in order of ascending inhibitory potency. IFNα-mediated induction was more effectively inhibited than IFNβ-mediated induction. Treating HD PBMCs with JDM patient plasma induced Siglec-1, which could be effectively inhibited. Siglec-1 induction by patient plasma correlated with global disease activity (r_s=0.98, p=0.0004). **Conclusion.** Our findings identify distinct disease trajectories and show the potential of IFN-induced biomarker CXCL10 to predict upcoming flares. In addition, our in vitro results underscore the potential of targeting the IFN pathway with novel therapies providing a molecular basis for precision treatment of JDM.

O-10

JUVENILE SCLEROMYOSITIS OVERLAP PATIENTS DEMONSTRATE A UNIQUE PERIPHERAL BLOOD IMMUNOPHENOTYPE USING BULK RNA SEQUENCING

Amanda D. Robinson[1,5], Gabrielle A. Morgan[2], Giffin Werner[1], Anwesha Sanyal[1], Haley Havrilla[1], Srilakshmi Chaparala[3], Lauren M. Pachman[2,4*], Kathryn S. Torok[1*]

*co-senior authors

[1]Pediatric Rheumatology, University of Pittsburgh Medical Center, Children's Hospital of Pittsburgh, Pittsburgh, PA, USA; [2]Pediatric Rheumatology, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA; [3]Molecular Biology Information Service, Health Science Library System, University of Pittsburgh, Pittsburgh, PA, USA; [4]Northwestern University Feinberg School of Medicine, Chicago, IL. USA; [5]Pediatric Rheumatology, University of Utah, Salt Lake City, UT, USA

Background. Juvenile systemic sclerosis (jSSc) and juvenile dermatomyositis (JDM) are rare autoimmune diseases sharing similar age of onset, heavy cutaneous disease burden, and frequent internal organ involvement. A proportion of jSSc and JDM patients have features of both diseases, scleromyositis overlap disease (jOverlap). Analysis of a single center cohort of jSSc demonstrated that jOverlap was common, associated with more frequent musculoskeletal involvement including myositis, and was enriched for U1RNP and PM-Scl autoantibody positivity. This study utilizes bulk RNA sequencing (RNA-Seq) with differentially expressed gene (DEG) analyses to evaluate the peripheral blood immunopheno-

type of jOverlap patients compared to healthy controls, jSSc, and JDM. **Methods.** Peripheral blood bulk RNA-Seq was performed on children with jSSc (n=25), JDM (n=25), jOverlap (n=26), and age/sex matched healthy controls (HCs) (n=21). Samples were collected at two tertiary care referral centers with dedicated jSSc and JDM clinics, each contributing jOverlap samples. Disease category was determined by the treating physician. Demographics, clinical manifestations, treatment status, and autoantibody profile were extracted. RNA was isolated from peripheral blood and sequenced using the Illumina NextSeq 500 platform. Data processing and analyses were performed using Partek Flow software and DESeq2 platform. Significant DEGs were identified based on a $\log_2$ fold cut-off value of ≤1.5 or ≥1.5 and a false discovery rate (FDR) step up of <0.1. **Results.** Overlap patients were predominantly White females and exhibited a unique autoantibody distribution enriched for PM-Scl, U1RNP, and U3RNP autoantibodies. jOverlap demonstrate differential gene expression when compared to HCs, jSSc, and JDM (Fig. 1A). Multiple type 1 INF signaling genes were upregulated in jOverlap compared to both HCs and SSc, an immune signature well documented in both adult and juvenile dermatomyositis. When compared to JDM, jOverlap exhibited upregulated expression of genes previously reported to be associated with a sclerosing neurologic diseases (other RAB GTPases) (1, 2), inflammatory arthritis (MMEL1) (3), and idiopathic pulmonary fibrosis (MMP19) (4). Clustering analyses using t-SNE demonstrate jOverlap in all four unique clusters (Fig. 1B). **Conclusion.** Scleromyositis overlap patients demonstrate a unique immunophenotype compared to HCs, jSSc, and JDM. This pattern of differential gene expression may explain the distinct clinical phenotype seen in these patients. Though HCs, jSSc, and JDM clustered well separately, jOverlap was found in all clusters identified, suggesting disease category is not the only modifier responsible for differential gene expression. Additional analyses of the relationship between DEGs with age, autoantibody positivity, clinical manifestations, and disease activity are needed to further characterize this unique patient population.

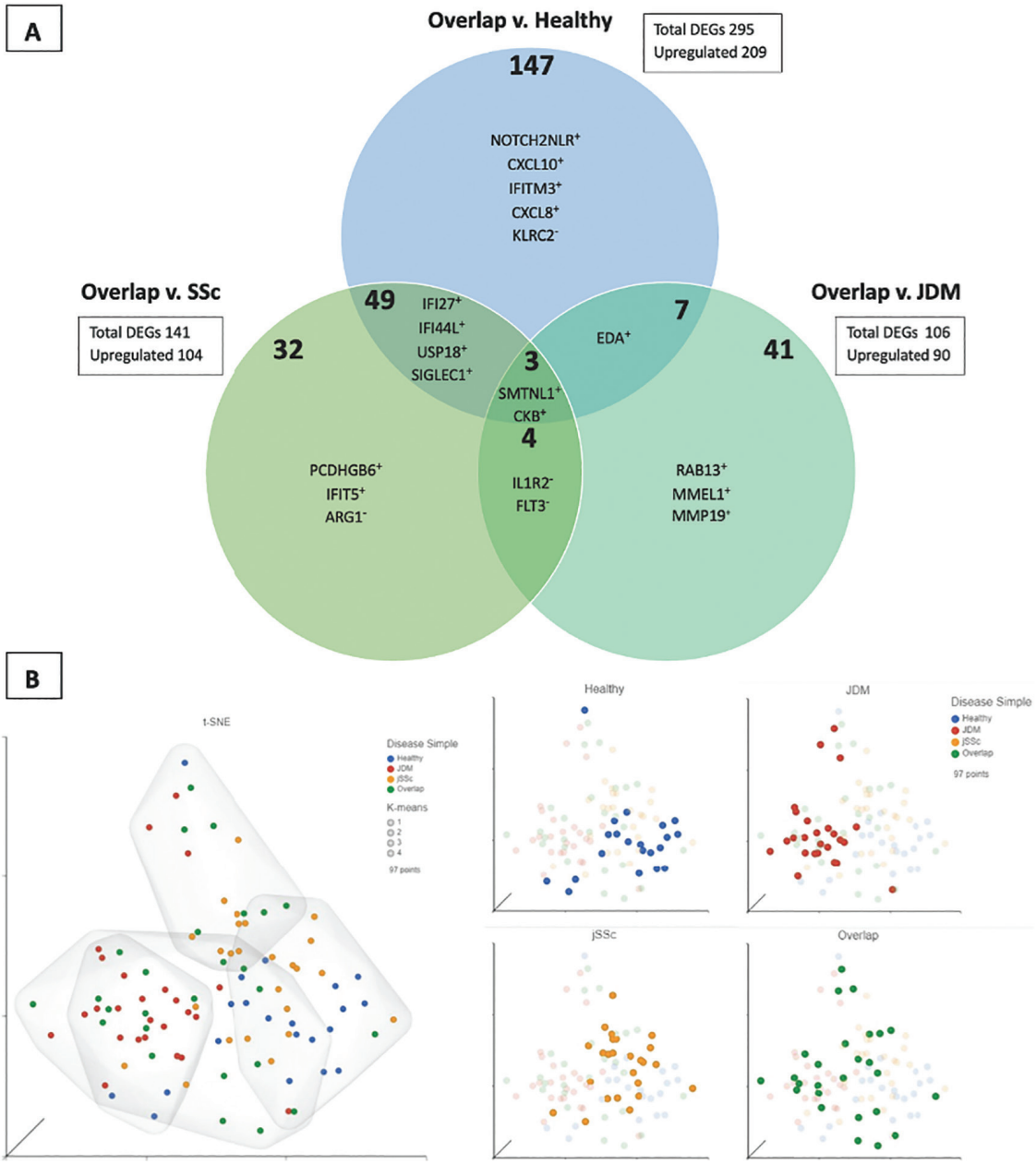


Fig. 1. A: Venn diagram of differentially expressed genes (DEGs) of scleromyositis overlap disease compared to healthy controls (blue circle), overlap compared to SSc (green circle), and overlap compared to JDM (teal circle). Boxes list the total number and number of upregulated DEGs in each analysis. Bolded numbers within circles are the number of protein-coding DEGs found in each analysis. Overlapping areas represent genes found in more than one analysis. Top DEGs of interest are listed with superscripts noting direction of differential expression.
B: t-SNA plot of bulk RNA-seq data for jOverlap, jSSc, JDM, and HC. (left), split by disease category (right).

References

1. PARAKH S, PERRI ER, JAGARAJ CJ, RAGAGNIN AMG, ATKIN JD: Rab-dependent cellular trafficking and amyotrophic lateral sclerosis. *Crit Rev Biochem Mol Biol* 2018; 53(6): 623-51. https://doi.org/10.1080/10409238.2018.1553926
2. HAILE Y, DENG X, ORTIZ-SANDOVAL C *et al*.: Rab32 connects ER stress to mitochondrial defects in multiple sclerosis. *J Neuroinflammation* 2017; 14(1): 19. https://doi.org/10.1186/s12974-016-0788-z
3. DANOY P, WEI M, JOHANNA H *et al*.: Association of variants in MMEL1 and CTLA4 with rheumatoid arthritis in the Han Chinese population. *Ann Rheum Dis* 2011; 70(10): 1793-97. https://doi.org/10.1136/ard.2010.144576
4. YU G, KOVKAROVA-NAUMOVSKI E, JARA P *et al*.: Matrix metalloproteinase-19 is a key regulator of lung fibrosis in mice and humans. *Am J Respir Crit Care Med* 2012; 186(8): 752-62. https://doi.org/10.1164/rccm.201202-0302OC

Clinical Trials

O-11

STUDY OF THE MUSCLE DAMAGE DURING ANTI-SYNTHETASE SYNDROME THROUGH SPATIAL TRANSCRIPTOMICS: INVOLVEMENT OF TYPE II IFN AND MACROPHAGES IN B LYMPHOCYTE SURVIVAL

Samuel Malartre[1], Julian Dal Cin[1], Céline Anquetil[1], Frank Letourneur[2], Angéline Madelaine[3], Sarah Léonard-Louis[1], Danielle Seilhan, Olivier Benveniste[1], Yves Allenbach[1].

[1]Center of Research in Myology, UMRS974, Institut National de la Santé et de la Recherche Médicale, Sorbonne Université, Paris, France; [2]Plateforme Séquençage et Génomique, Institut Cochin, Paris, France; [3]Myology Institute, Neuromuscular Morphology Unit, Reference Center of Neuromuscular Diseases Nord-Est-IDF, GHU Pitié-Salpêtrière, Paris, France Sorbonne Université, Paris, France

Background. Anti-synthetase syndrome (ASS) represents a significant subgroup of idiopathic inflammatory myopathies primarily characterized by myositis associated with interstitial lung disease and the presence of anti-synthetase autoantibodies. The significance of B cells and plasma cells in muscle pathophysiology has been underscored by recent studies but also by the successful outcomes observed with Rituximab or anti-CD19 CAR-T cell treatments. Despite these advancements, the intricacies of B cell pathogenicity and their developmental processes within muscle tissue remain poorly understood. A better understanding of these mechanisms would aid in defining therapeutic targets.
Methods. To characterize the phenotypes of inflammatory cell populations and their interactions in muscle tissue, we performed spatial transcriptomics (Visium, 10x Genomics) on biopsies from patients with anti-Jo1 antibody-positive ASS. We compared these biopsies to histologically normal muscle biopsies. This technique allows transcriptomic analysis for each tissue domain (spot) of 50 µm in diameter.
Results. We analyzed 5 ASS biopsies and 5 from healthy donors, representing a total of 6,210 tissue domains. Unsupervised analysis identified 13 clusters, including 3 clusters specific to ASS tissue domains. Among these 3 clusters, two were mainly characterized by the overexpression of immunoglobulin genes (IGLC7, JCHAIN), as well as MS4A1 (CD20) and SDC1 (CD138), indicating the presence of B lymphocytes and plasma cells. The third cluster contained transcripts corresponding to regenerating muscle cells (MYH3, MYH8), fibroblasts of fibro-adipogenic progenitor type (COL1A1, PDGFRA), and M1-polarized macrophages (SPP1, SOD2, C1QA, CD68). This cluster also exhibited a type II IFN signature (CD74, CXCL9, IFI30, SOD2) and the expression of cytokines BAFF and APRIL involved in B lymphocyte survival and maturation. In a public single-cell transcriptomics dataset of macrophages (1), we identified a subtype of macrophages, IL4I1-macrophages, responsible of BAFF production. These macrophages originated from an IFNγ-dependent monocyte population. We then found the transcriptomic signature of these IL4I1-macrophages in our third cluster (IL4I1, IRF1, STAT1, C1QA). This signature was also present in contact with our tissue domains containing B lymphocytes and plasma cells (Fig. 1).
Conclusion. Spatial transcriptomics data suggest a type II IFN response contributing to the polarization of monocytes into IL4I1-macrophages in the muscle. These macrophages are involved in cytokine production necessary for the maturation and survival of B lymphocytes and plasma cells observed in the muscles of ASS patients.

Reference

MULDER K, PATEL AA, KONG WT *et al*.: Cross-tissue single-cell landscape of human monocytes and macrophages in health and disease. *Immunity* 2021; 54(8): 1883-900.e5.

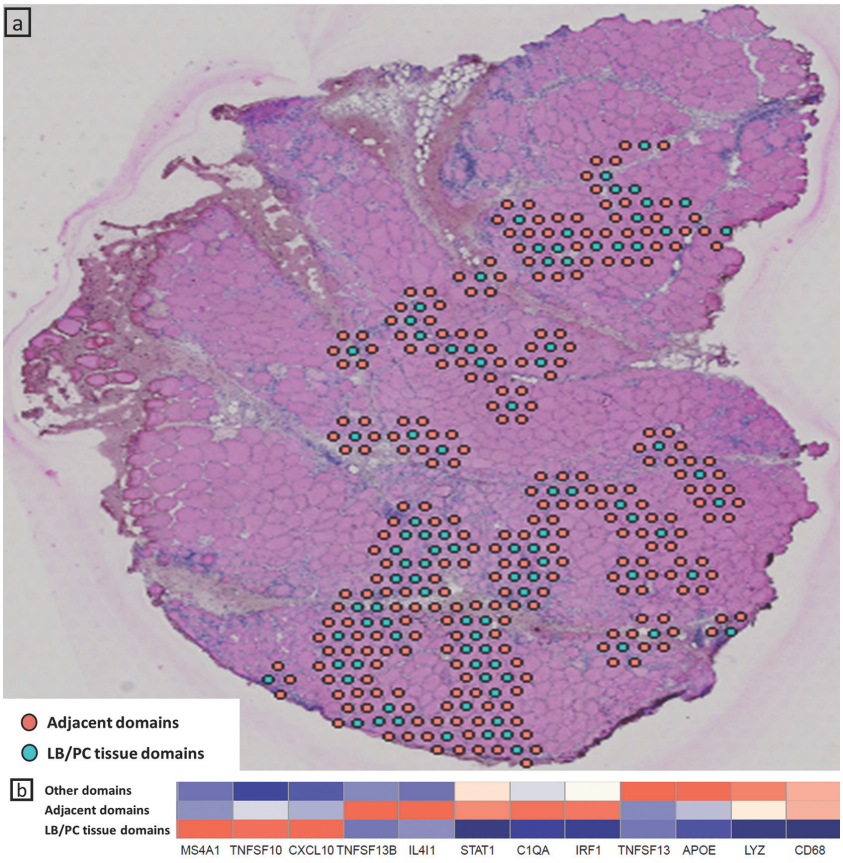


Fig. 1. **b**: Heatmap representing gene expressions in different groups of tissue domains (**a**): tissue domains containing B lymphocytes (LB) and plasma cells (PC), tissue domains in contact with LB/PC domains: <Adjacent domains> and other tissue domains. The transcriptomic signature of IL4I1 macrophages (IL4I1, STAT1, CIQA, IRF1) is found in the <adjacent domains> where TNFS13B (BAFF) production is highest.

O-12

IMPAIRED FORCE GENERATING CAPACITY BY SINGLE SKELETAL MUSCLE FIBERS FROM IMMUNE-MEDIATED NECROTIZING MYOPATHY PATIENTS

Tom J. Kerkhoff[1,2,3], Sanna Luijcx[1,2], Daan Hoomoedt[1,2], Lotta Plomp[1,2], Anneke J. van der Kooi[4], Eleonora M. Aronica[5], Joost Raaphorst[4], Coen A.C. Ottenheijm[1,2]

[1]Amsterdam UMC location Vrije Universiteit, Physiology, De Boelelaan 1117, Amsterdam, The Netherlands; [2]Amsterdam Cardiovascular Sciences, Pulmonary Hypertension & Thrombosis, Amsterdam, The Netherlands; [3]Amsterdam Movement Sciences, Musculoskeletal Health, Amsterdam, The Netherlands; [4]Amsterdam UMC location University of Amsterdam, Neurology, Meibergdreef 9, Amsterdam, The Netherlands; [5]Amsterdam UMC location University of Amsterdam, Pathology, Meibergdreef 9, Amsterdam, The Netherlands

Background. Immune-mediated necrotizing myopathy (IMNM) is the most severe myositis subtype in terms of muscle weakness. Immunosuppressive therapies are still insufficient and there is a need for better and personalized therapies. IMNM is also associated with myositis specific autoantibodies against signal recognition protein-54 (SRP) and 3-hydroxy-3-methylglutaryl CoA reductase (HMGCR), which have been suggested to play a pathogenic role. To date the muscle weakness has been ascribed to necrosis, but the proportion of necrotic fibers is too low to account for the clinical muscle weakness. This raises the question whether impaired fiber contractility plays a role.
Methods. A muscle biopsy was obtained from treatment naive patients with IMNM anti-SRP$^+$ patients (n=6), IMNM anti-HMGCR$^+$ patients (n=7) and from healthy controls (n=12). Intact skeletal muscle fibers (a minimum of 20 per biopsy), with a normal looking striation pattern, were mechanically dissected from the corresponding glycerinated biopsy. Fibers were clipped in between aluminum foil T-clips and subsequently permeabilized. Afterwards, the fibers are mounted between a force transducer and length motor in the first of eight chambers. By use of a bath controller, fibers were moved to chambers with higher Ca^{2+}-containing solutions and therefore activated (without potential confounding effects of Ca^{2+} cycling in and out the sarcoplasmatic reticulum). Generated forces are measured to assess sarcomere contractility and Ca^{2+} sensitivity. Afterwards, the fiber is stored in a buffer for gel electrophoresis to determine myosin heavy chain composition.
Results. Our data show a significant decrease in the maximum force generating capacity, *i.e.* force normalized for cross-sectional area, in both groups, indicating impaired sarcomere contractility (Fig. 1A). The data also show a reduced calcium sensitivity of force, i.e. more calcium is needed to produce a given level of force, only shown in the anti-SRP$^+$ IMNM patients compared to healthy controls and not in the anti-HMGCR$^+$ IMNM patients (Fig. 1B).
Conclusion. The force generating capacity of skeletal muscle fibers is impaired in anti-SRP$^+$ and anti-HMGCR$^+$ IMNM patients. Furthermore, calcium sensitivity is only altered in the anti-SRP$^+$ group and not in the anti-HMGCR$^+$ group. These data suggest that the reduced muscle weakness in patients not only results from necrotic fibers, but also from sarcomere dysfunction in muscle fibers which display a healthy morphology.

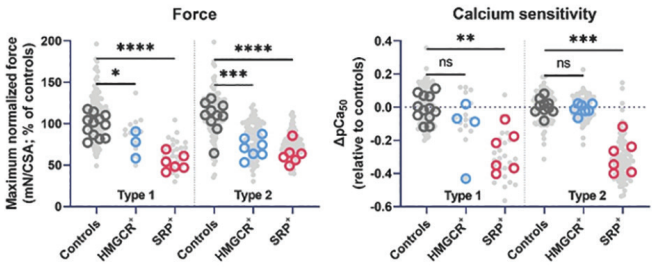


Fig. 1.

Imaging and Biomarkers

O-13

AUTOANTIBODIES AND DAMAGE IN PATIENTS WITH IDIOPATHIC INFLAMMATORY MYOPATHIES: A LONGITUDINAL MULTICENTER STUDY FROM THE MYONET INTERNATIONAL NETWORK

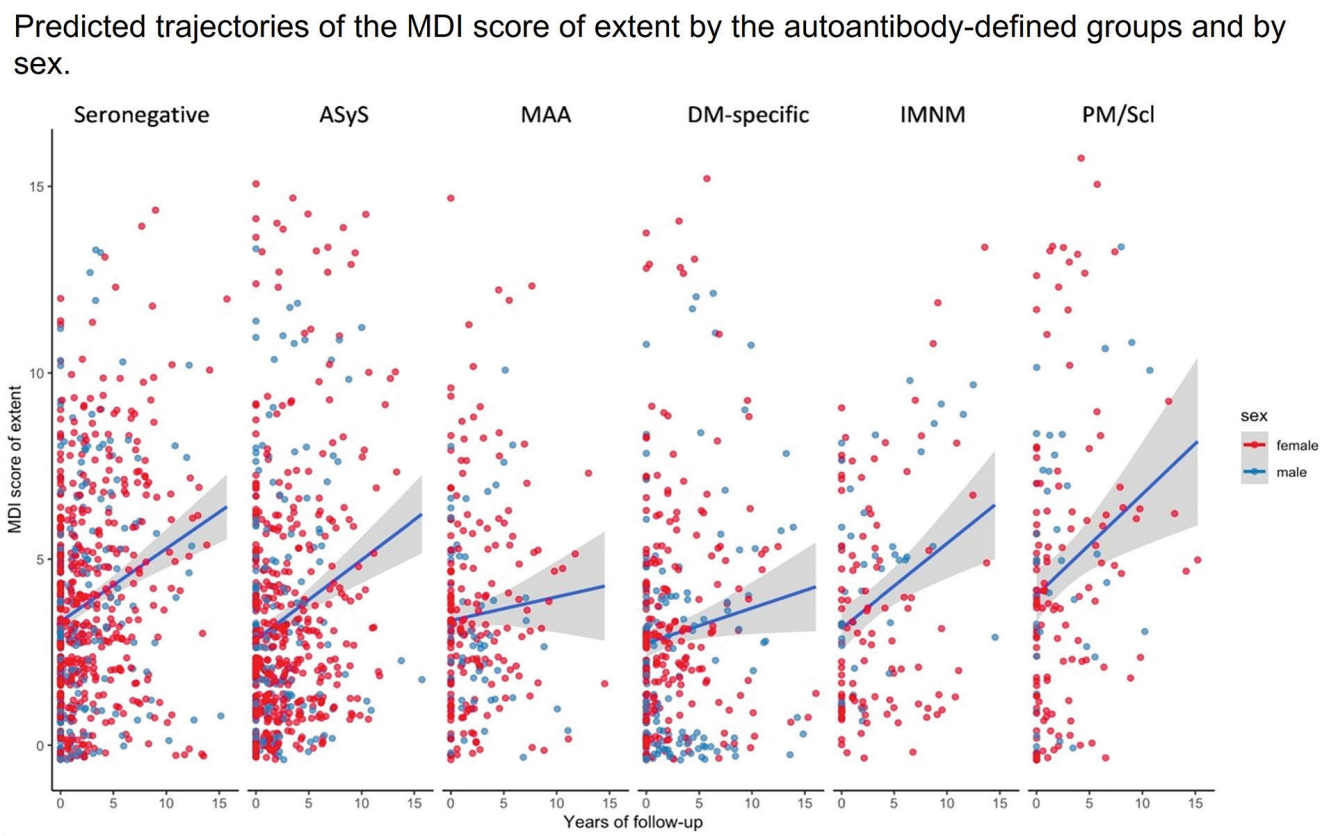
Fabricio Espinosa-Ortega[1,2], Karin Lodin[1,2], Maryam Dastmalchi[1,2], Jiri Vencovsky[3], Louise P Diederichsen[4] Samuel Katsuyuki Shinjo[5], Albert Selva-O'Callahgan[6], Marianne de Visser[7], Zoltan Griger[8], Angela Ceribelli[9,10], Diana Gómez-Martin[11], Helena Andersson[12], Monica Vázquez-Del Mercado[13], Hector Chinoy[14,15], James Lilleker[14,15], Paul New[14,15], Niels S Krogh[16], Ingrid E Lundberg[1,2], Helene Alexanderson[1,2], on behalf of all MYONET contributors

[1]Division of Rheumatology, Department of Medicine, Solna, Karolinska Institutet, Stockholm, Sweden; [2]Department of Gastro, Dermatology and Rheumatology, Karolinska University Hospital, Stockholm, Sweden; [3]Institute of Rheumatology and Department of Rheumatology, 1st Medical Faculty, Charles University, Prague, Czech Republic; [4]Center for Rheumatology and Spine Diseases, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark. Department of Rheumatology, Odense University Hospital, Odense, Denmark; [5]Division of Rheumatology, Faculdade de Medicina FMUSP, Universidade de Sao Paulo, Sao Paulo, SP, Brazil; [6]Systemic Autoimmune Diseases Unit, Vall d'Hebron Hospital, Universitat Autonoma de Barcelona; [7]Department of Neurology, Amsterdam University Medical Center, University of Amsterdam, Amsterdam Neuroscience, Amsterdam, The Netherlands; [8]Department of Medicine, Division of Clinical Immunology, University of Debrecen, Hungary; [9]Division of Rheumatology and Clinical Immunology, IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy; [10]Department of Biomedical Sciences, Humanitas University, Milan, Italy; [11]Department of Immunology and Rheumatology, Instituto Nacional de Ciencias Médicas y Nutrición Dr Salvador Zubirán, Mexico City; [12]Department of Rheumatology, Oslo University Hospital, Oslo, Norway; [13]División de Medicina Interna, Servicio de Reumatología, Hospital Civil Dr Juan I Menchaca, Universidad de Guadalajara, Guadalajara, Jalisco, Mexico; [14]National Institute for Health Research Manchester Biomedical Research Centre, Manchester University NHS Foundation Trust, The University of Manchester, Manchester, UK; [15]Department of Rheumatology, Salford Royal Hospital, Northern Care Alliance NHS Foundation Trust, Manchester Academic Health Science Centre, Salford, UK; [16]Zitelab Aps, Copenhagen, Denmark

Background. Patients with idiopathic inflammatory myopathies (IIM) may harbor autoantibodies that associate with well-defined clinical phenotypes. The association of these autoantibodies with organ damage is unknown. Therefore, we aimed to study the relationship of autoantibodies on the trajectories of organ damage over time using a large international cohort of patients with IIM.
Methods. We conducted a longitudinal analysis using the MyoNet registry including patients classified as IIM (1) who were tested for autoantibodies and had at least one assessment of damage (Myositis Damage Index, MDI). This index varies between 0-38, where 0 indicates no damage. (2) Patients were sub-grouped by their autoantibody status. The primary outcome was the change on MDI extent of damage over the entire follow-up time (up to 16 years) analyzed by linear mixed models. We used the autoantibody status as independent variable. The time point for the first MDI assessment registered was defined as the index date.
Results. In total, 769 patients were included, mean age at diagnosis was 50 years, and median time of disease duration at index date was 1.67 years (IQR 0.54–5.0). The overall mean MDI score at index date was 3.17 (SD 2.18) and 85% of patients had at least 1 item of damage registered at index date. Compared with the seronegative group, patients with Dermatomyositis-specific autoantibodies registered less damage over time (on average 0.54 less score, p=0.05) while patients with anti-PM/Scl autoantibodies registered higher damage (on average 0.83 higher score, p=0.026) independent of disease duration from diagnosis, age at diagnosis and sex (Fig. 1). Disease duration had an estimated score increase of 0.11 in the MDI extent per year of disease duration since diagnosis, independent of the antibody-status.
Conclusion. Our study is the first to describe patterns and trajectories of change of damage over time in relation to autoantibody status in a large international multicenter cohort of patients with IIM. These findings indicate that the autoantibody status is useful as predictor of organ damage in these patients.

References

1. LUNDBERG IE, TJÄRNLUNDA, BOTTAI M *et al*.: 2017 European League Against Rheumatism/American College of Rheumatology classification criteria for adult and juvenile idiopathic inflammatory myopathies and their major subgroups. *Ann Rheum Dis* 2017; 76(12):1 955-64.
2. SULTAN SM, ALLEN E, COOPER RG *et al*.: Interrater reliability and aspects of validity of the myositis damage index. *Ann Rheum Dis* 2011; 70: 1272-76.



O13 - Fig. 1. Each point represents a patient. The blue lines represent the predicted trajectory of the change on the MDI score of extent using linear regression. The grey shadow represents the confidence interval. Years of follow-up since the index date.
ASyS: anti-synthetase, MAA: myositis associated autoantibodies, DM-specific: dermatomyositis specific autoantibodies, IMNM: immune-mediated necrotizing myopathy autoantibodies, PM/Scl: anti-PM/Scl

O-14

SERUM LEVELS OF CASPASE 8 AS A NOVEL MARKER FOR IDIOPATHIC INFLAMMATORY MYOPATHIES-ASSOCIATED INTERSTITIAL LUNG DISEASES

Liubing Li[1], Chenxi Liu[3], Songxin Yan[4], Min Liu[1], Qing Xi[2]
[1]Department of Laboratory Medicine, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China; [2]Department of Gastroenterology, The First Affiliated Hospital of Guangdong Pharmaceutical University, Guangzhou, China; [3]Department of Laboratory Medicine, West China Second University Hospital, Sichuan University, Chengdu, China; [4]Department of Laboratory Medicine, Fujian Key Laboratory of Laboratory Medicine, Gene Diagnosis Research Center, Fujian Clinical Research Center for Clinical Immunology Laboratory Test, The First Affiliated Hospital, Fujian Medical University, Fuzhou, China

Background. Interstitial lung disease (ILD) is the most common extramuscular manifestation of idiopathic inflammatory myopathies (IIM). Although anti-aminoacyl-transfer RNA synthetase (ARS), melanoma differentiation-associated gene 5 (MDA5) autoantibodies as well as Krebs Von den Lungen-6 (KL-6) have an important role in IIM-ILD, these biomarkers have limited diagnostic values for the determination of ILD. Thus, there is still an unmet need for discovery and clinical verification of novel biomarkers for IIM-ILD.
Methods. We adopted a two-step approach with a marker discovery and a marker verification phase. For the marker discovery phase, a panel of 92 inflammatory proteins were assessed in sera from 19 IIM patients and 15 age- and sex-matched healthy controls using the Olink Protein Extension Assay. For the marker verification phase, a candidate protein was verified in sera from 76 IIM-ILD patients, 42 IIM-non-ILD patients and 30 healthy controls using enzyme-linked immunosorbent assay (ELISA). The association between the candidate protein and demographic, clinical and laboratory characteristics of IIM patients, and the values of the candidate protein in the diagnosis and prognosis of patients were also investigated..
Results. In the discovery phase, 18 candidate proteins were differentially expressed between IIM and healthy controls, including 11 up-regulated and 7 down-regulated proteins. After GO enrichment, KEGG pathway enrichment and PPI network analyses, a candidate protein, namely caspase 8 (CASP-8), was identified. In the verification phase, serum CASP-8 levels were significantly higher in the sera of patients with IIM compared with those of healthy controls (median, 12.0 *vs*. 3.0 ng/mL, $p<0.001$, as well as in the sera of patients with IIM-ILD compared with those of patients with IIM-non-ILD (median, 32.8 *vs*.6.4 ng/mL, $p<0.001$). The receiver operating characteristic (ROC) analysis revealed an optimal cut-off value of 9.8 ng/mL to distinguish IIM-ILD from IIM-non-ILD, with a sensitivity of 85.5% and specificity of 100% and the area under the curve (AUC) of 0.919 (95% CI 0.867–0.970, $p<0.001$). A combination of serum CASP-8 and KL-6 levels increased the sensitivity and specificity to distinguish IIM-ILD from IIM-non-ILD. Furthermore, there was no association between CASP-8 levels and prevalence of anti-MDA5 autoantibody. High CASP-8 levels are associated with poor prognosis in patients with IIM.
Conclusion. This study provides insights into the potential feasibility and clinical utility of serum CASP-8 for diagnosis, monitoring and outcome prediction of patients with IIM.

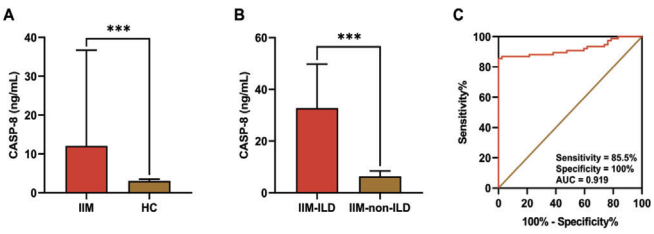


Fig. 1.

Malignancy

O-15

ANTI-SP4 AND ANTI-CCAR1 AUTOANTIBODIES IN UK VS. US PATIENTS WITH ADULT AND JUVENILE-ONSET MYOSITIS

Fionnuala McMorrow[1], Lucy R. Wedderburn[2,3], Hector Chinoy[4,5], Alexander Oldroyd[4,5], Janine A. Lamb[6], Lisa G. Rider[7], Andrew Mammen[8], Livia Casciola-Rosen[9], Neil J McHugh[1], Sarah L Tansley[10]

[1]University of Bath, Bath, UK; [2]UCL GOS Institute of Child Health, London, UK; [3]NIHR Biomedical Research Centre at GOSH, London, UK; [4]Department of Rheumatology, Salford Royal Hospital, Northern Care Alliance NHS Foundation Trust, Manchester Academic Health Science Centre, Salford, UK; [5]Division of Musculoskeletal and Dermatological Sciences, Faculty of Biology, Medicine and Health, The University of Manchester, Manchester, UK; [6]Division of Population Health, Health Services Research & Primary Care, Faculty of Biology, Medicine and Health, The University of Manchester, Manchester, UK; [7]Environmental Autoimmunity Group, National Institute of Environmental Health Sciences, Bethesda, Maryland, USA; [8]National Institute of Arthritis and Musculoskeletal and Skin Diseases, Bethesda, Maryland, USA; [9]Johns Hopkins University School of Medicine, Baltimore, Maryland, USA; [10]Royal National Hospital for Rheumatic Diseases, Bath, UK

Background. Anti-TIF1γ autoantibodies are important diagnostic and prognostic biomarkers and are strongly associated with cancer associated myositis (CAM) in adult patients. It has recently been demonstrated that cancer risk is attenuated if patients with anti-TIF1γ are also positive for anti-specificity protein 4 (Sp4) or anti-cell division cycle apoptosis regulator protein 1 (CCAR1). In US myositis patients with anti-TIF1γ, the frequencies of anti-CCAR1 and anti-Sp4 are 32% (1) and 43% (2) in adults and 9% (unpublished) and 19% (3) in juveniles, respectively. Anti-Sp4 positive juveniles exhibit milder muscle weakness and a higher prevalence of Raynaud's phenomenon (3). This study aims to identify the frequency of anti-Sp4 and anti-CCAR1 in adult and juvenile UK myositis populations and report any observed clinical associations.
Methods. Autoantibody status was initially determined by radio-immunoprecipitation (IP). In patients with 155/140kDa bands, anti-TIF1γ positivity was confirmed using anti-TIF1γ ELISA (MBL, Japan). 65 UK JDM (median age 6, 56% female, 73% Caucasian), 22 US JDM (demographic data not available), and 52 UK adult myositis (81% female, median age 49) anti-TIF1γ positive patients and 24 healthy control samples were screened for anti-Sp4 and anti-CCAR1 autoantibodies by ELISA (protocols provided by Mammen and Casciola-Rosen research groups).
Results. 22 (42%) of the 52 UK adult myositis anti-TIF1γ positive patients had cancer. Two (4%) of the myositis adults had anti-Sp4 (neither with cancer) and eight (16%) had anti-CCAR1, two (25%) with CAM. Both patients with anti-Sp4 were also positive for anti-CCAR1. Anti-Sp4 autoantibodies were detected in five (23%) of the US JDM cohort, but none of the UK JDM cohort. Two (9%) US JDM patients and seven (11%) UK JDM patients had anti-CCAR1 autoantibodies. Anti-CCAR1 positive US JDM patients were also positive for anti-Sp4 autoantibodies. There was no statistically significant difference in CAM frequency between UK anti-TIF1γ patients with or without anti-CCAR1 autoantibodies. There were no significant clinical or demographic differences between anti-TIF1γ patients with or without anti-CCAR1 or anti-Sp4 in UK myositis cohorts.
Conclusion. Anti-CCAR1 is less common in the adult UK myositis population compared to US. UK and US juvenile myositis populations appear to have similar anti-CCAR1 frequencies. Our results suggest anti-Sp4 autoantibodies are less frequent in both adult and juvenile UK myositis cohorts compared to US. The small sample size of anti-CCAR1 and anti-Sp4 autoantibodies makes it challenging to draw firm conclusions on the influence of the autoantibodies on cancer risk.

References

1. FIORENTINO D *et al*.: Association of anti-CCAR1 autoantibodies with decreased cancer risk relative to the general population in patients with anti-transcriptional intermediary factor 1γ-positive dermatomyositis. *Arthritis Rheumatol* 2023; 75(7): 1238-45.
2. HOSONO Y *et al*.: Coexisting autoantibodies against transcription factor Sp4 are associated with decreased cancer risk in patients with dermatomyositis with anti-TIF1γ autoantibodies. *Ann Rheum Dis* 2023; 82(2): 246-52.
3. SHERMAN MA *et al*.: Autoantibodies recognizing specificity protein 4 co-occur with anti-transcription intermediary factor 1 and are associated with distinct clinical features and immunogenetic risk factors in juvenile myositis. *Arthritis Rheumatol* 2023; 75(9): 1668-77.

O-16

TUMORS FROM CANCER-ASSOCIATED MYOSITIS HARBOR GENETIC EVENTS IN MYOSITIS-SPECIFIC AUTOANTIGENS

Albert Gil-Vila[1], Ana Belén Moreno-Cárdenas[2], Javier Ros[3], Debayan Datta[2], Roberta Fasani[4], Garazi Serna[4], Jose Jimenez[4], Ernesto Trallero-Araguás[5], Cristina Viaplana[6], Julia Lostes[3], José César Milisenda[7], Josep Maria Grau-Junyent[7], Raquel Lopez-Perez[8], Iago Pinal-Fernández[9,10], Paolo Nuciforo[4], Rodrigo A. Toledo[2], Albert Selva-O'Callaghan[1]

[1]Systemic Autoimmune Diseases, Vall d'Hebron General Hospital. Departament de Medicina, Universitat Autònoma de Barcelona, Barcelona, Spain; [2]Biomarkers and Clonal Dynamics Group, Vall d'Hebron Institute of Oncology (VHIO), Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain; [3]Medical Oncology Department, Vall d'Hebron University Hospital, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain; [4]Molecular Oncology Group, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; [5]Rheumatology Department, Vall d'Hebron General Hospital, Barcelona, Spain; [6]Oncology Data Science Group, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; [7]Muscle Research Unit, Internal Medicine Service, Hospital Clinic de Barcelona, Barcelona, Spain; [8]Radiology Department, Vall d'Hebron University Hospital, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain; [9]Muscle Disease Unit, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, USA; [10]Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Background. In autoimmunity, the immune system loses tolerance to self, while in cancer it fails to recognize transformed (mutated) self. Both contrasting poles of the immune spectrum co-occur in paraneoplastic syndromes such as cancer-associated myositis (CAM), providing an opportunity to explore the complex interplay between tumor immunity and autoimmunity. The aim of this study was to identify somatic mutations that could explain the potential relationship between the tumor and the development of CAM.
Methods. Eight patients diagnosed with CAM were included in this study. Myositis specific antibodies and associated cancer type are described in Table I. Whole-exome library preparation and sequencing was performed using the ImmunoID NeXT platform®. For somatic mutation detection, core single-nucleotide variants (SNVs) and SNV quality metrics were generated using GATK's HaplotypeCaller.
Results. Most (87.5%, 7/8) patients with CAM presented somatic alterations (mutations or copy-number variation) in the autoantigens corresponding their respective myositis-specific autoantibodies. The tumor samples from patients DM8, DM1 and DM12 with anti-TIF1g antibodies presented somatic alterations (mutations or LOH) in TRIM33 and TRIM66, part of the transcriptional intermediary factor 1 (TIF1) family proteins. In addition, we identified mutations in genes targeted by other CAM-related autoantibodies. Patient DM15, who presented anti-NXP2 autoantibodies was found to have a LOH in MORC2 and a somatic mutation in MORC3, the protein recognized by anti-NXP2 autoantibodies. Similarly, patient DM4, with anti-Mi2 autoantibodies presented LOH in the CHD4 gene, corresponding to Mi2b. Patient DM3, with anti-SAE autoantibodies, presented a gain in the whole chromosome 19, the genomic region that contains SAE1. Patient DM2 with anti-MDA5 antibody carried a missense somatic mutation in the IFIH1 gene, encoding MDA5. Of note, somatic genetic variants in CAM-related genes such as TRIM33, TRIM24, TRIM28, TRIM66, IFIH1, MORC2, MORC3, and CHD4 genes were detected in only 131 (1.2%) 135 (1.2%), 108 (1.0%), 78 (0.7%), 140 (1.3%), 146 (1.3%), 132 (1.2%), and 406 (3.7%) amongst the 10,967 tumor samples of the TCGA PanCancer Atlas Study. The highly frequent genetic alterations in these genes in tumors from patients with CAM greatly contrast with tumors from general cohorts, supporting a CAM disease-specificity of these events.
Conclusion. The high prevalence of genetic alterations in myositis-specific autoantigens in patients with CAM strengthens the evidence suggesting that tumoral mutations may induce the development of myositis autoantibodies.
Acknowledgements. Vall d'Hebron investigators are supported by the Instituto de Salud Carlos III grant PI22/00708 co-financed by the European Regional Development Fund (ERDF).

Table I.

Patient ID	Tumor type	Myositis specific antibody	Somatic alterations in CAM-related genes
DM1	Squamous cervix carcinoma	anti-TIF1γ	TRIM66 (LOH)
DM2	Nasopharyngeal carcinoma	anti-MDA5	IFIH1 (mutation)
DM3	Colonic NET	anti-SAE	chromosome 19 amplification
DM4	Small cell lung cancer	anti-Mi2	CHD4 (LOH)
DM5	Small cell lung cancer	anti-TIF1γ	Not detected
DM8	Small cell lung cancer	anti-TIF1γ	TRIM33 (mutation)
DM12	Thymic Carcinoma	anti-TIF1γ	TRIM66 (LOH); TRIM24 (LOH)
DM15	Small cell lung cancer	anti-NXP2	MORC2 (LOH); MORC3 (mutation)

O-17

GASTROINTESTINAL INVOLVEMENT IN NXP2 DERMATOMYOSITIS: A RETROSPECTIVE MULTICENTRIC COHORT

Orane Demuynck[1], Camille Rasmussen[2], Mohamed-Yacine Khitri[3], Philippe Blanche[2], Nicolas Limal[4], Laure Gallay[5], Benjamin Terrier[6], Mario Boisseau[7], Laurent Gilardin[8], Antoine Dossier[9], Yoan Crabol[10], Nathalie Costedoat-Chalumeau[11], Anne Tournadre[12], Alain Meyer[13], Olivier Benveniste[3], Yves Allenbach[3]

[1]CHU de Lille, Lille; [2]France, Hôpital Cochin, Paris, France; [3]Hôpital Pitié Salpêtrière, Paris, France; [4]Hôpital Henri Mondor, Créteil, France; [5]Hospices Civils de Lyon, Lyon, France; [6]Hôpital Cochin, Paris, France; [7]Hôpital privé d'Antony - Ramsay Santé, Antony, France; [8]Hôpital Jean-Verdier, Bondy, France; [9]Hôpital Bichat-Claude Bernard, Paris, France; [10]C.H. Bretagne Atlantique, Vannes, France; [11]Hôpital Cochin, Paris, France; [12]CHU Gabriel-Montpied, Clermont-Ferrand, France; [13]CHU de Strasbourg, France

Background. Gastrointestinal involvement in myositis was first reported in the 1970s as severe extramuscular manifestations with potentially fatal outcomes. However, limited studies have detailed these manifestations, marked by nonspecific symptoms like abdominal pain, diarrhea, and vomiting. NXP2 dermatomyositis is distinguished by vasculopathic features, including edema, calcinosis and perivascular infiltration or ischemic muscular lesions on biopsy. Recent case reports have particularly highlighted gastrointestinal involvement in NXP2-positive cases. Thus, our focus is on describing gastrointestinal implications in NXP2 dermatomyositis.
Methods. In a retrospective multicentric cohort of NXP2 dermatomyositis (ENMC criteria), the prevalence of gastrointestinal involvement was assessed. It was defined as any lesion in the gastrointestinal tract with macroscopic evidence or scannographic findings at diagnosis or during the disease. Dysphagia was excluded because it could be due to potential muscular dysfunction. Further details on gastrointestinal lesions were outlined within a subset of patients treated at a single center.
Results. The multicentric cohort comprised 44 patients, with 32% (14/44) exhibiting gastrointestinal lesions, often associated with increased severity at diagnosis. In the monocentric group 8 patients had gastrointestinal lesions, resulting in 10 events. Gastrointestinal events manifested a median of 2 months after the onset of muscular or cutaneous symptoms. It primarily occurred at disease relapse in 60% (6/10) of cases. The majority of patients (77.8%; 7/9) experienced simultaneous muscular or cutaneous symptoms with gastrointestinal manifestations. Manifestations included abdominal pain (60%), nausea (30%), and bleeding (30%), with predominant lesions being perforations (3/10), ulcers (7/10), gastritis (4/10), and colonic lesions (5/10). Lesions were distributed across the intestinal tract (mouth 20%, esophagus 30%, stomach 30%, small intestine 10%, colon 40%). Surgical intervention was required for 50% (4/8) of patients, leading to three transfers to the intensive care unit due to complications. Biopsies predominantly indicated lymphocyte infiltration (50%) and were normal in 37.5% of cases. Notably, 77.8% (7/9) of events occurred while patients were already on steroids or immunosuppressive agents.
Conclusion. In conclusion, gastrointestinal involvement is prevalent and potentially severe in NXP2 dermatomyositis, with manifestations occurring concurrently with or after the onset of muscular and cutaneous symptoms. Despite specific dermatomyositis treatment, severe gastrointestinal lesions may necessitate surgical intervention.

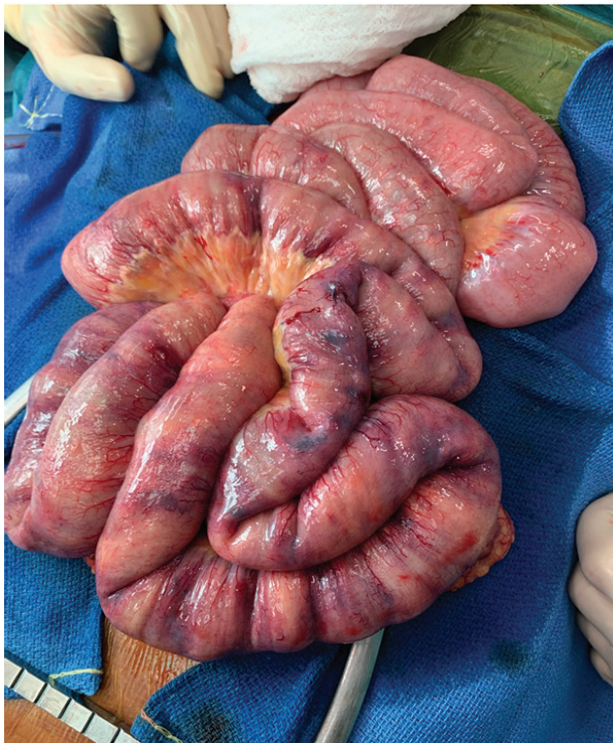


Fig. 1.

Pathogenesis of Inflammatory Myopathy

P-1

DISTINCT CYTOKINE PROFILE WITH ELEVATED TYPE I/III INTERFERONS IN CIRCULATION FROM PATIENTS WITH ANTI-MDA5 ANTIBODY-POSITIVE DERMATOMYOSITIS

Akira Yoshida[1], Takahisa Gono[1,2], Yuka Okazaki[1], Masataka Kuwana[1,2]
[1]Department of Allergy and Rheumatology, Nippon Medical School Graduate School of Medicine, Tokyo, Japan; [2]Scleroderma and Myositis Center of Excellence, Nippon Medical School Hospital, Tokyo, Japan

Background. Anti-melanoma differentiation-associated gene 5 (MDA5) antibody-positive dermatomyositis (DM) is often complicated with rapidly progressive interstitial lung disease (RP-ILD) and associated with early mortality. Previous studies indicated the role of type I interferons (IFNs) in the pathogenesis of anti-MDA5 antibody-positive DM (1). Recently, the similarity of clinical features and serum cytokine profiles between anti-MDA5 antibody-positive DM-ILD and severe coronavirus disease 2019 (COVID-19) pneumonia has been noted. In severe COVID-19, serum IFN-λ3 (a type III IFN) is elevated in the early disease course and suggested as a prognostic biomarker (2). In this context, we explored a characteristic serum cytokine profile in patients with anti-MDA5 antibody-positive DM, with a particular focus on type I/III IFNs, in comparison with other systemic autoimmune rheumatic diseases and COVID-19 pneumonia.

Methods. Consecutive patients with anti-MDA5 antibody-positive DM (n=10), anti-synthetase antibodies (n=6), anti-transcription intermediary factor 1-γ (TIF1-γ) antibody-positive DM (n=6), systemic lupus erythematosus (SLE) (n=6), and COVID-19 pneumonia (n=3), who visited Nippon Medical School Hospital from September 2020 to August 2023, were enrolled. Pre-treatment serum IFN-α, IL-1β, IL-6, and TNF-α were measured by cytometric bead array, while IFN-β and IFN-λ3 were measured by enzyme-linked immunosorbent assay.

Results. The median age of 10 patients with anti-MDA5 antibody-positive DM was 57 years old and 80% were female. Of these, nine were classified as amyopathic DM according to the 2017 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for idiopathic inflammatory myopathies. All the 10 patients had ILD and two were complicated with RP-ILD.

As shown in Figure 1, IFN-α was elevated in SLE (median 52.2 [interquartile range (IQR) 16.5–60.9] pg/mL), while IFN-β was elevated in two patients with classic DM and anti-TIF1-γ antibodies (30.6, 76.6 pg/mL). In patients with anti-MDA5 antibody-positive DM, IFN-α (23.1 [4.1–34.8] pg/mL), IFN-β (10.2 [5.7–11.8] pg/mL), and IFN-λ3 (77.4 [42.4–103.5] pg/mL) were all elevated. COVID-19 pneumonia was characterized by higher levels of IL-6 (COVID-19 pneumonia: 291.2 [170.2–507.9] pg/mL vs. anti-MDA5 antibody-positive DM: 16.9 [8.5–29.8] pg/mL) and IFN-λ3 was elevated in one patient (26.4 pg/mL). The elevation of type I/III IFNs was minimal in patients with anti-synthetase antibodies. There was no significant difference in the level of IL-1β and TNF-α between the diseases.

Conclusion. Patients with anti-MDA5 antibody-positive DM exhibited a distinct cytokine profile with elevated type I/III IFNs.

References

1. GONO T, OKAZAKI Y, KUWANA M: Antiviral proinflammatory phenotype of monocytes in anti-MDA5 antibody-associated interstitial lung disease. *Rheumatology* (Oxford) 2022; 61(2): 806-14. https://doi.org/10.1093/rheumatology/keab371. PMID: 33890985.
2. SUZUKI T, IWAMOTO N, TSUZUKI S *et al*.: Interferon lambda 3 in the early phase of coronavirus disease-19 can predict oxygen requirement. *Eur J Clin Invest* 2022; 52(9): e13808. https://doi.org/10.1111/eci.13808

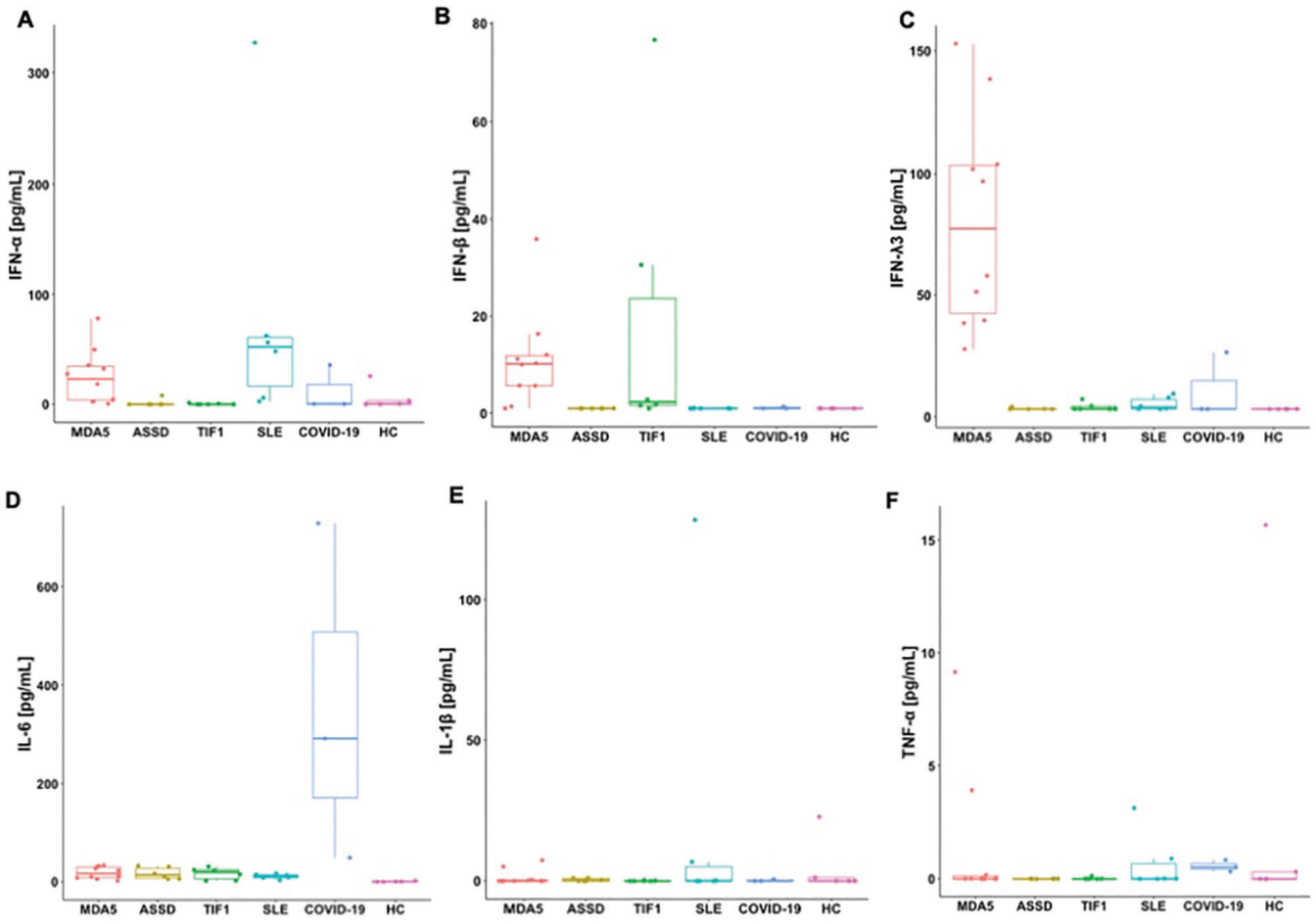


Fig. 1.

P-2

ANTI-FHL1 AUTOANTIBODIES IN ADULT PATIENTS WITH MYOSITIS: A LONGITUDINAL FOLLOW-UP ANALYSIS

Angeles S. Galindo-Feria[1,2,3], Karin Lodin[1,2,3], Begum Horuluoglu[1,2], Sepehr Sarrafzadeh-Zargar[1,2], Edvard Wigren[1,4], Susanne Gräslund[1,4], Olof Danielsson[5], Marie Wahren-Herlenius[1,2,6], Maryam Dastmalchi[1,2,3], Ingrid E. Lundberg[1,2,3], the SweMyoNet Consortium

[1]Division of Rheumatology, Department of Medicine, Solna, Karolinska Institutet, Stockholm, Sweden; [2]Center for Molecular Medicine, Karolinska Institutet, Karolinska University Hospital, Solna, Stockholm, Sweden; [3]Department of Gastro, Dermatology and Rheumatology, Karolinska University Hospital. Stockholm, Sweden; [4]Structural Genomics Consortium, Division of Rheumatology, Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden; [5]Division of Neurology, Department of Biomedical and Clinical Sciences, Faculty of Medicine and Health Sciences, Linkoping University, Linkoping, Sweden; [6]Broegelmann Research Laboratory, Department of Clinical Science, University of Bergen, Norway

Background. One recent autoantigen identified in patients with IIM is a muscle-specific antigen, Four-and-a-half-LIM-domain 1 (FHL1), which is highly expressed in skeletal and heart muscle. FHL1 is involved in the normal development and differentiation of cytoskeletal proteins in skeletal muscle. We have previously reported presence of anti-FHL1 autoantibodies in patients with autoimmune diseases, with higher frequency in patients with IIM (1, 2). In this study, our aim was determine prevalence and clinical associations of anti-FHL1 autoantibodies in patients with idiopathic inflammatory myopathies (IIM), to evaluate autoantibody levels over time and to identify its presence in other autoimmune and neuromuscular diseases.
Methods. Sera at the time of diagnosis from patients with IIM (n=449), autoimmune disease controls (DC, n=130), neuromuscular diseases (NMD, n=16) and healthy controls (HC, n=100) were analyzed for anti-FHL1 autoantibodies by Enzyme-Linked ImmunoSorbent Assay (ELISA). Patients with IIM FHL1+ and FHL1- were included in a longitudinal analysis. Serum levels were correlated to disease activity.
Results. Autoantibodies to FHL1 were more frequent in patients with IIM (122/449, 27%) compared to 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 NMD [0.48 (0.36-0.80)] $p<0.001$. Anti-FHL1+ patients with IIM were younger at time of diagnosis compared to the anti-FHL1- group ($p=0.05$) and were seronegative for other autoantibodies in 25%. In the first follow-up anti-FHL1+ sample 20/33 (60%) positive at baseline had turned negative for anti-FHL1 autoantibodies. Anti-FHL1 autoantibodies rarely appeared after initiating treatment. Anti-FHL1 autoantibody levels correlated with CK (r=0.62, $p=0.01$), disease activity measure MYOACT (n=14, $p=0.004$) and inversely with manual muscle test-8 (r=-0.59, $p=0.02$) at baseline.
Conclusion. Anti-FHL1 autoantibodies were present in 27% of patients with IIM, of these 25% were negative for other autoantibodies. Other autoimmune diseases had lower frequencies and levels. Anti-FHL1 levels often decreased with immunosuppressive treatment, correlated with disease activity measures at diagnosis and rarely appeared after start of treatment.

References

1. ALBRECHT I, WICK C, HALLGREN *et al*.: Development of autoantibodies against muscle-specific FHL1 in severe inflammatory myopathies. *J Clin Invest* 2015; 125(12): 4612-24.
2. GALINDO-FERIA AS, HORULUOGLU B, DAY J *et al*.: Autoantibodies against Four-and-a-Half-LIM Domain 1 (FHL1) in inflammatory myopathies: results from an Australian single-center cohort. *Rheumatology* 2022.

P-3

DYSREGULATION OF ER IMPORT PROTEINS IN IMNM WITH PARTICULAR DIFFERENCES BETWEEN SRP54+ AND HMGCR+ PATIENTS

Corinna Preusse[1,2], Andreas Hentschel[3], Theo Marteau[4], Susanne Morales-Gonzalez[5], Albert Sickmann[3], Yves Allenbach[6], Olivier Benveniste[6], Carsten Dittmayer[1], Markus Schülke-Gerstenfeld[2], Werner Stenzel[1], Andreas Roos[4,7,8]

[1]Charité - Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Department of Neuropathology, Berlin, Germany; [2]Charité - Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Department of Paediatrics, Berlin, Germany; [3]Leibniz-Institut für Analytische Wissenschaften - ISAS - e.V., Dortmund, Germany; [4]Department of Pediatric Neurology, Centre for Neuromuscular Disorders, Centre for Translational Neuro- and Behavioral Sciences, University Duisburg-Essen, Essen, Germany; [5]Charité - Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, CharitéCrossOver, Berlin, Germany; [6]Department of Internal Medicine and Clinical Immunology, Pitié-Salpêtrière University Hospital, Paris, France; [7]Pediatric Neurology, University Children's Hospital, University of Duisburg-Essen, Faculty of Medicine, Essen, Germany; [8]Department of Neurology, Medical Faculty, Heinrich Heine University Düsseldorf, Duesseldorf, Germany

Background. Immune mediated necrotizing myopathies (IMNM) are part of the idiopathic inflammatory myopathies and are precisely defined by international consensus. Criteria are based on clinical, morphological as well as serological features and the main characteristics include proximal lower limb-predominant muscle weakness, substantially increased serum CK levels and detection of the pathognomonic myositis-specific auto-antibodies anti-SPR54 or -HMGCR. However, 1/3 of IMNM patients remain without a positive serostatus for these antibodies. Notably, both auto-antibodies target proteins of the endoplasmic reticulum (ER) / sarcoplasmic reticulum (SR). Impaired protein processing may lead to ER/SR-stress and consequently activation of the unfolded protein response (UPR). Indeed, perturbed ER-integrity and UPR-activation was recently demonstrated in muscle biopsy specimens derived from IMNM patients in the context of our previous studies. Now we aim to expand the previous data set of ER pathology and it´s mechanisms by focussing on proteins crucial for the import of nascent polypeptides into the ER/SR (such as SRP54), as well as on ribosomal proteins and thus to explore the impact on protein synthesis in the molecular aetiology of IMNM.
Methods. In comparison to non-disease controls (NDC) we have analysed SRP54+ or HMGCR+ IMNM patients, using histology, proteomics, transcriptional analyses and immunoblotting.
Results. Proteomic profiling on whole muscle tissue showed 283 proteins (belonging to multiple pathways) being significantly dysregulated in IMNM patients compared to NDC. Notably, 13% (37) of these proteins are involved with the endoplasmic reticulum, ER-stress, protein processing at the ER and nuclear/cytosolic chaperones. Besides the previously demonstrated increased abundances of UPR-related proteins, we identified multiple import proteins as being dysregulated and our immunofluorescence studies revealed differences in staining intensity / pattern between the two subgroups. Moreover, our transcript studies revealed in HMGCR+ patients, among others, an up-regulation of Calumenin, encoding a calcium-binding protein localized within the ER/SR, which is involved in protein folding and sorting, as well as an up-regulation of SEC61B and SEC63. Latter transcripts encode for proteins, which are central for ER-mediated protein translocation. Interestingly, this increase was not detected in SRP54+ patients. Our protein studies using histological staining, immunofluorescence and immunoblotting confirmed these findings.
Conclusion. These combined studies show a pathophysiological difference between the two IMNM subgroups, not only increasing our understanding of the underlying pathophysiology but also providing new aspects in the stratification of IMNM patients by introducing biomarker candidates.
Acknowledgements. French Muscular Dystrophy Association (AFM-Telethon)

P-4

PROTEOMIC PROFILING TO DEFINE IIM-ASSOCIATED MARKER PROTEINS IN CULTURED HUMAN MYOBLASTS

Christopher Nelke[1*], Corinna Preusse[2*], Akinori Uruha[2,3], Andreas Hentschel[4], Vera Dobelmann[1], Christina B. Schroeter[1], Werner Stenzel[2], Yves Allenbach[3], Tobias Ruck[1#], Olivier Benveniste[3#], Andreas Roos[1,5,6#]

[1]Department of Neurology, Heinrich Heine University Düsseldorf, Dusseldorf, Germany; [2]Department of Neuropathology, Charité-Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Germany; [3]Sorbonne Université, Assistance Publique - Hôpitaux de Paris, Inserm U974, Department of Internal Medicine and Clinical Immunology, Pitié-Salpêtrière University Hospital, Paris, France; [4]Leibniz-Institut für Analytische Wissenschaften -ISAS- e.V., Dortmund, Germany; [5]Department of Neuropediatrics, Center for Translational Neuro- and Behavioral Sciences (C-TNBS), University Hospital Essen, Essen, Germany; [6]Brain and Mind Research Institute, Children's Hospital of Eastern Ontario Research Institute, Ottawa, Canada

Background. Idiopathic inflammatory myopathies (IIM) represent a group of chronic, autoimmune conditions primarily affecting skeletal muscles, although a variety of extramuscular manifestations are known. The most common types are dermatomyositis (DM), immune mediated necrotizing myopathy (IMNM), sporadic inclusion body myositis (sIBM), and antisynthetase Syndrome (ASys). Typically, patients present with sub-acute to chronic onset of proximal muscle weakness and histological analysis of muscle biopsy specimen is part of the routine diagnostic work-up. Patient stratification in terms of delineation of the phenotype and confirmation of diagnosis includes laboratory testing of myositis specific antibodies (MSA). Although the individual IIM-myopathologies are widely studied on muscle biopsy level, there is still a considerable lack of knowledge regarding the pathobiochemistry of myoblasts indicating predisposing pathophysiological events. Moreover, apart from MSA there is still a lack of muscular biomarker enabling an IIM-subtype differentiation based on pathophysiological hallmarks such as protein dysregulation.

Methods. To systematically address this gap of knowledge, we analyzed the proteomic signature of IIM-myoblasts cultured from muscle biopsies by making use of liquid chromatography coupled to tandem mass spectrometry.

Results. Our mass spectrometric approach revealed the significant dysregulation of proteins in all entities (DM: increase of 16 and decrease of 73; IMNM: increase of 4 and decrease of 13; sIBM: increase of 16 and decrease of 10; ASys: increase of 5 and decrease of 9). A Partial Least-Squares Discriminant Analysis displayed an overlap of sIBM and ASyS and partially with IMNM, while controls and DM cluster separately. Heatmap analysis unveiled a general more pronounced increase of dysregulated proteins in myoblasts derived from sIBM-patients compared to the other IIM-subtypes and controls. MOESIN, SON, CLIP3, PICALM, CACYBP and RPN1 are generally decreased in IIM-patients compared to controls. Of note, PSMA1, GOLGA2 and JPT2 are only increased in DM-patient derived myoblasts highlighting their potential to serve as proteinogenic markers. Interestingly, three of the molecular determinants (CLIP3, PICALM & GOLGA2) are related to function and maintenance of the Golgi apparatus. Other proteins are involved in functions of the endoplasmic reticulum (RPN1 & JPT2) or proteasome-based proteolysis (PSMA1 & CACYBP).

Conclusion. Our proteomic data unravelled molecular determinants of IIM indicative for pathobiochemical processes taking place already in cultured myoblasts. Additionally, for DM three specific marker proteins were identified, which might serve as muscular biomarker. Functions of marker proteins suggest a profound role of ER-Golgi based protein quality control and proteolysis in the etiology of IIM.

Acknowledgements. AR and AH acknowledge the support from the "Ministerium für Kultur und Wissenschaft des Landes Nordrhein-Westfalen" and "Der Regierende Bürgermeister von Berlin, Senatskanzlei Wissenschaft und Forschung". This work was also supported by a grant of the French Muscular Dystrophy Association (AFM-Téléthon; #23216) to WS and AR. Parts of this study were financed in the framework of the NME-GPS project by the European Regional Development Fund (ERDF).

P-5

INVESTIGATING OVERLAP MYOSITIS WITH POSITIVE KU- ANTIBODY - HISTOPATHOLOGICAL FEATURES AND AUTOPHAGY ASPECTS

Marie-Therese Holzer[1], Udo Schneider[2], Andreas Roos[3], Andreas Hentschel[4], Anne Schänzer[5], Sarah Léonard-Louis[6], Olivier Benveniste[7], Joachim Weis[8], Kristl G. Claeys[9,10], Benedikt Schoser[11], Federica Montagnese[11], Akinori Uruha[12,13], Melanie Huber[14], Laure Gallay[15], Natalie Streichenberger[16], Corinna Preuße[12*], Martin Krusche[1*], Werner Stenzel[12*]

*shared last authorship

[1]Division of Rheumatology and Systemic Inflammatory Diseases, III. Department of Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [2]Department of Rheumatology, Charité - Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany; [3]Department of Neuropediatrics, Developmental Neurology and Social Pediatrics, Centre for Neuromuscular Disorders in Children, University Children's Hospital Essen, University of Duisburg-Essen, Essen, Germany; [4]Leibniz-Institut für Analytische Wissenschaften -ISAS- e.V., Dortmund, Germany; [5]Institute of Neuropathology, Justus-Liebig-University, Gießen, Germany; [6]Reference Center of Neuromuscular Pathology Paris-Est, Pitié-Salpêtrière University Hospital, Paris, France; [7]Department of Internal Medicine and Clinical Immunology, Pitié-Salpêtrière University Hospital, Paris, France; [8]Institute of Neuropathology, Medical Faculty, RWTH Aachen University, Aachen, Germany; [9]Department of Neurology, University Hospitals Leuven, Leuven, Belgium; [10]Department of Neurosciences, Laboratory for Muscle Diseases and Neuropathies, KU Leuven, and Leuven Brain Institute (LBI), Leuven, Belgium; [11]Friedrich-Baur-Institute, Department of Neurology, Ludwig-Maximilians-University, Munich, Germany; [12]Department of Neuropathology, Charité - Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany; [13]Department of Neurology, Tokyo Metropolitan Neurological Hospital, Tokyo, Japan; [14]Department for Rheumatology, Campus Kerckhoff of Justus-Liebig University Gießen, Bad Nauheim, Germany; [15]Department of Internal Medicine, Edouard Herriot University Hospital, Hospices Civils de Lyon, Lyon, France; [16]Department of Neuropathology, Groupment Hospitalier Est, Hospices Civils de Lyon, Lyon, France

Background. Ku+ myositis is a rare form of myositis and patients can have various underlying connective tissue diseases. Accordingly, clinical presentations vary considerably. A few histopathological studies have so far identified inflammatory and necrotizing aspects, but a precise and exhaustive morphological analysis of Ku+ myositis is still lacking. The aim of this study was therefore to carry out a detailed histopathological, transcriptional and proteomic examination of muscle samples from anti-Ku antibody positive patients in a multicenter study in order to uncover possible pathomechanisms.

Methods. Muscle biopsies from 23 patients with anti-Ku antibodies and clinical/morphological signs of myositis were analyzed by immune histochemistry, transcriptomic and proteomic studies. Furthermore, a comparison was made with biopsies from non-disease controls and biopsies from patients with immune-mediated necrotizing myopathy (IMNM).

Results. Clinically, 91% of the patients were female with a mean age of 55 years. Isolated myositis was reported in 35% of the patients, overlap with systemic sclerosis with 30%. CK elevation was present in 91% of the patients, with higher CK mean levels in isolated myositis compared to overlap with systemic sclerosis.

Histopathological examinations showed a wide spectrum from mild to very pronounced myositis. Sarcolemmal MHC-class I staining was diffuse, and focally enhanced in all samples, while MHC-class II staining was spotty in 74% of the biopsies. In 87% of samples, we noted varying degrees of myofiber necrosis with concurrent endomysial lymphomonocytic infiltration in 83% of the samples. Small vacuoles were seen in 59% of biopsies and p62+ or LC3+ and myotilin+ aggregates were present in 60-76%. We identified a striking upregulation of proteins and genes involved in autophagy pathways by proteomic and transcriptomic analysis. In line with this, immunofluorescence identified co-localization of p62 or LC3 with the intermediate filaments myotilin and desmin, or the chaperone proteins HSP70 and alpha B crystallin. Ultrastructural studies of the sarcoplasmic aggregates identified granulofilamentous disruption of the contractile apparatus, which is at stark variance with the ultrastructure of IMNM (fine autophagolysosomal compartments), and inclusion body myositis (IBM) (extensive vacuolar debris and tubulofilaments).

Conclusion. Here, we identified Ku+ myositis morphologically being characterized by diffuse necrosis, MHC-class I and class II positivity, variable endomysial inflammation, as well as specific protein aggregation, which varies from those know in IBM and IMNM. These results show that Ku+ myositis features unique, often extensive sarcoplasmic protein aggregation on an acquired basis being functionally associated with impaired chaperone function and autophagy.

Acknowledgement. This project was partly funded by the Deutsche Gesellschaft für Muskelkranke (DGM). MTH received a project scholarship by the Arbeitsgemeinschaft Junge Rheumatologie Deutschland (AGJR) (Working Group Young Rheumatology from the German Society for Rheumatology).

P-6

LIPID DROPLETS IN IMMUNE-MEDIATED NECROTIZING MYOSITIS

Jose Milisenda[1,3,4,5*], Iago Pinal-Fernandez[1,2*], Katherine Pak[1*], Maria Casal-Dominguez[1,2*], Sandra Munoz-Braceras[1], Jiram Torres-Ruiz[1], Maria D. Cano[3], Ana Matas-Garcia[3], Gloria Garrabou[3,4,5], Josep Maria Grau[3,4,5], Iban Aldecoa[3], Albert Selva-O'Callaghan[6,7], Andrew L. Mammen[1,2,8]

*co-first authors

[1]Muscle Disease Unit, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD, USA; [2]Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, USA; [3]Muscle Research Unit, Internal Medicine Service, Hospital Clinic, Barcelona, Spain; [4]Barcelona University, Barcelona, Spain; [5]CIBERER, Barcelona, Spain; [6]Systemic Autoimmune Disease Unit, Vall d'Hebron Institute of Research, Barcelona, Spain; [7]Autonomous University of Barcelona, Barcelona, Spain; [8]Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Background. Muscle lipids, seen through stains like Oil Red O, accumulate mainly in type 1 fibers at the periphery. Primary lipid disorders include systemic carnitine deficiency, acyl-CoA dehydrogenase deficiency, and neutral lipid storage disease. This histological change has not been systemically studied in inflammatory myopathies.
Methods. All patients diagnosed with myositis at the Hospital Clínic de Barcelona from August 2010 to January 2022 were included. Muscle biopsy slides processed for clinical purposes underwent Oil Red O histochemistry and digitization. Immunofluorescence utilized a primary Laminin antibody and secondary Goat-antihuman IgG 488 and fluorescent staining with Nile Red. Imaging was performed using a Leica SP8 confocal microscope. Biopsies from immune-mediated necrotizing myopathy (IMNM) patients were compared with dermatomyositis (DM), antisynthetase syndrome (AS), inclusion body myositis (sIBM), and myositis associated with checkpoint inhibitors (ICI). Patients met either Lloyd's criteria for IBM or the Casal and Pinal criteria for other autoantibody-positive inflammatory myopathies. They tested positive for myositis-specific autoantibodies: anti-Jo1, anti-SAE, anti-NXP2, anti-Mi2, anti-TIF1γ, anti-MDA5, anti-SRP, or anti-HMGCR.
Results. A total of 140 muscle biopsies stained with Oil Red O histochemistry were included in the study. Among these, 51 were derived from individuals with DM (18 TIF1γ, 8 MDA5, 15 Mi2, 7 NXP2, and 3 SAE), 25 with sporadic inclusion body myositis (sIBM), 30 with IMNM (20 HMGCR and 10 SRP), 14 AS, and 20 were ICI. The average age of patients was 53.4 years (S.D 18.5), with those diagnosed with sIBM being the oldest at 63.9 years (S.D 12.5). Out of all cases, 28 exhibited lipid droplets with Oil Red O histochemistry, with 18/20 being associated with HMGCR (90%) and 3/10 with SRP (30%), 3/18 with TIF1γ (17%), 3/14 with Jo1 (21%), and 1/7 with NXP2 (14%).Within the analyzed myositis cases, it was observed that the presence of lipid deposits is significantly associated with anti-HMGCR autoantibodies (90% [18/20] *vs*. 8.3% [10/120], $p<0.001$). Muscle biopsies from patients with anti-HMGCR autoantibodies also showed cytoplasmic deposits of antibodies in the sarcoplasm. However, autoantibody deposits were inversely associated to the accumulation of lipids (areas with antibody deposits did not show deposits of lipids and vice versa).
Conclusion. There is an accumulation of lipids and antibodies in the sarcoplasm of patients with anti-HMGCR IMNM. The dysfunction of HMGCR induced by the autoantibodies may be related to this observation.

References

1. SELVA-O'CALLAGHAN A, PINAL-FERNANDEZ I, TRALLERO-ARAGUÁS E, MILISENDA JC, GRAU-JUNYENT JM, MAMMEN AL: Classification and management of adult inflammatory myopathies. *Lancet Neurol* 2018; 17(9): 816-28. doi: 10.1016/S1474-4422(18)30254-0. PMID: 30129477.
2. PINAL-FERNANDEZ I, MILISENDA JC, PAK K *et al*.: Transcriptional derepression of CHD4/NuRD-regulated genes in the muscle of patients with dermatomyositis and anti-Mi2 autoantibodies. *Ann Rheum Dis*

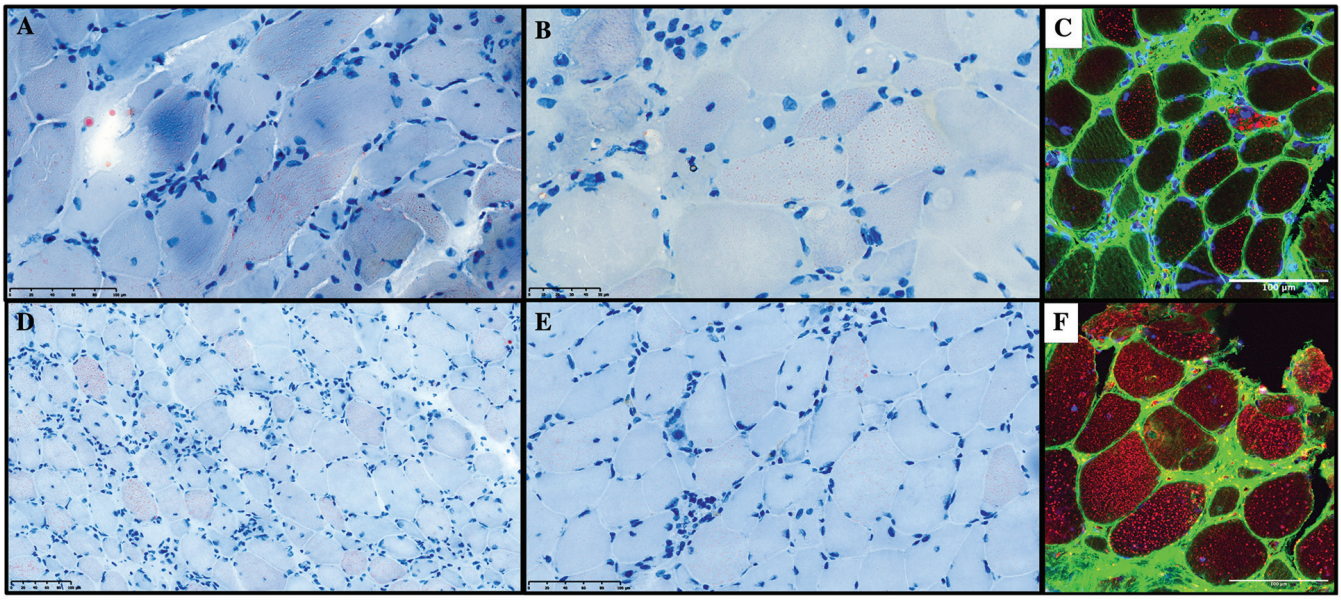


Fig. 1. A, B, D, and E. Oil Red O histochemistry from four different cases of IMNM associated with HMGCR. Lipid deposition is observed in the sarcoplasm. C and F. Immunofluorescence of a case of IMNM associated with HMGCR. Nuclei are observed in blue, human anti-IGG in green, and lipids in red.

P-7

AUTOMATED MORPHOMETRIC ANALYSIS OF MHC-1, MHC-2 AND ICAM-1 EXPRESSION PROVIDES DETAILED MORPHOLOGICAL CLASSIFICATION OF MYOSITIS SUBTYPES

Anna Nishimura[1], Christopher Nelke[2], Melanie Huber[3], Alexander Mensch[4], Angela Roth[1], Eva Neuen-Jacob[5], Werner Stenzel[6], Ulf Müller-Ladner[3], Tobias Ruck[2], Anne Schänzer[1]

[1]Institute of Neuropathology, Justus-Liebig University Giessen, Germany; [2]Department of Neurology, Medical Faculty, Heinrich-Heine-University, Düsseldorf, Germany; [3]Department of Rheumatology and Clinical Immunology, Campus Kerckhoff, Justus-Liebig-University, Giessen, Germany; [4]Department of Neurology, Martin-Luther-University, Halle-Wittenberg, Germany; [5]Institute of Neuropathology, Heinrich-Heine-University, Düsseldorf, Germany; [6]Department of Neuropathology, Charité - Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany

Background. Immunological pathways are different in idiopathic inflammatory myopathies (IIMs) subtypes and the correct morphological characterization of the muscle biopsy is necessary to provide the best therapeutic strategy for the individual patient. In addition to IIM subtypes such as dermatomyositis (DM), immune-mediated necrotizing myopathy (IMNM), anti-synthetase syndrome (ASyS) and inclusion body myositis (IBM), hereditary or acquired myopathy can show myositis-like features and mimic IIMs.
Methods. Our objective was to establish an automated morphometric analysis of quantification of protein expression on myofiber and endomysial vessels using immunofluorescent detection on muscle sections and to determinate whether MHC-1 (HLA-ABC), MHC-2 (HLA-DR) and ICAM-1 are expressed differently in IIM subtypes and myopathies with myositis-like morphology such as dysferlinopathy (DYSF), COVID-19 associated myopathy (COVID-19), neurogenic atrophy (NA), as compared to healthy controls (HC). From digitalized sections, protein expression of MHC-1, MHC-2 and ICAM-1 on myofibers was analyzed using Manders' Overlap Coefficient (MOC). With mean grey value (MGV), the intensity of ICAM-1 expression on endomysial capillaries was quantified. The results were validated by mass spectrometry (MS) on samples from IIM subtypes.
Results. MOC of MHC-1 and MHC-2 was expressed significantly higher in IIM subtypes compared to HC with higher expression in IBM and lower expression in IMNM. These results were confirmed by MS showing higher normalized protein abundance of HLA-A, HLA-B and HLA-C in IBM compared to IMNM. HLA-DR was not detected due to low levels. MOC of ICAM-1 was significantly higher in all IIMs and COVID-19 compared to HC and NA. Interestingly, ICAM-1 expression on endomysial capillaries (MGV) was high in ASyS, DM and COVID-19 highlighting a vascular pathology in these conditions. Whereas with normalized protein abundance of ICAM-1, no differences between the IIM subtypes were detected.
Conclusion. Our study shows that automated morphometric analysis provides detailed quantitative and qualitative data of immune-associated protein expression on myofiber and endomysial capillaries in muscle biopsies. These findings highlight the different immune mechanisms in IIM subtypes and the use of MHC-2 and ICAM-1 as diagnostic markers for muscle biopsies.

P-8

LOW PREVALENCE OF NEUTRALIZING AUTOANTIBODIES AGAINST TYPE I INTERFERONS IN IDIOPATHIC INFLAMMATORY MYOPATHIES

José Luis Gomez-Vazquez[1], Àngels SierraFortuny[1] Arnau Antolí[1,2], Xavier Solanich[1,2], Ernesto Trallero-Araguás[3], Ariadna Anunciación-Llunell[4], Albert Gil-Vila[4,5], Albert Selva.O'Callaghan[4,5]

[1]The Systemic, Vascular Diseases and Ageing group, Institut d'Investigació Biomédica de Bellvitge (IDIBELL), L'Hospitalet de Llobregat, Barcelona, Spain; [2]Internal Medicine Department, Bellvitge University Hospital, L'Hospitalet de Llobregat, Barcelona, Spain; [3]Rheumatology Department, Vall d'Hebron Hospital, Barcelona, Spain; [4]Systemic Autoimmune Diseases Unit, Internal Medicine Departament, Vall d'Hebron Hospital, Barcelona, Spain; [5]Universitat Autónoma de Barcelona, Barcelona, Spain

Background. Dysregulated type I interferon (IFN) responses play crucial roles in the development of multiple forms of autoimmunity. A prominent IFN signature has been identified in the skin, muscle, and blood of patients with adult and juvenile dermatomyositis (DM). The IFN-I genes signature also seems to correlate with disease activity in adult DM. Neutralizing autoantibodies (auto-Abs) against IFN-I have been described in 10-20% of systemic lupus erythematosus patients. It is worth highlighting that it is not known whether these antibodies are present in idiopathic inflammatory myopathies (IIM) so we aimed to test for auto-Abs against IFN-I in a cohort of IIM patients. We hypothesize that neutralizing autoantibodies against IFN-I may play a role in patients with anti-MDA5-positive DM-associated rapidly progressive interstitial lung disease, as it has been reported in critical patients with SARS-Cov2 pneumonia.
Methods. A total of 34 patients attended at Vall Hebron University Hospital in Barcelona who met the 2017 EULAR/ACR classification criteria for IIM were selected and their serum was collected. The determination of auto-Abs against type I IFNs were performed at Bellvitge University Hospital – IDIBELL. Firstly, auto-Abs against type I IFNs (IFN-α2, IFN-ω and IFN-β) were tested by a home-made enzyme-linked immunosorbent assay (ELISA) according to St. Giles procedure (cut-off >2 SD healthy population). Subsequently, we investigated the ability of these auto-Abs to neutralize high concentrations (10 ng/mL) of the three types I IFNs and also more physiological concentrations (100 pg/mL) of IFN-α2 and IFN-ω by a luciferase reporter assay.
Results. We analyzed serum from patients with the following phenotypes: 24 DM (13 MDA5, 5 Mi2, 5 SAE, 1 TIF1γ), 5 Immune Mediated Necrotizing Myopathy (4 HMGCR, 1 SRP), 5 overlap myositis (3 Jo1, 2 Ku). Only one (3%) anti-Mi2 DM patient showed auto-Abs with neutralizing activity against 100 pg/mL IFN-α2. Due to the low prevalence found, it cannot be analyzed whether there are clinical differences between patients with auto-Abs against IFN-I compared to the negative ones.
Conclusion. Neutralizing antibodies against type I IFNs do not seem to play a role in the pathogenesis of patients with IIM. The fact these antibodies were not detected in any of the anti-MDA5-positive DM-associated rapidly progressive interstitial lung disease argues against a viral etiology in these patients. Despite this, the presence of these antibodies should be analyzed in other series to determine their true prevalence and its clinical significance.
Acknowledgements. HUB-IDIBELL investigators are supported by La Marató de TV3 foundation (202115–30-31), GILEAD research grant (GLD22/00128) and the Carlos III National Health Institute (PI23/00651). Vall d'Hebron investigators are supported by the Instituto de Salud Carlos III grant PI22/00708 co-financed by the European Regional Development Fund (ERDF).

P-9

SINGLE CELL RNA SEQUENCING OF MUSCLE INFILTRATING T CELLS REVEALS ELEVATED HOBIT EXPRESSION IN PATIENTS WITH INCLUSION BODY MYOSITIS

Alexandra Argyriou[1,2], Begum Horuluoglu[1,2], Angeles Shunashy Galindo-Feria[1,2,3], Juan Sebastian Diaz-Boada[1,2], Annika van Vollenhoven[1,2], Antonella Notarnicola[1,2,3], Maryam Dastmalchi[1,2,3], Ingrid E. Lundberg[1,2,3], Lina-Marcela Diaz-Gallo[1,2], Karine Chemin[1,2]

[1]Division of Rheumatology, Department of Medicine, Solna, Karolinska Institutet, Stockholm, Sweden; [2]Center for Molecular Medicine, Karolinska Institutet, Stockholm, Sweden; [3]Department of Gastro, Dermatology and Rheumatology, Karolinska University Hospital, Stockholm, Sweden

Background. T cells play an important role in the pathogenesis of idiopathic inflammatory myopathies (IIM). We recently described the presence and clonal expansion of tissue resident memory T cells (T_{RM}) in the skeletal muscle of patients with IIM (1). Still, how these T_{RM} cells differ across IIM subtypes remains unclear and might unravel different mechanisms of pathogenesis across IIM subtypes. Here, we analysed the transcriptome of T_{RM} in patients with inclusion body myositis (IBM) and anti-synthetase syndrome (ASyS).
Methods. We performed deep Smart-seq3 single-cell RNA sequencing on muscle-infiltrating T cells from muscle biopsies from four patients with IBM and two patients with ASyS and we retrieved TCR alpha/beta CDR3 sequences using TraCeR.
Results. We identified a unique population of T_{RM} characterized by high expression of ZNF683 (encoding for HOBIT), together with a tissue resident memory signature including, CD69, CXCR6, ITGAE, XCL1 and XCL2, suggesting that these cells remain in the tissue overtime. Importantly in this cluster, the cells expressing ZNF683 were only derived from

patients with IBM, a characteristic probably related to the pathogenesis of IBM. Furthermore, a direct comparison of the transcriptomic T-cell profile in IBM against ASyS revealed ZNF683 as one of the most significantly differentially expressed genes, upregulated in muscle-infiltrating T cells in IBM. Finally, in IBM, most of the clonally expanded T cells within the muscle were identified within HOBIT+ T_{RM} and cytotoxic T cells. **Conclusion.** Overall, our data identify the transcription factor HOBIT highly expressed in T_{RM} in muscle biopsies from patients with inclusion body myositis as compared to ASyS. This finding suggests that different mechanisms might drive tissue-resident T cell formation in different IIM subsets. Further experiments will investigate if this signature could be used as an additional diagnostic tool in patients with IBM.

P-10

INVESTIGATION OF HISRS SPECIFIC AUTOREACTIVE CD4+ T CELLS IN PATIENTS WITH MYOSITIS

Begum Horuluoglu[1], Angeles S. Galindo-Feria[1,2], Ravi Kumar Sharma[1], Genadiy Kozhukh[1], Anatoly Dubnovitsky[1], Juan Sebastian Diaz Boada[1], Daniel Ramsköld[3], Karine Chemin[1], Vivianne Malmström[1], Ingrid E Lundberg[1,2]
[1]Division of Rheumatology, Center for Molecular Medicine, Department of Medicine, Solna, Karolinska Institutet, Stockholm, Sweden; [2]Department of Gastro, Dermatology and Rheumatology, Karolinska University Hospital, Stockholm, Sweden; [3]Department of Cell and Molecular Biology, Karolinska Institutet, Stockholm, Sweden

Background. One of the most common autoantibodies in patients with myositis is anti-Jo1, targeting histidyl-transfer RNA synthetase (HisRS) with a prevalence of 25-35 %. Importance of T-cells in disease is established by their presence at sites of inflammation such as the muscle. Moreover, genetic association of HLA-DRB1*03:01 further implicates the recognition of autoantigens by $CD4^+$T-cells. However, the presence of antigen specific $CD4^+$T-cells has not yet been shown in patients with myositis. The aim of this project is to identify HisRS specific $CD4^+$T-cells using HLA Class-II tetramers (Tmr) and single T cell receptor (TCR) sequencing.
Methods. HLA-DRB1*03:01 monomers with selected HisRS- and tetanus peptides as controls were produced in *E.coli*. The peptides were covalently linked to the HLA b-chain via a flexible peptide linker and HLA-tetramers were assembled using APC or PE labeled streptavidin. Peripheral blood cells from anti-Jo1 positive patients that were HLA-DRB1*03 (n=10) were stimulated with tetanus and HisRS peptides followed by tetramer staining. Tmr positive cells were single cell sorted and T cell receptor (TCR) alpha and beta (a/b) chain sequencing was performed. T cells sharing the same CDR3 sequence on both a/b chains were considered belonging to the same clone.
Results. We detected HisRS+$CD4^+$T cells from five out of ten patients using tetramers upon stimulation with HisRS peptide. The levels of IFNγ in the supernatants where Tmr+ cells were detected were significantly higher compared to cultures where no Tmr+ cells were present further supporting the activation of T cells. TCR a/b chains of HisRS+$CD4^+$T cells were sequenced (n=538) from five patient. The clonality analysis revealed presence of expanded T cell clones in 4 out of 5 patients. Moreover, expanded T cells had high mean fluorescent intensity values (MFI) for Tmrs, suggesting the responsiveness of autoreactive T-cells to HisRS. We detected persistence of HisRS+ $CD4^+$T cells from two of these patients after 1 year of treatment with conventional immunosuppressive treatment. TCR sequence analysis revealed expanded T-cell clones in both patients and only one shared clone between both time points in one of the patients.
Conclusion. Myositis are rare, chronic autoimmune disorders with no available cure. Previous studies indicate the importance of T cells in this disease. However, the phenotype and role of these cells in the disease pathogenesis has not been fully established. Our results indicate the presence of HisRS+$CD4^+$T-cells in myositis which will introduce the possibility of new targeted treatment approaches.

P-11

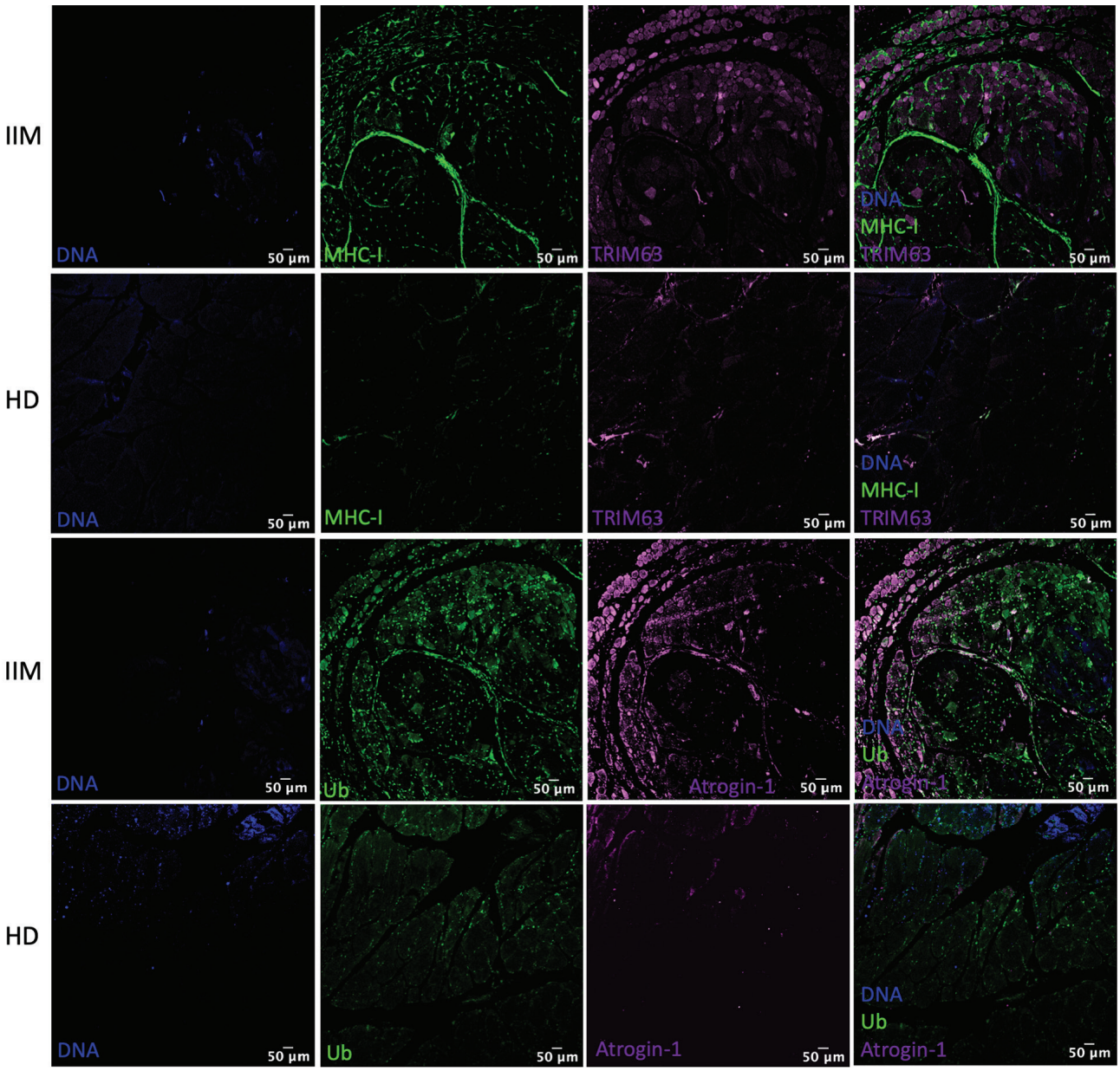
TRIM63 AND ATROGIN-1 CORRELATE WITH SYSTEMIC AND MUSCLE INFLAMMATION IN PATIENTS WITH IDIOPATHIC INFLAMMATORY MYOPATHIES

Jiram, Torres-Ruiz[1], Abdiel, Absalón-Aguilar[1], Nancy, R. Mejía-Domínguez[2], Alfredo, Pérez-Fragoso[1], Juan Alberto, Reyes-Islas[1], Fabiola, Cassiano-Quezada[1], Alejandro, Alfaro-Goldaracena[3], Mariana, Chávez-Villa[4], Miguel, Tapia-Rodríguez[5], Carlos, Núñez-Alvarez[1], Guillermo, Juarez-Vega[2], Diana, Gomez-Martin[1]
[1]Department of Immunology and Rheumatology. Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico; [2]Red de Apoyo a la Investigación. Coordinación de Investigación Científica, Universidad Nacional Autónoma de México, Mexico City, Mexico; [3]Department of Surgery. Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico; [4]Department of transplantation. Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico; [5]Microsopy Unit, Instituto de Investigación Biomédica Básica. Universidad Nacional Autónoma de México, Mexico City, Mexico

Background. The ubiquitin proteasome system is the main mediator of inflammation-induced muscle atrophy through the expression of TRIM63 and Atrogin-1. The aim of this study was to address the expression of these ubiquitin ligases and their relationship with inflammatory and atrophy parameters of patients with idiopathic inflammatory myopathies (IIM).
Methods. We recruited 37 adult IIM patients and registered their clinical features. We assessed the proportion of peripheral blood mononuclear cells (PBMC) subsets expressing TRIM63 and Atrogin-1 and the serum amount of theses ubiquitin ligases, cytokines, and chemokines, using multiparametric flow-cytometry, ELISA and luminometry respectively. We evaluated the expression of TRIM63, Atrogin-1, ubiquitin, K48, and different IFN-related proteins in muscle biopsies using confocal microscopy and Western Blot (WB). For the experiments involving peripheral blood, we recruited 10 age and sex-matched healthy donors, and we used commercially available healthy muscle slides and lysates as controls for the tissue experiments. We compared the quantitative variables with the Kruskal-Wallis and Mann-Whitney U tests and assessed the correlations with Spearman Rho.
Results. IIM patients had a higher proportion of TRIM63+ PBMC (3.03 (1.08-16.65) *vs*. 1.52 (0.20-2.79), P=0.042), TRIM63+ CD4+ T cells (24.56 (7.71-53.23) *vs*. 2.55 (0.42-4.51), $p<0.0001$), TRIM63+ CD8+ T cells (15.1 (3.22-37.40) *vs*. 1.06 (0.83-2.45), $p=0.0002$), TRIM63+ monocytes (14.09 (3.25-29.80) *vs*. 1.97 (0.59-7.64), $p=0.011$), Atrogin-1+ PBMC (5.35 (1.09-32.60) *vs*. 0.33 (0.22-2.05), $p=0.011$), Atrogin-1+ CD4+ T cells (27.30 (6.61-64.19) *vs*. 2.55 (0.42-4.51), $p<0.0001$), Atrogin-1+ CD8+ T cells (14.88 (5.99-34.30) *vs*. 2.33 (0.60-8.01), $p=0.001$), and Atrogin1+ monocytes (17.38 (8.93-47.37) *vs*. 1.41 (0.79-3.77), $p<0.0001$). In muscle from IIM patients, we found a higher expression of TRIM63 (29.25 AU (6.02-52.21) *vs*. 2.97 (1.71-3.77), $p=0.0079$), Atrogin-1 (0.45 AU (0.30-0.46) *vs*. 0.17 (0.13-0.29), $p=0.0317$), total ubiquitin (100.8 AU (68.52-305.6) *vs*. 13.31 (9.41-20.42), $p=0.0043$) (Fig. 1) and K48 (72.0 AU (46.05-187.4) *vs*. 2.72 (1.69.4.32), $p=0.0079$). TRIM63+ CD8+ T cells mainly correlated with serum IL-2 (r=0.56, $p<0.05$), IL-4 (r=0.5, $p<0.05$), IL-8 (r=0.61, $p<0.05$), IL-10 (r=0.58, $p<0.05$), G-CSF (r=0.58, $p<0.05$) and TNF-a (r=0.58, P<0.05). In muscle biopsies, ISG-15 showed a strong correlation with TRIM63 (r=0.8, $p<0.05$) and a moderate correlation with Atrogin-1 (r=0.51, $p<0.05$).
Conclusion. TRIM63 and Atrogin-1 are expressed in PBMC and muscle from patients with IIM and correlate with serum cytokines, chemokines and with muscle proteins showing an interferon signature. These ubiquitin ligases may contribute to the inflammation-induced muscle atrophy, which is frequently observed in IIM.

References

1. FELDON M, FARHADI PN, BRUNNER HI *et al*.: Predictors of reduced health-related quality of life in adult patients with idiopathic inflammatory myopathies. *Arthritis Care Res* (Hoboken) 2017; 69: 1743-50. https://doi.org/10.1002/acr.23198
2. RIDER LG, LACHENBRUCH PA, MONROE JB *et al*.: Damage extent and predictors in adult and juvenile dermatomyositis and polymyositis as determined with the myositis damage index. *Arthritis Rheum* 2009; 60: 3425-35. https://doi.org/10.1002/art.24904
3. PONYI A, BORGULYA G, CONSTANTIN T, VANCSA A, GERGELY L, DANKO K: Functional outcome and quality of life in adult patients with idiopathic inflammatory myositis. *Rheumatology* (Oxford) 2005; 44: 83-8. https://doi.org/10.1093/rheumatology/keh404



P-11. Fig. 1. Expression of TRIM63 and Atrogin-1 in muscle biopsies.

P-12

THE ROLE OF PROTEIN PHOSPHOTASE 1 IN INCLUSION BODY MYOSITIS

Donya Abdennebi[1], Sara Walli[1], Derya Cengiz[1], Vera Dobelmann[1], Corinna Preuße[2], Werner Stenzel[2], Anna Brunn[3], Andreas Roos[4], Christopher Nelke[1], Sven G. Meuth[1], Tobias Ruck[1]

[1]Department of Neurology, Medical Faculty, Heinrich Heine University Duesseldorf, Düsseldorf, Germany; [2]Department of Neuropathology, Charité-University Medicine Berlin, Berlin, Germany; [3]Institute of Neuropathology, Heinrich Heine University, University Hospital of Düsseldorf, Düsseldorf, Germany; [4]Department of Neuropediatrics, University of Duisburg-Essen, Essen, Germany

Background. Idiopathic inflammatory myopathies (IIMs) are rare autoimmune disorders characterized by persistent muscle inflammation, including inclusion body myositis (IBM), anti-synthetase syndrome (ASYS), dermatomyositis (DM), and immune-mediated necrotizing myositis (IMNM). Despite substantial progress in this field, understanding the interplay of inflammatory and metabolic factors in immune system dysregulation remains unclear. Here, we performed unlabelled proteomic analysis of skeletal muscle biopsies from IIM patients to better understand the underlying pathophysiology. **Methods.** Muscle biopsies from IBM (n=18), ASYS (n=5), DM (n3), and IMNM (n=5) were analysed by unlabelled mass-spectrometry based proteomics. We utilized sparse Partial Least Squares Discriminant Analysis (sPLS-DA) for dimensional reduction to detect unique proteomic signatures for each disease. These findings were collaborated by immunofluorescence analysis. **Results.** The proteomic analysis revealed distinct profiles among patients with IBM, ASYS, DM, and IMNM patients. Enrichment analysis demonstrated mitochondrial damage in IBM, with the interferon gamma pathway emerging as the most upregulated pathway. Interestingly, the protein that was most consistently downregulated in IBM was PPP1R27, a subunit of the protein phosphatase 1 (PP1). This could be confirmed through immunofluorescence staining, as lower levels of PP1 were observed in muscle biopsies from IBM patients in comparison to the other IIM subgroups and non-diseased controls. **Conclusion.** Phosphorylation is a crucial regulatory mechanism in cells. A dysregulation of PP1 could lead to abnormal phosphorylation states, thereby contributing to the metabolic abnormalities in IBM. We are planning to perform further experiments for a better understanding of PP1's role in IBM.

P-13

MITOCHONDRIAL-MEDIATED NEUTROPHIL ACTIVATION IN DERMATOMYOSITIS (DM) AND INCLUSION BODY MYOSITIS (IBM): INSIGHTS INTO PATHOGENESIS AND THERAPEUTIC IMPLICATIONS

Jorge Armando Gonzalez-Chapa[1], Jemima Albayda[2], Begum Horuluoglu[3], Despina Michailidou[1], Marina Barguil Macedo[1], Lisa Christopher-Stine[2], Ingrid Lundberg[4], Christian Lood[1]

[1]University of Washington, Seattle, WA, USA; [2]Johns Hopkins University, Baltimore, MD, USA; [3]Karolinska Institutet, Stockholm, Sweden; [4]Division of Rheumatology, Department of Medicine, Karolinska Institutet; Department of Gastroenterology, Dermatology, Rheumatology, Karolinska Universitetssjukhuset, Stockholm, Sweden

Background. Dermatomyositis (DM) and inclusion body myositis (IBM) are characterized by muscle weakness and inflammation, with emerging evidence of mitochondrial and neutrophil involvement. Prior work from our group has demonstrated the role of mitochondrial-derived danger-associated molecular patterns in promoting neutrophil activation. In the current study, we aimed to investigate whether patients with myopathies had elevated levels of extracellular mitochondrial biomarkers promoting neutrophil-mediated inflammation and its clinical association.

Methods. Plasma samples were obtained from patients with IBM, n=46, DM, n=40, and healthy individuals (HC, n=40) from Karolinska Institutet, Stockholm, Sweden; Johns Hopkins, Baltimore, USA; and University of Washington, Seattle, USA. DM was divided by MDA5 (n=19) and TIF1-gamma autoantibodies (n=21). We measured calprotectin, and neutrophil elastase-DNA complexes (NE-DNA) as neutrophil activation markers. For mitochondrial markers, we measured GDF-15, and N-formyl methionine (fMET) using ELISA. GraphPad Prism 9.4.0 facilitated statistical analysis. The Mann-Whitney U test and Spearman's correlation coefficient were utilized for statistical analysis.

Results. In DM and IBM patients, levels of mitochondrial fMET and GDF-15 were higher than in HCs (Fig.1A-B), supporting a role for mitochondrial extrusion. GDF-15 and fMET levels correlated in DM but not in IBM (Fig. 1C-D)**.** Elevated levels of calprotectin were noted in DM, especially in the MDA5 subtype (Fig. 1E)**,** while levels of calprotectin in IBM were similar to those in the HC group. In contrast, levels of neutrophil extracellular traps, NETs, were elevated in both DM and IBM patients, as compared to HC (Fig. 1F). Of note, levels of fMET correlated with calprotectin levels in both DM and IBM (Fig. 1G-H) suggesting a potential role for neutrophil FPR1 signaling (fMET receptor) in myopathies. MAA-negative IBM patients showed a significant inverse correlation between fMET and MMT8 scores, contrasting with the less robust CK correlation (Fig. 1 I-J), suggesting fMET may be a novel and superior, candidate for evaluating muscle involvement in IBM.

Conclusion. Distinct biomarker profiles in DM and IBM highlight mitochondrial dysfunction and neutrophil involvement in these diseases and fMET, as a potential novel prognostic biomarker for IBM, underscores this link. Future research is crucial for understanding their roles in disease progression and monitoring.

Acknowledgments. Gratitude is extended to the Lood Lab at the University of Washington Rheumatology Division, Johns Hopkins University, Karolinska Institutet, Cure JM Foundation, and the National Institutes of Health for their support.

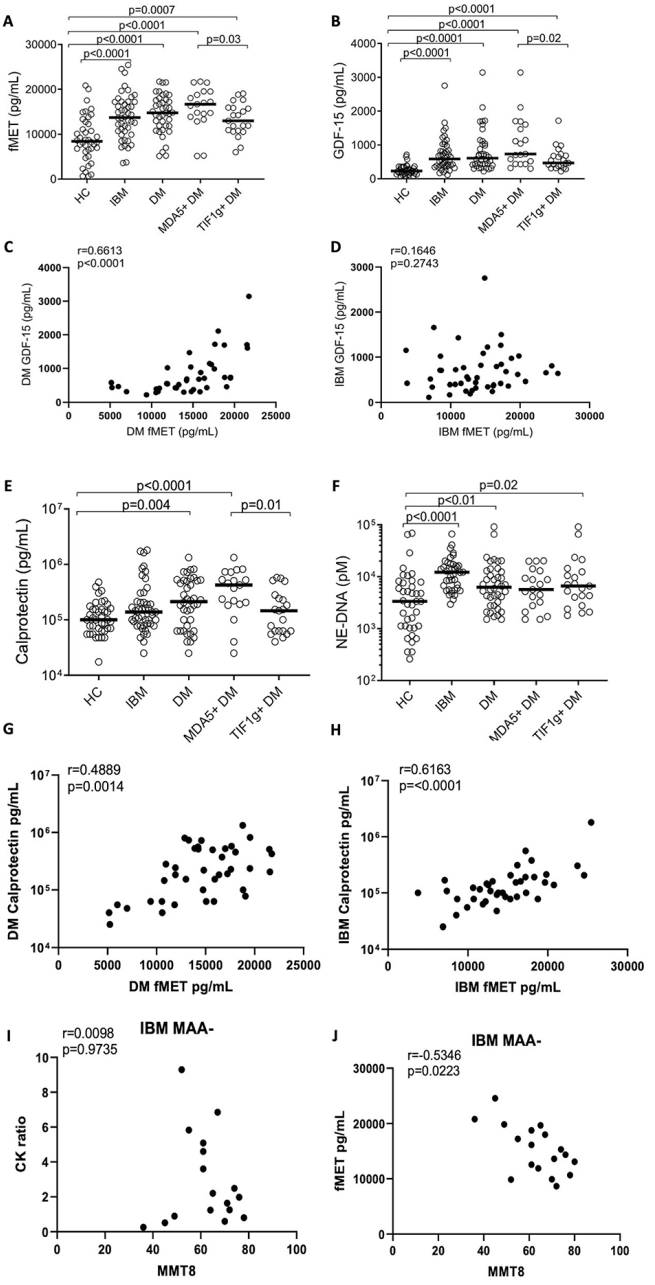


Fig. 1. Comparative analysis of fMET and GDF-15 as biomarkers in IBM and DM. Levels of A) fMET, B) GDF-15, E) Calprotectin, and F) NE-DNA were assessed in patients with Inclusion Body Myositis (IBM), Dermatomyositis (DM), and Healthy Controls (HC). Within the DM group, patients were subdivided into MDA5 (n=19) and TIF-1 gamma (n=21) subgroups. The Mann-Whitney U test was utilized for statistical analysis. Correlations were examined between GDF-15 and fMET in C) DM and D) IBM, calprotectin and fMET in G) DM and H) IBM, and IBM MAA negative patients between MMT8 scores and CK in I) and fMET in J), using Spearman's correlation coefficient.

References

1. DUVVURI B, PACHMAN LM, MORGAN G *et al.*: Neutrophil extracellular traps in tissue and periphery in juvenile dermatomyositis. *Arthritis Rheumatol* 2020; 72(2): 348-58. https://doi.org/10.1002/art.41078
2. WISCHHUSEN J, MELERO I, FRIDMAN WH: Growth/differentiation factor-15 (GDF-15): from biomarker to novel targetable immune checkpoint. *Front Immunol* 2020; 11: 951. https://doi.org/10.3389/fimmu.2020.00951
3. DE PAEPE B, VERHAMME F, DE BLEECKER JL: The myokine GDF-15 is a potential biomarker for myositis and associates with the protein aggregates of sporadic inclusion body myositis. *Cytokine* 2020; 127: 154966. https://doi.org/10.1016/j.cyto.2019.154966

P-14

PROFILING GRANZYMES IN INFLAMMATORY MYOPATHIES

Derek Wu[1], Michael Lane[1,2], Matthew Fliss[3], Hongyan Zhao[1,2], Karen Jung[1,2], Kristine Chapman[4], Michelle Mezei[4], Kristin Jack[4], Cameron Mitchell[3], Kun Huang[5], Fergus To[5], Katherine Beadon[4], Peter Schutz[2], Michael J Berger[1,6], David J Granville[1,2]

[1]International Collaboration on Repair Discoveries (ICORD), University of British Columbia, Vancouver, Canada; [2]Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, Canada; [3]School of Kinesiology, Faculty of Education, University of British Columbia, Vancouver, Canada; [4]Division of Neurology, Department of Medicine, University of British Columbia, Vancouver, Canada; [5]Division of Rheumatology, Department of Medicine, University of British Columbia, Vancouver, Canada; [6]Division of Physical Medicine & Rehabilitation, Department of Medicine, University of British Columbia, Vancouver, Canada

Background. Inflammatory myopathies are rare autoimmune conditions best characterized by muscle weakness and atrophy, leading to substantial disability. Granzymes are a family of serine proteases historically known for their intracellular, cytotoxic functions. In recent years, extracellular roles for granzymes in autoantigen generation, barrier dysfunction, extracellular matrix remodeling, and general inflammation have been revealed. Many studies have demonstrated that granzyme levels are typically low or undetectable in healthy tissues, but upregulated in autoimmune and inflammatory conditions. Moreover, granzymes may be implicated in the pathogenesis of inflammatory myopathies, as granzyme B substrates include FHL-1 and Mi-2, two major autoantigens of inflammatory myopathy. As such, we hypothesized that granzymes are elevated in patients with inflammatory myopathies and correlate to disease severity.

Methods. Muscle biopsies from healthy donors (n=2) and individuals with inflammatory myopathies (n=24; Dermatomyositis n=6; Inclusion body myositis n=5; Polymyositis n=3; Necrotizing HMG-CoA+ myositis n=4; Unspecified inflammatory myositis n=6) were analyzed using established immunohistochemistry protocols and digital pathology analysis pipelines (QuPath with Cellpose extension) for granzymes A, B, H, K, and M. Patient inclusion criteria required the participant to be 18 or older and possess a confirmed inflammatory myopathy diagnosis and classification through clinical features and histopathological muscle biopsy findings. The granzyme levels were then correlated with patient clinical and laboratory measurements (creatine kinase levels, C-reactive protein levels, alanine transaminase levels, aspartate transaminase levels, and Medical Research Council muscle strength score).

Results. All five granzymes (A, B, H, K, and M) were detected in the inflammatory myopathy samples. Preliminary analyses suggest that the numbers of granzymes A, B, and M-positive cells are increased in inflammatory myopathies by 17-fold (p=0.018), 3-fold (p>0.05), and 3-fold (p>0.05), respectively, compared to healthy muscle tissues. Moreover, the subtypes of inflammatory myopathy were also observed to have differing granzyme level profiles, with inclusion body myositis exhibiting higher numbers of granzyme A, B, and M-positive cells relative to the other disease subtypes. Granzyme levels did not correlate with patient clinical or disease measurements.

Conclusion. We demonstrated that granzymes A, B, and M are elevated in inflammatory myopathy muscle biopsies. While granzyme levels do not correlate with patient clinical or disease measurements, elevations in granzymes A, B, and M positivity show promise as a categorical marker. Analysis of 11 additional healthy muscle control samples for further inferential investigations is ongoing.

Acknowledgements. This project was funded by the Muscular Dystrophy Canada Translational Seed Grant.

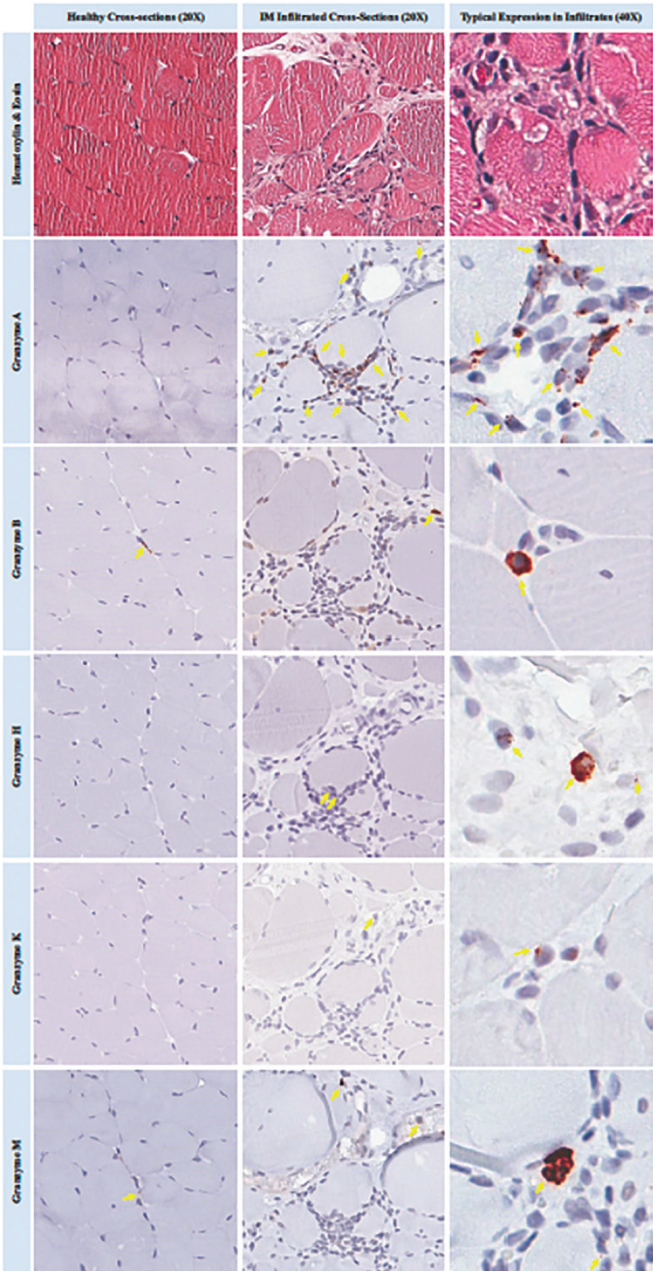


Fig. 1. Granzymes
A, B, H, K and Mininflammatory myopathy inflammatory myopathy c healthy donors. Hematoxylin-eosin staining and immunostaining for granzymes A, B, H, K, and M were performed on formalin-fixed paraffin-embedded muscle tissues of IM patients and healthy donors. The left-most column of panels depicts cross-sectional regions of healthy muscle tissue from a healthy muscle donor. Cross-sectional regions of IM muscle biopsies with characteristic histological patterns associated with IM are illustrated in the center column. The right column portrays the magnified and most typical infiltrate expression pattern of the stained granzyme in IM tissue. Hematoxylin and eosin staining is provided in the first row to providea better histological orientation of the muscle tissue. Positive staining for the respective granzyme is indicated by yellow arrows. The magnification of the left and central columns is 20x, while the magnification of the right column is 40x. Note: Granzyme expression levels in IM tissues can differ in both number of expressing cells and amount of granzymes expressed.

P-15

FOXP3+ T-REGULATORY CELLS HAVE DECREASED EXPRESSION OF NOTCH 2 FOLLOWING CARDIOTOXIN-INDUCED MUSCLE INJURY IN FOXP3EGFP MICE

Lisa A. Kimpler, Sara E. Sabbagh
Department of Pediatrics, Medical College of Wisconsin, Milwaukee, WI, USA

Background. Foxp3+ T-regulatory (T-reg) cells are essential regulators of muscle repair and regeneration. Following muscle injury, T-regs play a key role in the phenotypic switch of macrophages from a pro-inflammatory to a regulatory phenotype. This process is under the regulation of tissue-specific Notch expression in T-regs in non-muscle tissue, such as lung. However, the role of Notch in T-reg cell signaling following muscle injury has not yet been described. Here we investigate expression of different Notch receptors (Notch1, -2, -3, and -4) on T-regs isolated from inguinal lymph nodes following muscle injury in Foxp3^{EGFP} mice.

Methods. 10-week-old Foxp3^{EGFP} mice (Jackson Laboratories) that express eGFP (enhanced green fluorescent protein) under the control of the mouse Foxp3 promoter were injected with 50ul of 10uM cardiotoxin (Sigma Aldrich) or DPBS (Dulbecco's phosphate buffered saline) in the tibialis anterior (TA) muscle. TA and ipsilateral inguinal lymph nodes were harvested on day 2 and 4 following cardiotoxin or DPBS injection or in untreated Foxp3^{EGFP} mice. Muscle tissue was flash frozen in supercooled 2-methylbutane and stored at -80ºC for future sectioning. Muscle injury was confirmed by staining sections with hematoxylin and eosin-Y. Single cell suspensions from harvested lymph nodes were incubated with antibodies against CD4, CD8a (Thermo Fisher) and Notch1, Notch2, Notch3, or Notch4 (BioLegend). After washing, cells were fixed in 1% paraformaldehyde. Flow cytometry data were acquired on a Cytek Aurora spectral cytometer utilizing SpectroFlo software (Cytek Biosciences) and analyzed using FlowJo software (Tree Star). All experiments were performed according to the guidelines of the Institutional Animal Research Committees at the Medical College of Wisconsin.

Results. There was no expression of Notch1, Notch3, or Notch4 on Foxp3+ T-regs isolated from the inguinal lymph nodes in the untreated, DPBS treated, or cardiotoxin treated mice at any time point. There were low levels of Notch2 expression in CD4+ Foxp3+ cells in the inguinal lymph nodes of both untreated and DPBS-injected animals (5.58% and 3.51%, respectively). Comparatively, we found reduced Notch2 expression on CD4+ Foxp3+ cells at both day 2 and day 4 following cardiotoxin injection (0.74% and 1.35%, respectively).

Conclusions Our preliminary data show Notch2 expression on local Foxp3+ T-regs following muscle injury may play a role in regulation of muscle repair. Importantly, we did not find expression of Notch receptors 1, 3, and 4 in CD4+ Foxp3+ from the inguinal lymph nodes in the untreated or DPBS treated controls or in the cardiotoxin experimental groups. Additional experiments are needed to confirm these findings and investigate the role of Notch2 expression on muscle specific T-regs in regard to macrophage polarization, Treg recruitment and function, and muscle regeneration.

References

1. HARB H, BENAMAR M, LAI PS *et al*.: Notch4 signaling limits regulatory T-cell-mediated tissue repair and promotes severe lung inflammation in viral infections. *Immunity* 2021; 54(6): 1186-99 e7.
2. BURZYN D, KUSWANTO W, KOLODIN D *et al*.: A special population of regulatory T cells potentiates muscle repair. *Cell* 2013; 155(6): 1282-95. https://doi.org/10.1016/j.cell.2013.10.054 24

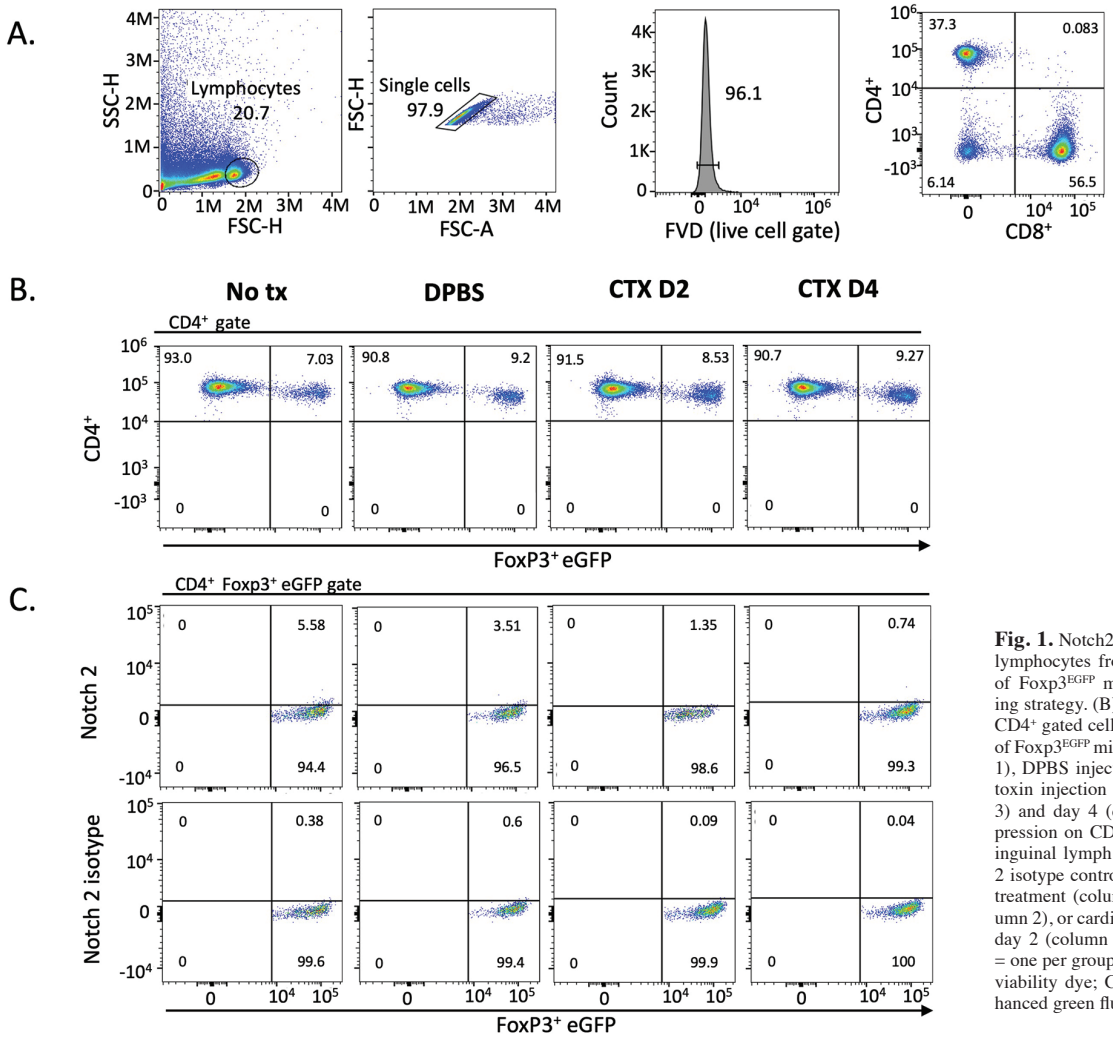


Fig. 1. Notch2 expression on CD4+ Foxp3+ lymphocytes from the inguinal lymph node of Foxp3^{EGFP} mice (A) Representative gating strategy. (B) CD4+ FoxP3+ expression of CD4+ gated cells in the inguinal lymph node of Foxp3^{EGFP} mice after no treatment (column 1), DPBS injection (column 2), and cardiotoxin injection harvested on day 2 (column 3) and day 4 (column 4). (C) Notch 2 expression on CD4+ Foxp3+ gated cells in the inguinal lymph node as compared to Notch 2 isotype control in Foxp3^{EGFP} mice after no treatment (column 1), DPBS injection (column 2), or cardiotoxin injection harvested on day 2 (column 3) and day 4 (column 4). N = one per group. Abbreviation: FVD: fixable viability dye; CTX: cardiotoxin; eGFP: enhanced green fluorescent protein.

P-16

MYOSITIS-SPECIFIC AUTOANTIBODIES INDUCE DISTINCT TRANSCRIPTOMIC SIGNATURES IN HUMAN SKELETAL MUSCLE MYOBLASTS

Sandra Muñoz-Braceras[1*], Iago Pinal-Fernandez[1,2*], Maria Casal-Dominguez[1,2#], Katherine Pak[1#], Jiram Torres-Ruiz[1,3#], Stefania Dell'Orso[4], Faiza Naz[4], Gustavo Gutierrez-Cruz[4], Shamima Islam[4], Ana Matas-Garcia[5,6,7], Joan Padrosa[7], Gloria Garrabou[5,6,7], Ernesto Trallero-Araguás[8,9], Brian Walitt[10], Julie J. Paik[11], Jemima Albayda[11], Lisa Christopher-Stine[2,11], Thomas E Lloyd[2], Josep Maria Grau-Junyent[5,6,7], Albert Selva-O'Callaghan[8,9], J. José C. Milisenda[1,5,6,7‡], Andrew L. Mammen[1,2,11‡]

*#‡These authors contributed equally to this project.

[1]Muscle Disease Unit, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD, US; [2]Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, USA; [3]Department of Immunology and Rheumatology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico; [4]Genomic Technology Section, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD, USA; [5]Muscle Research Unit, Internal Medicine Service, Hospital Clinic, Barcelona, Spain; [6]Barcelona University, Barcelona, Spain; [7]CIBERER, Barcelona, Spain; [8]Systemic Autoimmune Disease Unit, Vall d'Hebron Institute of Research, Barcelona, Spain; [9]Autonomous University of Barcelona, Barcelona, Spain; [10]National Institute of Neurological Diseases and Stroke, National Institutes of Health, Bethesda, Maryland, USA; [11]Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

Background. The idiopathic inflammatory myopathies (IIMs) are group of autoimmune diseases affecting the skeletal muscle. The major types of IIM include dermatomyositis, immune-mediated necrotizing myopathy, antisynthetase syndrome, and inclusion body myositis. Myositis-specific autoantibodies (MSAs) have been shown to identify clinical unique groups of patients with IIM. Muscle biopsies from patients with distinct MSAs show characteristic gene expression patterns, suggesting a potential mechanistic role of the MSAs in the observed transcriptomic signatures. Here, we aimed to determine whether internalized MSAs can lead to the same specific transcriptomic changes in muscle cells *in vitro*.

Methods. Immunoglobulins were isolated from the sera of IIM patients with different MSAs (anti-Mi2, anti-MDA5, anti-TIF1γ, anti-NXP2, anti-HMGCR, anti-SPR, and anti-Jo1), inclusion body myositis patients, and healthy individuals. The purified immunoglobulins, containing the MSAs, were introduced into cultured human skeletal muscle myoblasts by electroporation, and the transcriptomic profiles of the treated cells were studied by bulk RNA sequencing. The results from the differential expression analysis of electroporated cells were subsequently compared to those observed in muscle biopsies for each type of MSA-defined IIM.

Results. Skeletal muscle myoblasts electroporated with immunoglobulins from patients with MSAs showed an induced expression of genes that are also specifically upregulated in muscle biopsies from patients with the same MSAs. For example, SCRT1 and CAMK1G were upregulated in muscle biopsies from patients with anti-Mi2 and anti-Jo1 autoantibodies, respectively, and myoblasts electroporated with immunoglobulins from patients with anti-Mi2 and anti-Jo1 autoantibodies also upregulated SCRT1 and CAMK1G, respectively. Myoblasts electroporated with anti-Mi2 containing immunoglobulins showed a higher number of specifically differentially expressed genes than myoblasts treated with any of the other MSA-containing immunoglobulins. Of note, electroporation of immunoglobulins from patients with anti-MDA5 autoantibodies led to a significant upregulation of IFNB1 and interferon-upregulated genes.

Conclusion. The internalization of immunoglobulins from patients with MSAs into cultured myoblasts recapitulated distinct transcriptomic signatures observed in muscle biopsies from patients with the same MSAs. This finding suggests that MSAs can enter muscle cells and induce the transcriptomic signatures that have been described in different types of MSA-defined IIM. Further work will be required to demonstrate whether the transcriptomic changes induced by the MSAs contribute to muscle and/or other end organ damage in patients with IIM.

P-17

AUTOANTIBODIES RECOGNIZING AIRE DETECTED IN ANTI-MI2-POSITIVE DERMATOMYOSITIS

Jon Musai[1*], Sahana Jayaraman[2*], Katherine Pak[1], Iago Pinal-Fernandez[1,2], Maria Casal-Dominguez[1], Eric Cho[1], Fa'alataitaua M. Fitisemanu[1], José César Milisenda[3], Lisa G. Rider[4], Tom Lloyd[2], Lisa Christopher-Stine[2], H. Benjamin Larman[2†], Andrew L. Mammen[1,2†]

*co-first authors

†co-contributing Principal Investigators

[1]Muscle Disease Unit, National Institute of Arthritis and Musculoskeletal and Skin Disease, National Institutes of Health, Bethesda, MD; [2]Johns Hopkins University School of Medicine, Baltimore, MD; [3]Muscle Research Unit, Internal Medicine Service, Hospital Clinic, Barcelona, Spain; [4]National Institute of Environmental Health Sciences, National Institutes of Health, Bethesda, MD, USA

Background. Dermatomyositis (DM) is an idiopathic inflammatory myopathy (IIM). IIMs are a heterogenous family of autoimmune diseases that affect skeletal muscle, skin, lungs, and/or joints. Myositis-specific autoantibodies (MSAs) define unique disease phenotypes. For example, compared to other DM patients, DM patients with anti-Mi2 autoantibodies have more severe muscle weakness and greater myofiber necrosis (1). This study sought to identify novel myositis autoantibodies.

Methods. Phage Immunoprecipitation Sequencing (PhIP-Seq) is a serological screening technique that can identify novel antibodies. PhIP-Seq was performed using sera from 804 healthy controls and 411 IIM patients from the NIH Childhood Heterogeneity Collaborative Study and the Johns Hopkins Myositis Center. Multiple sequence alignment between autoimmune regulator (AIRE) and Mi2 peptide sequences was performed using ClustalW and Multiple Sequence Comparison by Log-Expectation. Sera from 63 healthy controls and 49 DM, 9 antisynthetase syndrome (ASyS), 6 inclusion body myositis (IBM), and 9 immune-mediated necrotizing myopathy (IMNM) adult and juvenile patients sourced from the NIH and the Clinic Hospital in Barcelona were screened for AIRE recognition by enzyme-linked immunosorbent assay (ELISA).

Results. PhIP-Seq identified autoantibodies that recognize AIRE in patients with anti-Mi2 autoantibodies. The screening cohort included 73 total DM, ASyS, IBM, and IMNM sera samples. Among these, 27 (40.0%) samples were positive for AIRE autoantibodies by ELISA. Of the 28 anti-Mi2-positive DM patients, 26 (92.9%) demonstrated AIRE recognition. By comparison, no sera with anti-MDA5, anti-NXP2, or anti-TIF1γ autoantibodies (other common DM autoantibodies) detected AIRE. Interestingly, multiple sequence alignment revealed regions of high homology between AIRE and Mi2 peptide sequences.

Conclusion. We demonstrate that patients with anti-Mi2-autoantibodies also have autoantibodies that recognize AIRE, suggesting the development of an anti-AIRE response in anti-Mi2-positive DM. Future work will investigate if there is a distinct anti-AIRE autoantibody or if anti-Mi2-autoantibodies directly bind AIRE. AIRE is a transcription factor that maintains central tolerance by negative selection of self-reactive T cells (2). Given the robust muscle disease activity in anti-Mi2-positive DM and AIRE's role in preventing autoimmune reactions, autoantibodies recognizing AIRE may

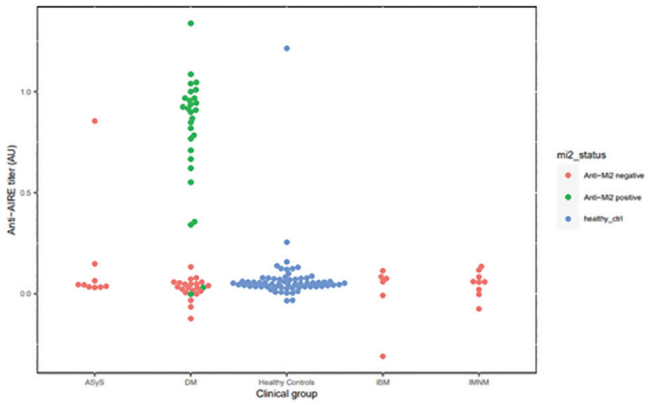


Fig. 1. Anti-AIRE autoantibody titers determined by ELISA in sera from 9 ASyS (8 anti-Jo1-positive and 1 Pl-7-positive), 49 DM (28 anti-Mi2-positive, 9 anti-MDA5-positive, 7 anti-NXP2-positive, and 5 anti-TIF1γ-positive), 6 IBM, 9 IMNM patients (5 anti-HMGCR-positive and 4 anti-SRP-positive), and 63 healthy controls.

contribute to the severe muscle disease in anti-Mi2-positive DM. We hope to further explore if autoantibodies recognizing AIRE directly contribute to anti-Mi2-positive DM pathophysiology.

References

1. PINAL-FERNANDEZ I, MECOLI CA, CASAL-DOMINGUEZ M *et al*.: More prominent muscle involvement in patients with dermatomyositis with anti-Mi2 autoantibodies. *Neurology* 2019; 93(19): e1768-e77. https://doi.org/10.1212/wnl.0000000000008443
2. PETERSON P, ORG T, REBANE A: Transcriptional regulation by AIRE: molecular mechanisms of central tolerance. *Nat Rev Immunol* 2008; 8(12): 948-57. https://doi.org/10.1038/nri2450

P-18

DECIPHERING THE LINK BETWEEN INTERFERON STIMULATED GENES AND REGENERATION USING SPATIAL TRANSCRIPTOMICS IN DERMATOMYOSITIS BIOPSIES

Linda Chenane[1], Julian Dal-Cin[1], Céline Anquetil[1], Hossein Khademian[1], Damien Amelin[1], Bérénice Tendrel[1], Angéline Madelaine[2], Sarah Leonard-Louis[1,3], Yves Allenbach[1,2], Olivier Benveniste[1,2]

[1]Sorbonne University-INSERM-Center of Research in Myology-UMRS 974, Paris, France; [2]Department of Internal Medicine and Clinical Immunology-Sorbonne Université-Pitié-Salpêtrière, Paris, France; [3]AP-HP-Pitié-Salpêtrière Hospital-Neuropathologie Laboratory-Reference Center for Muscle Diseases Paris-Est-Myology Institute, Paris, France

Background. Dermatomyositis (DM) is an Idiopathic Inflammatory Myopathy (IIM) characterized by progressive symmetrical proximal myopathy, and skin manifestations. Interferon-Stimulated Genes (ISGs) are among the most up-regulated genes in DM. Histological analysis shows also that DM muscles exhibit continuous attempts of regeneration ($CD56^+$ fibers) and in vitro cultures showed that Muscle Stem Cells derived from DM muscle (DM-MSC) have defects in their capacity to implement myogenesis comparing to control Muscle Stem Cells (C-MSC). It is widely admitted that inflammation is necessary during the first steps of regeneration can induce in vitro muscle atrophy. However, the link between Interferon Stimulated Genes and regeneration during dermatomyositis is not well understood.
Methods. To assess if there is a correlation between the histological aspect of muscle regions in DM biopsies and the presence of ISGs, we used spatial transcriptomics on 4 controls and 5 dermatomyositis biopsies. We cultured myoblasts derived from both C-MSC and DM-MSC to determine their ability to proliferate and to quantify by RTq-PCR the expression of genes linked to the first steps of regeneration.
Results. Here we show an upregulation of both ISGs and genes related to regeneration/myogenesis in DM samples. Moreover, we found an anticorrelated expression of these two groups of genes within the muscle. Interestingly, labeling of histological areas in DM biopsies and differential gene expression between atrophied and non-atrophied regions showed a specific enrichment of Interferon signaling (ISG15, IFI6, IFIT1) in atrophied DM regions and a downregulation of key markers of regeneration (MYH3 and ACTC1). Finaly, RT-qPCR results showed and impeded capacity of DM-MSC in vitro to proliferate associated to a decreased expression of factors necessary to differentiation (MEF2C, MYOG).
Conclusion. Taken together, these data show a potential negative effect of ISGs on both muscle homeostasis and regeneration in dermatomyositis affected muscle and an intrinsic default at the mRNA level of regeneration factors suggesting a transcriptional regulation of the first step of regeneration in dermatomyositis muscle stem cells.

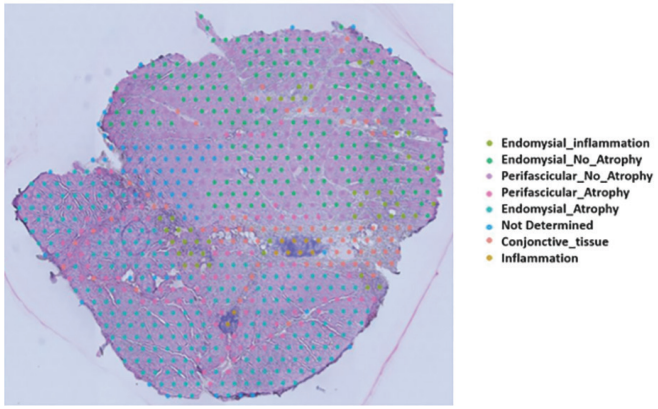


Fig. 1. H&E-stained dermatomyositis (DM) musle from one representative sample with spatial transcriptomics spot of histological labeling visualized on tissue-covered area.

P-19

BLOOD LEVELS OF INTERFERONS A, B, Γ AND TOLL-LIKE RECEPTORS 7, 9 CORRELATE POSITIVELY WITH MUSCLE STRENGTH IN PATIENTS WITH IDIOPATHIC INFLAMMATORY MYOPATHIES

Piotr Szczesny, Sebastian Miernik, Marzena Olesinska

National Institute of Geriatrics, Rheumatology and Rehabilitation, Warsaw, Poland

Background. The potential role of interferons (IFN) and toll-like receptors (TLR) in pathogenesis of idiopathic inflammatory myopathies (IIM) has been examined in previous studies, however their impact on phenomenon of muscle weakness, which is the foremost feature of this group of diseases, remains unknown.
Methods. Patients from a tertiary center in the capital city of Poland were recruited into the study. They needed to be diagnosed with IIM according to the latest classification criteria from 2017 with at least moderate muscle weakness, control group comprised of age and sex matched individuals with no muscle nor inflammatory disease documented. Peripheral blood and muscle tissue were collected from all patients. Expression of molecules was measured from the whole blood and whole muscle samples. Disease activity was assessed using tools included in Core Set Measures.
Results. 23 patients were recruited to the study group and 25 to the control group. A moderate negative correlation was found between manual muscle test (MMT) 8 and creatine kinase (CK) (rho -0.418, *p*-value 0.047). Blood analyzes showed a statistically significant difference between the level of expression of TLR7, TLR9 molecules in patients diagnosed with IIM and the control group. There was no distinction between both groups in terms of the expression of interferons α, β or γ. Patients with greater muscle strength measured by MMT8 had higher expression levels of IFNα, IFNβ, IFNγ, TLR7 and TLR9. The expression of IFNα, IFNβ negatively correlated with PhGA. IFNβ expression negatively correlated with extramuscular activity. Muscle tissue comparisons did not show similar meaningful results.
Conclusion. Although patients with higher disease activity constituents had higher CK levels, they also had lower blood expression of IFNs and TRLs. These results suggest, that IFNs and TLRs play role in regeneration processes in myositis or that the muscle tissue reaction to IFNs in IIM differs from that of a healthy person. Further studies are required, including isolation of inflammatory cells and analysis of the concentration of these molecules.

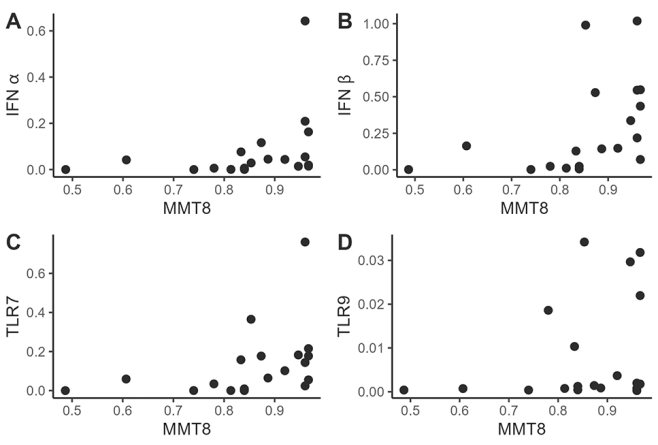


Fig. 1.

P-20

EFGARTIGIMOD PREVENTS NECROSIS AND ALLOWS FOR MUSCLE FIBER REGENERATION IN A HUMANIZED MOUSE MODEL OF IMMUNE-MEDIATED NECROTIZING MYOPATHY (IMNM)

Sarah Julien[1], Emma Briand[1], Bas van der Woning[2], Leentje De Ceuninck[3], Rachid Zoubari[1], Olivier Benveniste[4], Laurent Drouot[1], Olivier Boyer[1,5]
[1]Univ Rouen Normandie, INSERM, UMR1234, FOCIS Center of Excellence, PAn'THER, F-76000, Rouen, France; [2]argenx, Zwijnaarde, Belgium; [3]argenx, Issy les Moulineaux, France; [4]AP-HP, Pitié-Salpêtrière University Hospital, Department of Internal Medicine and Clinical Immunology, Paris, France; [5]Rouen University Hospital, Department of Immunology and Biotherapy, Rouen, France

Background. Immune-mediated necrotizing myopathy (IMNM) is a severe form of myositis characterized by muscle weakness and elevated creatine kinase levels in serum. 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 two separate mechanisms: 1) myolysis following complement activation; and 2) impairment of muscle fiber regeneration. Efgartigimod is an IgG1 Fc fragment targeting the neonatal Fc receptor (FcRn). We evaluated the therapeutic effects of IgG clearance by efgartigimod in a humanized murine model of IMNM.

Methods. Groups of Rag2 deficient (Rag2-/-) mice received daily intraperitoneal injections of IgG-depleted human serum as a source of human complement. 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). Rag2-/- mice were treated with efgartigimod 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 a therapeutic setting, administration of efgartigimod fully restored grip strength and muscle strength in mice treated with pathogenic anti-HMGCR$^+$ IgG (p<0.05). Total IgG and specific anti-HMGCR$^+$ IgG aAb became undetectable in serum since day 18, *i.e.* 9 days after efgartigimod administration. Histological analyses demonstrated that efgartigimod reduces IgG deposits, prevents further necrosis and allows for muscle fiber regeneration.

Conclusion. Efgartigimod reduces circulating IgG levels and rapidly eliminates pathogenic anti-HMGCR+ in a humanized mouse model of IMNM, preventing further necrosis and allowing muscle fiber regeneration, resulting in regain of muscle performance. These results support investigating the therapeutic efficacy of efgartigimod through a clinical trial in IMNM patients.

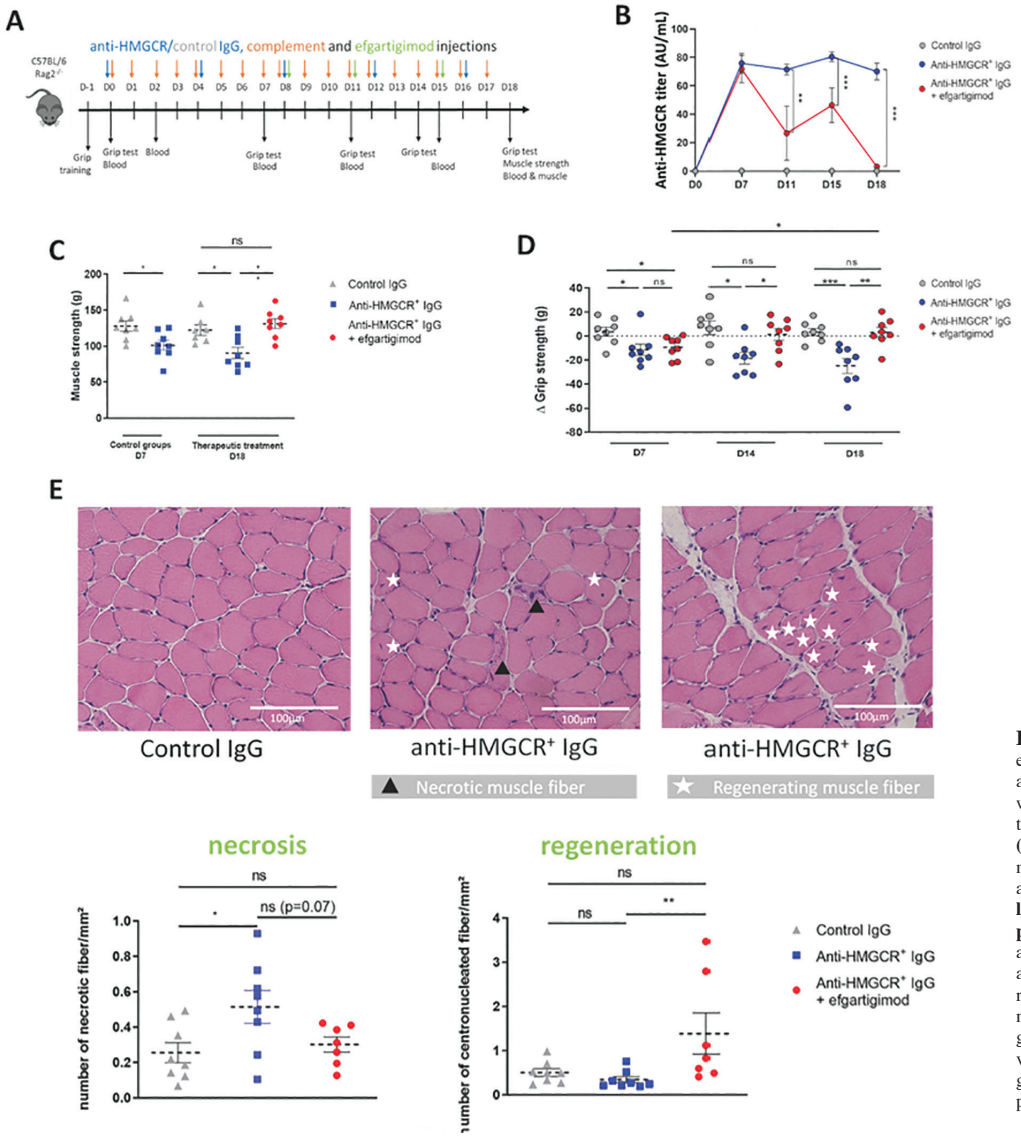


Fig. 1. Rag2$^{-/-}$ mice were treated with efgartigimod in a curative setting (green arrows on day 8, 11, 15), after disease was induced by anti-HMGCR+ IgG injections (blue arrow on day 0, 4, 8, 12, 16) **(A)**. Efgartigimod treatment rapidly eliminated pathogenic anti-HMGCR+ IgGs **(B)** and fully restored muscle strength **(C, left panel)** and grip strength **(C, right panel)** in mice treated with pathogenic anti-HMGCR+ IgG (p<0.05). Histological analyses demonstrated that efgartigimod reduced IgG deposits, prevented further necrosis and allowed for muscle fiber regeneration **(E)**. These results support investigating the therapeutic efficacy of efgartigimod through a cinical trial in IMNM patients.

P-21

DEVELOPMENT OF A NOVEL AUTOANTIBODY PANEL FOR THE DETECTION OF INTERSTITIAL LUNG DISEASE (ILD) ASSOCIATED TO SYSTEMIC AUTOIMMUNE DISEASES

Chelsea Bentow[1], Mary Ann Aure[1], Carlos Ramirez[1], Laura Martinez-Prat[2], Carmen Pilar Simeón Aznar[3], Alfredo Guillén Del Castillo[3], Thierry Vincent[4], Alexandre Jentzer[4], Alessandra Melegari[5], Maria Teresa Mascia[6], Dilia Giuggioli[6], Michael Mahler[1]

[1]Research and Development, Headquarters & Technology Center Autoimmunity, Werfen, San Diego, CA, USA; [2]Autoimmunity Research Unit, Technology Center OEM, Werfen, Barcelona, Spain; [3]Systemic Autoimmune Diseases Unit, Internal Medicine Service, University Hospital Vall d'Hebron, Barcelona, Spain; [4]Department of Immunology, St Eloi Hospital, Montpellier University, CHRU de Montpellier, Montpellier, France; [5]Autoimmunity Unit, Laboratory Department Azienda USL Modena, Modena, Italy; [6]Rheumatology Unit, Azienda Ospedaliero Universitaria Policlinico di Modena, University of Modena and Reggio Emilia, Modena, Italy

Background. Interstitial lung disease (ILD) is a common organ involvement in patients with systemic autoimmune rheumatic diseases (SARD) and represents one of the main risk factors for mortality. Several autoantibodies have been associated with ILD and hold promise as diagnostic and prognostic tools. A total of 12 autoantibody markers have been considered for interstitial pneumonia with autoimmune features (IPAF) including antinuclear antibodies, rheumatoid factor (RF), anti-CCP, anti-dsDNA, anti-SS-A/Ro, anti-SS-B/La, anti-RNP, anti-Sm, anti-Scl-70, antisynthetase antibodies, anti-PM/Scl and anti-MDA-5 antibodies.[1] In addition, with the availability of novel anti-fibrotic treatments, patient stratification is of outmost importance, especially due to the lack of cost-effectiveness of such drugs. Here we aimed to develop and validate a multi-analyte panel for the detection of antibodies associated with SARD-ILD.
Methods. Serum samples from a total of 208 patients with ILD together with healthy (n=67) and disease controls (n= 262) were tested. Of the ILD patients, 188 had a diagnosis of systemic sclerosis (SSc-ILD), and 20 patients had idiopathic inflammatory myopathy (IIM-ILD). Autoantibodies to a wide range on antigenic targets were measured using a novel particle-based multi-analyte technology (PMAT), including antibodies to dsDNA, RNP, Sm, Ro52, Ro60, SS-B, Scl-70, Jo-1, Centromere, DFS70, Ribo-P, Ku, RNA Pol III, Rpp25 (Th/To), PM/Scl, BICD-2, U11/U12 RNP (RNPC3), MDA5, Mi-2, TIF1-γ, PL12, SAE1, EJ, HMGCR, PL-7, SRP, and NXP2.
Results. Autoantibodies were found in 186/208 (89.4%) of the ILD patients. The prevalence of individual autoantibodies ranged from 0.48% to 43.8% (for TIF1-γ and Scl-70, respectively). The prevalence of autoantibodies most pronounced in SSc-ILD and IIM-ILD are shown in the table below.

Category	SSc-ILD (n=188) No pos/ % pos	IIM-ILD (n=20) No pos/ % pos	ILD Total (n=208) No pos/ % pos
Ro52	45/23.9%	4/20.0%	49/23.6%
MDA5	12/6.4%	7/35.0%	19/9.1%
Th/To	4/2.1%	0/0.0%	4/1.9%
RNP	25/13.3%	3/15.0%	28/13.5%
Scl-70	91/48.5%	0/0.0%	91/43.8%
Centromere	15/8.0%	0/0.0%	15/7.2%
PM/Scl	33/17.6%	0/0.0%	33/15.9%
RNPC3	8/4.3%	2/10.0%	10/4.8%
Other MSA	22/11.7%	4/20.0%	26/12.5%

Conclusion. Profiling of autoantibodies might represent a promising approach for the management of patients with SARD-ILD. Further studies are warranted to validate the panel in larger cohorts.

Reference

1. FERNANDES L, NASSER M, AHMAD K, COTTIN V: Interstitial Pneumonia with Autoimmune Features (IPAF). *Front Med* (Lausanne). 2019; 6: 209. https://doi.org/10.3389/fmed.2019.00209

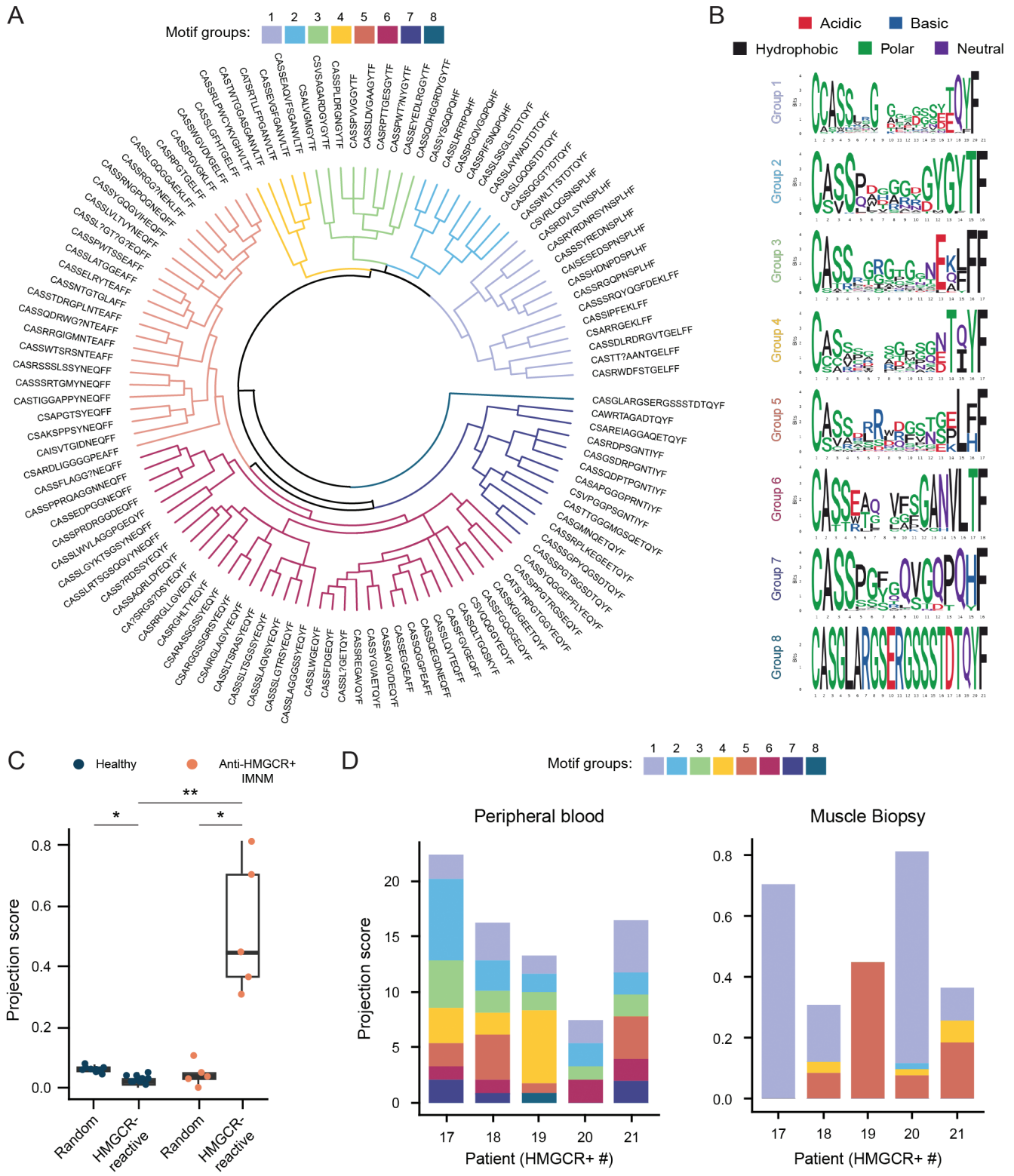
P-22

PRECISE IDENTIFICATION AND TRACKING OF HMGCR-REACTIVE CD4+ T CELLS IN THE TARGET TISSUE OF PATIENTS WITH ANTI-HMGCR IMMUNE MEDIATED NECROTIZING MYOPATHY

Eleni Tiniakou[1], Alexander A. Girgis[1,2], Myma Albayda[1], Brit Adler[1], Julie Paik[1], Christopher Mecoli[1], Lisa Christopher-Stine[1], Andrew L. Mammen[1,3,4†], Erika Darrah[1†]

[1]Division of Rheumatology, Johns Hopkins University, School of Medicine, Baltimore, MD, USA; [2]Biomedical Engineering, Johns Hopkins University, School of Medicine, Baltimore, MD, USA; [3]Division of Neurology, Johns Hopkins University, School of Medicine, Baltimore, MD, USA; [4]NIAMS, National Institutes of Health, Bethesda, MD, USA

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 track these cells in the affected muscle of these patients.
Methods. Peripheral blood mononuclear cells (PBMCs) from 10 patients with anti-HMGCR+ IMNM and 10 patients with dermatomyositis (DM) were screened for activation status in response to stimulation with HMGCR protein, as well as naturally presented HMGCR peptides identified with Natural Antigen Processing Assay (NAPA), based on CD154 upregulation. Subsequently, utilizing next generation T cell receptor (TCR) sequencing, HMGCR-reactive T cells were sorted based on CD154 upregulation and matched with TCRs identified in the muscle biopsy tissue of the respective patients (n=5).
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). There was a positive correlation between anti-HMGCR antibody titers and the frequency of HMGCR-specific CD4+ T cells (r^2=0.5141, p=0.0453). A total of 7 different naturally processed HMGCR peptides were identified using NAPA. 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). The muscle biopsies were found to contain several HMGCR-reactive TCRs (Fig. 1A). Using TCR clustering algorithm GIANA, 8 motif groups specific to HMGCR-reactive TCRs, which appeared more frequently in the muscle biopsies compared to motifs of whole blood TCRs (projection score 0.044 *vs*. 0.528, p=0.0072) (Fig. 1B, C, D, E).
Conclusion. Our findings represent the first report of antigen-specific CD4+ T cells in anti-HMGCR+ IMNM. HMGCR-specific CD4+ T cells correlated with the levels of anti-HMGCR antibodies. Furthermore, leveraging NAPA, we were able to define a core set of naturally presented HMGCR peptides which were relevant autoantigenic CD4+ T cell epitopes, and using TCR sequencing, we tracked HMGCR-reactive TCRs in the target muscle tissue, suggesting a targeted and active role in the disease process.


A
Motif groups: 1 2 3 4 5 6 7 8
B
Acidic
Basic
Hydrophobic
Polar
Neutral
Group 1
Group 2
Group 3
Group 4
Group 5
Group 6
Group 7
Group 8
C
Healthy
Anti-HMGCR+ IMNM
Projection score
Random
HMGCR-reactive
Random
HMGCR-reactive
D
Motif groups: 1 2 3 4 5 6 7 8
Peripheral blood
Muscle Biopsy
Projection score
Patient (HMGCR+ #)
Patient (HMGCR+ #)

P-22 Fig. 1.

P-23

VITAMIN D RECEPTOR GENE EXPRESSION IN MUSCLE TISSUE AND PRIMARY MUSCLE CELLS IS ASSOCIATED WITH MUSCLE FUNCTION PARAMETERS AND LIPID METABOLISM IN PATIENTS WITH MYOSITIS AND HEALTHY CONTROLS

Lucia Vernerová[1], Martina Vokurková[1], Nikoleta Alchus Laiferová[4], Michal Nemec[4], Maja Špiritović[1,3], Oksana Mytiai[4,5], Sabína Oreská[1,2], Martin Klein[1,2], Michal Tomčík[1,2], Jozef Ukropec[4], Barbara Ukropcová[4,5], Jiří Vencovský[1,2]

[1]Institute of Rheumatology, Prague, Czech Republic; [2]Department of Rheumatology, First Faculty of Medicine, Charles University, Prague, Czech Republic; [3]Department of Physiotherapy, Faculty of Physical Education and Sport, Charles University, Prague, Czech Republic; [4]Institute of Experimental Endocrinology, Biomedical Research Center, Slovak Academy of Sciences, Bratislava, Slovakia; [5]Institute of Pathophysiology, Faculty of Medicine, Comenius University, Bratislava, Slovakia

Background. Idiopathic inflammatory myopathies (IIM) patients suffer from progressive muscle weakness that may persist even after pharmacological suppression of inflammation. Vitamin D is essential for the maintenance of skeletal muscle. The binding of biologically active 1,25(OH)D to vitamin D receptor (VDR) induces transcriptional modulation of target genes involved in calcium/phosphate homeostasis, cellular proliferation/differentiation, and immune and mitochondrial function. The aim was to analyse VDR in the muscle tissue of IIM patients and healthy individuals (HC) and relate it to metabolic and muscle health parameters.
Methods. Muscle biopsies from m. vastus lateralis were obtained from 7 IIM patients before/after the 24-week training program, 13 non-exercising IIM patients, and 21 HC. Primary muscle cell cultures were established. Gene expression of VDR was determined by qPCR in muscle tissue and primary muscle cells. Oxidative metabolism was assessed in muscle (mRNA, qPCR) and in primary muscle cells (radioactive assays).
Results. Lower serum level of active 1,25(OH)D was observed in IIM patients compared to HC (125.0±45.4 *vs*. 164.7±49.2 pmol/l; $p<0.0001$). Numerically higher gene expression of VDR was found in muscle tissue and primary muscle cells in IIM compared to HC. After the 24-week training, gene expression of VDR in primary muscle cells decreased ($p=0.031$). VDR gene expression in muscle tissue was associated with MMT8 (IIM: r=-0.559, $p=0.013$), serum myoglobin (IIM: r=0.510, $p=0.026$; HC: r=0.473, $p=0.035$), creatin kinase (HC: r=0.484, $p=0.031$), triacylglycerols (HC: r=0.657, $p=0.001$), and HDL cholesterol (HC: r= -0.501, $p=0.021$). VDR mRNA in differentiated muscle cells correlated negatively with the complete oxidation of saturated palmitic fatty acid (CO2 production, R= -0.531, $p=0.028$), non-oxidative palmitate disposal (R= -0.685, $p=0.001$), total palmitate disposal (oxidative + non-oxidative palmitate disposal, R= -0.667, $p=0.001$) as well as with the relative content of mitochondrial complex V (% of the sum of all five OxPHOS complexes) (R= -0.49, $p=0.046$), irrespective of the disease or training state of subjects.
Conclusion. Increased VDR gene expression in muscle of IIM patients is associated with worse muscle condition and lipid profile. Higher VDR expression in differentiated muscle cells is related to decreased in vitro parameters of lipid metabolism and a lower relative content of complex V, which plays a decisive role in the ATP-producing capacity of mitochondria. These findings may suggest a local vitamin D signalling response to vitamin D deficiency observed in IIM and an adaptation of energy-generating metabolism to adverse conditions.
Acknowledgment. This work was supported by the Ministry of Health of the Czech Republic grant nr. NU21-05-00322.

OP-1

TOLL-LIKE RECEPTOR 7/8 ACTIVATION OF IMMUNE AND NON-IMMUNE CELLS IN MUSCLE BY RNA-CONTAINING IMMUNE COMPLEXES CAN CONTRIBUTE TO INFLAMMATION AND THE PATHOGENESIS OF MYOSITIS

Yin Wu[1], Aditee Deshpande[1], Nicholas Geraci[1], Vera Sellers[1], Phanindra Velisetty[1], David Fiorentino[2], Kavita Y. Sarin[2], Andrew Bender[1]

[1]EMD Serono, Billerica, MA, USA; [2]Stanford University, Redwood City, CA, USA

Background. Tissue inflammation is a major disease driver in idiopathic inflammatory myopathies (IIM), leading to muscle weakness and, in the case of dermatomyositis (DM), a subtype of IIM, cutaneous manifestations. The upstream pathways causing inflammation in IIM are poorly characterized. Activation of endosomal toll-like receptors (TLR) may drive inflammation in IIM as hallmarks of TLR activation are observed in some patients, including high Type I interferon (IFN) and the presence of RNA-containing immune complexes. We studied the potential contribution of TLR7 and TLR8 in IIM pathogenesis.
Methods. Immune complexes from 69 patients with IIM, 15 patients with lupus and 18 healthy controls were tested for their ability to activate healthy donor peripheral blood mononuclear cells (PBMCs). The impact of the TLR7/8 inhibitor enpatoran on PBMC activation was evaluated in a subset of samples. Human myoblasts and satellite cells were treated with supernatants from TLR7/8-activated PBMCs and gene expression was evaluated by NanoString. Mice were dosed intramuscularly with the TLR7/8 agonist R848 and single cell RNA sequencing was run on the muscle to ascertain the cell types responding to TLR7/8 and the downstream effects.
Results. Immune complexes from patients with IIM and lupus stimulated the production of IFN-α from PBMCs and triggered significant gene expression changes, including induction of a Type I IFN-gene signature. IFN production was completely blocked by enpatoran. DM patients, specifically those with autoantibodies targeting Jo-1, had the highest prevalence of activating immune complexes. Histidyl-transfer RNA, which is associated with the Jo-1 autoantibody, activated PBMCs in a TLR7/8-dependent manner. Myoblasts and satellite cells were activated by supernatants from TLR7/8 agonist-treated PBMCs, as determined by gene expression changes including increased expression of cytokines/chemokines and decreased expression of some muscle cell markers. In vivo, monocytes/macrophages and endothelial cells in muscle were activated by R848. Both cell types produced inflammatory cytokines downstream of NF-ϰB and endothelial cells increased expression of adhesion molecules. There was also the appearance of an IFN-gene signature in multiple cell types.
Conclusion. TLR7/8 activation can lead to inflammation in muscle with deleterious effects. RNA in immune complexes from patients with IIM, particularly Jo-1-positive DM patients, may activate TLR7/8. These data suggest that enpatoran may reduce inflammation in myositis that is triggered by TLR7/8 activation.
Acknowledgements. The healthcare business of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945) sponsored this study and medical writing support by Bioscript Group Ltd.

OP-2

SKELETAL MUSCLE FORCE DECLINE AFTER EXPOSURE TO SERA FROM PATIENTS WITH IDIOPATHIC INFLAMMATORY MYOPATHY

Cecilia Leijding[1], Stefano Gastaldello[1], Kristofer M. Andreasson[2,3], Tomas Schiffer[1], Suchada Kaewin[1], Takashi Yamada[4], Mattias Carlström[1], Ingrid E. Lundberg[2,5], Helene Alexanderson[2,3] Daniel C. Andersson[1,6]

[1]Karolinska Institutet, Department of Physiology and Pharmacology, Stockholm, Sweden; [2]Karolinska Institutet, Department of Medicine, Division of Rheumatology, Stockholm, Sweden; [3]Karolinska University Hospital, Allied Health Professionals, Medical Unit Occupational and Physical Therapy, Stockholm, Sweden; [4]Sapporo Medical University, Sapporo, Japan; [5]Karolinska University Hospital, Department of Gastro, Dermatology and Rheumatology, Stockholm, Sweden; [6]Karolinska University Hospital, Heart, Vascular and Neurology Theme, Cardiology unit, Stockholm, Sweden

Background. Idiopathic inflammatory myopathies (IIM) are a group of systemic autoimmune inflammatory muscle disorders characterized by sym-

metrical skeletal muscle weakness and accelerated fatigue (1). Although signs of inflammatory cell infiltrates in the muscles are commonly seen, correlation lacks between the degree of infiltrates and muscle weakness or fatigue (2). The mechanisms causing the muscle weakness in IIM remain unclear. Considering the systemic inflammation involved in IIM, our hypothesis proposes that blood-borne factors contribute to muscle dysfunction by affecting the contractile apparatus within muscle fibers

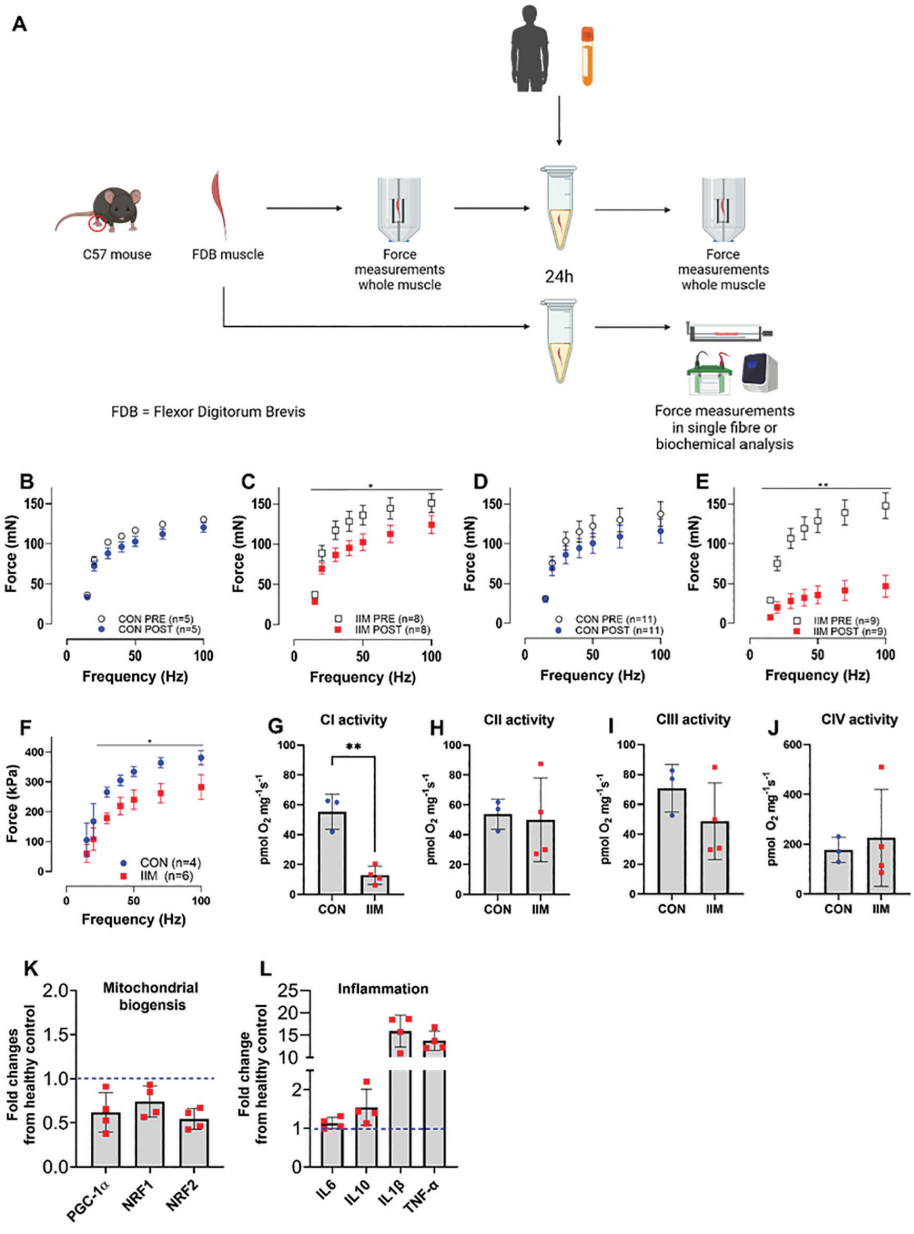
Methods. Isolated whole flexor digitorum brevis (FDB) muscles from female WT (C57BL/6JRj) mice were incubated in buffer (DMEM) containing either 10% or 50% of serum from patients with IIM or from healthy controls (Fig. 1A). The isolated whole muscles were incubated at room temperature for 24 h. Muscle force-frequency measurements were assessed before and after incubation of the muscles via repeated electrical stimulations at frequencies ranging between 15-100Hz. Force measurements were also performed in mechanically isolated muscle fibers from incubated FDBs to assess contractile function at single cell level. Mitochondrial respiration in permeabilized muscles was assessed with respirometry using the Oroboros technique. qPCR was conducted to measure gene expression to assess protein expression in incubated muscles.

Results. In whole muscles exposed to sera from patients with IIM, we found reduced force generation in a serum-dose dependent manner that was not observed after incubation in healthy control sera (Fig. 1B-E). Furthermore, the force decline after IIM sera was also evident at the single muscle fiber level suggesting that sera from patients with IIM affect the contractile machinery at cellular level (Fig. 1F). The activity of mitochondrial respiratory chain (complex I) was reduced (Fig.1G-J), and mitochondrial biogenesis regulatory genes (PGC1α, NRF1/2) displayed lower expression (Fig. 1K) after incubation with IIM sera when compared to healthy sera, indicating metabolic stress. Moreover, muscles increased their gene expression for inflammatory cytokine production following incubation with sera from patients with IIM, suggesting that local cytokine production is induced within the muscle fiber by IIM sera (Fig. 1L).

Conclusion. Sera from patients with IIM can initiate a phenotype of inflammatory activation, muscle weakness and metabolic dysfunction in an intact isolated healthy skeletal muscle preparation. By using isolated mouse muscle preparations in sera from human patients with IIM, we have developed an experimental platform to study physiological as well as molecular mechanisms that could contribute to muscle weakness in patients with IIM.

References

1. LUNDBERG IE, FUJIMOTO M, VENCOVSKY J *et al*.: Idiopathic inflammatory myopathies. *Nat Rev Dis Primers* 2021; 7(1): 86.
2. DORPH C, ENGLUND P, NENNESMO I, LUNDBERG IE: Signs of inflammation in both symptomatic and asymptomatic muscles from patients with polymyositis and dermatomyositis. *Ann Rheum Dis* 2006; 65(12): 1565-71.



OP-2 Fig. 1. A, Experimental platform. B-E, Force-frequency curves from FDB muscles before and after exposure to 10% or 50% sera from patients with Idiopathic inflammatory myopathies (IIM) (red) and healthy controls (CON) (blue). F, Force-frequency curves from single fibers after exposure to IIM patient sera (red) or CON (blue). F-J, Mitochondrial respiratory chain function in FDB muscles after exposure to 50% sera from IIM patients (red) and CON (blue). K-L, Gene expression in FDB muscles after exposure to sera, fold change in IIM serum exposed muscles compared to control (dotted line). Graphics (A) created with BioRender.com

OP-3

DISTRIBUTION AND CLINICAL RELEVANCE OF ANTI-NXP2 ANTIBODY ISOTYPES IN PATIENTS WITH DERMATOMYOSITIS

Xinxin Zhang[1,2,3], Sang Lin[2,3,4], Chao Sun[1,2,3], Qiwen Jin[1,2,3], Xixia Chen[1,2,3], Yuetong Xu[2,3,4], Wei Jiang[2,3], Shanshan Li[2,3], Xiaoming Shu[2,3], Xin Lu[2,3], Guochun Wang[1,2,3,4], Qinglin Peng[1,2,3,4]

[1]Peking University China-Japan Friendship School of Clinical Medicine, Beijing, China; [2]Department of Rheumatology, Key Myositis Laboratories, China-Japan Friendship Hospital, Beijing, China; [3]Beijing Key Lab for Immune-Mediated Inflammatory Diseases, China-Japan Friendship Hospital, Beijing, China; [4]China-Japan Friendship Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China

Background. This study aims to investigate the distributions and clinical significance of anti-NXP2 antibody isotypes, including IgM, IgA, IgG and its subclasses in the patients with anti-NXP2-positive dermatomyositis (anti-NXP2+ DM).
Methods. Seventy-nine anti-NXP2+ DM patients tested as anti-NXP2 IgG antibody positive by immunoblotting were retrospectively collected. Enzyme-linked immunosorbent assay (ELISA) was performed to detect anti-NXP2 antibody isotypes, and the associations between theses antibodies with clinical features and patients' prognosis were analyzed.
Results. In anti-NXP2+ DM patients, ELISA revealed positivity rates of 65.82 %,74.68 % and 100 % for anti-NXP2 IgM, IgA and IgG antibodies, respectively. The presence of anti-NXP2 IgM antibody significantly correlated with subcutaneous edema occurrence (p=0.012). Meanwhile, anti-NXP2 IgA antibody was strongly linked to the incidence of interstitial lung disease (ILD) (p=0.01) and impaired muscle functionality (p<0.05) in anti-NXP2+ DM patients. Furthermore, the analysis of anti-NXP2 IgG subclasses predominately showed IgG1 (82.28 %) and IgG2 (59.49 %) subtypes and, to a lesser extent, IgG3 (36.71 %) and IgG4 (29.11 %). Elevated level of anti-NXP2 IgG1 antibody indicated more pronounced and refractory muscle damage (all p<0.05) and was independently associated with mortality (p=0.039) in anti-NXP2+ DM patients.
Conclusion. Anti-NXP2 antibody isotypes can serve as biomarkers for stratifying anti-NXP2+ DM patients with distinct clinical specificities. High level of anti-NXP2 IgG1 antibody is a prognostic marker associated with increased mortality in anti-NXP2+ DM patients.

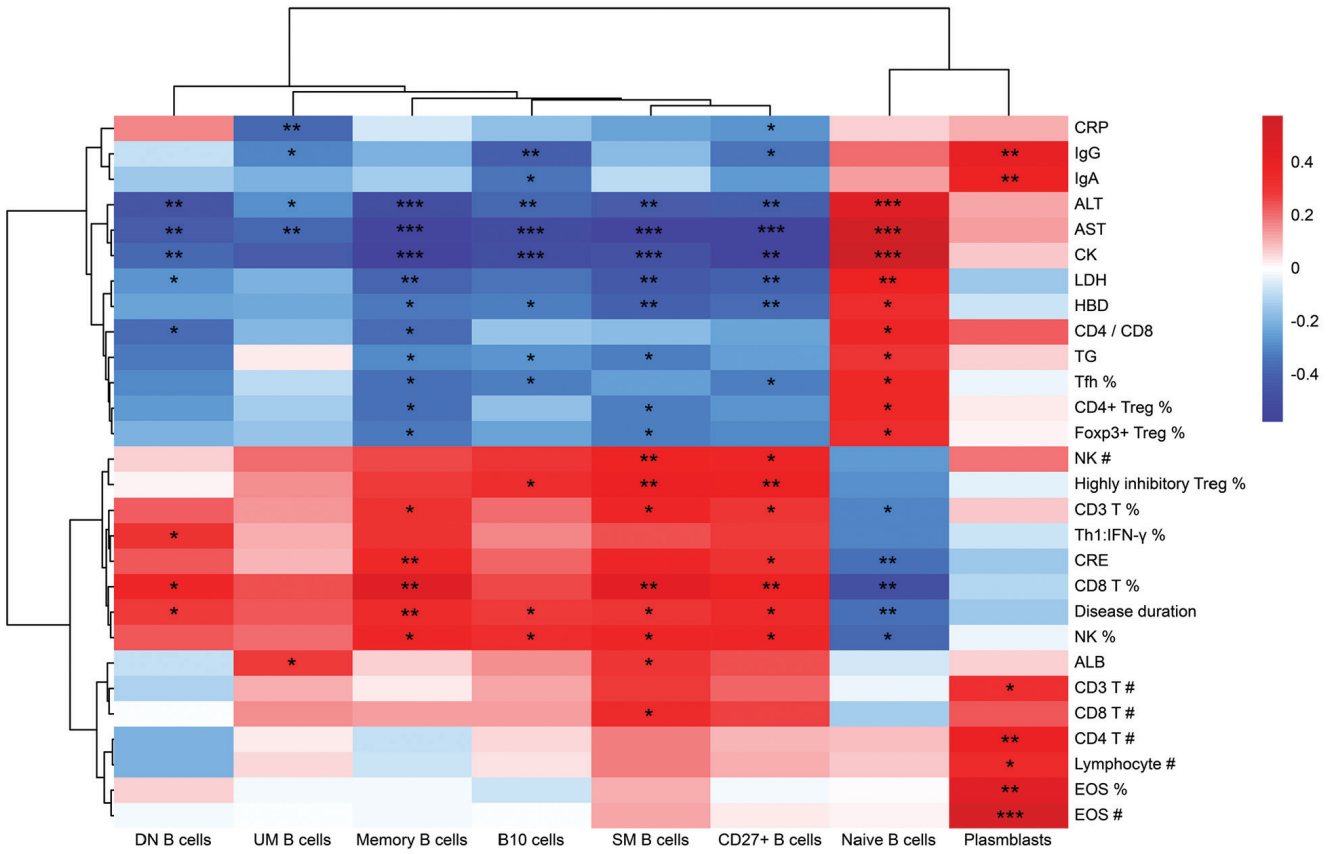
OP-4

FREQUENCIES OF B CELL SUBSETS SUGGEST CLINICAL MANIFESTATIONS IN IDIOPATHIC INFLAMMATORY MYOPATHIES

Wanxing Mo[1], Xiaoyan Xing[1], Xiao Wang[2], Xiao Tan[1], Jingtian Li[3], Yihong Dai[4], Yulong Wang[4], Jing He[1], Yuhui Li[1]

[1]Department of Rheumatology and Immunology, Peking University People's Hospital, Beijing, China; [2]Department of hematology, Rheumatology and Immunology, Xishuangbanna People's Hospital, Xishuangbanna, China; [3]Department of Orthopedics and Trauma, Peking University People's Hospital, Beijing, China; [4]Department of Nephrology, Peking University People's Hospital, Beijing, China

Background. Abnormal alterations of B cell subset frequencies in idiopathic inflammatory myopathies (IIM) have been described but their roles were rarely investigated. This study aimed to analyze the relationship between B cell subsets and clinical manifestations and provide evidence for diagnosis and treatment based on B cell subset detection.
Methods. 55 IIM patients who underwent the detection of peripheral B cell subsets were enrolled. B cells were classified into plasmablasts



OP-4 Fig. 1. Correlation matrix among B cell subsets and clinical manifestations of DM patients.
*p<0.05, **p<0.01, ***p<0.001.
CRP: C-reactive protein; Ig: immunoglobulin; ALT: alanine aminotransferase; AST: aspartate transaminase; CK: creatine kinase; LDH: lactate dehydrogenase; HBD: hydroxybutyrate dehydrogenase; TG: triglyceride; Tfh: T follicular helper cell; Treg: regulatory T cell; NK: natural killer cell; IFN: interferon; CRE: creatinine; EOS: eosinophil; DN B cells: double-negative memory B cells; UM B cells: unswitched memory B cells; SM B cells: switched memory B cells.

(CD19+CD20–CD27hi), naive B (NB) cells (CD19+CD27–lgD+), double-negative memory B (DN) cells (CD19+CD27–lgD–), unswitched memory B (UM) cells (CD19+CD27+lgD+), switched memory B (SM) cells (CD19+CD27+lgD–), and B10 cells (CD24hiCD27+) based on surface phenotype. Correlations between B cell subset frequencies and clinical manifestations were analyzed. Moreover, unbiased cluster analysis based on B cell subset frequencies was performed to divide IIM patients into three groups and their clinical manifestations were compared.

Results. Clinical manifestations correlating with B cell subset frequencies mainly included liver enzymes, muscle enzymes, immunoglobulins (Ig) and lymphocyte proportions (Fig. 1). The frequency of total B cells in lymphocytes (B%) correlated positively with heliotrope rash, V/shawl sign and perionychia. Memory B (MB) cell frequency correlated negatively with V/shawl sign, perionychia and muscle weakness. B10 cell frequency correlated negatively with myalgia, muscle weakness but positively with dyspnea. SM cell frequency correlated negatively with V/shawl sign, perionychia and muscle weakness. UM cell frequency correlated negatively with muscle weakness but positively with dyspnea. NB cell frequency correlated positively with V/shawl sign, perionychia and muscle weakness. B% in patients with interstitial lung disease (ILD) was significantly lower and receiver operating characteristic curve showed that area under curve was 0.671 (95% Cl 0.515–0.828) and the cutoff for ILD with maximum Youden index was B%<6.375%. Intriguingly, IIM patients could be divided into three groups that featured distinct B cell subset frequencies: group 1 rich in NB cells, group 2 rich in B10 cells and group 3 rich in MB cells, which differed in clinical manifestations including disease duration, aspartate aminotransferase, creatine kinase, creatinine, proportions of CD3 and CD8 T cells. Patients in group 1 had more muscle weakness but less dyspnea compared with two other groups, while patients in group 2 had more dyspnea but less heliotrope rash.

Conclusion. B cell subset frequencies are associated with intramuscular and extramuscular involvement in IIM and B% might serve as an indicator for screening ILD. Classification of IIM patients based on B cell subset frequencies can help with understanding and treatment of IIM.

Genetic and Enviromental Risk Factors

P-24

INTERFERON STIMULATED GENE SCORE AT BASELINE PREDICTS DISEASE ACTIVITY AT SIX MONTHS IN THE MYOPROSP COHORT, AND CORRELATES WITH NUCLEIC ACID SENSOR GENE EXPRESSION

Francisca Bozan[1], Xia Lyu[2,3,4], Hector Chinoy[3,5], Janine A. Lamb[4]
[1]Section of Rheumatology, Department of Medicine, Hospital Clínico Universidad de Chile, Santiago, Chile; [2]Department of Rheumatology, Renji Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China; [3]Division of Musculoskeletal and Dermatological Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, UK; [4]Epidemiology and Public Health Group, School of Health Sciences, University of Manchester, Manchester, UK; [5]Department of Rheumatology, Salford Royal Hospital, Northern Care Alliance NHS Foundation Trust, Manchester Academic Health Science Centre, Salford, UK

Background. Idiopathic inflammatory myopathies (IIM) are a group of heterogeneous autoimmune rheumatic diseases that can be divided into clinical subtypes: dermatomyositis (DM), polymyositis (PM), immune-mediated necrotizing myopathy (IMNM), inclusion body myositis (IBM), anti-synthetase syndrome (ASyS) and overlap myositis (OL). Several studies have demonstrated that interferons (IFNs) have important roles in the pathophysiology of IIMs and may help to differentiate clinical subtypes. We assessed the relationship of interferon stimulated gene (ISG) expression to disease activity and nucleic acid sensing gene expression in a real-world multi-centre cohort with different IIM subgroups.

Methods. The MYOPROSP study prospectively recruited a UK-based cohort with adult-onset IIM within two years of diagnosis between 2016 and 2020. Baseline and serial clinical and laboratory variables were collected. We analyzed RNA sequencing gene expression data from peripheral blood for 46 MYOPROSP samples at baseline and assessed an ISG signature for IFN I (the mean of five genes) and IFN II (the mean of three genes). Patients were grouped according to clinical, serological, and histological findings. Disease activity was measured with MYOACT and MITAX clinical assessment tools. Linear regression was conducted to evaluate the correlation between baseline ISG signature and disease activity at baseline and at six months. Interferon stimulated gene score was also correlated with the expression of nucleic-acid sensing genes.

Results. Differential ISG expression was observed in different IIM subgroups. The number of patients in each clinical subgroup were: 10 DM, 4 PM, 12 IMNM, 1 IBM, 13 ASyS, 6 OL. Baseline ISG signature positively correlated with MYOACT at six months for both IFN I (p=0.005, R^2=0.231) and IFN II (p=0.037, R^2=0.137). Similar results were observed for MITAX score, showing a positive association with both IFN I (p=0.028, R^2=0.134) and IFN II (p=0.023, R^2=0.144).

IFN I ISG score strongly correlated only with the cytosolic RNA sensing nucleic acid receptor RIG1 (DDX58) expression (p<0.001). IFN II ISG score correlated strongly with both expression of DDX58 and the DNA sensor, STING1 (p<0.001 for both).

Conclusion. IFN signature differs among IIM subgroups and a higher baseline ISG signature could predict worse clinical outcomes, such as increased disease activity score at six months. ISG signature could be a useful biomarker to improve the clinical monitoring of patients with IIMs.

P-25

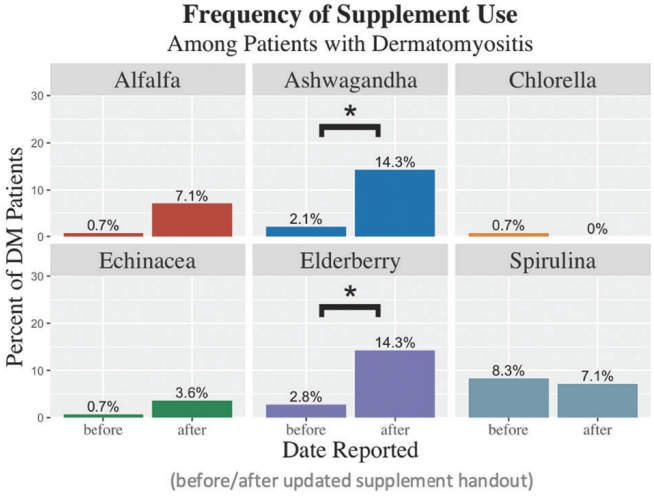
FREQUENCY OF HERBAL SUPPLEMENT USE AMONG PATIENTS WITH DERMATOMYOSITIS

Daniella Forman Faden[1], Lillian Xie[1], Caroline Stone[1], Laís Lopes Almeida Gomes[1], Victoria P. Werth[1,2]
[1]Department of Dermatology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [2]Department of Dermatology, Corporal Michael J. Crescenz VA Medical Center, Philadelphia, PA, USA

Background. Herbal supplement sales skyrocketed during the COVID 19 pandemic for their purported immune benefit (1, 2). Prior studies have shown a high prevalence of herbal supplement use among patients with dermatomyositis (DM) despite several reports of DM exacerbation following such use (3-6). In vitro studies have further demonstrated that spirulina stimulates the TLR4 pathway to a greater extent in DM blood compared to controls (7). Given the surge in prevalence of herbal supplement use and the associated risk of immune dysregulation, we sought to identify the most commonly used supplements among patients with DM since the start of the pandemic.

Methods. A retrospective chart review was performed on patients enrolled in the Penn Dermatomyositis Database after March 20, 2020. Patients were asked about supplement use in a stepwise manner and then given a handout on immunostimulatory supplements to avoid. Any reported supplement use was documented in their chart. Fisher's exact tests were performed to compare the frequency of supplement use between groups. Results were reported at a significance level of 0.05.

Results. Of the 173 patients, 43 (25%) reported taking herbal supplements, increased from 19% reported in a pre-pandemic study (3). 76% of patients who reported taking herbal supplements were White. However, the rela-



P-25 Fig. 1.

tiveproportion of herbal supplement use between races did not differ significantly. Among herbal supplement users, the prevalence of supplements used in descending order were spirulina (33%), elderberry (14%), ashwagandha (14%), alfalfa (7%), Echinacea (5%), and chlorella (2%). Despite elderberry and ashwagandha's herbal market dominance since the start of the pandemic, their popularity was not reflected in our cohort until both were added to our handout on June 27, 2023. Of the 28 patients who enrolled afterwards, 14 (50%) reported taking herbal supplements, 8 (57%) of whom reported taking elderberry or ashwagandha. A significant difference was seen in reported use of ashwagandha (OR=7.74, 95% CI 1.2, 56.2; p=0.01) and elderberry (OR=5.78, 95% CI 1.01, 33.3; p=0.02) after their inclusion in our handout, with increases from 2.1% to 14.3% and 2.8% to 14.3% respectively (Fig. 1).

Conclusion. Herbal supplement use among patients with DM is substantial and has increased since the pandemic despite the associated risk of DM exacerbation. Our study suggests an underestimation of the true prevalence, as indicated by the significant shift in reported usage after including elderberry and ashwagandha in the handout. This highlights the need for thorough screening and counseling on supplement use, particularly those with known immunostimulatory effects.

References

1. TYLER SMITH VE, MORTON REYNOLDS C: Herbal Supplement Sales in US Increase by Record-Breaking 17.3% in 2020. 2021, HerbalGram.
2. foodnavigator, u.c. Elderberry supplement sales skyrocketed to $320 million in 2020: ABC report. foodnavigator-usa.com 2021 2021/09/15/; Available from: https://www.foodnavigator-usa.com/Article/2021/09/15/Elderberry-supplement-sales-skyrocketed-to-320-million-in-2020-ABC-report.
3. RAVISHANKAR A *et al*.: Frequency of immunostimulatory herbal supplement use among patients with autoimmune skin disease. *J Am Acad Dermatol* 2022; 87(5): 1093-95.
4. BAX CE *et al*.: The effects of immunostimulatory herbal supplements on autoimmune skin diseases. *J Am Acad Dermatol* 2021; 84(4): 1051-58.
5. LEE AN, WERTH VP: Activation of autoimmunity following use of immunostimulatory herbal supplements. *Arch Dermatol* 2004; 140(6): 723-7.
6. ZEIDI M, CHANSKY PB, WERTH VP: Acute onset/flares of dermatomyositis following ingestion of IsaLean herbal supplement: Clinical and immunostimulatory findings. *J Am Acad Dermatol* 2019; 80(3): 801-4.
7. BAX CE *et al*.: Herbal supplement Spirulina stimulates inflammatory cytokine production in patients with dermatomyositis in vitro. *iScience* 2023; 26(11): 108355.

Inclusion Body Myositis

P-26

SENESCENT FIBRO-ADIPOGENIC PROGENITORS ARE POTENTIAL DRIVERS OF PATHOLOGY IN INCLUSION BODY MYOSITIS

Christopher Nelke[1] Christina B. Schroeter[1] Lukas Theissen[1] Corinna Preusse[2] Marc Pawlitzki[1] Saskia Räuber[1] Vera Dobelmann[1] Derya Cengiz[1] Felix Kleefeld[3] Andreas Roos[4] Benedikt Schoser[5] Anna Brunn[6] Eva Neuen-Jacob[6] Jana Zschüntzsch[7] Sven G. Meuth[1] Werner Stenzel[2], Tobias Ruck[1]

[1]Department of Neurology, Medical Faculty, Heinrich Heine University Duesseldorf, Duesseldorf, Germany; [2]Department of Neuropathology, Charité-University Medicine Berlin, Berlin, Germany; [4]Department of Neuropediatrics, Developmental Neurology and Social Pediatrics, Centre for Neuromuscular Disorders in Children, University Hospital Essen, University of Duisburg-Essen, Essen, Germany; [5]Friedrich Baur Institute at the Department of Neurology, LMU University Hospital, LMU Munich, Munich, Germany; [6]Institute of Neuropathology, Heinrich Heine University, University Hospital of Düsseldorf, Düsseldorf, Germany; [7]Department of Neurology, University Medical Center Göttingen, Göttingen, Germany

Background. Inclusion body myositis (IBM) is unique across the spectrum of idiopathic inflammatory myopathies due to its refractoriness to current treatment approaches. One explanation for this resistance may be the engagement of cell-autonomous mechanisms that sustain or promote disease progression of IBM independent of inflammatory activity. In this study, we focused on senescence of tissue-resident cells as potential driver of disease.

Methods. We compared IBM patients to non-diseased controls (NDC) and immune-mediated necrotizing myopathy (IMNM) patients using single-nuclei RNA sequencing, immunohistochemistry and immunofluorescence analysis.

Results. Histopathological analysis suggested that cellular senescence is a prominent feature of IBM, primarily affecting non-myogenic cells. In-depth analysis by single nuclei RNA sequencing allowed for the deconvolution and study of muscle-resident cell populations. Among these, we identified a specific cluster of fibro-adipogenic progenitors (FAPs) that demonstrated key hallmarks of senescence, including a pro-inflammatory secretome, expression of p21, increased β-galactosidase activity, and engagement of senescence pathways. FAP function is required for muscle cell health with changes to their phenotype potentially proving detrimental. In this respect, the transcriptomic landscape of IBM was also characterized by changes to the myogenic compartment demonstrating a pronounced loss of type 2A myofibers and a rarefication of acetylcholine receptor expressing myofibers. IBM muscle cells also engaged a specific pro-inflammatory phenotype defined by intracellular complement activity and the expression of immunogenic surface molecules. Skeletal muscle cell dysfunction may be linked to FAP senescence by a change in the collagen composition of the latter. Senescent FAPs lose collagen type XV expression, which is required to support myofibers' structural integrity and neuromuscular junction formation in vitro. Taken together, this study demonstrates an altered phenotypical landscape of muscle-resident cells and that FAPs, and not myofibers, are the primary senescent cell type in IBM.

Conclusion. Taken together, this study demonstrates an altered phenotypical landscape of muscle-resident cells and that FAPs, and not myofibers, are the primary senescent cell type in IBM.

Reference

1. NELKE C, SCHROETER CB, THEISSE L *et al*.: Senescent fibro-adipogenic progenitors are potential drivers of pathology in inclusion body myositis. *Acta Neuropathol* 2023; 146: 725-45. https://doi.org/10.1007/s00401-023-02637-2

P-27

PERIOSTIN LEVEL IN SPORADIC INCLUSION BODY MYOSITIS: A STUDY OF BLOOD AND MUSCLE

Vera Dobelmann[1], Yves Allenbach[2], Corinna Preuße[3], Matthias Vorgerd[4], Andreas Hentschel[5], Anne-Katrin Güttsches[4], Felix Kleefeld[6,7], Christopher Nelke[1], Werner Stenzel[3], Olivier Benveniste[2*], Tobias Ruck[1*], Andreas Roos[8,9*]

*shared last authorship

[1]Department of Neurology, Medical Faculty and University Hospital, Heinrich Heine University Düsseldorf, Duesseldorf, Germany; [2]Sorbonne Université, Assistance Publique - Hôpitaux de Paris, Inserm U974, Department of Internal Medicine and Clinical Immunology, Pitié-Salpêtrière University Hospital, Paris, France; [3]Charité - Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Department of Neuropathology, Berlin, Germany; [4]Department of Neurology, Heimer Institute for Muscle Research, University Hospital Bergmannsheil, Ruhr University Bochum, Bochum, Germany; [5]Leibniz-Institut für Analytische Wissenschaften - ISAS - e.V, Dortmund, Germany; [6]Berlin Institute of Health at Charité - Universitätsmedizin Berlin, BIH Biomedical Innovation Academy, BIH Charité Clinician Scientist Program, Berlin, Germany; [7]Charité - Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Department of Neurology, Berlin, Germany; [8]Department of Paediatric Neurology, Center for Neuromuscular Disorders in Children and Adolescents, University Clinic Essen, University of Duisburg-Essen, Duisburg-Essen, Germany; [9]Children's Hospital of Eastern Ontario (CHEO) Research Institute, Ottawa, Canada

Background. Sporadic inclusion body myositis (sIBM) is the most prevalent idiopathic inflammatory myopathy after the age of 50. Pathologically, sIBM is characterized by endomysial infiltrations by terminally differentiated T cells, myodegenerative changes, protein aggregates and fibrosis. Currently, no established blood biomarkers exist, and there is no specific therapy for this condition. However, a phase III trial for sIBM treatment with sirolimus is set to commence. In the current study we assessed the potential of the fibrosis-modulating protein periostin to serve as a blood biomarker for sIBM diagnosis and therapy response.

Methods. We collected blood samples from sIBM patients (n=56) and non-disease controls (NDC, n=24). Further, biopsy samples from sIBM (n=4) and PM-Mito (Polymyositis with mitochondrial pathology, n=3) patients were included. We performed label free global proteomics, qPCR, immunohistochemistry studies and ELISA. Additionally, serum samples from a phase IIb trial (NCT02481453), in which sIBM patients were treated either with rapamycin (n=21) or placebo (n=23) were investigated by ELISA. Moreover, we included serum samples at different time points from one patient that showed significant improvements in muscle activity under rapamycin treatment.

Results. We identified increased levels of periostin in sIBM muscles com-

pared to NDC based on immunohistochemistry, proteomics and qPCR experiments. Staining studies revealed enrichment within fibrotic scars. In contrast, analyses of serum samples from different cohorts of sIBM patients revealed decreased periostin levels (34.57±17.85 ng/mL; $p<0.0001$) compared to NDC (57.92±23.49 ng/mL). In the phase IIb study cohort, we observed that periostin serum levels rose with improvements in forced vital capacity, 6-minute-walking-test and health assessment questionnaire disability index in the rapamycin group. Furthermore, periostin levels in the serum samples derived from the successfully treated sIBM patient positively correlated with the improving muscle strength, which was tested via the manual muscle test 8 (MMT8).

Conclusion. Our study provides preliminary evidence that periostin is a potential blood biomarker for sIBM. Periostin levels correlate with clinically measurable improvements under treatment leading us to postulate that periostin may also serve as an indicator for therapy response. Further studies are warranted to understand the molecular background and to define the applicability in clinical practice.

P-28

IMPROVED PHYSICAL FUNCTION USING A POWER ENHANCING GLOVE IN PERSONS WITH IBM

Malin Regardt[1#], Helene Alexanderson[2#], Stephanie Hunn[3], Lindsay N Alfano[4], Roland Mischke[5], Ingrid de Groot[6], Anneli Dihkan[7], Therésia Danielsson[8], Annika Rydgård[8], Lesley-Ann Saketkoo[9]

On behalf of MIHRA Exercise and Rehabilitation Scientific Working Group.

[#] shared first author

[1]Department of Neurobiology, Care Sciences and Society, Division of Occupational Therapy, Karolinska Institutet, Stockholm, Sweden and Women´s Health and Allied Health Professionals Theme, Medical Unit Occupational Therapy and Physiotherapy, Karolinska University Hospital, Stockholm Sweden; [2]Department of Medicine, Solna, Division of Rheumatology, Karolinska Institutet, Stockholm, Sweden and Women´s Health and Allied Health Professionals Theme, Medical Unit Occupational Therapy and Physiotherapy, Karolinska University Hospital, Stockholm Sweden; [3]Department of Neurology, Neuromuscular Division, Washington University School of Medicine, St. Louis, United States; [4]The Abigail Wexner Research Institute at Nationwide Children's Hospital, Center for Gene Therapy, Columbus, OH, United States; The Ohio State University College of Medicine, Department of Pediatrics, Columbus, United States; [5]Patient Research Partner, Deutsche Gesellschaft für Muskelkranke e.V." , DGM, Taunusstein, Germany; [6]Patient Research Partner, Spierziekten Nederland (Dutch patient association for NMD), Rotterdam, The Netherlands; [7]Patient Research Partner, The Swedish Rheumatism association, Stockholm, Sweden; [8]Bioservo Technologies AB, Stockholm, Sweden; [9]Louisiana State University and Tulane University Schools of Medicine, New Orleans Scleroderma and Sarcoidosis Patient Care and Research Center, University Medical Center Comprehensive Pulmonary Hypertension Center and Interstitial Lung Disease Clinic Programs, New Orleans, USA

Background. Individuals with IBM have reduced hand function leading to limitation in daily activities. There is an urgent need to develop therapies and assistive devices to improve every-day function and quality of life for individuals with IBM.

We aimed to investigate if a power enhancing glove is feasible to use in persons with IBM.

Methods. Data were collected during The Myositis Association's (TMA) patient conference in September 2023. The study was open to interested people with idiopathic inflammatory myopathies who perceived hand weakness. For the purposes of this analysis, we are focusing on people with IBM. The glove's assistive force in grip and pincer strength is triggered by an 'intention-detection' logic that reacts to and supports the follow-through of a hand movement initiation by the user.

Physical function (IBM-Patient Reported Outcome Upper Extremity Function Scale (IBM-PRO), IBM-Functional Rating Scale (IBM-FRS)), pain (numeric rating scale) and grip strength (Jamar) were measured to assess degree of impairment.

Subsequently three activities listed in the modified IBM-PRO that participants perceived as difficult were selected. The participants performed the activities rating their perceived limitation on a 5-point scale (0 = "unable to do", 4= "without any difficulty") first without the glove and then upon using the glove. The glove was fitted individually to the left or right hand. After testing the glove, the participants answered a series of open-ended questions regarding their perception of the glove.

Results. The study included 40 persons with IBM. Median age 69 years, 52% male. The participants had reduced grip strength (kg)(md;range) (3.75;1.3-10.7) and physical function (IBM-FRS 20;2-38, IBM-PRO 23;1-44). The three most commonly selected IBM-PRO activities, with pre-and post-glove ratings are shown in Table I.

Table I. Measures on difficulty in chosen activities without and with the glove. (0="unable to do", 4= "without any difficulty").

Chosen activity	Without the glove	With the glove	Z (p-value)
Lift a heavy bag from the floor n=15	2 (2-2)	4 (4-4)	3.305 ($p<0.001$)
Open previously open jars, n=16	1 (1-2)	4 (3-4)	2.634 ($p<0.008$)
Lifting free weights, n=16	2 (1-2)	4 (3.25-4)	3.317 ($p<0.001$)
Lifting and holding a frying pan, n=11	1 (1-2)	3 (3-4)	2.858 ($p<0.004$)
PIcking a coin from a tsble, n=8	2 (11.3-3)	3.5 (2.3-4.0)	2.060 ($p<0.039$)

All activities were perceived easier to perform with the glove. In the open-ended questions, participants documented that the glove would be beneficial for use in everyday tasks, lifting objects, grocery shopping, stabilizing the hand and would increase independence. Most of the participants did not foresee activities in their daily routine where it might not work, however, some persons conveyed foreseeing some difficulty of glove use during personal hygiene and social activities. A few showed an interest to use the glove on both hands.

Conclusion. Based on this preliminary analysis the glove appears to increase hand function and might improve physical function in persons with IBM who experience impaired hand-function. A prospective intervention study is planned to further investigate the usefulness of the glove.

P-29

UPDATE IN SIROLIMUS IN IBM TRIAL – ONGOING CHALLENGES BUT A CASE FOR OPTIMISM IN IBM: AN MSG STUDY

M. Needham[1-4], U. Badrising[5], O. Benveniste[6], K. Beer[1,4], A. Heim[7], Optimism in IBM Study Group, M. M. Dimachkie[7]

[1]Department of Neurology, Fiona Stanley Hospital, Western Australia, Australia; [2]Centre for Molecular Medicine & Innovative Therapeutics, Murdoch University, Western Australia, Australia; [3]School of Medicine, Notre Dame University, Western Australia, Australia; [4]Perron Institute for Neurological and Translational Science, Western Australia, Australia; [5]Leiden University Medical Center, Leiden, The Netherlands; [6]Sorbonne Université, Hôpital de la Pitié-Salpêtrière, Paris, France; [7]University of Kansas Medical Center, Kansas City, Kansas, USA

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 has been trialled in 44 French IBM patients in a proof-of-concept monocentric controlled phase 2 study. While the primary outcome was not met, secondary outcomes suggested a positive impact on disease progression, supporting further investigation within a larger phase 2b/3 trial.

Methods. Optimism in IBM (NCT04789070; ANZCTR: ACTRN12620001226998p) is a double-blind randomised placebo-controlled phase 3 trial investigating the 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 are comparing 2mg sirolimus vs placebo over 84 weeks in 140 participants across 14 trial sites in Australia, Europe, the United Kingdom, and the United States of America. Secondary outcomes include the 6- and 2- minute walk test, modified Timed-up-and-go, patient reported outcomes, manual and quantitative muscle tests, and measures to assess safety and tolerability.

Results. This study has commenced across Australia and the United States but is currently still in set-up in the United Kingdom, The Netherlands and Germany. Thus far, 50 patients have been enrolled. The prolonged set-up and recruitment phases highlight challenges in establishing an international multi-centre trial. These include obtaining sufficient funding for study costs and executing complex contracts across different regulatory environments. As the first participants approach completion, there is consideration of feasibility of open label extension studies versus real world observational stud-

ies. These important challenges are surmountable but time-consuming. We are fortunate to have a strong and collaborative study team and support from patients and advocacy groups.

Conclusion. A global network of collaborative clinicians, support staff and well-phenotyped patient cohorts provides a strong foundation for large clinical trials in IBM. However, even within established clinical trial networks, obstacles and delays remain, requiring tenacity and creativity to ensure completion of the study and a case for Optimism in IBM.

Acknowledgements. We acknowledge funding from the National Health and Medical Research Council (NHMRC) and other funding bodies. We thank Pfizer for providing sirolimus. We thank the Muscle Study Group (MSG), International Myositis Assessment & Clinical Studies (IMACS) group and Myositis Research Consumer Panel for reviewing the protocol.

P-30

STRAPPED FOR STRENGTH: A COMPARISON STUDY OF DYNAMOMETRY TECHNIQUES TO EVALUATE KNEE EXTENSOR STRENGTH IN INCLUSION BODY MYOSITIS (IBM)

Katie Schütze[1], Ian Cooper[2,3], Brook Galna[4], Kelly AL Beer[2,3], Timothy J Fairchild[2,4], Kathryn Hird[1], Anna Brusch[5,6], Merrilee Needham[1,2,3,7]
[1]School of Medicine, The University of Notre Dame Australia, Fremantle, Western Australia, Australia; [2]Centre for Molecular Medicine & Innovative Therapeutics, Murdoch University, Murdoch, Western Australia, Australia; [3]Perron Institute of Neurological and Translational Sciences, Nedlands, Western Australia, Australia; [4]School of Allied Health, Murdoch University, Murdoch, Western Australia, Australia; [5]Department of Immunology, Sir Charles Gairdner Hospital, Western Australia, Australia; [6]School of Medicine, The University of Western Australia, Claremont, Western Australia, Australia; [7]Department of Neurology, Fiona Stanley Hospital, Murdoch, Western Australia, Australia

Background. The ability to accurately measure quadriceps strength in Inclusion Body Myositis (IBM) patients is vital in tracking disease progression and providing a standardised tool to assess interventions in clinical trials. Isokinetic dynamometers are the current gold standard tool for measuring quadriceps strength. However, they are expensive and space-expansive, making them impractical for day-to-day clinical use. A cheaper, more portable tool would therefore have more widespread clinical and research applications.

Methods. Current practice in medical clinics and translational research is to use (operator-stabilised) handheld dynamometry but there are significant concerns around the accuracy of this method.

This study investigated whether strap-stabilisation of the handheld dynamometer improves agreement with the isokinetic dynamometer for measurement of knee-extensor strength in IBM patients.

Fifteen IBM participants had bilateral knee-extensor force measured using three methods of dynamometry on the same day: the isokinetic dynamometer, operator-stabilised handheld dynamometry, and strap-stabilised handheld dynamometry. A cross-over design was used to account for fatigue bias.

Results. Strap stabilisation of the handheld dynamometer consistently improved agreement and intraclass correlation with the isokinetic dynamometer compared to operator stabilised handheld dynamometry, although statistical significance was not achieved.

Conclusion. Strap-stabilised handheld dynamometry is more closely correlated than (traditional) operator-stabilised handheld dynamometry with gold standard measure of quadriceps strength in patients with IBM. This finding has important implications for disease assessment and monitoring of IBM patients. Strap-stabilised handheld dynamometry may be a more suitable assessment tool for IBM clinical trials where quadriceps strength is an important outcome measure.

P-31

UNCOVERING THE SIGNIFICANCE OF EXPANDED CD8+ LARGE GRANULAR LYMPHOCYTES IN INCLUSION BODY MYOSITIS: INSIGHTS INTO T CELL PHENOTYPE AND FUNCTIONAL ALTERATIONS, AND DISEASE SEVERITY

Emily McLeish[1], Anuradha Sooda[1], Nataliya Slater[1], Barbara Kachigunda[2], Kelly Beer[3], Shereen Paramalingam[4], Phillipa J. Lamont[5], Abha Chopra[1,6], Frank L. Mastaglia[3], Merrilee Needham[1,3,7,8], Jerome D. Coudert[1,3,7]
[1]Centre for Molecular Medicine and Innovative Therapeutics, Murdoch University, Murdoch, Western Australia (WA), Australia; [2]Harry Butler Institute, Centre for Biosecurity and One Health, Murdoch University Murdoch, WA, Australia; [3]Perron Institute for Neurological and Translational Science, Nedlands, WA, Australia; [4]Department of Rheumatology, Fiona Stanley Hospital, Murdoch, WA, Australia; [5]Neurogenetic unit, Dept of Neurology, Royal Perth Hospital, Perth, WA, Australia; [6]Institute for immunology and infectious Diseases, Murdoch University, Murdoch, WA, Australia; [7]School of Medicine, University of Notre Dame, Fremantle, WA, Australia; [8]Fiona Stanley Hospital, Department of Neurology, Murdoch, WA, Australia

Background. Inclusion body myositis (IBM) is a progressive inflammatory myopathy characterised by skeletal muscle infiltration and myofibre invasion by $CD8^+$ T lymphocytes. In some cases, IBM has been reported to be associated with a systemic lymphoproliferative disorder of $CD8^+$ T cells exhibiting a highly differentiated effector phenotype known as T cell Large Granular Lymphocytic Leukemia (T-LGLL).

Methods. We investigated the incidence of a $CD8^+$ T-LGL lymphoproliferative disorder in blood samples from 85 IBM patients and 56 aged-matched Healthy Controls (HC) by flow cytometry. Further, we analysed the phenotypical characteristics of the expanded T-LGLs and investigated whether occurrence was associated with particular HLA alleles or clinical characteristics.

Results. Expansion of T-LGLs was apparent in 34 of the 85 (40%) IBM patients. The T cell immunophenotype of $T\text{-}LGL^{HIGH}$ patients was characterised by increased expression of surface molecules including CD57 and KLRG1, and to a lesser extent of CD94 and CD56 predominantly in $CD8^+$ T cells, although we also observed modest changes in $CD4^+$ T cells and γδ T cells. Analysis of Ki67 in $CD57^+$ $KLRG1^+$ T cells revealed that a small proportion of these cells was proliferating. Comparative analysis of $CD8^+$ and $CD4^+$ T cells isolated from matched blood and muscle samples donated by three patients indicated a consistent pattern of more pronounced alterations in muscles, although not significantly due to small sample size. In the $T\text{-}LGL^{HIGH}$ patient group, increased frequencies of perforin-producing $CD8^+$ and $CD4^+$ T cells were moderately correlated to combined CD57 and KLRG1 expression. HLA haplotype analysis of 75 IBM patients identified that carriage of the HLA-C*14:02:01 allele was significantly higher in $T\text{-}LGL^{HIGH}$ compared to $T\text{-}LGL^{LOW}$ individuals. Clinically, the age at disease onset and disease duration were similar in the $T\text{-}LGL^{HIGH}$ and $T\text{-}LGL^{LOW}$ patient groups. However, metadata analysis of functional alterations indicated that patients with expanded T-LGL more frequently relied on mobility aids than $T\text{-}LGL^{LOW}$ patients indicating greater disease severity.

Conclusion. Altogether, these results suggest that the T-LGL expansion observed in IBM patients is correlated with exacerbated immune dysregulation and increased disease burden.

Acknowledgements. This project was supported by grants from the Brain Foundation and the Spinnaker health research foundation, Murdoch University Research Training Programme Scholarships and a Byron Kakulas Scholarship from the Perron Institute.

Ethical approval for the study was obtained from the Murdoch University Human Research Ethics Committee (2015/111).

P-32

SPORADIC INCLUSION BODY MYOSITIS CAUSES ACCELERATED SARCOPENIA WITH DETRIMENTAL CHANGES IN BODY COMPOSITION, PHYSICAL FUNCTION AND MUSCLE POWER

Kasper Y. Jensen^[1], Julian Alcazar^[2,3,4], Per Aagaard[5], Anders N. Jørgensen[5,6], Bryan Haddock[7], Charlotte Suetta*[2,8], Louise P. Diederichsen*[1,9]
^shared first authorship; *shared last authorship
[1]Copenhagen Research Center for Autoimmune Connective Tissue Diseases (COPEACT), Center for Rheumatology and Spine Diseases, Rigshospitalet, Copenhagen, Denmark; [2]Geriatric Research Unit, Department of Geriatric and Palliative Medicine, Copenhagen University Hospital, Bispebjerg and Frederiksberg, Copenhagen, Denmark; [3]GENUD Toledo Research Group, Universidad de Castilla-La Mancha, Toledo, Spain; [4]CIBER of Frailty and Healthy Aging (CIBERFES), Madrid, Spain; [5]Department of Sports Science and Clinical Biomechanics, University of Southern Denmark, Odense, Denmark; [6]Department of Clinical Research, University of Southern Denmark, Odense, Denmark; [7]Department of Clinical Physiology and Nuclear Medicine, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark; [8]Geriatric Research Unit, Department of Medicine, Copenhagen University Hospital, Herlev and Gentofte, Herlev, Denmark; [9]Department of Rheumatology, Odense University Hospital, Odense, Denmark

Background. Sporadic inclusion body myositis (sIBM) is an acquired disease within the idiopathic inflammatory myopathy spectrum, characterized clinically by progressive muscle atrophy, weakness and often severely impaired physical function. Despite this, muscle mass and physical function is not routinely assessed in patients with sIBM. Dual-energy x-ray absorptiometry is used to monitor bone mineral density (BMD). However, DEXA is also able to assess muscle and fat mass and with the addition of simple measures of physical function, we might have a testing battery that could be beneficial for monitoring the disease and its progression.
Methods. The study was a retrospective analysis of patients with sIBM (n=22), a healthy age-matched group (n=414) and a healthy cohort (n=1305) from The Copenhagen Sarcopenia Study (1). DEXA measures (muscle index (MI), fat index (FI) and BMD), Body mass index (BMI), physical function (gait speed and sit-to-stand (STS)) and leg power were analysed. Relative (normalized to body mass), allometric (normalized to height squared) and specific (normalized to legs lean mass) STS power was calculated (2). Z-score values were calculated for the sIBM patients based on the age- and sex-matched cohort of healthy people. Finally, sex-specific quadratic regression lines and their derived equations in the whole cohort of healthy people were used to estimate potential accelerated sarcopenia in the group of sIBM patients.
Results. Women with sIBM had accelerated ageing in BMI (3.5 years), BMD (9.3 years) and fat index (12.5 years), gait speed (14.8 years), STS performance (27.5 years), relative, allometric and specific STS power (18.5, 18.8 and 21.9 years, respectively), and relative LEP (27.9 years) (Fig. 1). Men with sIBM also exhibited accelerated ageing in BMI (12.3 years), BMD (42.5 years), appendicular and legs MI (20.2 and 16.4 years), fat index (5.1 years), gait speed (18.3 years), STS performance (23.7 years), relative, allometric and specific STS power (21.3, 18.8 and 21.4 years), and relative LEP (23.1 years) (Fig. 1).
Conclusion. Patients with sIBM are severely impaired compared to the healthy cohort. In terms of physical function and muscle power, patients with sIBM showed accelerated ageing of 15 years, while it was 45 years for total BMD in men with sIBM. These findings underline the severity of impairment caused by the disease.

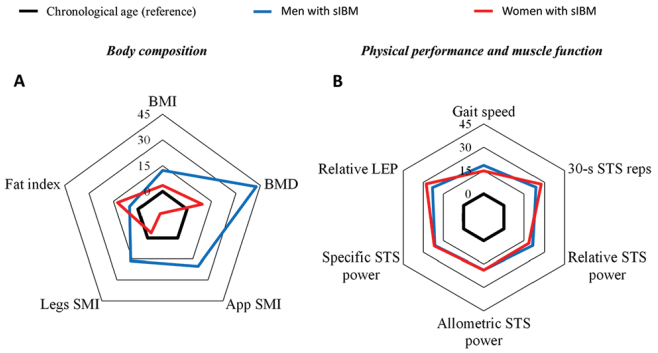


Fig. 1. Difference in outcomes (by years) between sIBM and healthy population visualised by spider graphs. A, Measures of body composition. B, Measures of physical performance and muscle function. BMI: body mass index; BMD: bone mineral density. App. SMI: appendicular skeletal muscle index; STS: sit-to-stand. Relative LEP: relative leg extension power; sIBM: sporadic inclusion body myositis.

References
1. SUETTA *et al.*: *J Cachexia Sarcopenia Muscle* 2019; 10(6): 1316-29.
2. ALCAZAR *et al.*: *Sci Rep* 2020; 10(1): 16337.

P-33

T-CELL RECEPTOR ANALYSIS OF MUSCLE-INFILTRATING AND BLOOD MEMORY T CELLS REVEALS DIVERSE PHENOTYPES IN SHARED AND EXPANDED CLONES IN PATIENTS WITH MYOSITIS

Begum Horuluoglu[1,2], Alexandra Argyriou[1,2], Juan Sebastian Diaz Boada[1,2], Angeles Galindo Feria[1,2,3], Annika van Vollenhoven[1,2], Daniel Ramsköld[4], Antonella Notarnicola[1,2,3], Lara Dani[1,2,3], Inger Nennesmo[5], Maryam Dastmalchi[1,2,3], Ingrid E. Lundberg[1,2,3], Lina-Marcela Diaz-Gallo[1,2], Karine Chemin[1,2]
[1]Division of Rheumatology, Department of Medicine, Solna, Karolinska Institutet, Stockholm, Sweden; [2]Center for Molecular Medicine, Karolinska Institutet, Stockholm, Sweden; [3]Department of Gastro, Dermatology and Rheumatology, Karolinska University Hospital, Stockholm, Sweden; [4]Department of Cell and Molecular Biology, Karolinska Institutet, Stockholm, Sweden; [5]Department of Oncology-Pathology, Karolinska University Hospital, Stockholm, Sweden

Background. The recombination of T-cell receptor (TCR) gene segments is the basis for the generation of a diverse T-cell repertoire where each T-cell is defined by a unique TCR sequence. TCR repertoire analysis is therefore a powerful tool to investigate adaptive immune responses. Our recent study revealed the presence of expanded and shared T-cell clones between muscle-infiltrating and peripheral blood (PB) memory T cells in patients with different myositissubtypes [1]. Here, we focused on T-cell clonality among an extended cohort of patients with inclusion body myositis (IBM) and anti-Jo1+ anti-synthetase syndrome (ASyS).
Methods. We performed Smartseq-2/3 single-cell RNA sequencing on muscle-infiltrating T cells and PB T cells from six patients with IBM, three patients with ASyS. TCRs were assembled and aligned using TraCeR and analysed with python and R. T cells sharing the same CDR3 sequence on both alpha and beta chains were considered belonging to the same clone.
Results. In IBM, the frequency of expanded T-cell clones tended to be higher among muscle-infiltrating T cells (37.4±10.8) compared to PB memory T cells (20±17.3), while in ASyS, similar frequencies were observed in both tissues (30.7±21.6 and 37.9±19.3 in muscle and PB respectively). Notably, we observed comparable frequencies of expanded clones in muscle-infiltrating T cells in IBM and ASyS while in PB the frequency of expanded clones was lower in patients with IBM. In patients with IBM (n=5/6) expanded clones exhibited a predominant tissue-resident memory T-cell (TRM) phenotype and these clones were not shared in PB. Conversely, in patients with ASyS, most expanded clones in PB were among cytotoxic T cells, which exhibited a similar phenotype in the muscle. Two ASyS patients had expanded clones among TRM in the muscle, and in one patient, these clones were also present among cytotoxic T cells in PB.
Conclusion. In conclusion our results unveil differences in TCR clonality and phenotype among patients with IBM and ASyS.suggestings that mechanisms governing T-cell infiltration into the muscle may vary based on myositis subtype. Importantly our observations validate and extend our previous report reinforcing the presence of shared clones between cytotoxic T cells and TRMs in patients with ASyS. This connection hints at a potential developmental link between these two cell subsets. Overall, our insights contribute to a more comprehensive understanding on the unique mechanisms leading to myositis.

P-34

CYTOSOLIC MITOCHONDRIAL DNA AS A POTENTIAL MEDIATOR OF INFLAMMATORY PATHWAYS IN INCLUSION BODY MYOSITIS

Sara Walli[1], Donya Abdennebi[1], Derya Cengiz[1], Vera Dobelmann[1], Corinna Preuße[2], Werner Stenzel[2], Anna Brunn[3], Sven G. Meuth[1], Tobias Ruck[1], Christopher Nelke[1]
[1]Department of Neurology, Medical Faculty, Heinrich Heine University Duesseldorf, Düsseldorf, Germany; [2]Department of Neuropathology, Charité-University Medicine Berlin, Berlin, Germany; [3]Institute of Neuropathology, Heinrich Heine University, University Hospital of Düsseldorf, Düsseldorf, Germany

Background. Inclusion body myositis (IBM) is a chronic inflammatory disease of the skeletal muscle in elderly patients, which is refractory to contemporary immunosuppressive approaches. Aside of autoimmune and neurodegenerative features, the pathogenesis involves mitochondrial dysfunction in skeletal muscle cells, as evidenced by ragged red fibers in staining of muscle specimens and mitochondrial DNA (mtDNA) alterations. Mitochondria may also mediate apoptosis through a process termed mitochondrial outer membrane permeabilization (MOMP). Here, mtDNA enters the cytosol through pores formed by BAX or BAK. Intriguingly, in the case of sub-lethal apoptotic stress, mtDNA may "leak" into the cytosol without triggering apoptosis, a condition termed minority MOMP (miMOMP). In this case, cytosolic mtDNA induces a plethora of effector functions including the engagement of the interferon-γ pathway. We hypothesize that miMOMP might provide a pathophysiological link between mitochondrial dysfunction and the interferon-γ response in IBM.
Methods. We used skeletal muscle specimens obtained from IBM patients. They were cut to 8µm sections and cryopreserved at -80°C prior to staining. We performed immunofluorescence stains with the following antibodies: DNA, TOMM20 (translocase of outer mitochondrial membrane 20) and BAX7. Protocol was also performed on immune mediated necrotizing myopathy (IMNM) muscle specimens as diseased controls as well as on non-diseased controls (n=3, respectively).
Results. In the skeletal muscle of IBM patients, cytoplasmatic DNA was found disengaged from the mitochondrial membrane, while cytosolic DNA was absent in non-diseased muscle. Expression of BAX7 suggested the formation of micropores in the mitochondrial membrane of IBM patients. The detection of cytosolic cytochrome C confirmed that mitochondria become "leaky" in IBM consistent with the concept of miMOMP.
Conclusion. Immunofluorescence analysis suggests the "leak" of mitochondrial DNA into the cytosol of muscle cells of IBM patients. Next, we plan to perform further stains and experiments investigating the biological consequences of the miMOMP in IBM. Confirmation of the role of mitochondria as promoters of an inflammatory status in the muscle of IBM could introduce new possible targets for therapy of this treatment-refractory disease.

P-35

THE MOLECULAR COMPOSITION OF CYTOSOLIC 5'-NUCLEOTIDASE 1A (CN1A) FILAMENTS IN CULTURED HUMAN CELLS

Fleur N. Brinkman[1], Chien-Yun Lee[2], Ger J.M. Pruijn[1]
[1]Radboud University, Nijmegen, the Netherlands; [2]Technical University of Munich, Munich, Germany

Background. The progressive autoimmune disease inclusion body myositis (IBM) causes asymmetrical muscle weakness in several parts of the body. IBM is characterized by rimmed vacuoles and protein accumulations in patients' muscle fibers. The etiology of IBM still has to be elucidated. Autoantibodies against cN1A (cytosolic 5'-nucleotidase 1A) are produced in 35-80% of IBM patients. The enzyme cN1A is involved in nucleotide metabolism, where it hydrolyses adenosine monophosphate to adenosine. It is most highly expressed in myotubes. Ectopic expression of cN1A in cultured human cells resulted in cN1A accumulation in filamentous structures. Since the origin of anti-cN1A autoantibodies in IBM patients is still unknown and these accumulations may mimic cN1A accumulation in IBM patient muscles, we characterized their composition to get more insight in the formation of cN1A-filaments.
Methods. APEX proximity labeling was used to identify proteins in close proximity of cN1A in transfected HEK-293T cells. cN1A was fused to the APEX2 enzyme and as a reference for cytosolic proteins a construct encoding APEX2 was fused to a nuclear export signal (NES). Upon activation of APEX2 in the presence of biotin-phenol, proximal proteins, in a radius of 10-20 nm, become biotinylated. The biotinylated proteins from three biological replicates were enriched by streptavidin. The resulting peptides were analyzed by mass spectrometry.
Results. Ectopic expression of APEX2-cN1A in cultured human cells showed dynamic, filamentous structures in the perinuclear region, which were similar to the accumulations observed with the GFP-cN1A fusion protein. APEX proximity labeling was assessed by western blotting, which revealed distinct biotinylated protein patterns for APEX2-cN1A and the reference, APEX2-NES. The proteomics analysis shows the differential abundance of more than 600 protein, in which 119 proteins were found to be significantly enriched in the cN1A samples (Fig. 1). Many of these proteins are known to be involved in mitochondrial ATP synthesis, gene expression and RNA modification. The colocalization of a selection of these proteins with cN1A in filaments will be assessed by immunofluorescence and fluorescence resonance energy transfer (FRET) and their importance for filament formation will be studied in knock-out models. Their co-localization in IBM patient muscles will be assessed by immunohistochemistry.
Conclusion. APEX proximity labeling allowed the identification of proteins in close proximity of APEX2-cN1A, which accumulates in perinuclear filaments, in HEK-293T cells. The highest scoring proteins have different activities in mitochondria and in the cytosol.

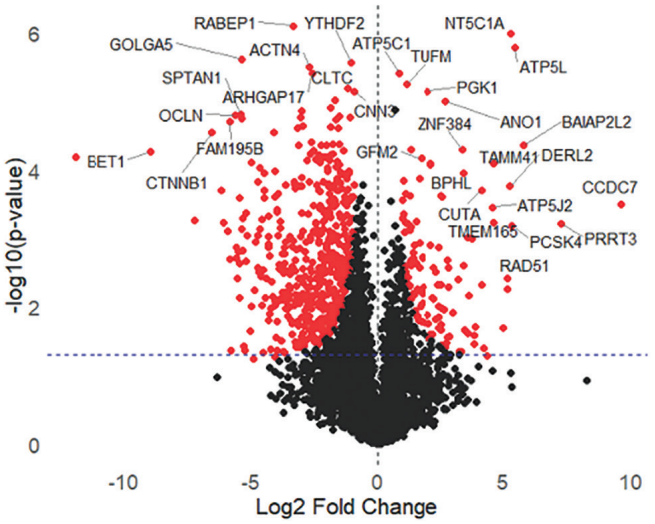


Fig. 1. Volcano plot showing the enrichment of proteins identified by APEX2-cN1A proximity labeling.

P-36

INCLUSION BODY MYOSITIS ASSOCIATED WITH SJOGREN'S SYNDROME: WHAT ARE THE CHARACTERISTICS?

Morgane Le Guen, Cecile Anquetil, Sarah Leonard-Louis, Xavier Mariette, Yves Allenbach, Olivier Benveniste
AP-HP, Paris, France

Background. Inclusion body myositis (IBM) is the most prevalent acquired myopathy, mostly affecting males over the age of 50. Sjögren's syndrome (SS) is an autoimmune disease characterized by sicca syndrome. The prevalence of IBM in SS patients is 0.5%, which is 500 times higher than in the general population. Conversely, the incidence of SS in IBM is 10-12%. Clinical heterogeneity between SS-IBM and sporadic IBM may impact treatment response, but limited data are available. Our objective is to identify the characteristics of the SS-IBM subgroup within a large cohort of IBM patients.
Methods. We conducted a retrospective analysis of clinical data from 210

patients followed at the Pitié-Salpêtrière University Hospital and Bicêtre University Hospital between 2015 and 2023, diagnosed with IBM based on Lloyd's criteria. The SS-IBM association was found in 22 patients according to EULAR/ACR criteria.

Results. Among the 210 patients meeting the inclusion criteria for IBM, we identified 22 cases (10.4%) of SS-IBM. Of these, 90.9% were women, with a median age of onset for muscular symptoms at 51.5 years, compared to 44.1% women in the IBM group (p<0.001), with a median age of 61 years (p=0.002). The time to diagnosis was longer in SS-IBM patients compared to IBM patients (7 years *vs*. 4 years, p=0.001), and CPK levels at diagnosis were significantly lower (233U/L *vs*. 500U/L, p=0.009). SS-IBM patients appeared to require more mobility aids at the last follow-up (61.9% *vs*. 46.5%), with 33% using a wheelchair, although not statistically significant. In terms of treatments, SS-IBM patients received corticosteroids significantly more frequently than IBM patients (72.7% *vs*. 40.9%, p=0.029) and had a greater number of immunomodulatory treatment lines (median 2.5 *vs*. 1). There was no difference in mortality rates (18.2% *vs*. 22.7%).

Conclusion. SS-IBM exhibits distinct features compared to sporadic IBM. It occurs more frequently in younger women, resembling the epidemiology of Sjögren's syndrome. Diagnosis often takes longer, and polymyositis is commonly misdiagnosed. In IBM patients, it is essential to screen for Sjögren's syndrome using a systematic approach (including dedicated clinical evaluation, accessory salivary gland biopsy, and autoantibody testing) to differentiate these patients from those with sporadic IBM and study their treatment response separately.

P-37
SPORADIC INCLUSION BODY MYOSITIS NOVEL AUTOANTIBODY AND BIOMARKER RESEARCH UTILIZING PROTEOME MICROARRAY AND MASS SPECTROMETRY PROTEOMICS ANALYSIS

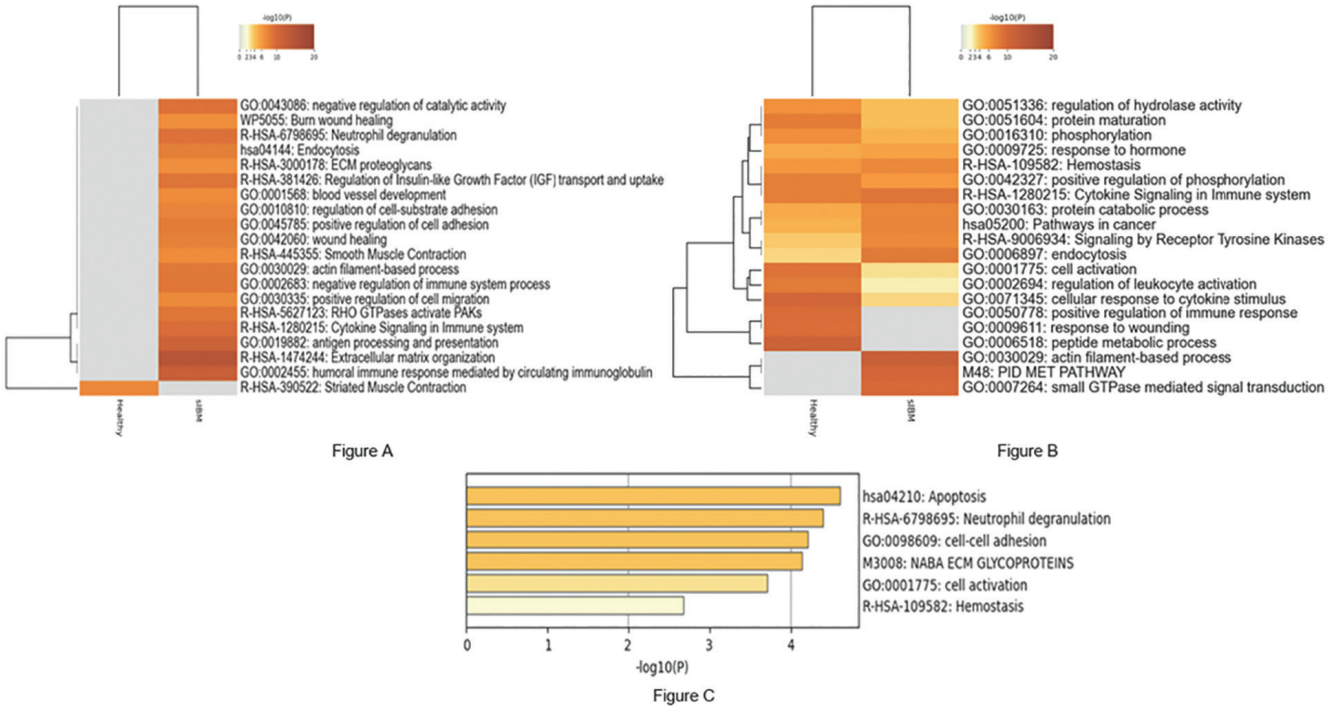
Farbod Moghaddam[1], Mark Tarnopolsky[2], Valerie Leclair[3], Marie Hudson[3], Ross Mitchell[4], Katherine A. Buhler[1], Erin Hatcher[2], Meifeng Zhang[1], Marvin J. Fritzler[1], Antoine Dufour[5], Luiz de Almeida[5], May Y. Choi[1]

[1]Division of Rheumatology, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada; [2]Division of Neuromuscular & Neurometabolic Disorders, Departments of Pediatrics and Medicine, McMaster University, Hamilton Health Sciences Centre (Hamilton, Canada); [3]Department of Medicine, Division of Rheumatology, McGill University, Montreal, Quebec, Canada; [4]Department of Medicine, Faculty of Medicine & Dentistry, University of Alberta, Edmonton, Alberta, Canada; [5]Division of Biochemistry and Molecular Biology, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada

Background. Sporadic inclusion body myositis (sIBM) is often challenging to diagnose because many patients have no detectable biomarkers (seronegative). We used machine learning (ML) to identify novel sIBM autoantibodies on a human proteome microarray (HuProt) and proteins in sera and muscle biopsies using mass spectrometry (MS)-based quantitative shotgun proteomics.

Methods. Sera from sIBM patients (n=10) were screened for novel autoantibodies using HuProt™ array (PEPperPRINT, Heidelberg, Germany). Sera (n=5) and muscle biopsy tissues (n=10) from sIBM patients were screened for novel proteins using MS. Traditional log-fold change method and ML feature selection techniques (permutation importance, select K best, recursive feature elimination) were used to select the most important biomarkers for differentiating between sIBM and healthy controls. We examined the potential function of selected biomarkers (absolute log-fold change threshold >2, p<0.05) in potential pathways of sIBM pathogenesis (autoimmune, inflammation, and degenerative pathways) using Genome Ontology (GO) analysis.

Results. We compared 12,319 autoantibodies detected using HuProt in both sIBM and controls, as well as 438 proteins detected in sera and 2462 proteins in muscle biopsies using MS. Significant autoantibodies and proteins included immune-related biomarkers involved in 1) complement activation



P-37 Fig. 1. Genome Ontology (GO) enrichment analysis of sporadic inclusion body myositis patients compared to healthy controls using A) muscle tissue proteins by mass-spectrometry-based quantitative shotgun proteomics, B) serum autoantibodies by HuProt, and C) serum proteins by mass-spectrometry-based quantitative shotgun proteomics. The most significantly (p<0.05) enriched GO terms are presented. All the adjusted statistically significant values of the terms were negative 10-base log transformed. The colour intensities indicate the level of enrichment score of each GO term. Figure 1A and 1B are displayed on a clustered heat map. Figure 1C is a bar graph of the six pathways that were identified were upregulated in sIBM compared to controls, ranked by fold enrichment (y-axis).

(decreased C3, C6, complement factor H related 3 expression) and 2) inflammation (increased cluster of differentiation 163 (CD163), signal transducer and activator of transcription 1 (STAT1), human leukocyte antigen A (HLA-A), cathepsin G, caspase 14, and guanylate binding protein 2 (GBP2)). Related to muscle function, there were biomarkers involved in 1) cytoskeleton organization (increased coronin 1A (CORO1A), gelsolin (GSN), and anti-myosin phosphatase Rho interacting protein (MPRIP) antibodies, as well as decreased actin alpha 1 (ACTA1), adenylosuccinate synthase 1 (ADSS1 – mutation causes distal myopathy)) and 2) muscle contraction (decreased calcium voltage-gated channel auxiliary subunit beta 1 (CACNB1) and calcium/calmodulin dependent protein kinase II beta (CAMK2B)). GO confirmed that apoptosis, neutrophil degranulation, cytokine signaling, antigen processing and presentation, and humoral immunity were upregulated in sIBM compared to controls (Fig. 1). There were also several pathways related to muscle function involved in sIBM including a downregulation of striated muscle contraction and upregulation of smooth muscle contractions and actin-filament based processes compared to controls.

Conclusion. We discovered several novel sIBM biomarkers involved in the immune, inflammatory, and degenerative pathways that may aid in the early diagnosis and our understanding of disease pathogenesis. These findings need to be validated in a larger cohort of sIBM patients before they can be developed onto a diagnostic platform available for clinical use.

P-38

THE MIKROIBIOM STUDY - COMPARISON OF GUT MICROBIOME OF SPORADIC INCLUSION BODY MYOSITIS (SIBM) PATIENTS AND UNAFFECTED SPOUSES

Maren Winkler[1], Waldemar Seel[2], Cornelia Kornblum[1], Marie-Christine Simon[2], Jens Reimann[1]

[1]Department of Neurology, Section of Neuromuscular Diseases, University Hospital of Bonn, Bonn, Germany; [2]Nutrition and Microbiota, Institute of Nutrition and Food Science, University of Bonn, Bonn, Germany

Background. Sporadic inclusion body myositis (sIBM) is a disorder with features of both inflammation and degeneration but yet without effective treatment. Influences of the gut microbiome on degenerative as well as inflammatory disorders and immune treatments are known. Curious whether the gut microbiome might influence the development or recalcitrance of sIBM, we appealed to sIBM patients and their unaffected spouses for stool samples and data on stool, gastrointestinal symptoms and nutrition.

Methods. We included 22 patients (n=2 clinically, n=20 clinico-pathologically defined; m:f 18:4; 51–83 years) and 21 controls (m:f 8:13; 53–82 years) for 16S rRNA V3V4 metagenomic analysis of their stool samples. In addition, modified Gastrointestinal Symptom Rating Scale, IBM Functional Rating Scale and Bristol Stool Scale were recorded. Bioinformatic analysis was performed using Qiime2 and MicrobiomeAnalyst software packages. LEfSe and Random Forest analysis were used to identify biomarkers, specific to the patient and control group. PICRUSt was used to perform pathway analysis.

Results. Checking across all controls vs patient samples showed no significant differences for various alpha and beta diversity metrics. But a significant (p<0.05) reduction in alpha diversity (observed features) was found for older (72+ years) patients compared to control. Increased abundances of the genera Lachnospira, Bacteroides, CAG-325, Defluviitaleacea (UCG-011) and Family XIII AD3011 group were detected for the patient group.

Conclusion. Our high-level microbiome analysis did reveal significant differences of the gut microbiome in patients only for older subjects, indicating that a more refined analysis may be needed. Cause-effect relationships are notoriously difficult to determine for microbiome changes in diseases, and our sIBM findings are no exception to this.

P-39

DEPRESSION IS A MORE SIGNIFICANT PREDICTOR FOR WELLBEING IN INCLUSION BODY MYOSITIS THAN PHYSICAL DISABILITY

Georgina Nunn.[1], Genevieve Glenister.[1], Kathryn Hird.[1], Kelly Beer.[2,3], Ian Cooper.[2,3], Anna Brusch.[3,4,5], Merrilee Needham.[2,3,4]

[1]University of Notre Dame Australia, Perth Australia; [2]Myositis Discovery Programme, Centre for Molecular Medicine & Innovative Therapeutics, Murdoch University, Perth Australia; [3]Perron Institute of Neurological and Translational Sciences, Perth Australia; [4]Department of Clinical Immunology, Sir Charles Gairdner Hospital, Perth Australia; [5]Department of Immunology, Pathwest Laboratory Medicine, Perth Australia. [6]Department of Neurology, Fiona Stanley Hospital, Perth Australia

Background. It is easy to assume that the more debilitating a person's disease, the worse their wellbeing is. Anecdotally, this does not seem to be the case. Many patients with severe disability limiting their function still report positive wellbeing. Conversely, patients with comparatively little disability can report a significant impact on their wellbeing and mental health.

Wellbeing is a person's emotional response to their life and is closely linked to physical and mental health. In Inclusion Body Myositis (IBM), where treatment options for disability are severely limited, greater emphasis could be placed on assessing and treating wellbeing and mental illness. The objectives of this study were to (1) determine if there is a correlation between wellbeing and disability in participants with IBM, (2) determine if there is a correlation between wellbeing and depression in participants with IBM, and (3) identify the prevalence of depression and reduced wellbeing in participants with IBM.

Methods. This was a cross-sectional exploration of wellbeing and depression in people with IBM, analysing data from 101 participants recruited across Australia. Participants completed the Personal Wellbeing Index (PWI), Neuromuscular Symptom Score (NSS), and Patient Health Questionnaire-9 (PHQ-9) surveys to serve as surrogate measures of wellbeing, physical disability, and depression respectively. Higher PWI scores indicate better wellbeing and higher NSS scores indicate better physical functioning. Higher PHQ-9 scores indicate more severe depression symptoms.

Results. Wellbeing was more strongly correlated with depression (Pearson's r value -0.702 (p-value <0.001)) than physical disability (Pearson's r value 0.265 (p-value 0.009)). Moderate to severe depression was reported in 78.2% of participants, and reduced wellbeing was reported in 98.9% of participants. Linear regression analysis showed that PHQ-9 (depression) significantly predicts PWI (wellbeing), however NSS (disability) does not (see table for values).

Table I. Linear regression values for predicting PWI using PHQ-9 and NSS.

Predictor	Estimate	SE	t	p
Intercept	83.5953	12.683	6.591	<0.001
PHQ-9	-2.7513	0.314	-8.771	<0.001
NSS	0.0575	0.191	0.301	0.764

Conclusion. In conclusion, depression is a more significant predictor of wellbeing than disability in participants diagnosed with IBM. Wellbeing was found to be most strongly correlated with depression, with a weak correlation to physical disability. There was a high prevalence of depression and reduced wellbeing in participants, highlighting the importance of assessing these factors to optimise holistic care in IBM.

Acknowledgements. Special thanks to the participants involved in this study and the Myositis Association of Australia (MAA) for their assistance.

P-40

THE MIND-MUSCLE TUSSLE: THE RELATIONSHIP BETWEEN PATIENT-REPORTED AND CLINICIAN-ASSESSED OUTCOME MEASURES IN INCLUSION BODY MYOSITIS - INSIGHTS FROM A RETROSPECTIVE COHORT STUDY

Madeline Schopp[1], Kathryn Hird[1], Kelly Beer[2,3], Ian Cooper[2,3], Katie Schütze[1], Anna Brusch[4,5], Merrilee Needham[1,2,3,6]
[1]School of Medicine, The University of Notre Dame Australia, Fremantle, Western Australia, Australia; [2]Centre for Molecular Medicine & Innovative Therapeutics, Murdoch University, Murdoch, Western Australia, Australia; [3]Perron Institute of Neurological and Translational Sciences, Nedlands, Western Australia, Australia; [4]Department of Immunology, Sir Charles Gairdner Hospital, Perth, Western Australia, Australia; [5]School of Medicine, University of Western Australia, Nedlands, Western Australia, Australia; [6]Department of Neurology, Fiona Stanley Hospital, Murdoch, Western Australia, Australia

Background. Inclusion body myositis (IBM) is an inflammatory myopathy, characterised by slow progression and a heterogeneous clinical presentation. This variability in disease progression and presentation complicates establishing reliable outcome measures for tracking clinical progress and intervention response in clinical trials. We aimed to identify the most useful suite of clinician-assessed and patient- reported outcome measures (PROMs) for use in clinical practice and trials.
Methods. We retrospectively analysed clinician-assessed outcome measures (manual muscle testing (MMT8, MMT12), right- and left-handed grip strength, modified timed up and go (mTUG), two-minute walk test (2MWT)); a clinician-administered patient-reported tool (IBM Functional Rating Scale (IBMFRS)); and PROMs including the eating assessment tool (EAT-10), neuromuscular symptom score (NSS)) from 20 participants.
Results. Correlation analysis revealed significant correlations between the IBMFRS, MMT8, MMT12, mTUG and 2MWT ($p<0.05$). The NSS strongly correlated with the MMT8, MMT12 and 2MWT ($p<0.05$). Univariate regression analyses revealed that 2MWT, MMT12 and mTUG were significant predictors of the IBMFRS and NSS, and backward stepwise linear regression highlighted that the 2MWT was a significant positive predictor for the IBMFRS ($p<0.001$).
Conclusion. Overall, we concluded that the IBMFRS, NSS, 2MWT and mTUG models were the best predictors of patient-perceived physical function in IBM.

P-41

GAIT ANALYSIS AND FALL PREDICTION IN PATIENTS WITH INCLUSION BODY MYOSITIS (IBM)

S. Hunn, C. Weihl
Washington University in St. Louis, USA

Background. Inclusion body myositis (IBM) is an inflammatory myopathy characterized by progressive weakness of the knee extensors and finger flexors. Ambulation becomes increasingly difficult, subjecting patients to higher fall risk and subsequent injury. While assistive devices and/or orthotics may improve gait and minimize fall risk in some patients with IBM, challenges remain in clinical decision making as to when certain devices or orthotics may be appropriate in addition to determining the optimal level of external assistance. Many factors must be taken into consideration when making these decisions, starting with identification of gait impairments. The goal of our study is to improve understanding and evaluating of gait kinematics in patients with IBM in order to improve fall prevention interventions and strategies using a wearable gait analysis system while performing the Timed Up and Go (TUG).
Methods. The Kinesis gait software involves patients wearing wireless sensors strapped just below the knees while performing a walking test, generating a report of various gait parameters to the connected tablet for analysis. It includes specific parameters for the TUG (qTUG) and estimates fall risk during each component of the test (rising from a chair, walking, turning, and sitting in a chair) based on each patient's gait kinematics compared to typical gait parameters. Patients seen in our IBM-specific clinic complete a series of patient reported outcome measures, including the Falls Efficacy Scale–International (FES-I), Neuro-Quality of Life Short Form (Neuro-QOL), and Fear of Falling Activity Avoidance Behavior Questionnaire (FFABQ), in addition to reporting the number of falls in the prior 6 months, muscle strength testing and completing the Kinesis-qTUG.
Results. We will report data from this ongoing prospective observational study.
Conclusion. Prior studies have described the impact of the IBM weakness pattern on gait kinematics using longer distances (*i.e.* 10-meter walk test); however, because the TUG involves transfers and movements of daily living known to be difficult in this population (i.e. rising from a chair), we hypothesize that the qTUG may be capable of improving fall risk prediction for IBM patients. We will report data from this ongoing prospective observational study.

P-42

EVALUATION OF RESPIRATORY INVOLVEMENT IN INCLUSION BODY MYOSITIS USING REAL-TIME MRI

Rachel Zeng[1], Omar Al-Bourini[2], Laura Plantenberg[1], Ulrike Olgemöller[3], Leonie Töpert[1], Leon Lettermann[4], Sabine Hofer[5], Jens Frahm[5], Martin Uecker[6], Ali Seif[2], Jens Schmidt[1,7]
[1]Department of Neurology, University Medical Center Göttingen, Germany; [2]Department of Diagnostic and Interventional Radiology, University Medical Center Göttingen, Germany; [3]Department of Cardiology und Pneumology, University Medical Center Göttingen, Germany; [4]BioQuant and Institute for Theoretical Physics, University of Heidelberg, Germany; [5]Biomedical NMR, Max Planck Institute for Multidisciplinary Sciences, Göttingen, Germany; [6]Institute of Biomedical Imaging, Graz University of Technology, Graz, Austria; [7]Department of Neurology and Pain Treatment, University Hospital of the Brandenburg Medical School Theodor Fontane, Immanuel Hospital Rüdersdorf, Rüdersdorf/ Berlin, Germany

Background. Inclusion body myositis (IBM) is typically characterized by insidious progression of atrophy and weakness in the extremities and swallowing muscles, while respiratory muscle weakness is considered to be rare and unusual. Several case reports suggested an involvement of respiratory muscles in IBM and demonstrated mild changes of diaphragm function in some of the cases. Respiratory impairment compromises quality of life and reduces life expectancy. Therefore, early diagnosis is important for therapeutic management of affected patients. Standard diagnostics such as pulmonary function tests often detect significant changes only in advanced stages of respiratory involvement. Real-time MRI (RT-MRI) offers a novel method for analysing complex respiratory movement patterns with a possibility of recognizing minor changes at an early stage. This new technique has been recently established and was first demonstrated in patients with Pompe disease, a muscle disease associated with characteristic diaphragm weakness (oral presentation at the 2023 MYO-MRI conference in Berlin; manuscript in preparation). Aim of this study in IBM patients was to assess the prevalence and extent of respiratory muscle involvement and to characterize a potential disease-specific pattern of breathing abnormalities.
Methods. A total of 22 patients with clinically and histologically confirmed IBM and 22 healthy controls (matched for age and BMI) underwent RT-MRI to examine respiratory motion patterns, with quantification of diaphragm and thoracic movements. All study participants received patient reported questionnaires on subjective respiratory complaints, MRC muscle strength assessment, diaphragm ultrasound, and standard pulmonary function tests.
Results. Analysis of respiratory mechanics and movement patterns of the diaphragm and thoracic muscles in IBM patients obtained by RT-MRI will be presented in comparison to the healthy control cohort. The RT-MRI data will be correlated with results from PROs, physical examination, diaphragm ultrasound, and pulmonary function tests.
Conclusion. This study provides a comprehensive analysis of respiratory function in IBM patients. The use of real-time MRI as a dynamic imaging method has the potential to improve the diagnosis and assessment of respiratory impairments in patients with neuromuscular diseases.

P-43

INVESTIGATING IMMUNOLOGIC MECHANISMS FOR THE ASSOCIATION BETWEEN INCLUSION BODY MYOSITIS AND RHEUMATOID ARTHRITIS

Tara Fallah Rastegar[1], Hong Wang[1], Brit Adler[1], Jemima Albayda[1], Julie Paik[1], Christopher Mecoli[1], Eduardo Gomez Banuelos[1], Andrew Mammen[2], Tom Lloyd[1], Lisa Christopher[1], Erika Darrah[1], Eleni Tiniakou[1]
[1]Department of Medicine, Division of Rheumatology, Johns Hopkins University, School of Medicine, Baltimore, Maryland, USA; [2]National Institutes of Health, Bethesda, Maryland, USA

Background. Inclusion body myositis (IBM) is a distinct type of inflammatory myopathy of unclear etiology with a combination of autoimmune and myodegenerative components. While typical myositis-associated antibodies are absent in IBM, the presence of other disease-associated antibodies, like rheumatoid arthritis, is unknown. We aimed to investigate the presence of an autoimmune response against autoantigens associated with rheumatoid arthritis. We screened for anti-cyclic citrullinated peptide (anti-CCP) and anti-peptidylarginine deiminase-4 (anti-PAD4) antibodies in patients with IBM.
Methods. Serum from patients with IBM (n=151), healthy controls (HC) (n=67), were tested for anti-cyclic citrullinated peptide (CCP) and anti-peptidyl-arginine deiminase 4 (PAD4) antibodies. The antibody prevalence was analyzed using the Chi-squared test and Mann-Whitney U-test. The degree of correlation between anti-CCP and anti-PAD4 was determined by the Pearson correlation test.
Results. 12 out of 151 patients with IBM (7.94%) tested positive for anti-CCP antibodies, while none of the 67 HC showed positivity (0%, p=0.02). Regarding anti-PAD4 antibodies, 22 out of 151 patients with IBM (14.56%) and 6 out of 67 healthy controls (7.89%) were positive, showing no significant difference (p=0.2). The median levels of anti-CCP and anti-PAD4 antibodies did not significantly differ between the patients with IBM and the healthy controls. Interestingly, we observed a moderate correlation (r=0.478, p<0.001) between anti-CCP and anti-PAD4 in patients with IBM. Among the IBM patients positive for anti-CCP antibodies, a subset of 4 patients also had a concurrent diagnosis of rheumatoid arthritis (RA).
Conclusion. Our findings revealed a statistically significant prevalence of anti-CCP antibodies in patients with IBM, indicating that citrullination of antigens may contribute to the pathogenesis of a subset of IBM patients. The presence of anti-CCP antibodies in IBM patients may serve as a potential marker for the development of rheumatoid arthritis in this specific population. Further research is warranted to gain a better understanding of the underlying mechanisms and clinical implications of this association. Such investigations will also help explore potential implications for the management and treatment strategies for patients with IBM and concurrent rheumatoid arthritis.

P-44

DEEP IMMUNOPROFILING IN INCLUSION BODY MYOSITIS AND TRAJECTORY ANALYSIS OF CYTOTOXIC CD8 CELLS

Bhaskar Roy, Rieke-Marie Hackbarth, Farhad Bahrassa, Minh Pham, Kevin C. O'Connor
Yale School of Medicine, New Haven, CT, USA

Background. Sporadic inclusion body myositis (IBM), the most common idiopathic inflammatory myopathy (IIM) in patients over the age of 50, presents with asymmetric muscle weakness, predominantly involving long finger flexors and quadriceps muscle. IBM does not respond to standard immunotherapy, and its pathophysiology remains controversial. Given treatment refractoriness and occasional degenerative features of IBM muscle biopsies, the autoimmune nature of IBM has been questioned. In general, CD8+ T cell invasion of muscle tissues is a prominent histological feature of IBM, and highly differentiated cytotoxic T cells are considered to be an important regulator of IBM pathogenesis. However, the drivers of such differentiation remain unclear.
Methods. We performed a deep profiling of peripheral blood mononuclear cells in IBM patients compared to healthy controls by examining the gene expression profile along with complete B cell repertoire (BCR) and T cell repertoire (TCR) analyses at a single cell level. Seurat platform was used for single-cell analysis. To examine the trajectory of the development of cytotoxic T cells, we used the Slingshot and tradeseq packages.
Results. We included four patients with IBM, three men, and one woman, with a mean age of 71.5±7.6 years and disease duration of 8±4.4 years in this preliminary analysis. Two healthy controls were recruited (both men, age 47.5±7.6 years). All the IBM patients fulfilled the ENMC criteria of IBM, and none of them were on immunosuppression. We noted differential gene expression in the IBM B cell compartment that were related to immunoglobulin production, leucocyte migration, and T-cell differentiation. As previously reported, there was a strong gene expression signature of highly differentiated cytotoxic T cells in IBM. Pseudo-time analysis reflected a distinct developmental trajectory of these T cells compared to healthy controls, which associated with a group of transcription factors (TF) including those found in the T-box family.
Conclusion. This preliminary analysis reinforces the autoimmune nature of IBM, further implicating a potential role for both B cells and uniquely developed cytotoxic T cells in the pathophysiology of IBM. A more detailed analysis with additional patients and healthy controls, along with a complete analysis of the BCR and TCR repertoires, will help to better understand disease pathophysiology in IBM and may identify new therapeutic targets.

P-45

B-CELLS AND INFLAMMASOME: INSIGHT INTO THE IMMUNOPATHOLOGY OF INCLUSION BODY MYOSITIS

Karsten Kummer[1], Per-Ole Carstens[2], Imke Bertram[2], Luisa Müllar[2], Arne Wrede[3,4], Sabrina Zechel[3], Martin Wachowski[5], Daniel Hoffmann[5], Almuth Brandis[6], Sabine Krause[7], Stephan Zierz[8], Jens Schmidt[1,9]
[1]Department of Neurology and Pain Treatment, Neuromuscular Center, Center for Translational Medicine, Immanuel Klinik Rüdersdorf, University Hospital of the Brandenburg Medical School, Rüdersdorf bei Berlin, Germany; [2]Department of Neurology, University Medical Center Göttingen, Göttingen, Germany; [3]Institute of Neuropathology, University Medical Center Göttingen, Göttingen, Germany; [4]Institute of Neuropathology, Saarland University Medical Center and Medical Faculty of Saarland University, Homburg, Germany; [5]Department of Trauma Surgery, Orthopaedics and Plastic Surgery, University Medical Center Göttingen, Göttingen, Germany; [6]Department of Pathology, Klinikum Region Hannover, Hannover, Germany; [7]Friedrich-Baur-Institute, Department of Neurology, Ludwig-Maximilians-University of München, München, Germany; [8]Department of Neurology, University Hospital Halle/Saale, Halle, Germany; [9]Faculty of Health Sciences Brandenburg, Brandenburg Medical School Theodor Fontane, Rüdersdorf bei, Berlin, Germany

Background. The pathogenesis of Inclusion body myositis (IBM) involves degenerative and inflammatory mechanisms. Proinflammatory cytokines lead to increased cell stress in muscle fibers and a dysregulated protein homeostasis. The inflammation is mainly driven by cytotoxic T cells attacking muscle fibers and triggering cellular inflammatory cell stress mechanisms through co-stimulatory molecules. Although some parts of the immunopathogenesis in chronic muscle inflammation in IBM are well understood, others haven't been studied in detail so far. Here we aimed to identify B-cell-mediated immunomechanisms in IBM and secondly focused on the NLRP3 inflammasome as a potential multiplicator of inflammation and mediator between inflammatory and myodegenerative pathology.
Methods. Regulation of the inflammasome and markers of B-cell activation were assessed in a well-established pro-inflammatory cell culture model by quantitative PCR, western blot and immunocytochemistry using primary human myotubes derived from orthopedic surgery. Diagnostic biopsy specimens from patients with IBM, other myositis subtypes and controls were analyzed for markers of B cell activation and recruitment (BAFF, APRIL, CXCL-12 and CXCL-13) and of the NLRP3 inflammasome. Results were compared to biopsy specimens without myopathic changes and hereditary muscular dystrophy.
Results. The mRNA expression of BAFF, APRIL, and CXCL-13 was significantly higher in IBM and Polymyositis (PM) compared to controls. Patients with IBM displayed the highest number of double positive muscle fibers for BAFF and CXCL-12 (48%) compared to PM (25%), muscular dystrophy (3%), and non-myopathic controls (0%). In vitro, exposure of human myotubes to pro-inflammatory cytokines led to a significant upregulation of BAFF and CXCL-12, but APRIL and CXCL-13 remained unchanged. In the cell culture model of IBM, the NLRP3 inflammasome was significantly overexpressed, as evidenced by western blot and quantitative PCR. Target genes that play a role in inflammasome assembly, T-cell migration,

and MHC-I expression were highly co-upregulated. NLRP3 was significantly overexpressed in muscle biopsies from IBM samples compared to disease controls, including other inflammatory myopathies.
Conclusion. These data support the concept that the pathophysiology of IBM involves B cell-associated mechanisms. Moreover, the inflammasome has been identified as part of the complex interplay between the inflammatory cascade and the protein accumulation in the muscle. Taken together, the results substantiate the hypothesis of a primarily inflammation-driven pathophysiology.

P-46

ROLE OF THE INFLAMMASOME IN INCLUSION BODY MYOSITIS

Carlo Serra, Andrew Wilson, Chiseko Ikenaga, Thomas E Lloyd
Department of Neurology and Neuroscience, Johns Hopkins University School of Medicine, Baltimore, MD USA

Background. Sporadic inclusion body myositis (IBM) muscle shows myofiber degeneration, infiltration of lymphocytes, mitochondrial abnormalities, and sarcoplasmic aggregation of TAR-DNA binding protein-43 (TDP-43), a DNA/RNA-binding protein. Although IBM is considered an autoimmune inflammatory myopathy, IBM may have etiological components in myofibers and muscle stem cells. Experimental models of amyotrophic lateral sclerosis (ALS) showed that TDP-43 may activate a pro-inflammatory response controlled by the cyclic GMP-AMP synthase (cGAS)/stimulator of interferon response CGAMP interactor 1 (STING1) pathway. During an infection, or upon cellular stress leading to the cytosolic release of endogenous DNA, both the cGAS/STING1 complex and members of the Toll-like receptors (TLRs) family activate the inflammasome to establish inflammatory responses. A typical inflammasome complex is composed of a sensor such as the NLR family pyrin domain containing 3 (NLRP3) or the absent in melanoma-2 (AIM2), a structural component like PYC and CARD domain containing protein (PYCARD), and an effector enzyme such as Caspase-1 (CASP1), which regulates the cellular release of mature interleukins through pores formed by the gasdermin proteins (GSDMDs) in the plasma membrane. We hypothesized that the inflammasome may play a role in IBM.
Methods. Muscle specimens collected from patients with IBM (n=12), dermatomyositis (DM) (n=5) and pathologically normal biopsies (Control) (n=7) were processed for immunofluorescence (IF) and qPCR analysis.
Results. IF assays showed increased numbers of STING1^{+} fibers, while qPCR analysis showed higher expression of both STING1 and cGAS genes in IBM muscles vs. DM and normal controls. IBM muscle displayed the sarcoplasmic accumulation of TLR9, with its increased gene expression, and the sarcolemmal accumulation of NLRP3, when compared to DM and normal control muscles. Activation of the inflammasome in IBM muscle was further supported by the upregulated expression of NLRP3, CASP1, PYCARD, GSDMD, and AIM2 genes, and of the interleukins IL1B and IL18 genes. IBM muscle also showed the increased expression of interferon-β1 (IFNB1), interferon-g (IFNG), and tumor necrosis factor-α (TNF) genes.
Conclusion. IBM muscle shows signs of the activation of inflammasome signaling. Further studies are necessary to identify the molecular mechanism of this activation, and to find the source (lymphocytes or myofibers) of the increased gene expression of inflammatory cytokines.
Funding. TMA to C.I; NIH (R01-NS082563 and R01- AR076390), MDA

P-47

INCLUSION BODY MYOSITIS ASSOCIATED WITH SJÖGREN'S SYNDROME (SS-IBM): HISTOPATHOLOGICAL CHARACTERISTICS

B.M.S. Proença[1], M. Le Guen[2], S. Leonard-Louis[2], C. Anquetil[2], X. Mariette[2], Y. Allenbach[2], A.M.S. Silva[1], E. Zanoteli[1], O. Benveniste[2]
[1]Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo - HC FMUSP, Brazil; [2]Hospital Pitié-Salpêtrière, AP-HP, Sorbonne Université, Paris, France

Background. Inclusion Body Myositis (IBM), an inflammatory myopathy prevalent after 50 years of age, primarily affects men (2:1). Lymphocytic infiltration, mitochondrial alterations, and rimmed vacuoles in histopathology reflect autoimmunity and degeneration. Sjögren's Syndrome (SS), an autoimmune disease predominantly affecting women (9:1), involves exocrine lymphocytic infiltration and rare extraglandular manifestations, including muscular involvement (2%). The coexistence of SS-IBM unveils immunological interrelations. Our objective is to compare histopathological features of SS-IBM and IBM.
Methods. We conducted a retrospective study analyzing data from 23 patients diagnosed with SS-IBM, employing Lloyd's and EULAR/ACR criteria, between 2015 and 2023. The data were collected from Pitié-Salpêtrière University Hospital and Bicêtre University Hospital in Paris, France, as well as Hospital das Clínicas da Universidade de São Paulo, Brazil. These patients were then compared with 46 age and sex-matched controls among IBM patients from France and Brazil. The histopathological comparison was based on evaluating the presence of invaded fibers, rimmed vacuoles, COX negative SDH positive fibers and the expression of TDP-43 or p62 reviewed in through the reports. Two independent reviewers examined muscle histological slides from a subset of 11 cases and 11 controls selected from the larger sample for a comparative quantitative analysis on inflammatory markers, oxidative reactions, and markers associated with muscular degeneration.
Results. At the time of IBM diagnosis, it was demonstrated that CPK levels were significantly more pronouced in the control group. The time between the onset of IBM symptoms and the muscle biopsy procedure was greater in the case IBM-SS group. There were no significant differences in muscular histopathology between the SS-IBM and IBM groups, considering oxidative reactions and markers of muscular degeneration. However, a significantly higher presence of invaded non necrotic fibers by lymphocytes was noted in the control group (p=0.028). The intensity of inflammatory reactions remained largely similar between the groups, except for a notably higher intensity of macrophage reaction assessed by CD68 immunohistochemistry, which was more pronounced in the control group compared to the SS-IBM group (p=0.040). There were no differences between neoplasic, hematologic and autoimmune comorbidities between the two groups.
Conclusion. The histopathological examination between SS-IBM and IBM cases revealed no significant differences in most findings, which suggests a parallel progression in both SS-IBM and IBM. However, in comparison with the ss-ibm group, we observed a higher intensity of macrophage reaction and a more frequent presence of invaded non-necrotic fibers in the control group, which may hint at potential distinctions in the underlying pathophysiology between these conditions. Further research is warranted to understand better these distinct subgroups' pathological mechanisms.

References

1. CHUNG SH, BENT EI, WEISS MD., GARDNER GC: Sporadic inclusion body myositis and primary Sjogren's syndrome: an overlooked diagnosis. *Clin Rheumatol* 2021. https://doi.org/10.1007/s10067-021-05740-5
2. NELKE C *et al*.: Inclusion body myositis and associated diseases: an argument for shared immune pathologies. *Acta Neuropathol Commun* 2022; 10: 84. https://doi.org/10.1186/s40478-022-01389-6
3. ZENG L *et al*.: Potential common molecular mechanisms between Sjögren syndrome and inclusion body myositis: a bioinformatic analysis and in vivo validation. Front Immunol 2023; 14: 1161476. https://doi.org/10.3389/fimmu.2023.1161476

P-48

IDENTIFICATION OF DISTINCT IMMUNE SIGNATURES IN INCLUSION BODY MYOSITIS BY PERIPHERAL BLOOD IMMUNOPHENOTYPING USING MACHINE LEARNING MODELS

Emily McLeish[1], Anuradha Sooda[1], Nataliya Slater[1], Kelly Beer[1,2], Ian Cooper[1,2], Frank L. Mastaglia[2], Merrilee Needham[1,2,3,4], Jerome D. Coudert[1,2,3]
[1]Murdoch University, Centre for Molecular Medicine and Innovative Therapeutics, Murdoch, Western Australia (WA), Australia; [2]Perron Institute for Neurological and Translational Science, Nedlands, WA, Australia; [3]University of Notre Dame Australia, School of Medicine, Fremantle, WA, Australia; [4]Fiona Stanley Hospital, Department of Neurology, Murdoch, WA, Australia

Background. Inclusion Body Myositis (IBM) is a progressive late-onset muscle disease characterised by preferential weakness of quadriceps femoris and finger flexors, with elusive causes involving immune, degenerative, genetic, and age-related factors. Overlapping with normal muscle ageing makes diagnosis and prognosis problematic.
Methods. We characterised peripheral blood leukocytes in 81 IBM patients and 45 healthy controls using flow cytometry. Using a Random Forest classifier, we identified immune changes in IBM compared to HC. K-means clustering and the Random Forest one-versus-rest model classified patients into three immunophenotypic clusters. Functional outcome measures including mTUG, 2MWT, IBM-FRS, EAT10, knee extension, and grip strength were assessed across clusters.
Results. The Random Forest model achieved a 94% AUC ROC with 82.76% specificity and 100% sensitivity. Significant differences were found in IBM patients, including increased $CD8^+$ T-bet+ cells, $CD4^+$ T cells skewed towards a Th1 phenotype, and altered γδ T cell repertoire with a reduced proportion of $V\gamma9^+V\delta2^+$ cells. IBM patients formed three clusters: (i) activated and inflammatory $CD8^+$ and $CD4^+$ T cell profile and the highest proportion of anti-cN1A positive patients in cluster 1; (ii) limited inflammation in cluster 2; (iii) highly-differentiated, pro-inflammatory T cell profile in cluster 3. Additionally, no significant differences in disease duration or severity, age, sex were detected between immunophenotype clusters.
Conclusion. These findings unveil distinct immune profiles in IBM, shedding light on underlying pathological mechanisms for potential immunoregulatory therapeutic development.
Acknowledgements. This project was supported by research grants from the Australian Brain Foundation, a Biobank support grant & a Research Excellence award from the Western Australian Future Health Research & Innovation Fund. Emily McLeish and Nataliya Slater are the recipients of a Murdoch University Research Training Programme Scholarship; Nataliya Slater is the recipient of a Byron Kakulas Scholarship funded by the Perron Institute for Neurological and Translational Science. Ethical approval for the study was obtained from the Murdoch University Human Research Ethics Committee (2015/111 and 2020/188).

OP-5

HIGH-RESOLUTION HLA GENOTYPING IN INCLUSION BODY MYOSITIS REFINES 8.1 ANCESTRAL HAPLOTYPE ASSOCIATION TO DRB1*03:01:01 AND HIGHLIGHTS PATHOGENIC ROLE OF ARGININE-74 OF DRB1 CHAIN

Nataliya Slater[1], Anuradha Sooda[1], Emily McLeish[1], Kelly Beer[1,2], Anna Brusch[5], Rakesh Shakya[5], Christine Bundell[5], Ian James[2,6], Abha Chopra[6], Frank L. Mastaglia[2,7], Merrilee Needham[1,2,3,4], Jerome D. Coudert[1,2,3]
[1]Murdoch University, Centre for Molecular Medicine and Innovative Therapeutics, Murdoch, WA, Australia; [2]Perron Institute for Neurological and Translational Science, Nedlands, WA, Australia; [3]University of Notre Dame Australia, School of Medicine, Fremantle, WA, Australia; [4]Fiona Stanley Hospital, Department of Neurology, Murdoch, WA, Australia; [5]PathWest Laboratory Medicine, Dept of Clinical Immunology, QEII Medical Centre, Nedlands, WA, Australia; [6]Murdoch University, Institute for Immunology and Infection Diseases, Murdoch, WA, Australia; [7]University of Western Australia, Centre for Neuromuscular & Neurological Disorders, Crawley, WA, Australia

Background. Inclusion body myositis (IBM) is a progressive inflammatory-degenerative muscle disease of older individuals. Previous studies have identified HLA region as the strongest genetic risk factor. Within that region, DRB1*03:01 and the 8.1 ancestral haplotype have been reported in association with IBM in Caucasians. Other reported associations included HLA-DRB1*01:01, A*03, and DQB1*05. Our study aimed to refine IBM genetic associations by high-resolution sequencing of HLA loci.
Methods. We recruited 113 Caucasian IBM patients and 112 ethnically-matched controls in Western Australia. DNA was extracted from blood or saliva and genotyped using Illumina next-generation sequencing. Alleles were called according to the latest IPD-IMGT/HLA nomenclature. Statistical analysis was conducted in RStudio using Genentech/MiDASand ggstatsplot. *p*-values were Bonferroni adjusted (denominated p_a) and considered statistically significant at $p_a<0.05$; odds ratios (OR) and likelihood ratios (LR) were calculated where appropriate.
Results. Our study confirmed an independent risk association of DRB1*03:01:01 ($p_a = 1.516\times10^{-8}$, OR=6.187) and protective association of DRB4*01:01:01 ($p_a = 2.371\times10^{-4}$, OR=0.225) and DQA1*01:02:01 ($p_a = 3.463\times10^{-3}$, OR=0.246).
We identified amino acid 74 within DRB1 locus as strongly associated ($p_a = 1.08\times10^{-11}$, LR=69.4). The frequency of arginine in that position was increased in patients (38.05% *vs*. 13.84%, $p_a = 1.547\times10^{-9}$, OR=6.159), whereas the frequency of glutamine was decreased (1.77% *vs*. 13.84%, $p_a = 1.050\times10^{-4}$, OR=0.096) compared to the control group.
Individuals carrying DRB1*03:01:01 but lacking both DRB4*01:01:01 and DQA1*01:02:01 faced a 14-fold increased risk of developing IBM over the general population (52.21% of IBM *vs*. 7.14% of controls, $p_a = 2.021\times10^{-13}$, OR=14.025) and were more likely to develop disease symptoms earlier in life (62 *vs*. 67 years, p=0.036), while carriage of at least one protective allele negated the risk effects of DRB1*03:01:01.
Conclusion. Our study determined that DRB1*03:01:01 of the 8.1 AH was the principal allelic component responsible for the genetic risk in IBM and identified combination of alleles that conferred the highest risk profile and impacted the age of symptom onset.
Acknowledgements. We thank participating patients and control donors, Ms Deborah Robertson, Ms Annik Panicker and staff of IIID sequencing platform for their outstanding professionalism. This project was supported by the Western Australian Future Health Research & Innovation Fund, Murdoch University Research Training Programme Scholarships and a Byron Kakulas Scholarship from the Perron Institute.
Murdoch University Human Research Ethics Committee approval #2015/111.

OP-6

POTENTIAL NEW AUTOIMMUNE TARGET IN INCLUSION BODY MYOSITIS

Antonella Notarnicola[1,2], Ceke Hellstrom[3], Begum Horuluoglu[1,2], Charlotta Preger[1], Francesco Bonomi[4], Boel De Paepe[5], Jan De Bleecker[5], Anneke J. Van der Kooi[6], Marianne De Visser[6], Sabrina Sacconi[7], Pedro Machado[8], Umesh A. Badrising[9], Anke Rietveld[10], Ger Pruijn[11], Simon Rothwell[12], James B. Lilleker[13], Hector Chinoy[13,14], Olivier Benveniste[15], Elisabet Svenungsson[1], Helena Idborg[1,2], Per-Johan Jakobsson[1,2], Peter Nilsson[3], Ingrid E. Lundberg[1,2]
[1]Karolinska Institutet and Karolinska University Hospital, Division of Rheumatology, Department of Medicine, Stockholm, Sweden; [2]Karolinska Institutet, Center for Molecular Medicine, Stockholm, Sweden; [3]KTH Royal Institute of Technology, Department of Protein Science, SciLifeLab, Stockholm, Sweden; [4]University of Florence-University Hospital Careggi, Department of Experimental and Clinical Medicine, Division of Rheumatology, Florence, Italy; [5]Ghent University Hospital, Department of Neurology and Neuromuscular Reference Center, Ghent, Belgium; [6]Amsterdam University Medical Centers, University of Amsterdam, Amsterdam Neuroscience, Department of Neurology, Amsterdam, The Netherlands; [7]Nice University Hospital/Institute of Research on Cancer and Aging of Nice, Research on Cancer and Aging , Nice, France; [8]University College London, Centre for Rheumatology & Department of Neuromuscular Diseases, London, UK; [9]Leiden University Medical Centre, Department of Neurology, Leiden, Netherlands; [10]Radboud University Medical Center, Department of Neurology, Center for Neuroscience Donders Institute for Brain, Cognition and Behaviour, Nijmegen, The Netherlands, 11 Radboud University; [11]Department of Biomolecular Chemistry, Institute for Molecules and Materials, Nijmegen, The Netherlands; [12]The University of Manchester, Division of Musculoskeletal & Dermatological Sciences, Manchester, UK; [13]The University of Manchester, Division of Musculoskeletal and Dermatological Sciences, Centre for Musculoskeletal Research, School of Biological Sciences, Manchester, UK; [14]Salford Royal Hospital, Northern Care Alliance NHS Foundation Trust, Manchester Academic Health Science Centre, Department of Rheumatology, Manchester, UK; [15]Pitié-Salpêtrière Hospital, Department of Internal Medicine and Clinical Immunology, Paris, France

Background. Autoantibodies are found in up to 80% of patients with idiopathic inflammatory myopathies (IIM) and are associated with distinct clinical phenotypes. Autoantibodies targeting cytosolic 5 ´-nucleotidase 1A

(anti-cN1A) are currently the only known serum biomarker for the subgroup inclusion body myositis (IBM), although detected even in other autoimmune diseases. The aim of the study was to identify new autoimmune targets in IIM by antigen bead array assay.

Methods. In a first cross-sectional exploratory study, 357 antigens were incubated with plasma samples from 219 IIM (108 Polymyositis (PM), 80 Dermatomyositis (DM) and 31 IBM) patients, 349 Systemic Lupus Erythematosus (SLE) patients and 306 population controls for screening of IgG reactivity by antigen bead array. All samples were identified in the local biobank of the Rheumatology clinic, Karolinska University Hospital. Interesting results for the IBM subgroup were then validated in an independent larger cohort of 287 patients with IBM followed at nine European rheumatological or neurological centers. IBM serum samples were explored by antigen bead array and results validated by western blot. As controls, sera from 29 patients with PM and 30 with DM, HLA-matched with the Swedish IBM cohort, were included. Demographics, laboratory, clinical, and muscle biopsy data of the IBM cohort was retrieved.

Results. In the exploratory study, IgG reactivity towards NADH dehydrogenase 1 α subcomplex 11 (NDUFA11), a subunit of the membrane-bound mitochondrial respiratory chain complex I, was discovered with higher frequency in the IBM (9.7%) than PM (2.8%) and DM samples (1.3%), although the difference was not statistically significant. Anti-NDUFA11 IgG was also found in 1.4% of SLE and 2% of population control samples. In the validation study, anti-NDUFA11 autoantibodies were detected in 10/287 IBM patients (3.5%), 0/29 PM and 0/30 DM patients. Reactivity against NDUFA11 could be confirmed by western blot (Fig. 1). No statistically significant differences were found between patients with and without anti-NDUFA11 antibodies when comparing clinical, laboratory and histological data. However, we observed a trend of higher frequency of distal lower extremity muscle weakness, CK levels at time of diagnosis and ragged red fibers in the anti-NDUFA11 positive group. Co-existence of anti-NDUFA11 and anti-cN1A antibodies was observed in three IBM patients.

Conclusion. Our results reveal a new autoimmune target in the mitochondrial respiratory chain complex I that might be specifically associated with IBM. This is of particular interest as mitochondrial abnormalities are known histological findings in muscle biopsies of IBM patients.

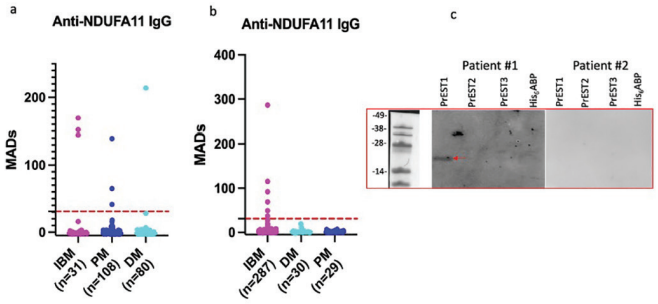


Fig. 1. Anti-NDUFAll reactivity in plasma and serum using a multiplex bead array. (a) Exploratory study: autoantibody reactivity against NDUFA11 protein fragment 1 (PrEST1) in plasma samples of IBM, PM, DM patients. (b) Validation study: autoantibody reactivity against NDUFA11 protein fragment 1 (PrESTI) in serum samples of IBM, DM and PM patients. Dotted red lines indicates cut-off that was calculated using the 98th percentile of the reactivity in the population controls. (c) Western blot showing the reactivity of two IBM patients against the NDUFA11 protein fragments (PrEST1,2,3) expressed with a His6ABP tag. Patient#1 was reactive to PrEST1 and not to PrEST2 and 3 in the bead array assay while patient#2 did not display any reactivity. NDUFA11: NADH dehydrogenase 1 α subcomplex 11; His6ABP: six histidine and albumin binding protein; IBM: inclusion body myositis; DM: dermatomyositis; PM: polymyositis; MADs: median absolute deviations; PrEST: protein epitope signature tag.

References

1. GALINDO-FERIA AS, WANG G, LUNDBERG IE: Autoantibodies: pathogenic or epiphenomenon. *Best Pract Res Clin Rheumatol* 2022; 36(2): 101767. 2.
2. HERBERT MK *et al*.: Disease specificity of autoantibodies to cytosolic 5'-nucleotidase 1A in sporadic inclusion body myositis versus known autoimmune diseases. *Ann Rheum Dis* 2016; 75(4): 696-701.

OP-7

DOES INSPIRATORY MUSCLE TRAINING IMPROVE LUNG FUNCTION AND QUALITY OF LIFE IN PEOPLE WITH INCLUSION BODY MYOSITIS? A PILOT STUDY

Ethan Williams[1,2], Ian Cooper[3], Kelly Beer[3], Kathryn Hird[1], Vinicius Cavalherid[4,5], Kathryn Watson[6], Merrilee Needhama[3,7,8]

[1]School of Medicine, The University of Notre Dame, Fremantle, Western Australia, Australia; [2]St John of God Midland, Public and Private Hospitals, Midland, Western Australia, Australia; [3]Perron Institute for Neurological and Translational Science, Western Australia, Australia; [4]Curtin School of Allied Health, Faculty of Health Sciences, Curtin University, Western Australia, Australia; [5]Allied Health, South Metropolital Health Service, Western Australia, Australia; [6]Physiotherapy Department, Fiona Stanley Fremantle Hospitals Group, Western Australia, Australia; [7]Department of Neurology, Fiona Stanley Fremantle Hospitals Group, Western Australia, Australia; [8]Centre for Molecular Medicine and innovative Technology (CMMIT) Murdoch University, Western Australia, Australia

Background. Inclusion Body Myositis is the most common acquired myositis in adults, predominantly weakening forearm flexor and knee extensor muscles. Subclinical respiratory muscle weakness has recently been recognised in people with Inclusion Body Myositis, increasing their risk of respiratory complications. Inspiratory muscle training, a technique which demonstrates efficacy and safety in improving respiratory function in people with neuromuscular disorders, has never been explored in those with Inclusion Body Myositis.

Methods. In this pilot study, six adults with Inclusion Body Myositis (age range: 53–81 years) completed eight weeks of inspiratory muscle training. Measures of respiratory function, quality of life, sleep quality and a two-minute walk test were performed pre- and post-intervention.

Results. All participants improved their respiratory function, with maximal inspiratory pressure, sniff nasal inspiratory pressure and forced vital capacity increasing by an average of 50% (p=0.002), 43% (p=0.018) and 13% (p=0.003) respectively. No significant change was observed in quality of life, sleep quality or two-minute walk test performance. No complications occurred due to inspiratory muscle training.

Conclusion. This pilot study provides the first evidence that inspiratory muscle training is safe and effective in people with Inclusion Body Myositis, potentially mitigating the complications of poor respiratory function.

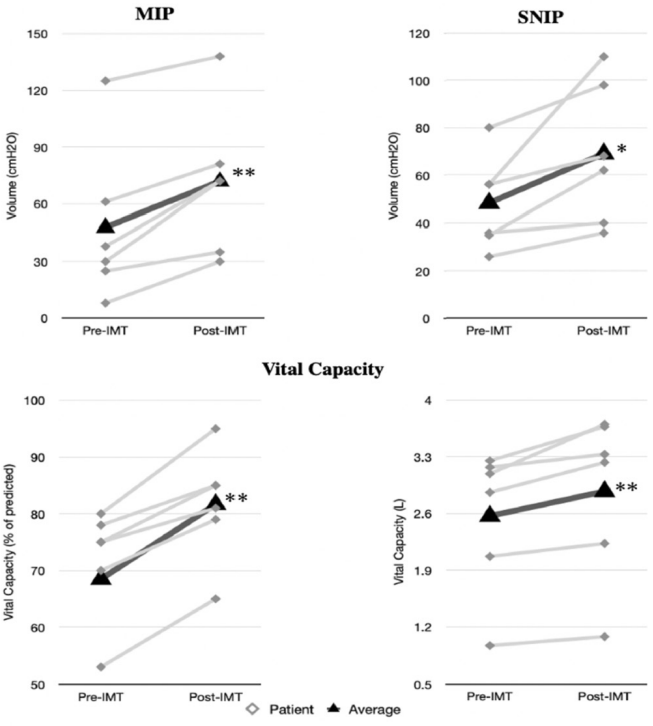


Fig. 1.

OP-8

MY MYOSITIS MENTAL HEALTH: UTILITY OF THE NOVEL THE MYOSITIS ASSOCIATION'S MENTAL HEALTH SUBSCALE AS A SCREENING TOOL FOR DEPRESSION AND ANXIETY

Louis J.F. Barter[1], Kelly A.L. Beer[2,3], Kathryn Hird[1], Ian Cooper[2,3], Merrilee Needham[1,2,3,4]

[1]School of Medicine, University of Notre Dame, Australia, Perth, Australia; [2]Centre for Molecular Medicine and Innovative Therapeutics, Murdoch University, Perth, Australia; [3]Perron Institute for Neurological and Translational Science, Perth, Australia; [4]Department of Neurology, Fiona Stanley Hospital, South Metropolitan Health Service, Perth, Australia

Background. Inclusion Body Myositis (IBM) is a chronic, progressive disease which leads to significant physical disability secondary to loss of muscle strength and function. Due to the current limitations of IBM treatment, clinical management primarily involves supportive care. Supportive care in IBM has traditionally been focused on reducing the burden of motor symptoms through physiotherapy and other rehabilitation methods. Although the level of physical impairment caused by IBM does influence perceived quality of life, the unique impact of mental health has become apparent. A significantly increased prevalence of both anxiety and depression has been reported in patients with IBM; furthermore, a significant portion of those with either anxiety or depression were not receiving mental health treatment. The increasing recognition of mental health aspects of IBM led to the inclusion of a mental health subscale within the "My Myositis Tracker" a quality-of-life assessment tool recently developed by the Myositis Association in 2020. This study aims to evaluate the utility of The Myositis Association's Mental Health Subscale (MHS) as a screening tool for both depression and anxiety in IBM.
Methods. A cross-sectional survey was conducted with 77 participants diagnosed with IBM. Participants completed the MHS and gold-standard diagnostic questionnaires: the Patient Health Questionnaire 9 (PHQ-9) and Generalized Anxiety Disorder 7 (GAD-7). Sensitivity and specificity in detecting anxiety and depression was calculated using graded diagnostic thresholds.
Results. The prevalence of depression (14.3%) and anxiety (10.3%) in the sample far exceeded age-matched controls. 50% of participants who met the diagnostic criteria for depression also registered a positive result for generalised anxiety. The MHS demonstrated good sensitivity (81%) and specificity (81%) for major depression when a threshold of three or more positive MHS responses. Similarly, 75% sensitivity and 78% specificity for generalised anxiety disorder were achieved using a total MHS score of 3 or more. Decreasing the diagnostic threshold to 2 or more positive responses increased sensitivity to 88% for anxiety and 100% for depression.
Conclusion. The MHS demonstrates utility as a rapidly administered screening tool for major depression and generalised anxiety disorder in IBM. Clinicians can utilise a threshold of two or more positive MHS responses to trigger further psychological evaluation of both depression and anxiety. Screening of mental health through the MHS is likely to identify individuals with IBM who could benefit from targeted psychological intervention.

Classification of Inflammatory Myopathies

P-49

CLINICAL PHENOTYPING IN PATIENTS WITH ANTI-SYNTHETASE ANTIBODIES USING CLUSTER ANALYSIS

Shintaro Yamamoto[1], Akira Yoshida[1], Yuka Okazaki[1], Takahisa Gono[1,2], Masataka Kuwana[1,2]

[1]Department of Allergy and Rheumatology, Nippon Medical School Graduate School of Medicine, Tokyo, Japan; [2]Scleroderma/Myositis Centre of Excellence, Nippon Medical School Hospital, Tokyo, Japan

Background. Patients with anti-synthetase antibodies present with different combinations of myositis, interstitial lung disease (ILD), arthritis, mechanic's hands, Raynaud's phenomenon, and/or unexplained fever, constituting a heterogenous disease spectrum. Anti-synthetase syndrome (ASSD) has been proposed as a distinct disease entity and international classification criteria are under development. We aimed to characterize clinically homogenous subgroups among unselected patients with anti-synthetase antibodies using cluster analysis to better understand the heterogeneity of this disease entity.
Methods. This study evaluated patients with anti-synthetase antibodies registered to two independent cohorts; 106 consecutive patients from a prospective, single-center cohort of the Scleroderma/Myositis Centre of Excellence (SMCE) of the Nippon Medical School Hospital were used as a derivation cohort, while 139 patients from the Multicenter Retrospective Cohort of Japanese Patients with Myositis-Associated ILD (JAMI) were used as a validation cohort. Anti-synthetase antibodies were identified by RNA immunoprecipitation assay. A multiple correspondence analysis using 13 variables covering the clinical manifestations associated with anti-synthetase antibodies followed by hierarchical clustering was performed in the SMCE cohort to aggregate the patients into homogenous subgroups. Clinical characteristics and outcomes of patients included in each cluster were compared. Subsequently, a simple-to-use classification tree was generated using classification and regression tree (CART) analysis, which was validated in the JAMI cohort.
Results. Three clusters were identified in the SMCE cohort (Table I): cluster #1 (n=48), the "interstitial pneumonia with autoimmune features/amyopathic dermatomyositis cluster", associated with an older age at onset and a higher frequency of malignancy; cluster #2 (n=46), the "dermatomyositis (DM) cluster", with younger age at onset and a higher prevalence of myositis, arthritis, DM-pathognomonic rashes, mechanic's hands, and fever; and cluster #3 (n=12), the "systemic sclerosis cluster", characterized by chronic ILD with usual interstitial pneumonia pattern on chest high-resolution computed tomography. There was no significant difference in overall survival or progression-free survival among the clusters. The CART analysis generated a simple classification tree based on the presence of myositis and Raynaud's phenomenon. The classification tree reproduced three clusters with clinical features consistent with the SMCE clusters in the JAMI cohort.
Conclusion. Patients with anti-synthetase antibodies were classified into three distinct phenotypes. Our results will help to improve our understanding of the substantial heterogeneity in this disease entity and provide information useful for the development of classification criteria for ASSD.
Acknowledgements. The authors are grateful to JAMI investigators for data collection.

Table I. Characteristics of three clusters identified in the SMCE cohort.

	Cluster 1 (n=48)	Cluster 2 (n=46)	Cluster 3 (n=12)	*p*-value
Demographics				
Age at diagnosis (years)	67 [55–72]	60 [50–68]	65 [62–69]	**0.033**
Female	30 (62.5%)	36 (78.3%)	7 (58.3%)	0.180
Clinical diagnosis				**0.002**
DM	0	15 (32.6%)	0	
ADM	10 (20.8%)	15 (32.6%)	0	
PM/IMNM	5 (10.4%)	8 (17.4%)	1 (8.3%)	
SSc	1 (2.1%)	0	3 (25.0%)	
IIM-SSc overlap	0	6 (13.0%)	3 (25.0%)	
IPAF	32 (66.7%)	2 (4.3%)	5 (41.7%)	
Anti-synthetase antibodies				0.105
Anti-Jo-1	7 (14.6%)	15 (32.6%)	2 (16.7%)	
Anti-PL-7	4 (8.3%)	10 (21.7%)	4 (33.3%)	
Anti-PL-12	6 (12.5%)	6 (13.0%)	0	
Anti-EJ	14 (29.2%)	10 (21.7%)	1 (8.3%)	
Anti-OJ	4 (8.3%)	2 (4.3%)	0	
Anti-KS	12 (25.0%)	3 (6.5%)	4 (33.3%)	
Clinical features				
Arthritis	4 (8.3%)	21 (45.7%)	1 (8.3%)	**<0.001**
Muscle involvement				**<0.001**
No myositis	48 (100.0%)	13 (28.3%)	12 (100.0%)	
Subclinical myositis	0	8 (17.4%)	0	
Clinical myositis	0	25 (54.3%)	0	
Onset of ILD				1.000
Acute	17 (35.4%)	15 (32.6%)	2 (16.7%)	
Subacute	9 (18.8%)	7 (15.2%)	1 (8.3%)	
Chronic	17 (35.4%)	16 (34.8%)	6 (50.0%)	
Asymptomatic/unclassified	5 (10.4%)	6 (13.0%)	1 (8.3%)	
HRCT pattern of ILD				**0.026**
UIP	3 (6.2%)	2 (4.3%)	2 (16.7%)	
NSIP and/or OP	40 (83.3%)	40 (87.0%)	6 (50.0%)	
DAD	4 (8.3%)	1 (2.2%)	0	
Unclassified/unknown	1 (2.1%)	1 (2.2%)	2 (16.7%)	
DM-specific rash	14 (29.2%)	35 (76.1%)	2 (16.7%)	**<0.001**
Mechanic's hands	20 (41.7%)	34 (73.9%)	3 (25.0%)	**0.001**
Fever	4 (8.3%)	17 (37.0%)	0	**0.001**
Raynaud's phenomenon	0	16 (34.8%)	9 (75.0%)	**<0.001**
Sclerodactyly	0	3 (6.5%)	8 (66.7%)	**<0.001**
Proximal scleroderma	0	2 (4.3%)	4 (33.3%)	**<0.001**
Malignancy	10 (20.8%)	2 (4.3%)	1 (8.3%)	**0.042**

ADM: amyopathic dermatomyositis; DAD: diffuse alveolar damage; DM: dermatomyositis; HRCT: high-resolution computed tomography; IIM: idiopathic inflammatory myopathy; ILD: interstitial lung disease; IMNM: immune-mediated necrotizing myopathies; IPAF: interstitial pneumonia with autoimmune features; NSIP: nonspecific interstitial pneumonia; OP: organizing pneumonia; PM, polymyositis; SMCE: Scleroderma and Myositis Center of Excellence; SSc: systemic sclerosis; UIP: usual interstitial pneumonia.
Continuous and categorical variables are shown as the median [IQR] and n (%), respectively.

P-50

CLINICAL PRESENTATION, COURSE, AND PROGNOSIS OF PATIENTS WITH MIXED CONNECTIVE TISSUE DISEASE: A MULTICENTER RETROSPECTIVE COHORT

Kevin Chevalier[1], Benjamin Thoreau[1], Marc Michel[2], Bertrand Godeau[2], Christian Agard[3], Thomas Papo[4], Karim Sacre[4], Raphaèle Seror[5], Xavier Mariette[5], Patrice Cacoub[6], Ygal Benhamou[7], Hervé Levesque[7], Cécile Goujard[8], Olivier Lambotte[8], Bernard Bonnotte[9], Maxime Samson[9], Félix Ackermann[10], Jean Schmidt[11], Pierre Duhaut[11], Jean-Emmanuel Kahn[12], Thomas Hanslik[12], Nathalie Costedoat-Chalumeau[1], Benjamin Terrier[1], Alexis Regent[1], Bertrand Dunogue[1], Pascal Cohen[1], Véronique Le Guern[1], Eric Hachulla[13], Benjamin Chaigne[1], Luc Mouthon[1]

[1]Department of Internal Medicine, National Reference Center for Rare Systemic Autoimmune Diseases, Hôpital Cochin, Assistance Publique-Hôpitaux de Paris, Université Paris Cité, Paris, France; [2]Department of Internal Medicine, Henri-Mondor University Hospital, Assistance Publique-Hôpitaux de Paris, Université Paris Est Créteil (UPEC), Créteil, France; [3]Department of Internal Medicine, Nantes University Hospital, University of Nantes, Nantes, France; [4]Department of Internal Medicine, Hôpital Bichat-Claude Bernard, Assistance Publique-Hôpitaux de Paris, Université Paris Cité, Paris, France; [5]Department of Rheumatology, Bicêtre hospital, Assistance Publique-Hôpitaux de Paris, Université Paris Saclay, Le Kremlin Bicêtre, France; [6]Department of Internal Medicine and Clinical Immunology, Groupe Hospitalier Pitié-Salpêtrière,Université Paris Sorbonne, Paris, France; [7]Department of Internal Medicine, CHU de Rouen, UniRouen, Rouen, France; [8]Université Paris Saclay, Department of Internal Medicine and clinical immunology, Bicêtre hospital, Assistance Publique-Hôpitaux de Paris, UMR1184 Inserm, CEA, Le Kremlin Bicêtre, France; [9]Department of Internal Medicine and Clinical Immunology, Dijon University Hospital, Dijon, France; [10]Department of Internal Medicine, Foch Hospital, Suresnes, France; [11]Department of Internal Medicine and RECIF, Amiens University Hospital, Université Picardie Jules Verne, Amiens, France; [12]Department of Internal Medicine, Ambroise Paré Hospital, Assistance Publique - Hôpitaux de Paris, Université de Versailles Saint-Quentin-en-Yvelines, Boulogne-Billancourt, France, [13]Department of Internal Medicine and clinical immunology, North-West National Reference Center for Rare Systemic Autoimmune Diseases iques et Auto-Immunes Rares du Nord-Ouest, Hôpital Claude Huriez, Université de Lille, France

Background. The mixed connective tissue disease is an entity defined by the positivity of antibodies directed against ribonucleoprotein U1 (anti-RNP) and the presence of several clinical and biological signs found in other differentiated connective tissue diseases. Myositis is one of the main criteria for mixed connective tissue disease, present in all four sets of current diagnostic criteria and involving 13.5-42% of patients at diagnosis; this frequency rose to 20-50% during follow-up.

Methods. The objective of this study is to better characterize the features and outcomes of a large population of patients with mixed connective tissue disease. We performed an observational retrospective multicenter cohort study in France. Patients who fulfilled at least one diagnostic criteria set for mixed connective tissue disease and none of the criteria for other differentiated connective tissue diseases were included.

Results. Three hundred and thirty patients (88% females, median [interquartile range] age of 35 years [26-45]) at diagnosis were included. Two hundred and eight (63.0%) patients were Caucasian, 97 (29.4%) of Afro-Caribbean origin and 21 (6.4%) of Asian origin. The diagnostic criteria of Sharp or Kasukawa were met by 97.3% and 93.3% of patients, respectively. None of the patients met other classification criteria without fulfilling Sharp or Kasukawa criteria. The most common manifestations at diagnosis were Raynaud's phenomenon (90%), arthralgia (84%), swollen fingers (49%) and myalgia (33%). During the course of the disease, we found that myalgia is present in 55 patients (31%) and was significantly more frequent in patients of African or Caribbean origin. One hundred and nine patients had an electromyogram with a myogenic pattern in 30 (27.5%). Muscle biopsy was performed in 40 patients with a myositis pattern in 26 of them (65%). After a median follow-up of 8 [3-14] years, 149 (45.2%) patients achieved remission. Eighty-five (25.8%) patients progressed to a differentiated connective tissue disease with a mean duration of 5 [2-11] years, mainly systemic lupus erythematosus (15.8%) or systemic sclerosis (10.6%). Myalgia or myositis were not associated with the progression toward a differentiated connective tissue disease.

Conclusion. This study shows that MCTD is a distinct entity that can be classified using Kasukawa and/or Sharp criteria, and that only 25.8% patients progress to a differentiated connective tissue disease during follow-up. It also shows that myalgia/myositis are one of the hallmarks of the disease.

P-51

CLINICAL CHARACTERISTICS OF ANTI-SYNTHETASE SYNDROME: ANALYSIS FROM THE CLASS PROJECT

Sara Faghihi-Kashani[1], Akira Yoshida[2], Francisca Bozan[3], Giovanni Zanframundo[4,5], Davide Rozza[6], Aravinthan Loganathan[7,8,9], Eduardo Dourado[10,11,12], Gianluca Sambataro[13], Iazsmin Bauer Ventura[14], Sangmee Sharon Bae[15], Darosa Lim[16], Daphne Rivero Gallegos[17], Yasuhiko Yamano[18], Albert Selva-O'Callaghan[19], Andrew Mammen[20], Carlo A Scirè[6,21], Carlomaurizio Montecucco[4,5], Chester V Oddis[22], David Fiorentino[23], Francesco Bonella[24], Frederick W Miller[25], Ingrid E Lundberg[26], Jens Schmidt[27,28], Jorge Rojas-Serrano[29], Marie Hudson[30], Masataka Kuwana[2], Miguel Angel González-Gay[31,32], Neil McHugh[8], Tamera Corte[33], Tracy Jennifer Doyle[34], Victoria Werth[16], CLASS project participating investigators, Rohit Aggarwal[22], Lorenzo Cavagna[4,5]

[1]Division of Immunology and Rheumatology, Stanford University Medical Center, Redwood City, CA, USA; [2]Department of Allergy and Rheumatology, Nippon Medical School Graduate School of Medicine, Tokyo, Japan; [3]Section of Rheumatology, Department of Medicine, Hospital Clínico Universidad de Chile, Santiago, Chile; [4]Department of Internal Medicine and Therapeutics, University of Pavia, Lombardy, Italy; [5]Rheumatology Division, Fondazione IRCCS Policlinico San Matteo, Pavia, Lombardy, Italy; [6]Epidemiology Research Unit, Italian Society for Rheumatology, Milan, Italy; [7]Royal National Hospital for Rheumatic Diseases, Bath, UK; [8]Department of Life Sciences, University of Bath, Bath, UK; [9]Arthritis Australia, Broadway, Glebe, NSW, Australia; [10]Rheumatology Department, Centro Hospitalar do Baixo Vouga, Aveiro, Portugal; [11]Aveiro Rheumatology Research Centre, Egas Moniz Health Alliance, Aveiro, Portugal; [12]Rheumatology Research Unit, Instituto de Medicina Molecular, Faculdade de Medicina, Universidade de Lisboa, Centro Académico de Medicina de Lisboa, Lisboa, Portugal; [13]Regional Referral Center for Rare Lung Disease, Policlinico "G. Rodolico-San Marco", University of Catania, Catania, Italy; [14]Section of Rheumatology, Department of Medicine, University of Chicago, Chicago, IL, USA; [15]Division of Rheumatology, Department of Medicine, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA, USA; [16]Department of Dermatology, Perelman School of Medicine & Corporal Michael J. Crescenz Department of Veterans Affairs Medical Center, Philadelphia, PA, USA; [17]Rheumatology service, National Institute of Respiratory Diseases, Ismael Cosío Villegas, Mexico City, Mexico; [18]Department of Respiratory Medicine and Allergy, Tosei General Hospital, Aichi, Japan; [19]Systemic Autoimmune Diseases Unit, Internal Medicine Department, Vall d'Hebron University Hospital, Barcelona, Spain; [20]National Institute of Arthritis and Musculoskeletal and Skin Disorders, and Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, USA; [21]School of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy; [22]Division of Rheumatology and Clinical Immunology, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA; [23]Department of Dermatology, Stanford University Medical Center, Redwood City, CA, USA; [24]Center for interstitial and rare lung diseases, Pneumology Department, Ruhrlandklinik University Hospital, University of Duisburg-Essen, Essen, Germany; [25]Environmental Autoimmunity Group, Clinical Research Branch, National Institute of Environmental Health Sciences, National Institutes of Health, Bethesda, MD, USA; [26]Division of Rheumatology, Department of Medicine, Solna, Karolinska Institutet, Stockholm, Sweden; [27]Department of Neurology, University Medical Center Göttingen; Department of Neurology and Pain Treatment, Immanuel Klinik Rüdersdorf, University Hospital of the Brandenburg Medical School Theodor Fontane, Rüdersdorf bei Berlin, Germany; [28]Faculty of Health Sciences Brandenburg, Brandenburg Medical School Theodor Fontane, Rüdersdorf bei Berlin, Germany; [29]Interstitial Lung Disease and Rheumatology Units, Instituto Nacional de Enfermedades Respiratorias, Ismael Cosío Villegas, México City, México; [30]Division of Rheumatology, Department of Medicine, Jewish General Hospital, McGill University, Montreal, Quebec, Canada; [31]Division of Rheumatology, IIS-Fundación Jiménez Díaz, Madrid, Spain; [32]Medicine and Psychiatry Department, University of Cantabria, Santander, Spain; [33]Department of Respiratory Medicine, Royal Prince Alfred Hospital, The University of Sydney, Sydney, Australia; [34]Division of Pulmonary and Critical Care Medicine, Department of Medicine, Brigham and Women's Hospital, Boston, MA, USA

Background. Anti-synthetase syndrome (ASSD) is a rare systemic autoimmune rheumatic disease (SARD) with significant heterogeneity (1), for which currently there are no shared classification criteria. The Classification Criteria for Anti-synthetase Syndrome (CLASS) project is an international collaborative study funded by the American College of Rheumatology and the European Alliance of Associations for Rheumatology to develop and validate data and consensus-driven classification criteria for ASSD. For the data-driven part of the project, we herein report the results of univariable analysis performed on the CLASS database aiming to identify clinical and serological variables suitable for inclusion in the classification criteria for ASSD.

Methods. We utilized the large, international, multi-center, CLASS database, which includes information on both ASSD patients and controls with mimicking conditions such as SARDs and interstitial lung disease (ILD), enclosed by 92 centers across 30 countries around the world. The diagnoses of ASSD and controls by local investigators were confirmed by the CLASS

project team members. Univariable logistic regression was performed to evaluate clinical and serological features associated with the ASSD diagnosis on a randomly selected subset of the whole cohort.

Results. Our analysis included 797 ASSD patients and 857 controls. Joint, muscle, lung, or cardiac involvement was more prevalent in ASSD than in controls, and a similar trend was observed for skin involvement. Specific variables associated with ASSD included arthritis (odds ratio (OR) 1.98 [95% confidence interval 1.61–2.42]), diffuse myalgia (OR 1.65 [1.35–2.02]), muscle enzyme elevation (OR 1.70 [1.39–2.07]), ILD (OR 8.16 [6.51–10.24]), mechanic's hands (OR 7.79 [5.85–10.38]), secondary pulmonary hypertension due to ILD (OR 4.53 [2.07–9.92]), Raynaud's phenomenon (OR 1.45 [1.17–1.79]), and unexplained fever (OR 1.64 [1.23–2.17]). From the serological point of view, anti-Jo-1 (OR 492.66 [122.04–1988.74]) and non-Jo-1 anti-synthetase autoantibodies (OR 156.53 [49.91–490.91]), anti-nuclear antibodies with cytoplasmic pattern (OR 3.20 [2.42–4.24]), and anti-Ro52/Ro60 or anti-Ro/SSA autoantibodies (OR 3.71 [2.98–4.62]) were associated with ASSD (Fig. 1). In contrast, isolated arthralgia, muscle weakness, dysphagia, electromyography/MRI/muscle biopsy findings suggestive of myopathy, dermatomyositis rashes, myocarditis, and pulmonary arterial hypertension did not differentiate ASSD from controls or were inversely associated with ASSD.

Conclusion. We identified key clinical and serological variables associated with ASSD, which will help clinicians and offer valuable insights for multivariable analyses aimed at establishing data-driven classification criteria for ASSD.

P-52

THE ROLE OF MULTI-CRITERIA DECISION ANALYSIS IN THE DEVELOPMENT OF CANDIDATE CLASSIFICATION CRITERIA FOR ANTISYNTHETASE SYNDROME: ANALYSIS FROM THE CLASS PROJECT

Giovanni Zanframundo[1,2]*, Eduardo Dourado[3,4,5]*, Iazsmin Bauer-Ventura[6], Sara Faghihi-Kashani[7], Akira Yoshida[8], Aravinthan Loganathan[9,10,11], Daphne Rivero-Gallegos[12], Darosa Lim[13], Francisca Bozán[14], Gianluca Sambataro[15], Sangmee Sharon Bae[16], Yasuhiko Yamano[17], Francesco Bonella[18], Tamera J. Corte[19], Tracy J. Doyle[20], David Fiorentino[21], Miguel A. Gonzalez-Gay[22], Marie Hudson[23], Masataka Kuwana[8], Ingrid E. Lundberg[24], Andrew Mammen[25,26], Neil McHugh[10], Frederick W. Miller[27], Carlomaurizio Montecucco[1,2], Chester V. Oddis[7], Jorge Rojas-Serrano[12], Jens Schmidt[28], Albert Selva O Callaghan[29], Victoria P. Werth[12], Paul Hansen[30], Davide Rozza[31], Carlo A. Scirè[32], Garifallia Sakellariou[33,34], the CLASS project contributing centres**, Lorenzo Cavagna[1,2]***, Rohit Aggarwal[7]***.

[1]Department of Internal Medicine and Therapeutics, Università di Pavia, Pavia, Italy, [2]Division of Rheumatology, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; [3]Rheumatology Department, Centro Hospitalar do Baixo Vouga, Aveiro, Portugal; [4]Aveiro Rheumatology Research Centre, Egas Moniz Health Alliance, Aveiro, Portugal; [5]Rheumatology Research Unit, Instituto de Medicina Molecular, Faculdade de Medicina, Universidade de Lisboa, Lisbon, Portugal; [6]Section of Rheumatology, Department of Medicine, University of Chicago, Chicago, IL, USA; [7]University of Pittsburgh School of Medicine, Pittsburgh, PA, USA; [8]Department of Allergy and Rheumatology, Nippon Medical School Graduate School of Medicine, Tokyo, Japan; [9]Royal National Hospital for Rheumatic Diseases, Bath, UK; [10]Department of Life Sciences, University of Bath, Bath, UK; [11]Arthritis Australia, Broadway, Glebe, NSW, Australia; [12]Rheumatology Clinic, Instituto Nacional de Enfermedades Respiratorias, Ismael Cosío Villegas, Mexico; [13]Department of Dermatology, Perelman School of Medicine

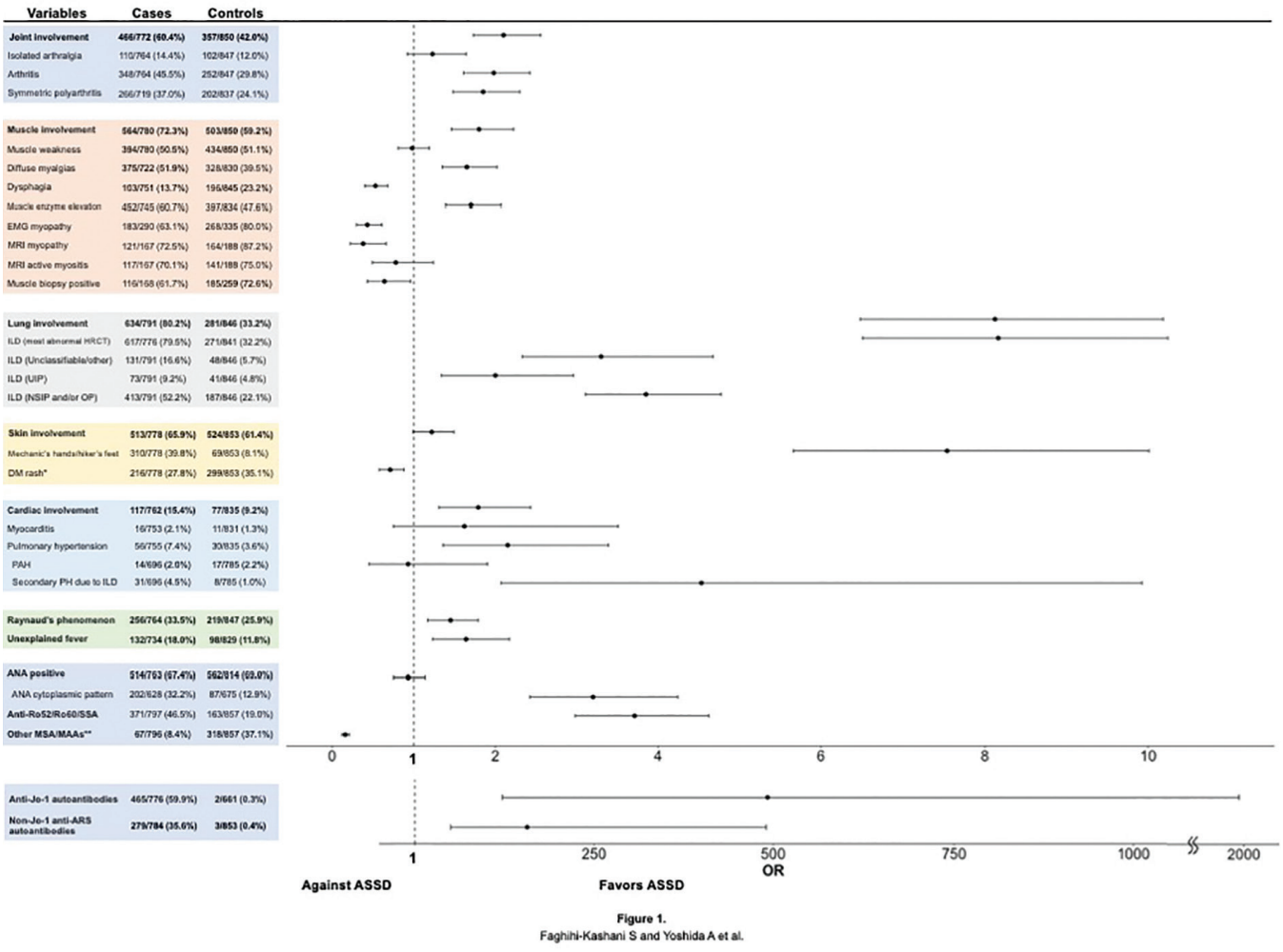


Figure 1.
Faghihi-Kashani S and Yoshida A et al.

P-51 Fig.1.

& Corporal Michael J. Crescenz Department of Veterans Affairs Medical Center, Philadelphia, PA, USA; [14]Section of Rheumatology, Department of Medicine, Hospital Clínico Universidad de Chile, Santiago de Chile, Chile; [15]Regional referral centre for Rare Lung Disease, Policlinico "G. Rodolico-San Marco", University of Catania, Catania, Italy; [16]Division of Rheumatology, Department of Medicine, David Geffen School of Medicine, University of California Los Angeles, LA, USA; [17]Department of Respiratory Medicine and Allergy, Tosei General Hospital, 160 Nishioiwake-cho, Seto, Aichi, Japan; [18]Unit for Interstitial and Rare Lung Disease at Ruhrlandklinik, University of Essen, Essen, Germany; [19]Department of Respiratory Medicine, Royal Prince Alfred Hospital Camperdown, NSW, Australia; [20]Department of Medicine, Brigham and Women's Hospital, Boston, MA, USA; [21]Department of Dermatology, Stanford University School of Medicine, Stanford, California, USA; [22]Rheumatology Department, Hospital Universitario Marqués de Valdecilla, Santander, Spain; [23] Division of Rheumatology, McGill University, Quebec, Canada; [24]Division of Rheumatology, Department of Medicine, Karolinska Institutet, Solna, Stockholm, Sweden; [25]Departments of Medicine and Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, USA; [26]National Institute of Arthritis and Musculoskeletal and Skin Disorders, National Institutes of Health, Bethesda, MD, USA; [27]Environmental Autoimmunity Group, Clinical Research Branch, National Institute of Environmental Health Sciences, National Institutes of Health, Bethesda, MD, USA; [28]Department of Neurology and Pain Treatment, Immanuel Klinik Rüdersdorf, University Hospital of the Brandenburg Medical School, Theodor Fontane, Rüdersdorf bei Berlin, Germany; [29]Vall d'Hebron Hospital, Universitat Autònoma de Barcelona, Barcelona, Spain; [30]University of Otago, Dunedin, New Zealand; [31]School of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy; [32]Epidemiology Unit, Italian Society for Rheumatology, Milan, Italy; [33]Department of Internal Medicine and Therapeutic, Università di Pavia, Pavia; [34]Istituti Clinici Scientifici Maugeri, University of Pavia, Pavia, Italy

Background. Previously proposed antisynthetase syndrome (ASSD) criteria lack validation and broad consensus. We aimed to develop and evaluate the performance of multi-criteria decision analysis (MCDA)-based candidate classification criteria for ASSD.
Methods. A list of variables associated with ASSD was developed using a systematic literature review and then refined into ASSD key variables list by international myositis and interstitial lung disease (ILD) experts. This list was used to create preferences surveys where experts were presented with a series of pairwise comparisons of fictional clinical vignettes with only two different variables. Assuming all other aspects were the same, experts were asked to select the clinical vignette that was more likely to represent an ASSD case. Expert's answers were analysed using the Potentially All Pairwise RanKings of All Possible Alternatives (PAPRIKA) method to determine the weights of the key variables to formulate the MCDA-based classification criteria. Clinical vignettes scored by the experts as consensus cases or controls were used to test the performance of candidate classification criteria using receiver operating characteristic curves.
Results. The experts recommended that exclusion criteria should be applied before using the classification criteria (Table I). The positivity for antisynthetase antibodies (anti-ARS) had the highest weight for ASSD classification, followed by ILD, myositis, mechanic's hands, arthritis, dermatomyositis-specific rashes, Raynaud's phenomenon, fever, and pulmonary hypertension. Given the sub-optimal performance of methods other than immunoprecipitation in detecting anti-ARS, especially for non-Jo1 anti-ARS, the experts considered the positivity for anti-Jo1 and non-anti-Jo1 anti-ARS as distinct domains in the candidate classification criteria original model. However, because anti-ARS antibodies are generally considered mutually exclusive, a modified model was also created by merging these two anti-ARS domains. The best cut-off for the original model had a sensitivity of 89.42%, specificity of 81.97%, positive predictive value (PPV) of 89.42%, negative predictive value (NPV) of 81.97%, Youden's index of 0.714 and an area under the curve (AUC) of 0.935 compared to the gold standard of expert consensus. The best cut-off for the modified model had a sensitivity of 89.42%, specificity of 81.97%, PPV of 89.42%, NPV of 81.97%, Youden's index of 0.714 and an AUC of 0.931.
Conclusion. The MCDA-based candidate classification criteria for ASSD performed well against the gold standard of expert consensus.

P-53

ANTI SYNTHETASE SYNDROME: WHAT'S IN A NAME?

Anushka Aggarwal[1], Parth Ladha[2], Srijan Mittal[3], Simran Nirmal[2], Saloni Haldule[2], Namratha Edpuganti[4], Nakul Jain[5], Rohit Aggarwal[6]
[1]Department of Rheumatology, Indraprastha Apollo Hospital, New Delhi, India; [2]Byramjee Jeejeebhoy Medical College, Pune, India; [3]Maulana Azad Medical College, New Delhi, India; [4]Mamata Medical College, Telangana, India; [5]Netaji Subhash Institute of Technology, New Delhi, India; [6]Arthritis and Autoimmunity Center and UPMC Myositis Center, Division of Rheumatology and Clinical Immunology, School of Medicine, University of Pittsburgh, Pittsburgh, USA

Background. Anti-synthetase syndrome constitutes a dynamically evolving subset of Idiopathic Inflammatory Myositis, marked by continual discoveries of novel antibodies, clinical parameters and treatment modalities. However, the nomenclature and appropriate abbreviations for this syndrome are plagued by heterogeneity and ambiguity, leading lack of consistency in literature. The aim of this study is to evaluate existing diversity in disease names and abbreviations within the current literature, with a future goal to develop consensus on the nomenclature.
Methods. A comprehensive search of PUBMED was conducted from January 1, 1984 (the initial description of anti-synthetase autoantibodies) to November 30, 2023, encompassing all pertinent articles published within this timeframe. The search terms employed were "antisynthetase syndrome", "anti synthetase syndrome", and "anti-synthetase syndrome". Inclusion criteria comprised all articles published in English, excluding animal studies and those solely focused on anti-synthetase autoantibodies rather than the syndrome itself. The articles were then screened for presence of terminology used for anti-synthetase syndrome and any abbreviations for the disease.
Results. The search yielded a total of n=936 items with the specified terms. After excluding 303 irrelevant articles and 58 non-English publications, the remaining n=575 articles underwent detailed review of the abstract and the full article. The data collected was representative of 47 nationalities from all over the globe. The term "anti-synthetase syndrome" made its inaugural appearance in 1992, and for the subsequent decade, no abbreviations were employed (until 2002). Out of n=575, there was variability in the terminology used as well with 54.7% (n=314) using 'antisynthetase syndrome' and 43.4% (n=249) preferring 'anti-synthetase syndrome' with few articles mentioning novel names.
Conclusion. A conspicuous discordance in nomenclature is evident, with about half using antisynthetase syndrome and other half using anti-synthetase syndrome. Moreover, significant heterogeneity exists in abbreviations with most employing ASS. There is a pressing need to bridge this disparity among the various terminology as well as abbreviation to establish a uniform identifier for the disease. Therefore, it is imperative to cultivate a consensus on an all-acceptable nomenclature to alleviate confusion and enhance clarity in communication.

References

1. SANTIAGO VILLALOBOS R, LÓPEZ-CAMPOS BODINEAU JL, RODRÍGUEZ BECERRA E, LASERNA MARTÍNEZ E, LUQUE CRESPO E, BORJA URBANO G: [Antisynthetase syndrome and interstitial lung involvement. Report of 6 cases]. *Arch Bronconeumol* 2002; 38(10): 495-8. Spanish. https://doi.org/10.1016/s0300-2896(02)75273-3
2. STURGESS A: Recently characterised autoantibodies and their clinical significance. *Aust N Z J Med* 1992; 22(3): 279-89. https://doi.org/10.1111/j.1445-5994.1992.tb02126.x
3. MAHLER M, MILLER FW, FRITZLER MJ: Idiopathic inflammatory myopathies and the anti-synthetase syndrome: a comprehensive review. *Autoimmun Rev*. 2014; 13(4-5): 367-71. https://doi.org/10.1016j.autrev.2014.01.022

Table I. Different nomenclature used for the disease name and abbreviation of anti-synthetase syndrome in the literature.

TERMINOLOGY	COUNT OF ARTICLES	% OF ARTICLES	ABBREVIATIONS	COUNT OF ARTICLES	% OF ARTICLES
antisynthetase syndrome	314	**54.7%**	ASS	255	**44.3%**
anti-synthetase syndrome	249	**43.4%**	AS	47	**8.2%**
anti-trna-synthetase syndrome	4	0.7%	ASSD	39	6.8%
anti-synthetase syndrome-overlap myositis	2	0.3%	ASyS	30	5.2%
anti Jo1 syndrome	1	0.2%	ARS	8	1.4%
polymyositis-synthetase overlap syndrome	1	0.2%	Anti-SS	7	1.2%
jo-1 antisynthetase syndrome	1	0.2%	ASA	3	0.5%
anti trna synthetase syndrome	1	0.2%	Anti-SS-OM	2	0.3%
anti-synthase antibody syndrome	1	0.2%	Anti-ARS	1	0.2%
antisynthetases syndrome	1	0.2%	SynS	1	0.2%
			Anti-ARS syndrome	1	0.2%
Grand Total	**575**	**100%**		**394**	**100%**

P-54

A COMPARATIVE ANALYSIS OF CLINICAL FEATURES OF ANTI-SYNTHETASE SYNDROME AND DERMATOMYOSITIS

Caroline J. Stone[1], Daniella Forman Faden[1], Lillian Xie[1], Darosa Lim[1], Lais Lopes Almeida Gomes[1], Victoria P. Werth[1,2]
[1]Department of Dermatology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [2]Corporal Michael J. Crescenz VA Medical Center, Philadelphia, PA, USA

Background. Anti-synthetase syndrome (ASSD) commonly manifests with the presence of positive anti-synthetase antibodies and a triad of symptoms, including interstitial lung disease (ILD), arthritis, and myositis (1). However, establishing clear classification criteria for ASSD remains an ongoing challenge. In a review conducted by Zanframundo *et al*. in February 2022, 85 proposed criteria for ASSD were identified across 82 studies (2). The ongoing debate revolves around whether ASSD should be regarded as a distinct entity, as a subset of dermatomyositis (DM) within the broader myositis spectrum, or if a patient can have both ASSD and DM. DM is characterized by classic cutaneous manifestations and can manifest with or without muscle pathology. Notably, both conditions share an increased risk of ILD, arthritis, and Raynaud's phenomenon (3).
Methods. We conducted a retrospective chart review of patients at the Penn autoimmune dermatology clinic and identified 16 patients exhibiting positive anti-synthetase antibodies and classic DM cutaneous patterns, ranging from mild to severe.
Results. These cases defied straightforward classification as DM or ASSD. The patients, ranging from 33 to 74 years old, included eleven Caucasians, four African Americans, and one Asian individual. All serologies were found to be positive for at least one of the following: Jo-1, PL-7, PL-12, and OJ. Myositis was present in fourteen, with ILD in eleven, arthritis in thirteen, and mechanic's hands in eight. Raynaud's phenomenon was prevalent in nine cases, and all cases displayed at least one characteristic DM dermatological hallmark – malar rash, Gottron's sign, V-sign, or heliotrope rash.
Conclusion. A previous study revealed differences in the interferon (IFN) signature between DM and ASSD when examining skin biopsies taken exclusively from mechanic's hands (4). Consequently, some experts consider ASSD a distinct entity separate from DM. However, a subsequent study on ASSD patients exhibiting DM-specific skin manifestations revealed that lesional biopsies from the shawl, V-neck, or Gottron's distributions displayed similarities in type 1 IFN, cytokine, and JAK-STAT pathways to pure DM patients (5). This suggests an overlap between these conditions, particularly in ASSD patients with DM-specific rashes. These cases underscore the challenge of categorizing ASSD and DM as separate entities and emphasize the overlap between these diseases.

Table I.

Case	Antibody	Myositis	ILD	Arthritis	Mechanic's Hands	Raynaud's Phenomenon	Malar Rash	Gottron's Sign + Papules	V-sign	Heliotrope Rash	Shawl Sign
1	Jo-1	✓	✓	✓	✓		✓	✓		✓	
2	Jo-1	✓	✓	✓	✓			✓			
3	PL-7	✓	✓	✓		✓	✓				
4	PL-7	✓	✓	✓		✓		✓	✓		✓
5	Jo-1	✓	✓	✓	✓	✓	✓	✓			✓
6	PL-7, PL-12	✓		✓		✓	✓	✓			
7	OJ	✓		✓		✓		✓			
8	OJ					✓	✓	✓	✓	✓	✓
9	PL-7	✓	✓	✓			✓	✓		✓	
10	PL-7	✓	✓	✓	✓	✓		✓		✓	
11	PL-12	✓	✓	✓	✓		✓	✓			
12	PL-12	✓	✓	✓	✓	✓	✓	✓		✓	
13	Jo-1		✓				✓	✓		✓	
14	PL-7	✓					✓			✓	
15	Jo-1	✓		✓	✓		✓	✓	✓		
16	Jo-1	✓	✓	✓	✓	✓	✓	✓		✓	

References

1. WELLS M *et al*.: A multidisciplinary approach to the diagnosis of antisynthetase syndrome. *Front Med* 2022; 9: 959653. https://doi.org/10.3389/fmed.2022.959653
2. ZANFRAMUNDO G *et al*.: Defining anti-synthetase syndrome: a systematic literature review. *Clin Exp Rheumatol* 2022; 40: 309-19. https://doi.org/10.55563/clinexprheumatol/8xj0b9
3. HUANG K, AGGARWAL R: Antisynthetase syndrome: A distinct disease spectrum. *J Scleroderma Relat Disord* 2020; 5: 178-91. https://doi.org/10.1177/2397198320902667
4. OKIYAMA N *et al*.: Distinct histopathologic patterns of finger eruptions in dermatomyositis based on myositis-specific autoantibody profiles. *JAMA Dermatol* 2019; 155: 1080-82. https://doi.org/10.1001/jamadermatol.2019.1668
5. PATEL J *et al*.: Identification of similarities between skin lesions in patients with antisynthetase syndrome and skin lesions in patients with dermatomyositis by highly multiplexed imaging mass cytometry. *Arthritis Rheumatol* 2022; 74: 882-91. https://doi.org/10.1002/art.42050

P-55

RE-CLASSIFICATION REVELATIONS: UNVEILING THE TRUE SUBTYPES BEHIND POLYMYOSITIS AND DERMATOMYOSITIS PARTICIPANTS IN THE UKMYONET STUDY

Choon-Guan Chua[1,2,3], Alexander Oldroyd[1,4], James B. Lilleker[1,5], Robert P. New[6], Sarah Tansley[7,8], Neil J. McHugh[7,9], Janine A. Lamb[10], Hector Chinoy[1,3]; on behalf of UKMYONET
[1]Division of Musculoskeletal and Dermatological Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, UK; [2]Department of Rheumatology, Allergy and Immunology, Tan Tock Seng Hospital, Singapore; [3]Department of Rheumatology, Salford Royal Hospital, Northern Care Alliance NHS Foundation Trust, Manchester Academic Health Science Centre, Salford, UK; [4]National Institute for Health Research Manchester Biomedical Research Centre, University of Manchester, Manchester, UK; [5]Manchester Centre for Clinical Neuroscience, Manchester Academic Health Science Centre, Salford Royal Hospital, Northern Care Alliance, NHS Foundation Trust, Salford, UK; [6]MRC/ARUK Institute of Ageing and Chronic Disease, University of Liverpool, Liverpool, UK; [7]Department of Rheumatology, Royal National Hospital for Rheumatic Diseases, Bath, UK; [8]Department of Life Sciences, University of Bath, Bath, UK; [9]Department of Pharmacy and Pharmacology, University of Bath, Bath, UK; [10]Epidemiology and Public Health Group, School of Health Sciences, The University of Manchester, Manchester, UK

Background. Distinct idiopathic inflammatory myopathies (IIM) clinical phenotypes have been defined since Peter/Bohan's description of polymyositis (PM) and dermatomyositis (DM), facilitated by mass-testing of myositis-specific and myositis-associated autoantibodies (MSAs/MAAs). However, patients continue to be diagnosed with PM and DM where another IIM-subtype designation would be more appropriate, hampering accurate clinical, genetic, and epidemiological studies on IIM. This study aims to review the IIM-subtype diagnoses ascribed to participants in the UKMYONET study.
Methods. We reviewed the proformas and serological records of all subjects labelled as PM and DM in UKMYONET (2000-2019). Where possible, clarifications on diagnoses and clinical information were sought from managing physicians. Diagnosis reassignment was based on: 2017 ACR/EULAR classification criteria for IIM, 2017 ENMC criteria for immune-mediated necrotising myopathy (IMNM), 2013 ENMC criteria for inclusion body myositis (IBM), Connors and Solomon's criteria for anti-synthetase syndrome (ASyS), MSAs/MAAs detected, and clinical judgement. Patients with an underlying connective tissue disease or MAA otherwise not defined in other diagnostic categories were diagnosed as overlap myositis (OM). MSAs/MAAs were detected through immunoprecipitation for 761 patients and line immunoblot assay (LIA), if tested, for others. Anti-HMGCR antibody was detected using ELISA and anti-Ro52 using ELISA, LIA or multiplex assay.
Results. Of the 1,952 participants in UKMYONET, 504 were originally diagnosed as PM and 568 DM (total 1072). 28/1072 were duplicate entries. Amongst 504 original PM patients, 302 (60%) were re-diagnosed as non-PM IIM: 143 ASyS, 86 OM, 52 IMNM, 19 DM, and 2 IBM. 6 (1%) patients retained PM diagnosis – 4 anti-mitochondrial and 2 anti-EIF3 antibody positive. We were unable to re-diagnose 154/504 patients: 131 seronegative for MSA/MAA, 23 had no MSA/MAA performed. 30 (6%) original PM patients were re-diagnosed with non-IIM myopathy including: hereditary myopathy (n=6), statin-related myotoxicity (n=1) and myalgia (n=1).

Amongst 568 original DM patients, 159 (28%) were re-diagnosed as non-DM IIM: 80 ASyS, 69 OM, 10 IMNM. Of the 389 (69%) retained DM, 58.9% were seropositive for MSA/MAA, 30% seronegative, and 11% had no available MSA/MAA.

The most common MSA detected for each re-diagnosed IIM-subtype were: DM (anti-TIF1γ, 21%); ASyS (anti-Jo1, 85%); IMNM (anti-SRP, 65%); OM (anti-PMScl, 44%). See Figure 1 for distribution.

Conclusion. A substantial proportion of participants originally diagnosed with PM and DM were re-diagnosed as other IIM-subtypes or non-inflammatory myopathy. Our study reinforces the importance of MSA/MAA and correlation with clinical features in diagnosing IIM-subtype accurately and may require the reanalysis of clinical and genetic studies using this data.

Acknowledgements. We express gratitude to all the patients and researchers participating in the UKMYONET study.

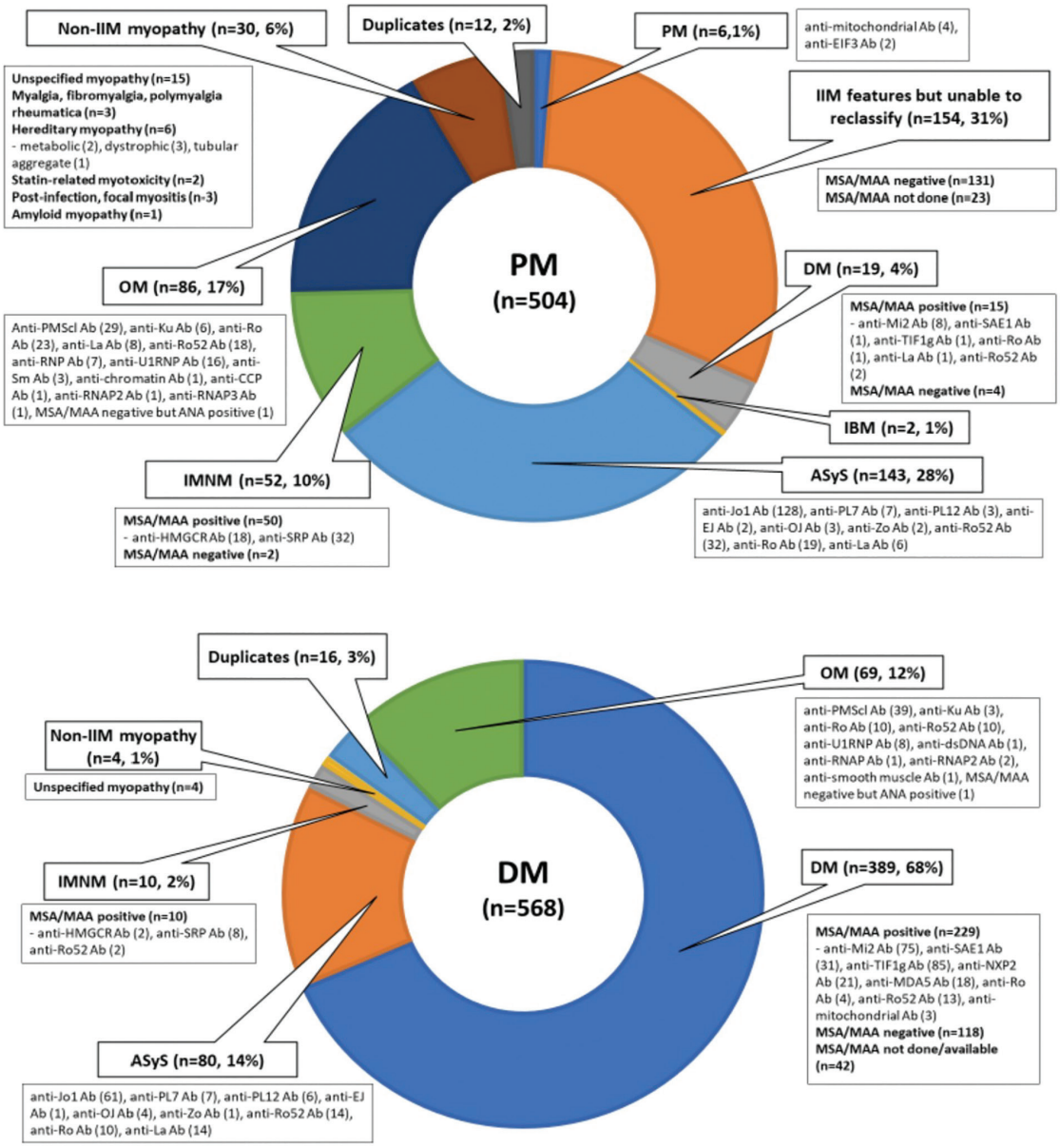


Table I.

P-56

EULAR/ACR 2017 CLASSIFICATION CRITERIA UNDERESTIMATE THE INCIDENCE OF INFLAMMATORY MYOPATHIES DUE TO THE IGNORANCE OF ANTISYNTHETASE SYNDROME AND SCLEROMYOSITIS: DATA FROM A QUADRUPLE SOURCES CAPTURE-RECAPTURE STUDY

Margherita Giannini[1], Léa Debrut[2], Benoit Nespola[3], Bernard Geny[4], Michel Velten[5], Jean Sibilia[6], Alain Meyer[7]

[1]Service de Physiologie et explorations fonctionnelles, CHU Strasbourg ; Centre de Référence des Maladies Autoimmunes Rares, CHU, Strasbourg; UR3072, Centre de Recherche en Biomédecine, University of Strasbourg, France; [2]University of Strasbourg, CNRS UMR7104, INSERM U1258, IGBMC, Illkirch, France; UR3072 Centre de Recherche en Biomédecine, University of Strasbourg, France; [3]Laboratoire d'immunologie, University Hospital of Strasbourg, France; [4]Service de Physiologie et explorations fonctionnelles, CHU Strasbourg; UR3072 Centre de Recherche en Biomédecine, University of Strasbourg, France; [5]INSERM UMR-S1113, Registre des cancers du Bas-Rhin, Fédération de Médecine Translationnelle, University of Strasbourg, France; [6]Service de Rhumatologie, Centre de Référence des Maladies Autoimmunes Rares, CHU Strasbourg, University of Strasbourg, France; [7]Service de Physiologie et explorations fonctionnelles, CHU Strasbourg; Service de Rhumatologie, Centre de Référence des Maladies Autoimmunes Rares, CHU Strasbourg; UR3072, Centre de Recherche en Biomédecine, University of Strasbourg, France

Background. Diagnosis criteria and method of cases ascertainment are two methodological issues in inflammatory myopathies (IM) epidemiology. EULAR/ACR 2017 criteria have been an important step forward in the diagnosis of IM, but some shortcomings in identifying the whole spectrum of IM remain (1). Using a four sources capture for cases ascertainment combined with the capture-recapture analysis, and the EULAR/ACR 2017 criteria, we have estimated the IM incidence in Eastern France to be 8.22/106 inhabitants/year [95% CI 6.76–9.69] (2). The aim of this study was to evaluate the potential underestimation of IM incidence due to the non-recognition of the non-anti-Jo-1 patients by EULAR/ACR criteria.

Methods. Among the patients identified by laboratory records and other sources (physicians, administrative hospital records, archives of the pathology department), the records of all the patients who lived in the study area during the study period, tested positive for IM autoantibodies, showed signs of connective tissue diseases (CTDs) incident during the study period but not fulfilled the IM EULAR/ACR 2017 criteria (consequently excluded from the incidence) were manually reviewed.

Results. Thirty-nine patients were identified. Most of them (34/39, 87.2%) had antisynthetases (15/39, 38.5%), anti-Ku (10/39, 25.6%) or anti-PM/Scl autoantibodies (9/39, 23.1%) as shown in Table I. All patients with antisynthetase antibodies fulfilled Connors's criteria for antisynthetase syndrome (ASyS) (3) (15/39, 38.5%). Anti-PM/Scl positive patients frequently showed clinical features of systemic sclerosis (SSc, including RP, puffy hands and sclerodactyly), but only one of them (11.1%) fulfilled SSc EULAR/ACR 2013 criteria, because of the absence of anti-centromere, -Scl-70, -RNA polymerase III antibodies. Thus, in addition to being not recognized in IM epidemiology, these patients (with anti-PM/Scl CTD or scleromyositis) were neither recognized in SSc epidemiology of the region. Anti-Ku positive patients, not fulfilling IM EULAR/ACR 2017 criteria, frequently fulfilled systemic lupus erythematosus EULAR/ACR 2019 criteria (4/10) or had isolated arthritis (3/10) or isolated ILD (1/10). These population-based data indicate that IM criteria miss 48% of ASyS and 60% of anti-PM/Scl associated CTD patients leading to underestimate IM incidence by at least 26%.

Of note, in 4/39 patients (10%), clinical phenotype was not consistent with the autoantibodies (anti-Mi2: n=3; -SRP: n=1), indicating the importance to consider the accuracy of autoantibodies testing when including them in diagnosis criteria.

Conclusion. These population-based data highlight that EULAR/ACR 2017 criteria miss an important part of IM spectrum. Considering non-anti-Jo-1 autoantibodies and clinical features, such as ILD, non-DM rash (skin thickening, mechanic's hands) and arthritis would enable the diagnosis of such patients.

Table I. Antisynthetase antibodies (ASy Abs) were anti-Jo1 (n= 7), -PL12 (n= 6), -PL7 (n= 2). CK: creatinekinase; DM: dermatomyositis; ILD: interstitial lung disease; IQR: interquartile range; SLE: systemic lupus erythematosus. All public and private laboratories were contacted by questionnaire letters with a stamped self-addressed return envelope asking to report all known patients with IM-associated autoantibodies (anti-Jo1, -PL7, -PL12, -EJ, -OJ, -EJ, -KS, -Zo, -SRP, -HMGCR, -Mi2, -MDA5, -Tif1γ, -NXP2, -PM/Scl, -Ku.

	ASy Abs (n=15)	Ku Abs (n=10)	PM/Scl Abs (n=9)
Age at diagnosis, median (IQR)	60 (41.8-69.5)	19 (14.3-30.5)	54 (46.8-60.5)
Female (ratio, %)	11/15 (73.3)	10/10 (100)	5/9 (55.6)
Proximal muscle weakness (ratio, %)	3/15 (20)	1/10 (10)	1/7 (14.3)
High CK (ratio, %)	3/14 (21.4)	1/10 (10)	4/7 (57.1)
Dysphagia (ratio, %)	1/13 (7.7)	0/8 (0)	0/6 (0)
ILD (ratio, %)	10/11 (90.9)	1/9 (11.1)	2/5 (40)
Arthralgia/arthritis (ratio, %)	8/12 (66.7)	7/8 (87.5)	7/9 (77.8)
DM rash (ratio, %) Heliotrope rash (ratio, %) Gottron papules/sign (ratio, %)	1/15 (6.7) 1/15 (6.7) 0/15 (0)	0/10 (0) 0/10 (0) 0/10 (0)	0/9 (0) 0/9 (0) 0/9 (0)
Mechanic's hands (ratio, %)	3/9 (33.3)	0/9 (0)	1/5 (20)
Raynaud's phenomenon (ratio, %)	9/10 (90)	4/9 (44.4)	2/6 (33.3)
Calcinosis (ratio, %)	0/8 (0)	0/8 (0)	0/3 (0)
Puffy hands (ratio, %)	0/9 (0)	0/9 (0)	2/6 (33.3)
Sclerodactyly (ratio, %)	4/10 (40)	0/9 (0)	2/5 (40)
Telangiectasia (ratio, %)	3/9 (33.3)	0/9 (0)	0/3 (0)
Pulmonary arterial hypertension (ratio, %)	2/11 (18.2)	1/9 (11.1)	0/5 (0)
Cancer (ratio, %)	5/15 (33.3)	0/10 (0)	4/7 (57.1)
Immunosuppressants (ratio, %)	10/11 (90.9)	7/10 (70)	8/9 (88.9)
Classification criteria Connors's criteria SLE EULAR/ACR 2019 criteria SSc EULAR/ACR 2013 criteria	 15/15 (100) 0/15 (0) 3/15 (20)	 0/10 (0) 4/10 (40) 0/10 (0)	 0/9 (0) 0/9 (0) 1/9 (11.1)

References

1. LUNDBERG IE, TJÄRNLUND A, BOTTAI M *et al*.: 2017 European League Against Rheumatism/American College of Rheumatology classification criteria for adult and juvenile idiopathic inflammatory myopathies and their major subgroups. *Ann Rheum Dis* 2017; 76(12): 1955-64.
2. DEBRUT L, GIANNINI M, KLEIN D *et al*.: Refining incidence and characteristics of inflammatory myopathies: a quadruple-source capture-recapture survey using the 2017 European League Against Rheumatism/American College of Rheumatology Classification Criteria. *Arthritis Rheumatol* 2023; 75(10): 1850-55.
3. CONNORS GR, CHRISTOPHER-STINE L, ODDIS CV, DANOFF SK: Interstitial lung disease associated with the idiopathic inflammatory myopathies. *Chest* 2010; 138(6): 1464-74.

Therapeutic Advances

P-57

PREDNISONE THERAPEUTIC EFFECT IN MYOSITIS DEPENDS ON B-ADRENERGIC PATHWAY ACTIVATION INDUCED BY MYOFIBRES

Margherita Giannini[1], Rovito Daniela[2], Léa Debrut[2,3], Céline Keime[2], Anne-Laure Charles[3], Béatrice Lannes[4], Bernard Geny[5], Daniel Metzger[2], Gilles Laverny[2], Alain Meyer[6]

[1]Service de Physiologie et Explorations Fonctionnelles, CHU Strasbourg; Centre de Référence des Maladies Autoimmunes Rares, CHU, Strasbourg ; UR3072, Centre de Recherche en Biomédecine, University of Strasbourg, France; [2]University of Strasbourg, CNRS UMR7104, INSERM U1258, IGBMC, Illkirch, France; [3]UR3072 Centre de Recherche en Biomédecine, University of Strasbourg, France; [4]Département de Pathologie, CHU Strasbourg, University of Strasbourg, France; [5]Service de Physiologie et Explorations Fonctionnelles, CHU Strasbourg; UR3072 Centre de Recherche en Biomédecine, University of Strasbourg, France; [6]Service de Physiologie et Explorations Fonctionnelles, CHU Strasbourg; Service de Rhumatologie, Centre de Référence des Maladies Autoimmunes Rares, CHU Strasbourg; UR3072, Centre de Recherche en Biomédecine, University of Strasbourg, France

Background. Glucocorticoids (GC) treatment in myositis is empirical and side effects are frequent. Both therapeutic and iatrogenic effects of GC are mediated by glucocorticoid receptor (GR) which is ubiquitously expressed. We have recently shown in experimental myositis (EM) induced in GR(i)skm-/- mice that prednisone (PDN) induces a myofibre-mediated anti-inflammatory phenotype in immune cells (1). Muscle transcriptomic analysis indicated that PDN induces myofibres release of epinephrine that could mediate therapeutic response. Epinephrine effect depends on its binding to the β-adrenergic receptors (β-AR). β2-AR are the most expressed in immune cells. The aim of this study was to investigate the importance of β-adrenergic pathway activation in the therapeutic response to PDN in preclinical models of myositis.

Methods. Human myotubes were treated with proinflammatory cytokines for 2 days. Then, PDN (or vehicle) was added with or without a GR inhibitor for 5 days. EM was induced at day 0 (D0) in 10-week-old mice through the immunisation against a polypeptide from skeletal muscle fast-type C protein. From D14 to D20, mice were treated with oral PDN at the dose of 1 mg/kg/day for 7 days (or vehicle), with or without a β-blocker at the same dose, or with an oral β2-agonist (6 mg/kg/day for 7 days). Muscle

strength was assessed at D0, D14 and D20 before the sacrifice (D21). Serum creatine-kinase (CK) levels were assessed at D21.
Results. PDN increased by 2-fold the epinephrine level in the supernatant of human myotubes treated with proinflammatory cytokines. This effect of PDN was suppressed when a GR inhibitor was added. In vehicle-treated EM mice, a 20% decrease in muscle strength was found at D14 (p=0.0001) up to D20 (p=0.0001) compared to D0. PDN-treated EM mice recovered muscle strength at D20 (p=0.008 *vs*. D14). This effect of PDN was abolished when a β-blocker was co-administered (p=0.0001 *vs*. D0). At sacrifice, CK serum levels were 2 times higher in vehicle-treated EM mice compared to unimmunized mice (p=0.004). PDN normalized CK serum levels in EM mice. This effect of PDN was suppressed when a β-blocker was co-administered (p=0.008 *vs*. unimmunized mice). Conversely, a treatment with a β2-agonist reproduced PDN therapeutic effect on muscle weakness as well as on CK level. These results show that PDN improves myositis in EM through myofibre production of epinephrine and β-adrenergic pathway activation.
Conclusion. Coadministration of β-blockers might decrease PDN therapeutic effect in myositis. Stimulation of β2-adrenergic pathway might represent a new therapeutic strategy for myositis.

Reference
1. GIANNINI M *et al*.: https://doi.org/10.1136/annrheumdis-2023-eular.5217

P-58

PREVALENCE OF URINARY AND BOWEL INCONTINENCE AMONG INDIVIDUALS WITH MYOSITIS: A CROSS-SECTIONAL STUDY

Genevieve M. Simkovics[1,2], Ian D. Cooper[3,4], Kelly A.L. Beer[3,4], Kerry J. Maclaurin[3,5], Kathryn M. Hird[2], Merrilee Needham[1,2,3,4]
[1]Fiona Stanley Hospital, Department of Neurology, Murdoch, AU; [2]The University of Notre Dame Australia, School of Medicine, Fremantle, AU; [3]Murdoch University, Centre for Molecular Medicine and Innovative Technologies, Murdoch, AU; [4]Perron Institute for Neurological and Translational Science, Myositis Discovery Programm, Nedlands, AU; [5]Myositis Research Consumer Panel, Australia

Background. No evidenced link exists between myositis and incontinence, however, myositis patients identify incontinence as an issue. This research was initiated in response to advocacy by consumers to investigate this topic. The objective was to determine the prevalence of urinary incontinence (UI) and bowel incontinence (BI) in the Australian myositis population, compared to an age-matched general Australian population.
Methods. The study included participants aged 18 years or older, with a self-declared, confirmed diagnosis of myositis, living in Australia. 151 participants commenced the online survey (response rate of 34%). 121 responses were validated. The mean age of participants was 75 years. 54% of participants were female. Previously published Australian general population data was used as the comparison group. Prevalence of incontinence was captured using validated International Consultation on Incontinence Questionnaires. Demographic data and physical function (via the Neuromuscular Symptom Scale (NSS)) was also captured. The survey was designed with the involvement of consumers and distributed by the Myositis Association of Australia to members.
Results. UI and BI prevalence was significantly higher (p<0.001) in the myositis population compared to the general Australian population. 87.7% of females and 66.1% of males reported UI, 73.8% of females and 53.6% of males reported BI. The most common type of UI was Mixed UI in female participants and Urge UI in males. No difference in disease duration existed between the continent and incontinent participants. Medications and the environment/setting were perceived by approximately 50% of participants as contributing factors, more than limb weakness. Difference existed in functional NSS scores only between BI and continent males (p=0.01). Two-thirds of incontinent myositis participants had never sought help for incontinence.
Conclusion. This consumer-driven study confirmed anecdotal reporting of increased prevalence of urinary and bowel incontinence within the myositis population. The significant impact of incontinence on this population and the relative silence around the topic warrants clinician awareness. Not only is the need for further research indicated, but the study also evidences the critical role of consumers in better understanding complex conditions and their impact.

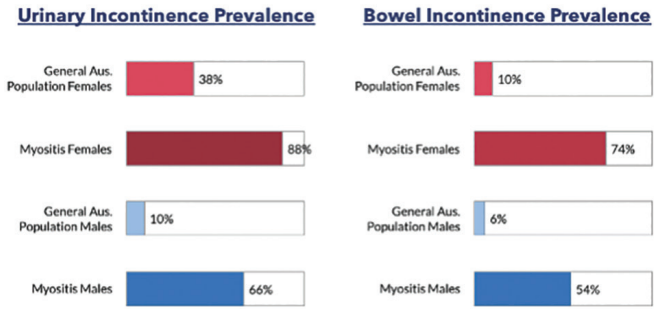


Fig. 1. Prevalence comparison of urinary incontinence and bowel incontinence in this myositis population and the general Australian population[1]

Reference
1. HAWTHORNE G: Measuring Incontinence in Australia. The University of Melbourne; 2006.

P-59

DAZUKIBART (PF-06823859), AN ANTI-INTERFERON BETA ANTIBODY, NORMALIZES GENE EXPRESSION PROFILES IN THE SKIN OF PATIENTS WITH DERMATOMYOSITIS IN A 12-WEEK STUDY

Karen Page[1], David Fiorentino[2], Ruth Ann Vleugels[3], Xingpeng Li[1], Cassandra Tierney[4], Kathleen McCauley[1], Craig Hyde[1], Wen He[1], Madhurima Saxena[1], Mikhail Salganik[1], Rohit Aggarwal[5], Victoria P. Werth[6], Aaron Mangold[7], Myron Chu[8], Elena Peeva[1], Michael Vincent[1]
[1]Pfizer Inc, Cambridge, MA, USA; [2]Department of Dermatology, Stanford University School of Medicine, Redwood City, CA, USA; [3]Department of Dermatology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA; [4]Pfizer Inc, Groton, CT, USA; [5]Department of Medicine, University of Pittsburgh, Pittsburgh, PA, USA; [6]University of Pennsylvania and the Corporal Michael J. Crescenz VA Medical Center, Philadelphia, PA, USA; [7]Department of Dermatology, Mayo Clinic Arizona, Scottsdale, AZ, USA; [8]Pfizer Inc, Collegeville, PA, USA

Background. In dermatomyositis (DM), interferon (IFN)-β levels have been shown to be positively correlated with type 1 IFN-inducible gene expression and disease activity. The effect of dazukibart (PF-06823859), a selective, humanized IFN-β neutralizing antibody, on IFN-induced and overall disease-associated gene expression in DM was assessed in a double-blind, placebo-controlled, phase 2 study (NCT03181893; exploratory endpoint).
Methods. Adults (18-80 years) with DM were randomized to placebo or intravenous dazukibart (150 or 600 mg). In this analysis, skin biopsies from patients with skin-predominant DM (Cutaneous Dermatomyositis Disease Area and Severity Index activity [CDASI-A] score ≥14; failed ≥1 standard of care systemic treatment) were collected at baseline (lesional skin [LS] and non-lesional skin [NL]) and Week 12 (LS). A 13-gene type 1 IFN signature (13GS) was used to measure IFN activity in the skin. Correlation of baseline 13GS to CDASI-A was assessed by fitting a linear model. Week 12 gene signature improvement (GSI) was calculated (change from baseline [CFB] at Week 12 in 13GS in LS divided by average difference of 13GS between baseline LS and NL). Differential gene expression analysis was used to evaluate the baseline gene expression between LS and NL. Week 12 CFB in the LS *vs*. NL disease-associated transcriptome was compared between treatment groups. Gene Set Variation Analysis (GSVA) was used to evaluate upregulated/downregulated gene sets in the representative transcriptome (LS compared with baseline NL).
Results. Skin biopsies from 48 patients were analyzed (placebo:11; dazukibart 150 mg:11; dazukibart 600 mg:26). At baseline, the 13GS differed significantly between LS and NL (p=1.192e–09) and correlated with CDASI-A in LS (p=0.0017). At Week 12, significant GSI in LS *vs*. average baseline levels with dazukibart 150 mg (120.7%; p<0.001) and 600 mg (131.0%; p<0.001) indicated recovery of LS 13GS to NL levels. At Week 12, genes that were over expressed in LS (compared with NL at baseline) were found to be downregulated, while genes that were under expressed in LS were upregulated with dazukibart 150 mg and 600 mg, indicating normalization at a transcriptome level. In addition, GSVA also showed normalization of transcriptomes from LS to NL levels with both doses of dazukibart (Fig. 1).
Conclusion. Overall DM transcriptome and 13GS expression in LS re-

versed to NL levels after 12 weeks of treatment with dazukibart. Normalization of LS gene expression supports further investigation of dazukibart as a therapeutic target for DM.

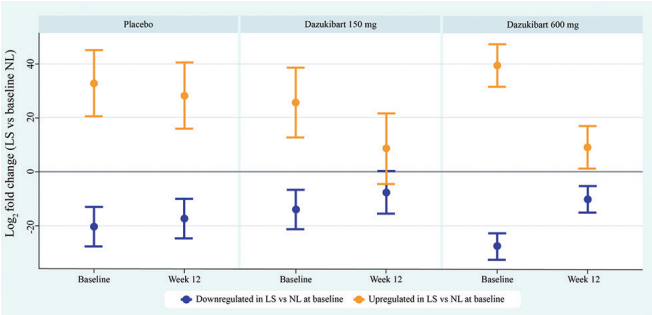


Fig. 1. GSVA of DM Transcriptome.
Upregulated and downregulatede gene sets in LS vs baseline NL were analyzed through GSVA (average p-scure) to evaluate hors gene expression in LS at Week 12 changes towards baseline NL levels. The error bars show 95% CI.
CI: confidence interval; DM: dermatomyositis; GSVA: Gene Set Variation Analysis; LS: lesional skin; NL: non-lesional skin.

P-60

BREPOCITINIB PREVENTS TYPE-I INTERFERON INDUCED DAMAGE IN CULTURED MYOCYTES AND ENDOTHELIAL CELLS INDICATING A POTENTIAL ROLE IN THE TREATMENT OF DERMATOMYOSITIS

Jiří Vencovský[1], Jolie Feldman[2], Alexandra S Goriounova[2], Lisa McConnachie[2], Brendan M Johnson[2]
[1]Institute of Rheumatology, Rheumatology, Prague, Czech Republic; [2]Priovant Therapeutics, Early Development, Durham, USA

Background. The pathogenesis of dermatomyositis (DM) involves dysregulation in signaling of Type I interferon (IFN-I), IFN-γ, IL-12, and IL-23. TYK2 and JAK1 are essential for the signaling pathway of these cytokines. Brepocitinib, a selective and potent dual TYK2/JAK1 inhibitor is in development for the treatment of DM and is expected to reduce signaling of these cytokines. A Phase 3 clinical trial of brepocitinib in adults with DM is ongoing (NCT05437263).
Methods. To evaluate the efficacy of brepocitinib in preventing IFN-I induced pathological changes characteristic of DM, human skeletal muscle myoblasts were cultured and differentiated into myotubes then treated with vehicle control or IFN-I to induce cellular damage. Myotubes were also preincubated for 1 hour with brepocitinib (1 μM or 130 nM, the latter represents the average free plasma concentration after brepocitinib 30 mg QD) prior to IFN-I treatment. Immunofluorescence staining followed by image analysis to determine myosin 4 surface area were conducted after 48 hours of IFN-I treatment. Human dermal microvascular endothelial cells (HMEC-1) were cultured and, once vascular networks were established, cells were treated with IFN-I or vehicle control. Cells were also preincubated for 1 hour with brepocitinib as described above. Under light microscopy 9 hours after treatment, the number of nodes, master segment length, and total mesh area were analyzed. One-way ANOVA followed by Tukey's multiple comparison post-hoc analyses were performed.

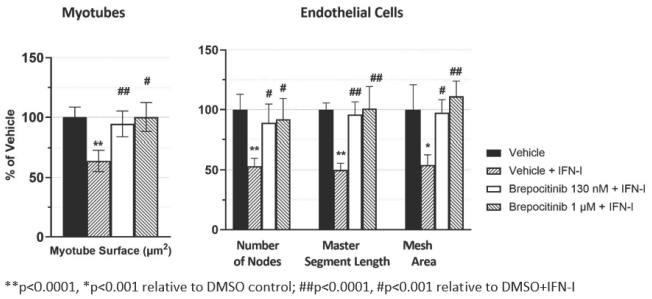


Fig. 1. Brepocitinib effects on IFN-I induced Myotube and endothelial cell damage.

Results. Myosin surface area was reduced by ~40%, relative to vehicle treated control, in myotubes exposed to IFN-I (p<0.0001). This cytokine induced damage was prevented by brepocitinib preincubation (both 130 nM and 1 μM) with mean myosin surface areas of 96% and 100% of the vehicle control, respectively. Similarly, HMEC-1 exposure to IFN-I significantly reduced the mean number of nodes, mean master segment length, and mean total mesh area by 47 to 50% relative to vehicle control (p<0.0001 nodes and segments, p<0.001 mesh area). With brepocitinib preincubation, this damage was prevented with the mean number of nodes, master segment lengths, and total mesh area ranging from 89 to 111% of vehicle control.
Conclusion. One of the most debilitating aspects of DM is muscle weakness resulting from perifascicular atrophy leading to significant impacts on quality of life for these patients. We report here the ability of brepocitinib to prevent IFN-I induced damage in both myocytes and microvasculature in culture at clinically relevant concentrations, providing further pharmacologic rationale for brepocitinib in the treatment of DM.

P-61

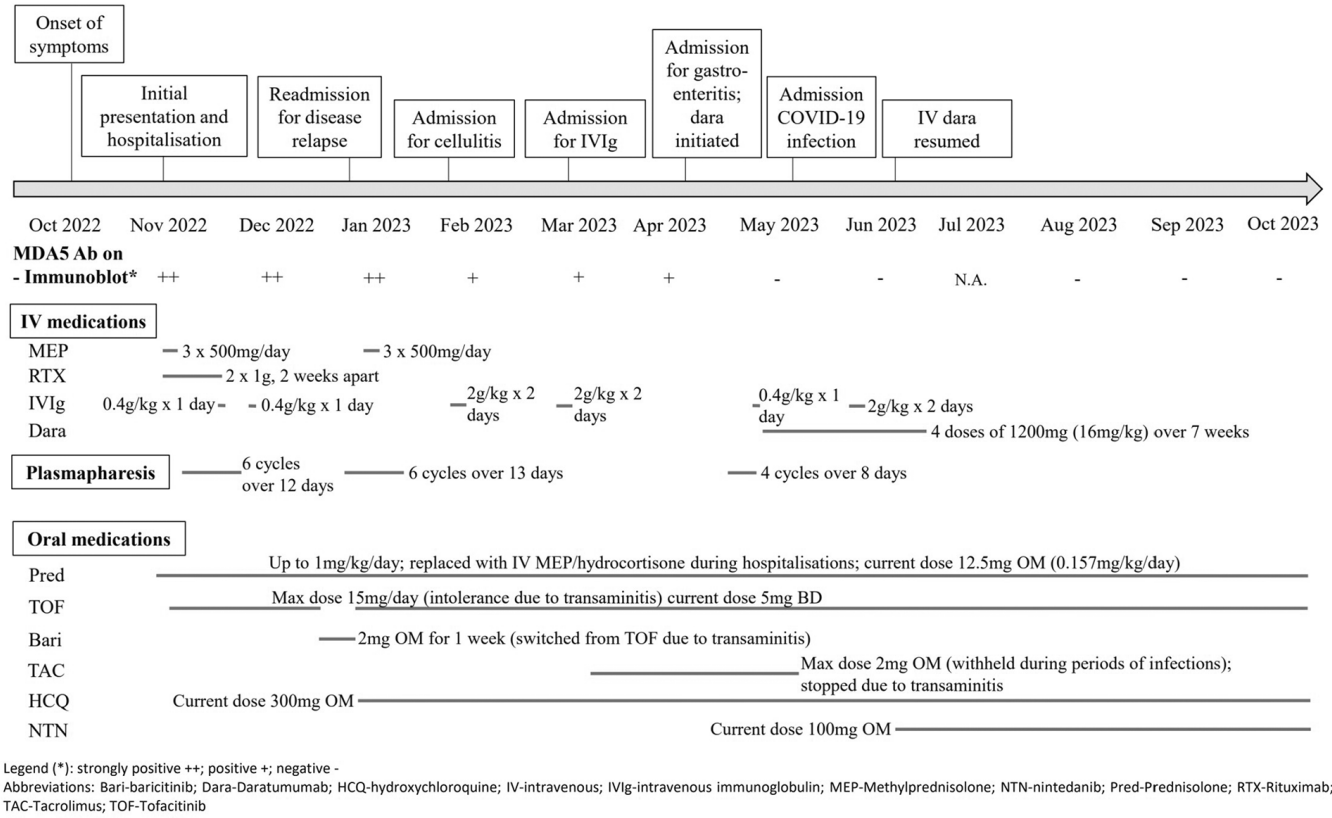
SUCCESSFUL RESCUE TREATMENT OF REFRACTORY ANTI-MDA5 AUTOANTIBODY POSITIVE DERMATOMYOSITIS WITH RAPIDLY PROGRESSIVE INTERSTITIAL LUNG DISEASE USING DARATUMUMAB

Choon-Guan Chua[1], Gin-Tsen Chai[2], Xin-Rong Lim[1], Mona Manghani[1], Bernard Pui Lam Leung[1,3], Li-Wearn Koh[1]
[1]Department of Rheumatology, Allergy and Immunology, Tan Tock Seng Hospital, Singapore; [2]Department of Respiratory and Critical Care Medicine, Tan Tock Seng Hospital, Singapore; [3]Health and Social Sciences, Singapore Institute of Technology, Singapore

Background. Anti-melanoma differentiation-associated 5 gene autoantibody (anti-MDA5 Ab) positive dermatomyositis (DM) with rapidly progressive interstitial lung disease (RP-ILD) (anti-MDA5 disease) is lethal and difficult to treat. Reported 6-month survival remains poor despite intensive treatment with glucocorticoids, various immunosuppressants, intravenous immunoglobulin (IVIg) and plasmapheresis. We report a patient with refractory anti-MDA5 disease that did not respond to Methylprednisolone-Rituximab-Tofacitinib (MEP-RTX-TOF) combination therapy and plasmapheresis, but eventually improved after receiving daratumumab.
Methods. A previously well 30-year-old Chinese man was hospitalised for 3-week history of intermittent fever, non-productive cough, lethargy, and myalgia with typical DM cutaneous changes. Physical examination revealed bilateral mid-to-lower zone inspiration crepitations with no proximal weakness or synovitis. Investigations revealed elevated creatine kinase, C-reactive protein, erythrocyte sedimentation rate, lactate dehydrogenase, ferritin, IL-18 and neutrophil-to-lymphocyte ratio of 5.52. Initial chest radiograph was normal. CT thorax 4 days later showed non-specific ground-glass opacities with consolidation in both lower lobes. Anti-MDA5 Ab was strongly positive on EUROLINE Inflammatory Myopathies 16 Ag (IgG) commercial line immunoblot.
Patient was transferred to our center one week later and was intubated on arrival for type I respiratory failure. MEP-RTX-TOF regime combination therapy was given alongside 6 cycles of plasmapharesis. Although his condition improved initially with successful extubation within one week, his anti-MDA5 disease remained active in the following months with several admissions for infections and progression of RP-ILD. He required a minimum prednisolone dose of 0.625mg/kg/day, and was given TOF, three further courses of IVIg, another 10 cycles of plasmapharesis, and tacrolimus. He remained positive for anti-MDA5 Ab on immunoblot and had persistently raised ferritin and IL-18. Given the persistent active anti-MDA5 disease, four weekly doses of intravenous daratumumab 1200mg (16mg/kg) was given to deplete long-lived plasma cells producing pathogenic autoantibodies.
Results. Three months after daratumumab treatment, patient's condition improved with prednisolone tapered to 0.157mg/kg/day, TOF, hydroxychloroquine and nintedanib (radiological signs of progressive fibrosis). His anti-MDA5 Ab turned negative on immunoblot, ferritin and IL-18 levels improved, and improvement in lung function tests and chest radiograph findings were seen. See Figure 1 for treatment summary.

Conclusion. Daratumumab is an anti-CD38 monoclonal antibody licensed for treatment of multiple myeloma which has been used off-label for other refractory autoimmune conditions like SLE. It is postulated that besides CD19/20 positive B cells, CD38 positive long-lived autoantibody-secreting plasma cells also drive chronic inflammation in these autoimmune diseases. In our patient, daratumumab use was well-tolerated and led to definite clinical and biochemic improvement.

Acknowledgements. We express gratitude to the patient for his consent and all the physicians who were involved in his care.



P-61 Fig. 1. Treatment summary.

P-62

INTERFERON BETA KNOCKDOWN USING NUCLEIC ACID THERAPEUTICS: A NOVEL APPROACH FOR TREATMENT OF JUVENILE AND ADULT DERMATOMYOSITIS

Joanna E. Parkes, Andres Correa-Sanchez, Mark Cunningham, Peter L. Oliver
MRC Nucleic Acid Therapy Accelerator, Didcot, UK

Background. The main treatments for adult and juvenile dermatomyositis (DM/JDM) are immunosuppressant drugs and corticosteroids, which have significant side effects and are not effective in all patients; therefore, identifying new therapeutic strategies for DM/JDM is an important clinical need. Type I Interferons (IFN) are a group of cytokines including IFN alpha and IFN beta. Type I IFN signalling is detected across myositis subtypes but is particularly strong in DM/JDM. There is increasing evidence that induction of IFN beta in DM/JDM correlates with disease severity. Therefore, an siRNA targeting the knockdown of expression of the human IFN beta gene IFNB1 is an attractive therapeutic target in DM/JDM.

Methods. A panel of siRNA targeting IFNB1 was designed with optimisation of GC content and predicted off-target effects, secondary structures, and thermodynamic stability. Fully chemically modified oligonucleotides were synthesised using solid phase synthesis. The oligonucleotides were then purified using reversed-phase HPLC, desalted, and quality control checks performed using LC-MS analysis.

In vitro screening was performed using immortalised myoblasts (Institut de Myologie, Paris). Cells were seeded at 50,000 cells per well of a 24-well plate. IFN beta expression was induced by transfection with 1ng/mL PolyIC for 24 hours using Lipofectamine™ 2000 (Invitrogen). Cells were then transfected with siRNA for a further 48 hours using Lipofectamine™ RNAiMAX (Invitrogen). Cells were then harvested and RNA isolated for RTqPCR for IFNB1 with HPRT1 as the reference gene.

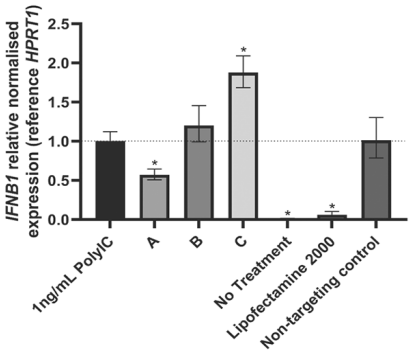


Fig. 1. Representative examples of normalised relative expression of IFNB1 with reference gene HPRT1 and control group 1ng/mL PolyIC. Immortalised myoblasts transfected with 1ng/mL PolyIC for 24hrs and then transfected with siRNA for 48hrs. Values calculated using Bio-Rad CFX Maestro software. * Indicates *p*-value <0.05.

Results. A panel of 30 siRNA were synthesised of which 27 passed quality control and were taken forward into in vitro screening. PolyIC treatment induced an 80-fold increase in IFNB1 expression compared to untreated cells at 72 hours. Treatment with the panel of siRNA for 48 hours produced a range of responses including no change, significant upregulation and significant knockdown of IFNB1 mRNA expression (Fig. 1). A selection of the siRNA demonstrating significant knockdown have been taken forward for further study to evaluate efficacy, toxicity and specificity in myoblasts, differentiated myotubes and keratinocytes.

Conclusion. In conclusion, knockdown of IFNB1 using siRNA is a promising approach as a novel therapeutic in DM/JDM and other diseases with elevated IFN beta.

Acknowledgements. Funding for this project was provided by a Cure JM Foundation grant.
Immortalised myoblasts (KM1421) derived from paravertebral muscle of a 13-year-old female were provided by the Platform for Immortalization of Human Cells, Institut de Myologie, Paris.

P-64

UPADACITINIB THERAPY IN REFRACTORY INFLAMMATORY MYOSITIS: A CASE SERIES OF 10 PATIENTS

Madelaine Beckett[1], Jan Dutz[2,3,5], Fergus To[3,5], Kun Huang[3,4,5,6]
[1]Department of Medicine, University of British Columbia, Vancouver, British Columbia, Canada; [2]Department of Dermatology, Faculty of Medicine, University of British Columbia, Vancouver, British Columbia, Canada; [3]Vancouver General Hospital, Vancouver, British Columbia, Canada; [4]Department of Medicine, Surrey Memorial Hospital, Surrey, British Columbia, Canada; [5]Division of Rheumatology, Faculty of Medicine, University of British Columbia, Vancouver, British Columbia, Canada; [6]Arthritis Research Canada, Vancouver, British Columbia, Canada

Background. JAK inhibitors have shown benefit in the treatment of refractory dermatomyositis cutaneous disease, with tofacitinib (JAK1/2/3) most commonly used in clinical setting. The approval of upadacitinib with high JAK1 selectivity introduces a second generation of JAK inhibitors with promise for minimization of JAK2 and JAK3 related side effects. Upadacitinib has not previously been used in inflammatory myositis. In this study, we reported a case series of 10 myositis patients who were treated with upadacitinib.
Methods. Patients with refractory inflammatory myositis treated with upadacitinib from a single urban center in Vancouver, British Columbia, Canada, were included from September 2020 to June 2023. The medical records of these patients were retrospectively reviewed.
Results. Ten total patients were identified for review, including five classic dermatomyositis (DM), three amyopathic DM (ADM), and two antisynthetase syndrome (ASSD). Their baseline characteristics, serologies and phenotypes as well as response to upadacitinib are summarized in Table I. The patients failed an average of four immunosuppressants before initiation of upadacitinib. In the classic DM and ADM aggregate group, upadacitinib offered clinically and statistically significant cutaneous improvement (statistics will be shown on the poster). Lack of active muscle disease at baseline precluded analysis of the effect of upadacitinib on muscle weakness. Three patients had previously undergone trials of tofacitinib at a dose of 5mg twice a day, who had either no or incomplete response to tofacitinib. After switching to upadacinitib, their individual CDASI scores improved from 7 to 1, 27 to 5, and 14 to 7, respectively. Five total patients had ILD at the time of diagnosis including two ASSD, and three anti-MDA5 DM. Three patients had mild dyspnea at baseline, and their respiratory status stabilized or improved on upadacitinib, measured by clinical status, PFT and chest CT. Nine patients remained on upadacitinib at the end of the study period. One patient discontinued upadacitinib due to severe facial acneiform rash.
Conclusion. To our knowledge, this represents the first report on the use of upadacitinib in myositis. Upadacitinib appears to be effective in targeting cutaneous manifestations of refractory inflammatory dermatomyositis. Our case series included three patients on upadacitinib who demonstrated significant improvement in cutaneous disease activity after failing tofacitinib, suggesting switching to upadacitinib may be worthwhile for those who have incomplete response to tofacitinib.Further research is still needed to validate its efficacy on a broader population scale.

References

1. PAIK JJ, CASCIOLA-ROSEN L, SHIN JY *et al.*: Study of tofacitinib in refractory dermatomyositis: an open-label pilot study of ten patients. *Arthritis Rheumatol* 2021; 73(5): 858-65.
2. PAIK JJ, SHNEYDERMAN M, GUTIERREZ-ALAMILLO L *et al.*: Long-term extension study of tofacitinib in refractory dermatomyositis. *Arthritis Rheumatol* 2022; 74(2): 371-2.
3. BECKETT M, TAN J, BONNARDEAUX E *et al.*: Tofacitinib therapy in refractory inflammatory myositis: a retrospective cohort study of 41 patients. Rheumatology (Oxford) 2023.
4. PAIK JJ, LUBIN G, GROMATZKY A, MUDD PN, JR., PONDA MP, CHRISTOPHER-STINE L: Use of Janus kinase inhibitors in dermatomyositis: a systematic literature review. *Clin Exp Rheumatol* 2022.
5. CHEN Z, WANG X, YE S: Tofacitinib in amyopathic dermatomyositis-associated interstitial lung disease. *N Engl J Med* 2019; 381(3): 291-3.
6. TAKANASHI S, KANEKO Y, TAKEUCHI T: Tofacitinib in interstitial lung disease complicated with anti-MDA5 antibody-positive dermatomyositis: a literature review. *Mod Rheumatol* 2022; 32(1): 231-7.

Table I. Patient baseline characteristics, treatments and individual response to upadacitinib therapy.

Age (current), sex	Race	Disease Phenotype	Duration of disease, years	Myositis Ab identified	Prior DMARDs	Prednisone dose (daily), pre-UPA	Current DMARDs	Prednisone dose (daily), current	Time on UPA (months)**	CDASI, pre-UPA	CDASI, current	MMT8, pre-UPA	MMT8, current
50, F	East Asian	CDM	2	Anti-MDA5, anti-Ro52	HCQ*, IVIG*, MMF*, MTX, TAC*	10mg	CP, TAC	2.5mg	8	12	4	126	150
39, F	East Asian	CDM	7	Negative	AZA, HCQ*, MMF, MTX*, QUI, TOF*	0	UPA, MTX	0	13	7	1	150	150
36, M	South Asian	CDM	4	Anti-SAE1, anti-Ro52	AZA, HCQ, IVIG*, MMF, RTX*, TAC, TOF	15mg	UPA, IVIG	4mg	10	27	5	150	150
86, F	Southeast Asian	CDM	3	Anti-TIF-1	AZA, MMF*	50mg	UPA	5mg	4	50	31	127	131
49, F	Southeast Asian	CDM	2	Anti-MDA5, anti-Ro52	CP, IVIG, MMF*, MTX, TAC*	10mg	UPA, MMF	0	3	2	0	150	150
77, F	White	ADM	1	Anti-MDA5	MMF*, MTX*	0	UPA	0	11	8	1	NA	NA
31, F	East Asian	ADM	1	Anti-MDA5, anti-Ro52	AZA*, MTX*	5mg	UPA, MTX	0	6	9	0	NA	NA
57, F	East Asian	ADM	11	Not done	HCQ, IVIG, MMF*, MTX, TOF	0	UPA, MMF	0	9	14	7	NA	NA
64, F	Southeast Asian	ASSD	6	Anti-PL12, anti- Ro52	AZA*, HCQ*, MTX*	10mg as needed	UPA	0	33	0	0	NA	NA
76, M	East Asian	ASSD	2	Anti-Jo1, anti-Ro52	LEF*, MTX*	5mg daily	UPA, MTX	0	18	0	0	NA	NA

P-65

PRECLINICAL SPECIFICITY AND ACTIVITY OF CABA-201, A FULLY HUMAN 41BB CONTAINING CD19 CAR T THERAPY FOR TREATMENT-RESISTANT MYOSITIS

Binghao J Peng, Andrea Alvarado, Hangameh Cassim, Ebony Cottman-Thomas, Ashley Martynchuk, Erica Devitt, Ivan Martinez, Jimmy Perry, Victoria Stratton, Vicky Li, Jonathan Willis, Julia SantaMaria, Sarmistha Banerjee, Tuhina Prasad, Yan Li, Chien-Chung Chen, Gwendolyn K Binder, Rebecca Dryer-Minnerly, Jinmin Lee, Samik Basu
Cabaletta Bio, Philadelphia, PA, USA

Background. Idiopathic inflammatory myopathies are a group of rare immune mediated diseases that affect primarily skeletal muscle and can also impact other organs including the skin, lungs, and joints. There is increasing evidence that B-cells play a central role in disease pathogenesis, based upon responsiveness to B-cell depletion by antibody-based therapeutics; however, responses are transient due to the incomplete depletion of B-cells in lymphoid tissue. Chimeric antigen receptor (CAR) T-cells are a novel gene-engineered cellular immunotherapy where a synthetic T-cell receptor is expressed to redirect the T-cell to a desired target. Several B-cell targeted CD19 CAR T-cell products have led to durable remissions of B-cell malignancies; four have been approved, each of which utilizes the murine derived CD19 scFv binding domain FMC63. Numerous studies have established the ability of these products to deeply deplete B-cells. An early clinical evaluation of an FMC63-41BB-CD3ζ CAR T-cell product, analogous to one of the approved therapies, in patients with treatment refractory myositis suggest the potential to safely achieve durable drug-free remissions in patients with treatment refractory disease.
Methods. CABA-201, a fully human 41BB-CD3ζ containing CD19 CAR T-cell, was generated both from healthy donor apheresis and from myositis patients' (dermatomyositis subtype) peripheral blood mononuclear cells (PBMCs) via standard ex vivo expansion using antibody coated beads and lentiviral transduction. CABA-201 in vitro activity was evaluated in co-culture assays with either CD19⁺ NALM6 cells or with patient-matched myositis CD19⁺ B-cells. Activity was measured by Luminex assay for cytokine release, cytotoxicity via flow cytometry, or CAR T-cell activation via flow cytometry. *In vitro* safety was assessed via CAR T-cell co-culture against selected primary human cells and via membrane proteome assay. *In vivo* studies assessed the function of CABA-201 in an NSG-NALM6 model.
Results. CABA-201 generated from healthy donors showed specific in vitro activity against CD19⁺ NALM6 cells. Furthermore, CABA-201 generated from myositis patient PBMCs demonstrated specific *in vitro* activity against matched B-cells (Fig. 1). The fully human CD19 binder CABA-201 had no off-target binding, and CABA-201 did not show any activity against selected non-B-cell primary human cells. Finally, *in vivo* studies confirmed the safety and activity of CABA-201 in the NSG-NALM6 model.
Conclusion. Together, these data support the safety and activity of CABA-201, and provide a clinically relevant benchmark for dose related potency in clinical studies.

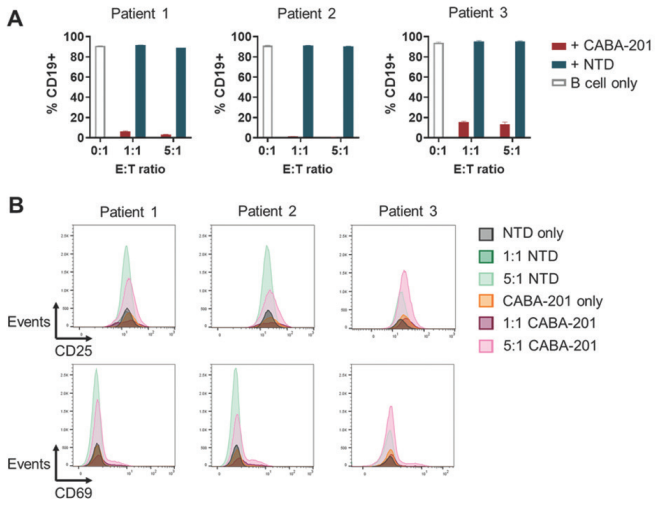


Fig. 1. Myositis patient derived CABA-201 T cells effectively kill their intended autologous patient target B cells. A) Effector T cells (CABA-201 or NTD T cells) generated from myositis donor PBMCs were co-cultured with B cells isolated from the same donor at the indicated E:T ratios for 24 hours. Percentage of CD19 positive cells is shown for each representative matched donor pair. Each bar represents mean ± SD of triplicates. B) Histogram of CD25 (upper panel) and CD69 (lower panel) surface expression on effector T cells is shown for each representative matched donor pair following co-culture. 1:1 = E:T ratio of 1:1, and 5:1 = E:T ratio of 5:1.

OP-9

EFFICACY AND SAFETY OF CALCINEURIN- AND JAK-INHIBITORS COMBOTHERAPY IN ANTI-MDA5 DM PATIENTS: A CASE CONTROL STUDY

V. Pagis[1], Q. Astouati[2], L. Pacoureau[3], Y. Nguyen[4], P. Bay[5], A. Roux[6], L. Gallay[7], B. Terrier[8], A. Meyer[9], C. Cerf[10], M. Neuvielle[10], B. Hervier[11], B. Suzon[12], O. Benveniste[1], Y. Uzunhan[5], Y. Allenbach[1]
[1]Department of Internal Medicine, Pitié-Salpêtrière University Hospital, AP-HP, Sorbonne University, Paris, France; [2]Department of Internal Medicine and Clinical Immunology, Lille University Hospital, Lille University, Lille, France; [3]Department of Internal Medicine, Bicêtre Hospital, AP-HP, Paris-Saclay University, Kremlin-Bicêtre, France; [4]Department of Internal Medicine, Beaujon Hospital, APHP, Paris Cité University, Clichy; [5]Department of Pneumology, Avicenne Hospital, AP-HP, Sorbonne University, Paris, France; [6]Department of Pneumology, Foch Hospital, Suresnes, France; [7]Department of Internal Medicine, Lyon Sud Hospital, Lyon Sud University, Lyon, France; [8]Department of Internal Medicine, Cochin Hospital, AP-HP, Paris Cité University, Paris, France; [9]Department of Physiology, Strasbourg University Hospital, Strasbourg University, Strasbourg, France; [10]Department of Reanimation, Foch Hospital, Suresnes, France; [11]Department of Internal Medicine, Saint-Louis Hospital, AP-HP, Paris Cité University, Paris, France; [12]Department of Internal Medicine, Martinique University Hospital, Fort-de-France, Martinique France

Background. To date, there are no guidelines to prevent the occurrence of severe forms of anti-melanoma differentiation-associated gene 5 dermatomyositis (anti-MDA5 DM), mainly related to their pulmonary involvement. JAK inhibitors seem to be a promising treatment, as anti-MDA5 DM pathophysiology involves interferon signaling. The aim of our study, was to assess the efficacy and safety of the association of JAK and calcineurins inhibitors (JAK-CNI) in patients with anti-MDA5 DM.
Methods. We performed a nested case-control study from a retrospective cohort of 234 patients with anti-MDA5 DM. Each patient receiving JAK-CNI was matched to 2 controls with respect to age at symptom onset, gender, New York Heart Association (NYHA) dyspnea score at diagnosis, existence of Raynaud's phenomenon and based on number of previous therapeutic lines. All-cause mortality or transplant within a year was compared using Cox proportional hazards regression models, adjusted for the occurrence of rapidly progressive interstitial lung disease. Specific mortality or transplantation within one year was also assessed, as was the occurrence of infectious or non-infectious side effects.
Results. Twenty-seven patients with JAK-CNI were compared to 54 matched controls. Almost all of these patients had pulmonary involvement. Thirty patients (37%) died (n=27) or were transplanted (n=3) during follow-up. JAK-CNI combination showed no improvement in terms of survival or reduction in the number of transplants within a year compared with standard treatment (HR 0.80 IC95% (0.36–1.77)). Results were similar whether patients were hospitalized in intensive care unit when treatment was introduced, and whether or not they were in first line of treatment. Six-month survival rate among patients receiving JAK-CNI was similar to those receiving triple therapy (corticosteroids, CNI and intravenous cyclophosphamide) (n=7) (70% *vs*. 60%). Infectious complications were frequent in both groups (n=41, 52%), with no excess risk in patients receiving JAK-CNI, notably regarding viral infections.
Conclusion. This study on large proportion of patients with severe forms of anti-MDA5 DM nuances the preliminary results concerning the use of JAK inhibitors. Previous results were obtained from smaller studies, with less severe forms of the disease and with inappropriate controls to account for disease severity. JAK-CNI association does not appear to be associated with an increased risk of infection, although this risk remains high and warrants particular attention and systematic prophylaxis.

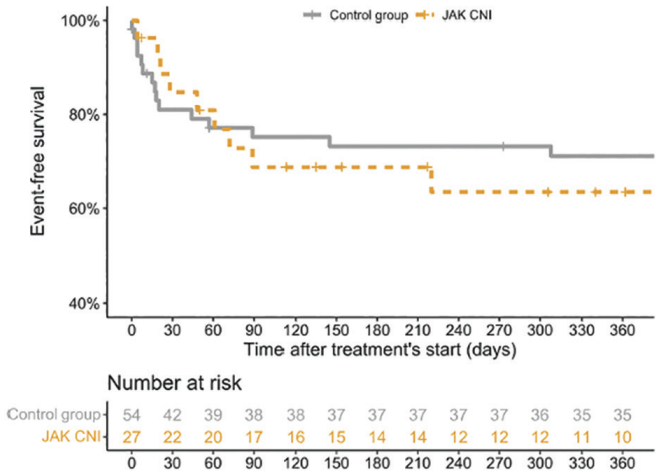


Fig. 1. Kaplan Meier curves for one-year survival and transplantation-free survival (primary outcome) according to treatment regimen.

References

1. CHEN Z, WANG X, YE S: Tofacitinib in amyopathic dermatomyositis-associated interstitial lung disease. *N Engl J Med* 2019; 381(3): 291-3
2. KURASAWA K, ARAI S, NAMIKI Y *et al*.: Tofacitinib for refractory interstitial lung diseases in anti-melanoma differentiation-associated 5 gene antibody-positive dermatomyositis. *Rheumatology* (Oxford) 2018; 57(12): 2114-19
3. TSUJI H, NAKASHIMA R, HOSONO Y *et al*.: Multicenter prospective study of the efficacy and safety of combined immunosuppressive therapy with high-dose glucocorticoid, tacrolimus, and cyclophosphamide in interstitial lung diseases accompanied by anti-melanoma differentiation-associated gene 5-positive dermatomyositis. *Arthritis Rheumatol* 2020; 72(3): 488 98.

OP-10

KINETICS OF MUSCLE STRENGTH RECOVERY DURING INITIAL THERAPY WITH GLUCOCORTICOIDS IN INFLAMMATORY MYOSITIS

Sasikala B, Anirudh Maslekar, Ramya Janardana, Vineeta Shobha

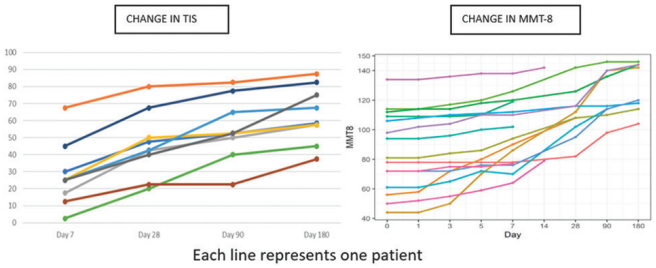
Department of Clinical immunology and rheumatology, St. John's Medical College Hospital, St. John's National Academy of Medical Sciences, Bengaluru, India.

Background. There is a lack of data regarding the kinetics of muscle strength change during the early part of illness after initiation of glucocorticoid therapy in idiopathic inflammatory myositis (IIM) patients and how this translates into subsequent muscle strength recovery and overall improvement. We undertook the current pilot study to document the early course of muscle strength changes in hospitalised IIM patients and to identify potential markers of early responsiveness.

Methods. This is a single-centre observational pilot study involving hospitalised IIM patients. Adult patients (>18 years), either newly diagnosed or with relapse, were included. All patients were administered parenteral pulse glucocorticoids for 3 days, followed by oral glucocorticoids (0.5-1 mg/kg body weight) as per physician discretion. Outcome parameters assessed were manual muscle testing (MMT-8), and at least one of muscle enzymes on at least 3 occasions in initial 28 days and subsequently on month 3 and 6. The improvement in IMACS (International Myositis Assessment and Clinical Studies Group) score in the domain of MMT-8 and the total improvement score (TIS) was calculated using the IMACS calculator.

Results. A total of 15 patients were included, predominantly women, with a mean age of 37.6±17 years. Subtypes of IIM were dermatomyositis (10), overlap myositis (2) and JDM(1). The autoantibody profile included Mi2α/β(2), TIF1-γ(1), NXP-2(1), Ro-52(5), and remaining were seronegative. Extra-muscular involvement was seen in 10 (83.3%) patients, largely in the lung and skin. Clinical improvement in MMT-8 was evident as early as day 3, and by day 7, an IMACS improvement score (muscle domain) of at least 10 was observed in 12 of 15 patients, 2 patients had a score of 27.5. These 2 patients continued to have higher improvement scores at day 28, 90 and 180. TIS also showed a similar trend as the muscle kinetics and patients with higher TIS at day 7 tended to have a higher TIS at day 90 and 180.

Conclusion. Improvement in muscle strength as measured by IMACS score (muscle domain) was observed as early as day 3 in hospitalised IIM patients on treatment with glucocorticoids. Patients with higher improvement scores at day 7 tend to have persistently higher improvement scores as well as higher TIS scores at 1 month, 3 months and 6 months. Early glucocorticoid responsiveness may be a useful tool to assess outcome and predict overall prognosis.



OP-10 Fig. 1. Trends of muscle strength recovery and total improvement score as per IMACS calculator in IIM patients.

Reference

1. JANARDANA R, SANGEETHA KN, BHAT V *et al*.: Long term outcomes in idiopathic inflammatory myositis: an observational epidemiologic study over 15 years. *Mediterr J Rheumatol* 2023 (in press).

OP-11

EFFECTIVENESS OF GENERIC TOFACITINIB IN IDIOPATHIC INFLAMMATORY MYOSITIS(IIM) - A RETROSPECTIVE ANALYSIS FROM INDIAN MYOSITIS REGISTRY (MYOIN)

Vineeta Shobha[1], Ramya Janardana[1], Ramya Kodali Sri[1], Sanjiv N. Amin[2], Banwari Sharma[3], Ruchika Goel[4], Arvind Ganapati[5], Ramnath Misra[6], Liza Rajasekhar[7]

[1]Department of Clinical Immunology and Rheumatology, St. John's Medical College Hospital, St. John's National Academy of Medical Sciences, Bengaluru, India; [2]Rheumatic Disease Clinic, Mumbai, India; [3]Niramaya Health Care, Jaipur, India; [4]Department of Clinical Immunology and Rheumatology, Christian Medical College, Vellore, India; [5]Department of Clinical Immunology and Rheumatology, All India Institute of Medical Sciences, Mangalagiri, India; [6]Department of Clinical Immunology and Rheumatology, Krishna Institute of Medical Sciences, Bhubaneshwar, India; [7]Department of Clinical Immunology and Rheumatology, Nizam's Institute of Medical Sciences, Hyderabad, India

Background. Blocking the intracellular signalling pathways with Janus kinase inhibitors (JAKi) is gaining momentum in the therapeutic armamentarium of refractory Idiopathic Inflammatory Myositis (IIM). We present retrospective analysis of generic tofacitinib prescription patterns and domain-based outcomes in IIM from members of Indian Myositis Registry (MyoIN).

Methods. Using a structured proforma, we retrospectively captured the demographic parameters, phenotype of IIM, autoantibody, prior immunosuppression used and the indication and duration for tofacitinib prescription. Further, we assessed the overall physician global assessment and response in individual domains of IIM at 3, 6 & 12 months. The skin and calcinosis improvement was as per the physician's judgement (PGA). The lung domain assessment was as per medical research council (MRC) dyspnoea scale and muscle improvement was assessed using MMT-8.

Results. We included 33 patients of IIM with a mean age 40.2 ± 15.1 years, 75.8% were women and the median duration of illness was 90(23:113.3) months. Indication for initiating tofacitinib was either refractory disease (n=27;81.2%) and or as steroid sparing agent (n=17;51.5%) among which indication in majority was cutaneous domain (n=18;54.5%). The IIM domains, autoantibody profile and prior immunosuppression and outcome responses are depicted in Figure 1. Overall complete and partial response was recorded in 18 (64.2%) patients at 3 months and in 23(88.5%) patients at 6 months following initiation of therapy with generic tofacitinib, the median duration of prescription being 17.7+11.7 months. The trends of improvement as depicted in bar and line diagrams in Fig1 suggest efficiency of tofacitinib in cutaneous and lung domains including calcinosis, but not in the muscle domain. Adverse effects of tofacitinib included Herpes zoster (n=2;6%) and dyslipidemia (n=4;12.5%).

Conclusion. Generic tofacitinib appears to be effective on short term in refractory IIM in the cutaneous and lung domains including calcinosis, however improvement is muscle strength was minimal.

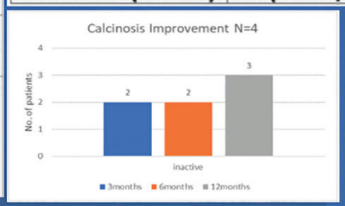
References

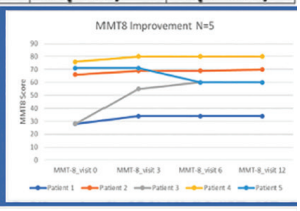
1. RAJASEKHAR L, SHOBHA V, NARASIMHAN A, BHAT V, AMIN SN, MISRA R: Prevalence and clinical correlates of myositis specific autoantibodies in idiopathic immune-mediated inflammatory myositis - Results from a Multicentric Cohort (MyoIN) from India. *J Assoc Physicians India* 2021; 69(1): 36-40.
2. GUPTA L, SRAVAN KA, JANARDANA R *et al*.: Meeting report: MyoIN – Pan-India Collaborative Network for Myositis Research. *Indian J Rheumatol* 2019; 14(2): 136-42. https://doi.org/10.4103/injr.injr_40_19
3. BECKETT M, TAN J, BONNARDEAUX E *et al*.: Tofacitinib therapy in refractory inflammatory myositis: a retrospective cohort study of 41 patients. *Rheumatology* (Oxford) 2023. https://doi.org/10.1093/rheumatology/kead404

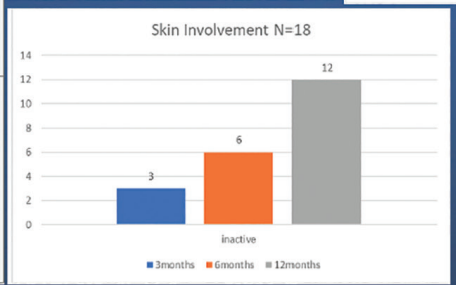
Patient characteristics at baseline	
Disease Phenotypes (N=32)	
Dermatomyositis	23(69.7%)
Overlap myositis.	6(18.2%)
Juvenile Dermatomyositis	3(9.1%)
Polymyositis	1(3%)
Median Total duration of illness (months)(IQR)	90 (23, 113.3)
Clinical domains (N=33)	
Muscle weakness	20/30(66.7%)
Mean MMT 8 (± SD)	63.2 ± 15.3
Skin Rash	31(93.9%)
Heliotrope Rash	13(39.4%)
Gottron's papule	9(27.3%)
Ulcers	7(21.2%)
Panniculitis	3(9%)
Calcinosis	13(39.4%)
HRCT evidence of ILD	9/20(45%)
Respiratory failure	1(3%)
GI involvement	3(9%)
Fever	9(27.3%)
Weight loss	20(60.6%)
Arthritis	15(45.5%)
Dysphagia	6(18.2%)
Dyspnea	4(12.1%)
Dysphonia	1(3%)
Raynauds	4(12.1%)
Laboratory/Imaging evidence	
Creatinine kinase (unit/l) (IQR)	1243.2(89.6,1332.7)
Lactate dehydrogenase (unit/l) (IQR)	494.8(223.5,718.3)
Aspartate aminotransferase(unit/l) (IQR)	56 (34,90)
Magnetic resonance imaging	12/14(85.7%)
Myopathy pattern on EMG	12/16(75%)
Muscle Biopsy evidence of myositis	5/6(83.3%)
Autoantibodies (N= 24)	
Mi-2	6(25%)
MDA 5	9(37.5%)
Ro 52	7(29.2%)
Pm-Scl	4(16.7%)
NXP2	3(12.5%)
Ku	4(16.7%)
SRP	3(12.5%)
PL7	1(4.2%)
TIF 1γ	1(4.2%)
SAE	1(4.2%)
Antibody distribution	
Single antibody positivity	15(62.5%)
>1 antibody positivity	8(33.3%)

Patient characteristics after starting tofacitinib	
Indication for initiation on Tofacitinib (N=33)	
Steroid sparing	
Muscle	4(12.1%)
Skin	8(24.2%)
Lung	2(6%)
Calcinosis	3(9%)
Refractory disease	
Muscle	3(9%)
Skin	10(30.3%)
Lung	2(6%)
Calcinosis	9(27.3%)
arthritis	3(9%)
Upfront Tofacitinib	3(9%)
Mean ± SD duration of tofacitinib usage(in months)	17.7 ± 11.7
Tofacitinib status till date (N =33)	
Continued	27 (81.8%)
Discontinued	6 (18.1%)
(Reasons Herpes Zoster-2)	
Previous immunosuppression (N=30)	
Methotrexate	22(73.3%)
Azathioprine	7(23.3%)
Mycophenolate mofetil	10(33.3%)
Rituximab	6(20%)
Tacrolimus	4(13.3%)
Cyclophosphamide	4(13.3%)
HCQ	5(16.6%)

Overall assessment (PGA)	Complete response	Partial response	No Response
3 months (N = 28)	2(7.1%)	16(57.1%)	10 (35.7%)
6 months (N = 26)	10(38.5%)	13(50%)	3(11.5%)







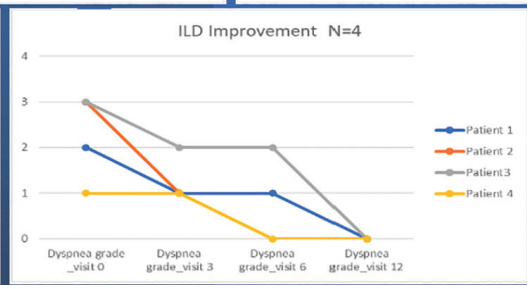


Fig. 1. Overview and short-term outcome of IIM patients treated with generic tofacitinib in an Indian Myositis Cohort (MyoIN).

OP-12

ANTI-CD19 CAR-T CELL THERAPY IN A BOY WITH REFRACTORY JUVENILE DERMATOMYOSITIS (JDM)

Rebecca Nicolai[1], Pietro Merli[2], Patricia Moran Alvarez[1], Claudia Bracaglia[1], Emiliano Marasco[1], Mattia Algeri[2], Maria G. Cefalo[2], Marco Becilli[2], Fabrizio De Benedetti[1], Franco Locatelli[2]
[1]Division of Rheumatology, IRCCS Ospedale Pediatrico Bambino Gesù, Roma, Italy; [2]Department of Hematology/Oncology, Cell and Gene Therapy, IRCCS Ospedale Pediatrico Bambino Gesù, Roma, Italy

Background. Treatment with autologous CAR T cells directed against CD19 has recently emerged as a promising therapy for systemic lupus erythematosus (SLE) and myositis, with 5 adults with SLE and 2 adult patients with antisynthetase syndrome reported. To our knowledge, we here describe the first case of a refractory JDM patient treated with anti-CD19 CAR T cell therapy.
Methods. A single infusion of fresh, autologous second-generation anti-CD19 CAR T product (lentiviral vector) manufactured on the Prodigy device was administered ($1x10^6$ CAR T cells/kg), after lymphodepletion with cyclophosphamide (CYC) (1000 mg/m^2 over 2 days) and fludarabine (90 mg/m^2 over 3 days).
Results. Treatment was given to a 12-year-old Caucasian boy diagnosed with JDM 6 years prior, who first presented at our attention at age 10 years, with a chronically active disease, refractory to multiple treatment lines and side effects from long-term glucocorticoid (GC) treatment. The boy had persistent severe skin and muscular disease activity (widespread rash, severe ulcerations, calcinosis universalis, inflammatory muscle edema on MRI and significant muscle weakness), despite previous treatment with high dose GCs, intravenous immunoglobulin, methotrexate, mycophenolate mofetil (MMF), cyclosporin A, CYC, plasmapheresis, rituximab. Before anti-CD19 CAR T cell therapy, the patient had active disease: PGA (Physician's Global Assessment of disease activity), 10/10; CMAS (Childhood Myositis Assessment Scale), 36/52 and CAT (Cutaneous Assessment Tool for myositis), 9/17. JDM treatment (GC, MMF and hydroxychloroquine) was withdrawn before CAR T infusion. The patient presented fever as part of mild cytokine release syndrome (G1), transient anemia (G2) and neutropenia (G4). No infection or neurotoxicity were observed. Circulating B cells at baseline were 154.11 cells/mL. CAR-T cells expanded significantly (peak at day 7, 32.69 cells/mL). Complete B-cell depletion was achieved on day 5 in blood and at wk 2 and 4 in bone marrow. Starting at wk 4, he presented progressive improvement of disease activity, reaching PGA 2/10, CMAS 41/52 and CAT activity score 3/17 at wk 16.
Conclusion. This JDM patient with severe chronic disease, refractory to multiple treatments, achieved sustained B-cell depletion (in blood and bone marrow) and ongoing immune-suppressive drug-free clinical and radiological improvement after a single infusion of anti-CD19 CAR-T cells. Long-term efficacy assessment is needed.

References

1. MACKENSEN A, MÜLLER F, MOUGIAKAKOS D *et al*.: Anti-CD19 CAR T cell therapy for refractory systemic lupus erythematosus. *Nat Med* 2022; 28(10): 2124-32.
2. MÜLLER F, BOELTZ S, KNITZA J *et al*.: CD19-targeted CAR T cells in refractory antisynthetase syndrome. *Lancet* 2023; 401(10379): 815-18.
3. PECHER AC, HENSEN L, KLEIN R *et al*.: CD19-targeting CAR T cells for myositis and interstitial lung disease associated with antisynthetase syndrome. *JAMA* 2023; 329(24): 2154-62.

Juvenile Myositis

P-66

EFFICACY AND SAFETY OF GROWTH HORMONE IN JDM CHILDREN WITH GLUCOCORTICOID RELATED GROWTH FAILURE

Wang Xiaolei, Wang Xinning, Chi Ying, Liu Yuan, Li Jianguo
Department of Rheumatology and Immunology, Children's Hospital Affiliated to Capital Institute of Pediatrics, Beijing China

Background. Juvenile dermatomyositis (JDM) is a chronic symmetrical inflammatory myositis. The standard treatment for JDM involves long-term use of glucocorticoids (GC), either alone or in combination with multiple biological agents and immunomodulators. Approximately 30% of JDM children experience growth failure. In recent years, growth hormone has been gradually utilized to improve GC related growth failure. Nevertheless, there are no existing reports on the efficacy and safety of growth hormone specifically in JDM children combine with growth failure. Therefore, we present a study involving sixteen Chinese JDM children with growth failure who received rhGH treatment.
Methods. Sixteen JDM children with associated growth failure were enrolled between September 2020 and March 2023. They underwent rhGH treatment at a dosage range of 0.10-0.15 IU/kg/day. The primary efficacy endpoint was significant changes observed in both growth velocity (GV) and height Z-score compared to baseline after 6 to 24 months.
Results. The mean age of the participants was (10.19±3.10) years old while the average duration of JDM was (52.88 ±16 .69) months prior to enrollment into this study. The height Z-score before treatment initiation stood at (-2 .3±1 .15). After 24 months of rhGH treatment, the height Z-score was (-0.77±0.57), and the Δheight Z-score was (1.61±0.79). The height Z-score gradually increased (p<0.001, p<0.01). In addition, the average GV was (2.74±1.53) cm/year before treatment. After 24 months of rhGH treatment, the GV was (9.75±1.39) cm/year, and the ΔGV was (6.42±3.39) cm/year. The GV of the patient gradually increased (p<0.001, p<0.01). No serious adverse events were related to recombinant human Growth Hormon growth hormone (rhGH) treatment. Compared with the recurrent rate of JDM without rhGH therapy, there was only one patient (1/16, 6.25%) recurred, indicating there were no risk of JDM recurrent, abnormal glycometabolism, and abnormal thyroid function in JDM children after rhGH treatment.
Conclusion. In this study, rhGH achieved significant improvement in GV, height Z-score and other growth-related variables, including IGF-1and AKP in children with JDM combined with glucocorticoid related growth failure. rhGH was safe and well tolerated. Of course, evaluation with larger prospective controlled studies is needed to answer remaining questions about rhGH dosing, timing of usage, and the long-term effect in JDM.

References

1. GARA S, JAMIL RT, MUSE ME *et al*.: Juvenile dermatomyositis 2023.
2. RHIM JW: Juvenile dermatomyositis. *J Rheum Dis* 2022; 29(1): 14-21
3. MAMYROVA G, KISHI T, SHI M *et al*.: Anti-MDA5 autoantibodies associated with juvenile dermatomyositis constitute a distinct phenotype in North America. *Rheumatology* (Oxford) 2021; 60(4): 1839-49.
4. PINOTTI CS, CANNON L, DVERGSTEN JA *et al*.: Calcinosis in juvenile dermatomyositis: Updates on pathogenesis and treatment. Front Med (Lausanne). 2023, 10: 1155839.
5. NEELY J, ARDALAN K, HUBER A *et al*.: Baseline characteristics of children with juvenile dermatomyositis enrolled in the first year of the new Childhood Arthritis and Rheumatology Research Alliance registry. *Pediatr Rheumatol Online J* 2022, 20(1): 50.
6. KIM H: Updates on interferon in juvenile dermatomyositis: pathogenesis and therapy. *Curr Opin Rheumatol* 2021, 33(5): 371-77.
7. DEAKIN CT, PAPADOPOULOU C, MCCANN LJ *et al*.: Identification and prediction of novel classes of long-term disease trajectories for patients with juvenile dermatomyositis using growth mixture models. *Rheumatology* (Oxford) 2021; 60(4): 1891-901.
8. NORDAL E, PISTORIO A, RYGG M *et al*.: Growth and puberty in juvenile dermatomyositis: a longitudinal cohort study. *Arthritis Care Res* (Hoboken) 2020; 72(2): 265-73.
9. PACHMAN LM, NOLAN BE, DERANIERI D *et al*.: Juvenile dermatomyositis: new clues to diagnosis and therapy. *Curr Treatm Opt Rheumatol* 2021; 7(1): 39-62
10. SENER S, CAM V, OZEN S *et al*.: Biologic drugs in the treatment of juvenile dermatomyositis: a literature review. *Clin Rheumatol* 2023.

P-67

CALCINOSIS IS ASSOCIATED WITH DISEASE DURATION, CUTANEOUS INFLAMMATION AND VASCULOPATHY IN A LARGE NORTH AMERICAN COHORT OF JUVENILE DERMATOMYOSITIS

Adam M. Huber[1], Gulnara Mamyrova[2], Payam N. Farhadi[3], Lisa G. Rider[3], Childhood Myositis Heterogeneity Study Grou
[1]IWK Health Centre and Dalhousie University, Halifax, Canada; [2]George Washington University School of Medicine, Washington, DC; [3]Environmental Autoimmunity Group, Clinical Research Branch, National Institute of Environmental Health Sciences, National Institutes of Health, Bethesda, USA

Background. Juvenile dermatomyositis (JDM) is a rare systemic autoimmune disorder with muscle inflammation and skin rashes. One of the most important morbidities is calcinosis. The goal of this study was to evaluate clinical and laboratory characteristics associated with calcinosis in a large, well characterized cohort.
Methods. 460 patients with probable or definite JDM by Bohan and Peter criteria were enrolled in National Institutes of Health investigational review board-approved natural history protocols from March 1989 to July 2019. More than 200 demographic, clinical, and laboratory variables were examined for their associations with development of calcinosis. Univariable analysis was performed using logistic regression with calcinosis as the dependent variable. Multivariable analysis was conducted with significant variables from the univariable analysis (p=0.10), using random forest analysis followed by logistic regression. Models were adjusted for disease duration.
Results. Calcinosis was seen in 154 (33.5%) participants. There were 323 females (70%) with a mean age at diagnosis of 8.1 years, and time since first symptom to diagnosis of 7.2 months (no difference between those with and without calcinosis). The median follow-up duration was 5.9 years (9.7 years with calcinosis, 4.1 years without). Most participants were white, 332 (72%). For those where a clinical course could be determined, it was monocyclic in 78 (17%), polycyclic in 86 (18.7%) and chronic continuous in 191 (41.5%).

Table I. Summary of univariable associations with calcinosis.

	Odds ratio (95% CI)	Calcinosis* (n=154)	No Calcinosis* (n=306)
Follow-up duration	1.20 (1.14, 1.27)	9.7 years	4.1 years
Demographics			
Black race	2.48 (1.24, 4.95)	22 (14.3%)	23 (7.5%)
Disease severity			
Polycyclic/Chronic Continuous	2.80 (1.45, 5.44)	128 (90.8%)	149 (69.6%)
Hospitalized	1.75 (1.11, 2.76)	97 (67.4%)	160 (53.9%)
Weight loss	1.73 (1.11, 2.69)	71 (47.0%)	105 (34.4%)
Cutaneous			
Lipoatrophy/lipodystrophy	4.25 (2.17, 8.33)	44 (29.0%)	16 (5.2%)
Panniculitis	10.81 (4.11, 28.38)	27 (17.5%)	6 (2.0%)
Skin ulcers	2.92 (1.77, 4.84)	51 (33.1%)	51 (16.7%)
Skin atrophy	3.86 (1.69, 8.81)	23 (14.9%)	11 (3.6%)
Heliotrope rash	2.31 (1.10, 4.84)	141 (92.2%)	255 (83.3%)
Linear extensor erythema	1.60 (1.03, 2.48)	74 (49.0%)	105 (34.8%)
V-Sign rash	1.67 (1.06, 2.64)	64 (41.8%)	82 (26.9%)
Photosensitivity	1.69 (1.09, 2.64)	91 (61.9%)	141 (47.0%)
Mucous membrane lesions	1.68 (1.07, 2.64)	56 (36.6%)	104 (34.2%)
Other erythematous rashes	1.97 (1.20, 3.23)	118 (76.6%)	202 (66.2%)
Pruritis	2.04 (1.11, 3.74)	28 (18.2%)	36 (11.8%)
Musculoskeleta			
Joint contractures	1.98 (1.25, 3.14)	112 (72.7%)	168 (55.3%)
Distal weakness	1.72 (1.11, 2.67)	91 (59.5%)	122 (40.9%)
Muscle atrophy	2.39 (1.52, 3.76)	81 (52.6%)	81 (24.8%)
Falling	1.93 (1.25, 2.99)	87 (57.2%)	114 (37.65)
Wheelchair use	3.96 (1.47, 10.68)	44 (30.3%)	45 (15.0%)
Laboratory			
Anti-MDA5 autoantibodies	2.48 (1.19, 5.19)	16 (10.5%)	20 (6.6%)
Treatment			
Proportion remission	0.99 (0.98, 1.0)	6.4%	7.8%
Proportion inactive disease	0.99 (0.99, 1.0)	16.8%	20.8%

*Denominator may vary depending on the degree of missing results. p=0.05 for all variables.

The univariable associations with calcinosis are summarized in the Table. In the multivariable analysis, the following variables (odds ratio, OR [95% confidence interval, CI]) were independently associated with calcinosis: disease duration (OR 1.16 [95% CI 1.07, 1.26]), panniculitis (OR 5.51 [95% CI 1.43, 21.19]), lipodystrophy/lipoatrophy (OR 4.08 [95% CI 1.68, 9.87]), skin ulcers (OR 2.70 [95% CI 1.31, 5.55]), falling (OR 2.13 [95% CI 1.16, 9.87]) and proportion of follow-up in remission (OR 0.99 [95% CI 0.98, 1.0]).
Conclusion. Calcinosis remains a common complication of JDM. These findings demonstrate associations of calcinosis with duration of active disease, cutaneous inflammation and vasculopathy, which may suggest potential pathogenic targets of therapy to prevent calcinosis.

P-68

INTERFERON SIGNALIZATION IN JUVENILE DERMATOMYOSITIS AND JUVENILE SCLERODERMA

Hulya Kose[1], Abdurrahman Simsek[2], Muhammed Ali Kizmaz[2], Tugce Bozkurt[2], Ferdi Ozturk[3], Sukru Cekic[1], Ferah Budak[2], Hayriye Sarıcaoglu[3], Sara Sebnem Kilic[1*]
[1]Bursa Uludag University Faculty of Medicine, Department of Pediatric Immunology and Rheumatology; [2]Bursa Uludag University Faculty of Medicine, Department of Immunology; [3]Bursa Uludag University Faculty of Medicine, Department of Dermatology, Turkey

Background. Juvenile scleroderma (JSc) is a heterogeneous group of diseases associated with sclerotic skin lesions, grouped as systemic sclerosis (SSc) and localized scleroderma (JLS). This study aims to measure the cytokine and chemokine levels involved in interferon signaling in patients with JSc and determine their correlation with disease severity.
Methods. Twenty-nine JLS, five SSc, and nine healthy controls were included in the study. Patients with morphea were scored according to the LoSCAT (activity index), LoSDI (damage index), and PGA-A (physician global assessment) indices. Cytokines and chemokines involved in interferon gene signaling (IFN-α, IFN-β, IFN-γ, TNF-α, IL-1, IL-6 IL-8, IP-10, MCP1 and CXCL-10) and interferon-stimulated genes (ISGs) including IFI27, IFI44, ISIG15, IFIT1, OAS1, RSAD2 were measured by ELISA and RT-PCR method respectively.
Results. A significant increase in IFN-α, IFN-β, IFN-γ, TNF-α, IL -1, IL -6 IL -8, IP-10, and MCP1 levels was observed in patients with SSc compared with the healthy control group. Furthermore, IFN-α and IP-10 were elevated in both JLS and SSc compared to the healthy control group. IFN-γ and IFN-α positively correlated with LoSAI and LoSDI levels, respectively. According to PGA-A analysis, IFN-β, IFN-γ, TNF-α, IL -8, IP10, MCP1, and CXCL11 were significantly higher in active disease than in the inactive state.
Conclusion. The results suggest that interferon signaling may be impaired in patients with JSc. Significant changes were observed in cytokines and genes related to IFN signaling, which may have a crucial role in monitoring disease activity. In addition, we have gained important insights into the possibility of using IFN-α and IFN-γ as biomarkers for monitoring JLS activity and damage.

References

1. ARSHANAPALLI A, SHAH M, VEERULA V, SOMANI AK: The role of type I interferons and other cytokines in dermatomyositis. *Cytokine* 2015; 73(2): 319-25.
2. MOLTENI M, DELLA BELLA S, MASCAGNI B *et al*.: Increased interferon-gamma (IFN-gamma) levels produced in vitro by alloactivated T lymphocytes in systemic sclerosis and Raynaud's phenomenon. *Clin Exp Immunol* 1999; 116(1): 164-8.
3. KAKKAR V, ASSASSI S, ALLANORE Y *et al*.: Type 1 interferon activation in systemic sclerosis: a biomarker, a target or the culprit. *Curr Opin Rheumatol* 2022; 34(6): 357-64.

P-69

TOFACITINIB IN REFRACTORY JUVENILE DERMATOMYOSITIS

Kelley S. Lee[1], Aarat M. Patel[1,2]
[1]Bon Secours Mercy Health, Richmond, Virignia, USA; [2]Department of Pediatrics, University of Virginia, Charlottesville, Virginia, USA

Background. Juvenile Dermatomyositis (JDM) is a systemic, autoimmune disease affecting the skin and proximal skeletal muscles in children. First and second line treatments including glucocorticoids are sometimes insufficient for controlling the disease, necessitating escalation of treatment. Several recent studies in adults with dermatomyositis (DM) have showed disease response to Tofacitinib, an oral Janus Kinase inhibitor. This is currently approved for the treatment of RA, JIA and other autoimmune disease. There are limited reports of the use of Tofacitinib in JDM. Due to the reported ability of JAK inhibitors to suppress type 1 interferon (IFN) signaling, which is suspected to be upregulated in JDM, we treated refractory patients with Tofacitinib.
Methods. Six patients with refractory JDM began treatment with Tofacitinib (at the approved JIA/RA dose) after they had failed or had adverse effects to standard of care immunosuppressive agents. Their medical records were reviewed, with improvement measured using the Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI) activity score. Throughout their treatment they were additionally monitored for improvement in laboratory values and the necessity for concomitant treatments. Patients were monitored for adverse effects to Tofacitinib treatment.

Table I.

Sex/ Age Ethnicity Subtype	Previous treatment	TOF start	Date of visit:	CDASI Activity Score	Concomitant treatment with TOF *Other outcomes
Female 10 Caucasian Classic	AZA, HCQ, IVIG, LEF, MTX, MMF, Prednisone, TAC	4/20	4/20	10	HCQ
			6/20	0	IVIG - 10/20
			8/20	1	
			11/20	6	Skin and muscle
			12/20	2	Flare 11/20 →
			1/21	0	regained response
			4/21	0	with IVIG → off
			5/21	0	IVIG 10/20
			6/21	0	
			10/21	0	
			2/22	0	
			5/ 22	0	
			9/22	0	
			1/23	0	
			5/23	0	
			11/23	0	
Female 8 Caucasian Classic	AZA, HCQ, IVIG, MTX, MMF, Prednisone, RTX	8/20	8/20	14	No response, stopped
			10/20	14	TOF → switched to Abatacept
Male 9 Caucasian Amyopathic	HCQ, MTX, Prednisone	10/20	10/20	16	
			1/21	11	
			4/21	7	
			6/21	5	
			10/21	4	
			3/22	3	
			8/22	5	
			6/23	0	
			9/23	0	
Male 8 Hispanic Classic	Prednisone	3/21	3/21	8	MTX (added for
			4/21	4	arthritis)
			6/21	1	
			9/21	1	Significant
			1/22	0	improvement in
			5/22	0	arthritis
			10/22	0	
			2/23	0	
			6/23	0	
Female 13 Caucasian Classic	IVIG, Medrol, MTX Prednisone	10/23	10/23	17	MTX
			11/23	6	
Male 16 Hispanic Classic	ACTH, IVIG, Medrol, MTX, Prednisone	2/23	2/23	54	MTX, IVIG, ACTH
			3/23	28	
			4/23	32	
			5/23	14	
			6/23	16	
			8/23	13	
			9/23	8	
			11/23	5	

Results. Five out of six patients within the case series showed significant improvement of their CDASI scores. One patient with classic JDM had no response to Tofacitinib and was switched to abatacept and is now in remission. Three of the patients have had a sustained response with no flare after over 2 years of treatment. Other outcomes noted included improved pruritus in three patients and improvement of calcinosis in one patient. No worsening muscle involvement or adverse effects were noted with Tofacitinib use.
Conclusion. Five out of six patients within this retrospective study showed significant improvement of cutaneous disease with Tofacitinib use. We demonstrate JAK inibition in JDM to have a sustained response with no flare or adverse effects. These results are consistent with other case series showing response to JAK inhibition in refractory JDM.

References

1. WILKINSON: *Pediatr Rheumatol Online J* 2021; 19(1): 146.
2. YU: *Rheumatology* 2021; 60(4): 1700-707.
3. ZHANG: *Arthritis Res Ther* 2023; 25(1): 204.

P-70

JUVENILE DERMATOMYOSITIS WITH INTERSTITIAL LUNG DISEASE AFTER COVID-19: A CASE REPORT

Takayuki Kishi[1], Kumiko Ishiguro[1], Kentaro Sano[2], Minobu Shichiji[1], Takatoshi Sato[1], Keiko Ishigaki[1], Satoru Nagata[1]
[1]Department of Pediatrics, Tokyo Women's Medical University Hospital, Tokyo, Japan; [2]Department of Pediatrics, Tokyo Women's Medical University, Yachiyo Medical Center, Yachiyo, Japan

Background. COVID-19 has been linked to various autoantibody production and the onset of autoimmune diseases. Of particular note are the Anti-MDA5 autoantibodies, pivotal in activating interferon-regulating receptors in the cytoplasm. This antibody is notably prevalent in patients with dermatomyositis (DM), especially in East Asian countries including Japan, and is often associated with rapidly progressive interstitial lung disease.
Methods. This report presents a case of anti-MDA5 autoantibody-positive juvenile dermatomyositis (JDM) complicated by interstitial lung disease triggered by a COVID-19 infection.
Results. [Case] A 4-year-old boy exhibited fatigue and muscle weakness shortly after a COVID-19 infection at 3 years and 7 months of age. One month later, he developed erythematous rashes on his elbows and knees. Persistent muscle symptoms ensued, along with characteristic skin manifestations of JDM, including heliotrope rash and Gottron's papules. After five months, he became unable to stand or sit independently, experiencing neck instability, had prolonged fever, and dry cough. In addition to these symptoms, elevated muscle enzymes (CK 306 U/L, aldolase 24.2 U/L), and high signal intensity on STIR images of skeletal muscle MRI confirmed the diagnosis of JDM. Two weeks later, due to worsening cough, he was transferred to our hospital. Anti-MDA5 autoantibodies were positive, and lung CT revealed ground-glass opacities and consolidation, consistent with interstitial lung disease. Treatment stated with two courses of methylprednisolone pulse therapy, followed by intravenous cyclophosphamide and subsequent maintenance therapy with oral prednisolone and cyclosporine. Markedly elevated levels of muscle enzymes, transaminases, and ferritin (3772 ng/mL) normalized rapidly after treatment initiation. Muscle weakness gradually improved, and the patient achieved walking one month after treatment initiation. He developed PCP infection during the disease course, however, oxygen therapy was successfully discontinued after two and a half months. Post-hospital discharge, symptoms continued to gradually improve, allowing for the discontinuation of prednisolone 8 months after treatment initiation, with continued favorable progress thereafter.
Conclusion. This case suggests that the patient's symptoms emerged shortly after a COVID-19 infection, indicating a potential trigger for the onset of JDM by SARS-CoV-2. Viral infections, including SARS-CoV-2, have been proposed as external triggers for JDM development. The timing of MDA5 autoantibody elevation was uncertain and genetic factors potentially influence in illness onset. However, in response to SARS-CoV-2 infection, an upregulation of MDA5 expression might lead to excessive autoantibody production resulting in autoimmune responses. While reports of adult dermatomyositis cases following SARS-CoV-2 infection exist, occurrences in juvenile patients are rare.

P-71

SINGLE CENTER EXPERIENCE IN ASSESSING PATIENTS WITH JUVENILE MYOSITIS USING TELEHEALTH

Ramona Khanna[1], Gulnara Mamyrova[2], Sonia Silinsky Krupnikova[2], Mohammed Albdulfatah[2], Marta Michalska-Smith[2], Kezia Daniel[2], Attiya Randolph[2], Michelle Best[2], Hanna Kim[2,3], Lisa G. Rider[2,4], Rodolfo V. Curiel[2]
[1]Department of Dermatology, George Washington University School of Medicine and Health Sciences, Washington DC, USA; [2]Department of Medicine, Division of Rheumatology, George Washington University School of Medicine and Health Sciences, Washington DC, USA; [3]Juvenile Myositis Pathogenesis and Therapeutics Unit, National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH, Bethesda, MD, USA; [4]Environmental Autoimmunity Group, Clinical Research Branch, National Institute of Environmental Health Sciences, NIH, Bethesda, MD, USA

Background. During the COVID-19 pandemic, telemedicine was introduced due to in-person encounter restrictions. The aim of our study was to evaluate the utility of telehealth in juvenile myositis patient assessment.
Methods. We conducted a retrospective chart review (April 2020-August 2023) of 66 patients, 28 telehealth and 38 in-person patients with probable or definite juvenile myositis seen at a myositis center and matched by age, sex, and physician global disease activity. To prepare for telehealth visits, a clinic coordinator contacted each family and instructed them on administration of the Manual Muscle Test (MMT), Childhood Myositis Assessment Scale (CMAS) and Child Health Assessment Questionnaire (C-HAQ). MMT and CMAS were administered remotely by physicians during telehealth appointments, with parental in-person assistance. Parents also actively participated by pointing to specific rashes, joints, and muscles via webcam.
Results. 28/66 (42%) patient visits were assessed via telehealth. Demographics and disease characteristics are shown in Table I.

Table I. Demographics and disease characteristics of juvenile myositis patients assessed by telehealth *vs*. in-person.

	Telehealth visit* n (%) mean (SD) n=28	In-person visit* n (%) mean (SD) n=38
Clinical diagnosis		
JDM	21 (75.0)	28 (73.7)
JPM	2 (7.1)	2 (5.3)
Overlap myositis	0 (0.0)	1 (2.6)
INMN	5 (17.9)	5 (13.2)
Anti-synthetase	0 (0.0)	2 (5.3)
Sex: Female	17 (60.7)	22 (57.9)
Age (years)	15.0 (8.1)	13.9 (4.3)
Disease duration (years)	5.0 (5.6)	4.7 (5.8)
Myositis specific antibodies		
NXP2	7 (28.0)	11 (33.3)
TIF1-γ	5 (20.0)	3 (9.1)
SRP	2 (8.0)	3 (9.1)
MDA5	1 (4.0)	3 (9.1)
HMGCR	3 (12.0)	2 (6.1)
Jol	0 (0.0)	2 (6.1)
Autoantibody negative	7 (28.0)	9 (27.3)
Not tested	3 (11.0)	5 (13.0)
Disease activity core set measures		
Physician Global Activity (Likert 0-4)	1.9 (0.8) n=28	1.6 (0.7) n=38
MMT-8 (0-150)	136.2 (17.4) n=14	136.6 (18.4) n=37
CMAS (0-52)	46.8 (9.3) n=24	46.4 (10.2) n=37
CHAQ (0-3)	0.4 (0.7) n=15	0.5 (0.7) n=30
Skin activity**		
Skin Global Activity (Likert 0.4)	1.2 (0.7) n=14	NA
CDASI Activity (0.100)	9.4 (5.9) n=14	8.8 (8.3) n=36

*There were no significant differences between the two groups. **For telehealth visits, CDASI was attempted first. If not possible, a Skin Global activity by Likert score was performed.
JDM: juvenile dermatomyositis; JPM: juvenile polymyositis; IMNM: immune mediated necrotizing myopathy; NXP2: nuclear matrix protein 2; TIF 1-γ: transcription intermediary factor 1 gamma; SRP: signal recognition particle; MDA5: melanoma differentiation associated gene 5; HMGCR: hydroxymethylglutaryl coenzyme A reductase; ARS: aminoacyl tRNA synthetase; MMT-8: Manual Muscle Testing; CMAS: Childhood Myositis Assessment Scale; C-HAQ: Childhood Health Assessment Questionnaire; NA: not assessed; CDASI: Cutaneous Dermatomyositis Disease Area and Severity Index.
Likert scale (0 - no disease activity, 1 - mild activity, 2 - moderate activity, 3 - severe activity, 4 - extremely severe activity).

14/28 (50%) patients received a full MMT8 exam *vs*. 37/38 (97%) of patients seen in-person ($p<0.0001$). For 11/28 telehealth patients, the average number of muscles tested was 10.9 (range 6–13) *vs*. 14.9 (range 13–15) for in-person visits ($p<0.0001$). Some muscles were not tested due to patient fatigue, muscle pain, lack of cooperation, and/or technical difficulties. Three telehealth patients were wheelchair-bound and reluctant to perform MMT8. In contrast, 24/28 (86%) telehealth patients underwent full CMAS exam *vs*. 37/38 (97%) of in-person patients ($p=0.15$). Three telehealth wheelchair-bound patients were reluctant to complete CMAS. There was no difference in mean MMT8 or CMAS scores for the two groups. Telehealth MMT8 and CMAS scores strongly correlated (r_s 0.74), similar to in-person visits (r_s 0.74). Due to limitations of camera quality, only 14/28 (50%) patients had skin examination by the Cutaneous Disease Area and Severity Index (CDASI) *vs*. 36/38 (95%) of in-person patients ($p<0.0001$). The remaining 14/28 telehealth patients were given a So semi-quantitative skin activity score by Likert Scale. C-HAQ scores were obtained only in 15/28 (54%) telehealth patients *vs*. 30/38 (79%) in-person ($p=0.035$).
Conclusion. Telehealth may be a feasible option to assess patients with mild to moderate juvenile myositis. Instructing families in advance on the clinical assessment tools may improve the ability to complete the evaluation. The CMAS may be used as a surrogate of muscle strength in this setting.
Acknowledgement. Cure JM Foundation, GWMFA, NIEHS, NIAMS, NIH for research support. Patients and their families for participation in the study.

P-72

PERIPHERAL BLOOD TRANSCRIPTOMIC CORRELATION WITH CLINICAL TRAITS IN JUVENILE DERMATOMYOSITIS (JDM) AND THE ANTI-TIF1 MYOSITIS-SPECIFIC AUTOANTIBODY (MSA) GROUP

Ujana Zajmi[1], Megan Darrell[1], Amy M. Kaneshiro[1], Adeline Chin[1], Adriana A. de Jesus[2], Stephen Brooks[3], Raphaela Goldbach-Mansky[2], Lisa G. Rider[4], Hanna Kim[1]
[1]Juvenile Myositis Pathogenesis and Therapeutics Unit, Pediatric Translational Research Branch, NIAMS, NIH, Bethesda, USA; [2]Translational Autoinflammatory Diseases Section, NIAID, NIH, Bethesda, USA; [3]Biodata Mining and Discovery Section, NIAMS, NIH, Bethesda, USA NIH; [4]Environmental Autoimmunity Group, Clinical Research Branch, NIEHS, NIH, Bethesda, USA

Background. Myositis-specific autoantibody (MSA) subgroups define phenotypes associated with specific clinical traits and outcomes within JDM, a clinically heterogeneous autoimmune disease. The pathogenesis of JDM is not fully understood. We examined correlation between co-expressed gene modules and clinical traits for JDM and anti-TIF1 autoantibodies (Ab+), the most frequent MSA group in JDM, in order to better understand pathogenic differences.
Methods. Whole blood RNA-seq was performed for 57 prevalent JDM patients with further analysis of the anti-TIF1 autoantibody (Ab) (n=22) subgroup. Modules of co-expressed genes from weighted gene co-expression network analysis (WGCNA) were correlated with clinical traits and top-correlating WGCNA-trait pairs were functionally annotated by BloodGen3 modules (Rinchai, 2021). We generated heatmaps of the highest significant absolute correlations (JDM r>0.70, anti-TIF1 r>0.65) between gene module-traits and functional annotations.
Results. JDM patients were 63% female, 65% white, and averaged 10.0 years old. They had a mean Physician Global Activity (PGA) by Visual Analogue Scale (VAS) score of 2.9/10, an average prednisone dose of 0.3 mg/kg/day, and an average disease duration of 26 months. Anti-TIF1 Ab+ patients were 86% female, 86% white, and had an average age of 10.0 years. They had a mean PGA of 2.9/10, an average prednisone dose of 0.2 mg/kg/day, and an average disease duration of 42 months. For overall JDM, PGA had strong correlations with interferon and complement pathway functions (Fig. 1A). Disease Activity Score (DAS) Muscle correlated with T-cell and lipid metabolism functions. Myositis Damage Index (MDI) Total correlated with cell cycle, T-cell, B-cell, erythroid cell, cell adhesion, and mitochondrial stress/proteasome functions. In anti-TIF1 Ab+ patients, DAS Total strongly correlated with cell cycle, platelets, oxidative stress, and prostanoids/prostaglandins functions, while PGA strongly correlated with cytotoxic lymphocyte function (Fig. 1B). CHAQ-HAQ strongly correlated with erythroid cells and oxidative phosphorylation functions. Myositis Disease Activity Assessment Tool (MDAAT) Cutaneous VAS strongly correlated with interferon and complement pathway functions. MDI Total strongly correlated with cell cycle, oxidative stress, T-cell, and erythroid cell functions.

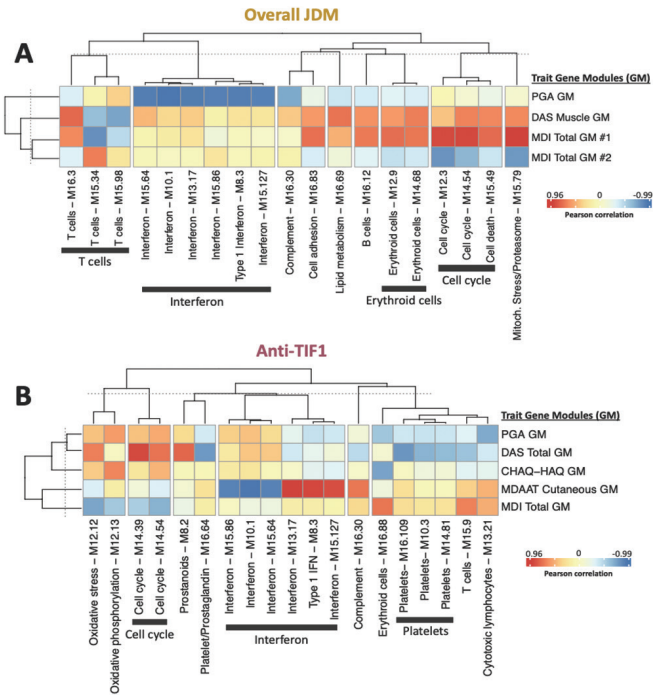


Fig. 1. Heatmap for functional annotation of WGCNA gene module-trait pairs in A) overall JDM and B) anti-TIF1 autoantibody patients.
Significant functional annotations are hierarchically clustered whitin their annotation type on the horizontal axis. Functional annotations are labeled as the function followed by the Bloodgen3 module number (Rinchai, 2021). The highest absolute correlating WGCNA modules are hierarchically clustered within their trait type on the vertical axis. WGCNA modules are labeled by the myositis clinical trait it is paired with Pearson correlation coefficients are noted inside each cell. We evaluated multiple clinical traits including all JDM Core Disease Activity Measures (Physician Global Activity by VAS. Patient/Parent Global Activity by VAS. Manual Muscle Testing (MMT). Childhood Myositis Assessment Scale (CMAS), (Childhood) Health Assessment Questionnaire (CHAQ-HAQ), Muscle enzymes (alanine aminotranferase (ALT), aldolase, aspartate aminotransferase (AST), creatine kinase (CK), lactate dehydrogenase (LDH), Extramuscular activity by VAS, and Disease Activity Score (DAS). Heatmaps include the highest significant absolute correlations between gene module-traits and functional annotations.
WGCNA: Weighted Gene Co-Expression Network Analysis; IFN: Interferon; GM: Gene Module; MDI: Muscle Damage Index; MDAAT: Myositis Disease Activity Assessment Tool assessed by Visual Analogue Scale (0-10); DAS: Disease Activity Score; PGA: Physician Global Activity assessed by VAS; CHAQ-HAQ; (Chilhood) Health Assessment Questionnaire; VAS: Visual Analog Scale

Conclusion. Interferon and complement pathway functions most strongly correlated with PGA gene module in overall JDM, but most strongly correlated with MDAAT Cutaneous VAS gene module in anti-TIF1 patients. MDI Total shares some functions (cell cycle, T-cell, erythroid cells, and mitochondrial stress/oxidative phosphorylation) in overall JDM and anti-TIF1 Ab+ patients, but functions do not fully overlap. These findings suggest JDM subgroups may have pathogenic distinctions.
Acknowledgments. Intramural Research Program of the NIH, NIAMS, NIAID, NIEHS, & the CC.

Reference

1. RINCHAI D, ROELANDS J, TOUFIQ M *et al.*: BloodGen3Module: blood transcriptional module repertoire analysis and visualization using R. *Bioinformatics* (Oxford) 2021; 37(16): 2382-89.

P-73

HIGH PREVALENCE OF SUBOPTIMAL EMOTIONAL HEALTH AND ADVERSE CHILDHOOD EXPERIENCES IN PATIENTS WITH JUVENILE DERMATOMYOSITIS AND LUPUS: INTERIM ANALYSIS OF THE LUPUS ERYTHEMATOSUS AND DERMATOMYOSITIS STRESS AND CARDIOVASCULAR HEALTH (LEADS-CV) COHORT STUDY

Kaveh Ardalan[1], Bryce B. Reeve[1], Christoph P. Hornik[1], M. Anthony Moody[1], Donald Lloyd-Jones[2], Eveline Y. Wu[3], Audrey Ward[1], Rebecca Sadun[1], Jeffrey Dvergsten[1], Ann M. Reed[1], Mark Connelly[4], Laura E. Schanberg[1]
[1]Duke University School of Medicine, Durham, NC, USA; [2]Northwestern University Feinberg School of Medicine, Chicago, IL, USA; [3]University of North Carolina School of Medicine, Chapel Hill, NC, USA; [4]Children's Mercy Kansas City/University of Missouri-Kansas City School of Medicine, Kansas City, MO, USA

Background. Studies of the emotional health of juvenile dermatomyositis (JDM) patients remain scant. We present interim analyses from the Lupus Erythematosus and Dermatomyositis Stress & Cardiovascular Health (LEADS-CV) study reporting prevalence of suboptimal emotional health, adverse childhood experiences (ACEs), and their associations with disease outcomes in JDM and juvenile lupus (JSLE) patients.
Methods. Patients with JDM/JSLE (5-22yo) completed PROMIS® self-report (≥8yo) and/or parent-proxy (≥5yo) emotional health measures (i.e. Psychological Stress Experiences [-Str], Depressive Symptoms [-Depr], Anxiety [-Anx], Positive Affect [-PosAff], Life Satisfaction [-LifeSat]). ACEs were assessed using the Center for Youth Wellness ACE Questionnaire (all parent-proxy except self-report by unaccompanied 18yo+ patients). Outcomes included physician/patient/parent global assessments of disease activity (PGA/Pt-GA/Par-GA) and self-report/parent-proxy PROMIS Mobility and Pain Interference. Relationships between PROMIS emotional health and disease outcomes were analyzed using Spearman correlations. Mann Whitney U test compared JDM vs JSLE emotional health and ACEs.
Results. Of 83 participants, n=35 (42%) had JDM. Most JDM/JSLE participants were female (n=66, 80%) and adolescent (median [IQR] age 16yo [12-18yo]). The cohort was racially/ethnically diverse, with n=38 (46%) identifying as Black, n=10 (12%) Hispanic/Latino/a/x, n=8 (10%) Asian, and n=26 (31%) non-Hispanic White. Disease activity was low (median [IQR] PGA 0.5 [0-2], Pt-GA 1 [0-4], Par-GA 1 [0-5]). Suboptimal emotional health, defined as ≥1 PROMIS self-report/parent-proxy emotional measure scoring worse than national severity threshold cutoffs, was prevalent (n=74, 89.2%). Rates of suboptimal emotional health on individual self-report/parent-proxy PROMIS measures ranged 36.4-58.1%. Of 72 participants with ACEs data, n=38 (53%) reported ≥1 ACEs, while n=18 (25%) reported ≥3 ACEs. Higher number of ACEs correlated with worse emotional health for all self-report PROMIS emotional health measures (Spearman's rho 0.275-0.41) and parent-proxy PROMIS-Str/-PosAff/-LifeSat (rho 0.313-0.349). PROMIS emotional health measures showed small-to-moderate correlations with most patient/parent-reported outcomes (Table I).

Table I. Spearman's Correlations of PROMIS Pediatric Emotional Health Measures with Outcomes in JDM/JSLE.

Self-report

	PGA	*p*-value	Pt-GA	*p*-value	PROMIS mobility	*p*-value	PROMIS pain interference	*p*-value
Psychological stress	0.05	0.66	0.41	<0.01	-0.21	0.08	0.44	<0.01
Depressive symptoms	-0.06	0.62	0.28	0.02	-0.24	0.04	0.42	<0.01
Anxiety	-0.13	0.27	0.25	0.03	-0.33	<0.01	0.56	<0.01
Positive affect	-0.02	0.85	-0.47	<0.01	0.35	<0.01	-0.33	<0.01
Life satisfaction	0.05	0.70	-0.37	<0.01	0.30	<0.01	-0.26	0.02

Parent-proxy

	PGA	*p*-value	Par-GA	*p*-value	PROMIS Mobility	*p*-value	PROMIS Pain Interference	*p*-value
Psychological stress	0.05	0.69	0.3	<0.01	-0.01	0.97	0.23	0.09
Depressive symptoms	-0.05	0.71	0.04	0.79	-0.38	<0.01	0.51	<0.01
Anxiety	0.09	0.54	0.26	0.05	-0.31	0.02	0.42	<0.01
Positive affect	0.01	0.92	0.06	0.68	0.22	0.10	-0.40	<0.01
Life satisfaction	0.06	0.65	-0.15	0.27	0.33	0.01	-0.54	<0.01

ACEs correlated with parent-proxy report PROMIS-PainInt (rho 0.366), but not other outcomes. PROMIS emotional health scores did not differ between JDM/JSLE, except for worse self-reported PROMIS-LifeSat in JSLE

(p<0.01) and higher number of ACEs in JSLE (p=0.05); however, there was possible confounding due to differences in age and race/ethnicity distributions of JDM/JSLE subgroups.
Conclusion. Suboptimal emotional health and ACEs are highly prevalent with JDM/JSLE. Poorer emotional health is associated with worse patient/parent-reported global assessments, mobility, and pain interference. Further study in multicenter inception cohorts will delineate associations of emotional health/ACEs and outcomes, predictors of suboptimal emotional health, and targets for intervention.

P-74

MAGNETIC RESONANCE IMAGING (MRI) FOR ASSESSMENT OF JUVENILE DERMATOMYOSITIS: A SCOPING REVIEW

Vitor T. Paula[1], Clarissa H. Omori[1], Adriana M. Elias[1], Julio B. Guimaraes[2], Samuel K. Shinjo[3], Daniel B. Araujo[4], Claudia Magalhaes[5], Simone Appenzeller[6], Tamima Arabi[1], Clarissa Carvalho[1], Jessica Day[7], Mickael Essouma[8], Edoardo Conticini[9], Mary Anne Riopel[10], Susan Shenoi[11], Edoardo Marrani[12], Andrea S. Doria[13]
[1]Instituto da Criança, Hospital das Clínicas, Faculdade de Medicina da Universidade de São Paulo, Brazil; [2]Escola Paulista de Medicina, Universidade Federal de São Paulo, Brazil; [3]Rheumatology Department, Hospital das Clínicas, Faculdade de Medicina da Universidade de São Paulo, Brazil; [4]Universidade Federal de Pelotas, Brazil; [5]Universidade Estadual Paulista, São Paulo, Brazil; [6]Universidade Estadual de Campinas, São Paulo, Brazil; [7]Royal Melbourne Hospital, VIC, Australia; [8]University of Yaounde I, Cameroon; [9]University of Siena, Italy; [10]Moravian University, Bethlehem, PA, United States; [11]Seattle Children's Hospital, WA, United States; [12]University of Florence, Florence, Italy; [13]SickKids - The Hospital for Sick Children, Toronto, ON, Canada

Background. An international Task Force from International Myositis Assessment and Clinical Studies Group (IMACS) conducted a comprehensive scoping review of the literature on analyzing MRI indications for patients with JDM, MRI techniques and protocols, and the adopted scoring systems. We also analyzed whether MRI was comparable to other measures used to assess disease activity, remission, or flares and whether MRI was accurate in achieving the proposed goals.
Methods. A comprehensive search for studies in the MEDLINE (via PubMed), EMBASE, and Cochrane databases was conducted from January 2000 to October 2023 using a combination of descriptors of interest. Two experienced imaging experts analyzed the MRI methodologies of these articles.
Results. Fifteen studies on patients with JDM under 18 years at disease onset were eligible and analyzed as part of the review. The objectives, methodologies, and analyses of these studies were heterogeneous. Moreover, the proposed scoring systems differ among themselves. Quantitative assessment was performed in one study, and semi-quantitative or qualitative analyses were performed in the other 14 studies. Whole-body MRI was performed in four studies, whereas thigh, pelvis, upper or lower limb dedicated MRI were performed in other studies. Muscle groups were assessed for symmetric or asymmetric distribution of edema, fatty infiltration, and muscle atrophy. Regarding whole-body MRI protocols, T1 weighted images acquired on coronal views were the sequences of choice to measure chronic inflammatory changes, such as hypotrophy and fat substitution of muscle bellies. In this review, T1 was used in all analyzed studies, except for one. Fluid-sensitive sequences such as T2 with fat saturation or short tau inversion recovery (STIR) were present in all studies and were also obtained on the coronal axis in most manuscripts. Fluid-sensitive sequences are the most relevant images for detecting soft tissue edema (high signal intensity) related to acute or subacute inflammatory findings. One study used additional diffusion-weighted and postcontrast sequences.
Conclusion. Further studies with an established whole-body MRI protocol are necessary to define not only the best tool for diagnostic and disease activity criteria but also to recommend a standardized model of imaging acquisition and analysis that can provide comparable results and optimized results to study and follow patients with JDM.

P-75

PROTEOMIC ANALYSIS REVEALS DIFFERENT PROTEIN MODULES AND FUNCTIONAL ANNOTATIONS WITH CLINICAL TRAITS IN JUVENILE DERMATOMYOSITIS (JDM) AND MYOSITIS-SPECIFIC AUTOANTIBODY (MSA) GROUP (ANTI-TIF1 AUTOANTIBODY)

Amy M. Kaneshiro[1], Adeline Y. Chin[1], Ujana Zajmi[1], Megan P. Darrell[1], Angélique Biancotto[2], Foo Cheung[2], Frederick W. Miller[3], Lisa G. Rider[3], Hanna Kim[1]
[1]Juvenile Myositis Therapeutic and Translation Studies Unit (JMPTU), Pediatric Translation Research Branch (PTRB), NIAMS, Bethesda, MD, USA; [2]Center for Human Immunology Autoimmunity and Inflammation (CHI), NIAID, Bethesda, MD, USA; [3]Environmental Autoimmunity Group, Clinical Research Branch, NIEHS, Bethesda, MD, USA

Background. JDM is a heterogenous systemic autoimmune disease with muscle and skin pathology, which can be categorized by MSA groups. The most common MSA in JDM is anti-TIF1 autoantibodies (Ab+). Pathogenesis is poorly understood. We aimed to better understand proteomic expression and correlations with clinical traits in JDM overall and MSA group.
Methods. The SomaLogic SOMAscan aptamer-based proteomic assay (Boulder, CO) analyzed 1,305 serum proteins in JDM patients. Weighted-gene co-expression analysis (WGCNA) was used to create protein co-expression modules, which were correlated with clinical traits. Highly correlated protein module-clinical traits pairs were functionally annotated by Gene Ontology Biological Processes (GOBP) overrepresentation analysis with clusterprofileR. Significant GOBPs (q<0.05) with 4+ proteins for JDM overall (n=39) and anti-TIF1 Ab+ (n=19) patients were grouped into functional categories (Fig. 1). Top overlapping traits were compared (anti-TIF1 Ab+ *vs*. rest of JDM) with Mann-Whitney U-test.
Results. JDM patients were 66% female, 58% Caucasian, mean age of 9.7 years, and had a mean Physician Global Activity (PGA) of 4.0/10. The Anti-TIF1 Ab+ subgroup of patients were 74% female, 84% Caucasian, mean age of 9.5 years, and had a mean PGA of 4.1/10.
Disease Activity Score (DAS) Total and Myositis Damage Index (MDI) Muscle were not significantly different (anti-TIF1 vs rest JDM).
DAS Total was annotated with epithelial and muscle cell activation, innate immune response, neuron development and wound healing in anti-TIF1 Ab+, but not JDM (Fig. 1). DAS skin was significantly higher in anti-TIF1 than rest of JDM, and had more annotations including innate and adaptive immune response and mitochondrial stress versus in JDM. More annotations were also seen for erythrocyte sedimentation rate (ESR) with anti-TIF1 including innate/adaptive immune response versus JDM overall, though ESR was lower in anti-TIF1 versus rest of JDM. MDI Muscle had more annotations in JDM including innate immune response, cell death, and wound healing.
Conclusion. Overall disease activity (DAS-Total) had more immune-cell and other functional annotations in anti-TIF1 not identified in JDM overall, though their DAS-Total levels were not different. DAS skin was higher in anti-TIF1, and demonstrated more functions in anti-TIF1 such as mitochondrial stress and wound healing, while ESR was lower in anti-TIF1 but still had more annotations. We identified distinct protein module functions with clinical traits in patients from a single MSA group (anti TIF1 Ab+) compared to overall JDM patients, which may have pathogenic and therapeutic implications.
Acknowledgments. NIH IRP, NIAMS, NIEHS, NIAID, CC, Cure JM.

A.
JDM

	Cell cycle	Immune/ Endo	Epi	Adaptive immune	Innate immune	Muscle Cell	Neuron	Wound healing	Cyto/ Chemo	Cell death	Mito/ Stress	IFN	Bone remodeling	Tissue Remodeling
DAS Total	x													
DAS Skin	x		x											
CHAQ/HAQ	x	x	x	x		x								
MDAAT Skeletal	x	x	x	x	x	x	x	x	x	x	x	x	x	x
ESR	x		x				x						x	
MDI Muscle	x	x	x	x	x		x	x	x	x		x		

B.
anti-TIF1 Ab+

	Cell cycle	Immune/ Endo	Epi	Adaptive immune	Innate immune	Muscle Cell	Neuron	Wound healing	Cyto/ Chemo	Cell death	Mito/ Stress	IFN	Bone remodeling	Tissue Remodeling	Neuro-inflammation
DAS Total	x	x	x		x	x	x	x							
DAS Skin	x	x		x	x			x	x	x	x				
CMAS	x	x													
MDAAT Constitutional	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
ESR	x	x	x	x	x	x		x	x	x	x	x			x
MDI Muscle	x	x		x		x	x		x						

P-75 Fig. 1. JDM and anti-TIF1 summary of traits and functional categories of GOBPs. A) JDM B) anti-TIF1 Ab+
The rows show each clinical trait, and the columns with an "x" are significant functional categories for each trait based on GOBPs. The columns are organized from left to righ by highest to lowest frequency. JDM (n=39) includes anti-MDA5 Ab+ (n=10), anti-NXP2 Ab+ (n=10) and anti-TIF1 Ab+ (n=19), with the anti-TIF1 Ab+ subgroup analyzed separately.
Ab+: Autoantibody+, Adaptive Immune: Adaptive Immune Response; Cell Cycle: Cell Cycle/Cell processes; CHAQ/HAQ: Childhood Health Assessment Questionnaire; CMAS: Childhood Myositis Assessment Scale; Cyto/Chemo: Cytokine/Chemokines; DAS: Disease Activity Score; Epl: Epithelial Cell Activation; ESR: Erythocyte Sedimentation Rate; GOBP: Gene Ontology Biological Processes; IFN: Interferon; Immune/Endo: Immune Response/Endothelial Cell Activation; Innate Immune: Innate Immune Response; MDAAT: Myositis Disease Activity Assessment Tool Measures by Visual Analogue Scale 0-10; MDI: Myositis Damage Index by VAS; Mito/Stress: Mitochondrial/Stress Response; Muscle Cell: Muscle Cell Activation; Neuron: Neuron Development; AS: Visual Analogue Scale 0-10.

P-76

TESTING OF PARENT-REPORTED OUTCOME MEASURES FOR REMOTE ASSESSMENT IN JUVENILE DERMATOMYOSITIS

Silvia Rosina[1], Ana Isabel Rebollo Giménez[1], Letizia Tarantola[2], Roberta Naddei[3], Alessandro Consolaro[1], Angela Pistorio[4], Angelo Ravelli[4]
[1]IRCCS Istituto Giannina Gaslini, UOC Reumatologia e Malattie Infiammatorie, Genova, Italy; [2]Università degli Studi di Genova, Dipartimento di Neuroscienze, Riabilitazione, Oftalmologia, Genetica e Scienze Materno-Infantili (DiNOGMI), Genova, Italy; [3]Università degli Studi di Napoli Federico II, Dipartimento di Scienze Mediche Traslazionali, Napoli, Italy; [4]IRCCS Istituto Giannina Gaslini, Direzione Scientifica, Genova, Italy

Background. The optimal care of patients with juvenile dermatomyositis (JDM) requires frequent assessments of disease activity over time. However, an adequately tight frequency of physicians' visits may not be always feasible. On the contrary, if the disease is stable or the child is off therapy, appointments may be deferred. In this scenario, the availability of well-established parent-reported outcomes (PROs) could allow for delivering remote symptom monitoring and telehealth, new emerging technologies that may lessen the financial burden to families, reduce the pressure on healthcare systems and help improving the quality of care. Aim of the study was to evaluate correlations between PROs potentially suitable for remote disease monitoring and physician-centered tools in JDM.
Methods. The following data were collected from parents of 263 JDM patients at the time of a visit at study center: 1) parent assessment of skin disease activity (Parent Skin Scale) on a 0–5 Likert scale, giving 1 point to the report of each of the following: i) rash on eyelids, ii) rash on nose/cheeks, iii) rash on knuckles, iv) rash on trunk/arms, v) skin ulceration; 2) parent assessment of muscle disease activity (Parent Muscle Scale) on a 0–5 Likert scale, giving 1 point to the report of i) fatigue/discomfort, ii) muscle weakness, iii) muscle pain, iv) voice change, v) difficulty swallowing; 3) parent assessment of child's fatigue on a 0-10 visual analogue scale (VAS); 4) parent global assessment of disease activity on a 0–10 VAS (PaGA). Correlations between these PROs and physician-centered measures (physician's global assessment of disease activity on a 0-10 VAS - PhGA, total DAS, skin DAS, muscle DAS, physician's assessment of skin and muscle disease activity on a 0–10 VAS, MMT8, hMC and CMAS) were calculated.
Results. Parent Skin Scale was moderately correlated with Skin DAS, Skin VAS, and total DAS, but poorly correlated with Muscle DAS, Muscle VAS, MMT8, hMC and CMAS. Parent Muscle Scale and fatigue VAS were moderately correlated with Muscle DAS, Muscle VAS, hMC and total DAS, and poorly correlated with Skin VAS e Skin DAS. Correlations for PaGA were moderate to high with all physician-centered tools.
Conclusion. The fair correlations found between the tested PROs and physician-centered tools in their respective (i.e. skin or muscle) domain suggest that parents' evaluations may serve as surrogate measures of disease activity when physician-centered assessments are not available. This finding supports the use of PROs for remote monitoring of JDM disease course over time.

P-77

TOWARDS THE DEVELOPMENT OF COMPOSITE PARENT-CENTERED DISEASE ACTIVITY SCORES FOR JUVENILE DERMATOMYOSITIS

Silvia Rosina[1], Ana Isabel Rebollo Giménez[1], Letizia Tarantola[2], Roberta Naddei[3], Alessandro Consolaro[1], Angela Pistorio[4], Angelo Ravelli[4]
[1]IRCCS Istituto Giannina Gaslini, UOC Reumatologia e Malattie Infiammatorie, Genova, Italy; [2]Università degli Studi di Genova, Dipartimento di Neuroscienze, Riabilitazione, Oftalmologia, Genetica e Scienze Materno-Infantili (DiNOGMI), Genova, Italy; [3]Università degli Studi di Napoli Federico II, Dipartimento di Scienze Mediche Traslazionali, Napoli, Italy; [4]IRCCS Istituto Giannina Gaslini, Direzione Scientifica, Genova, Italy

Background. Increasing attention has been recently paid to the development of parent-centered composite disease activity scores (DAS) for the assessment of health status of children with rheumatic diseases. The aim of our study was to develop and test an entirely parent-centered composite DAS for JDM, named parent Juvenile DermatoMyositis Activity Index (parJDMAI).
Methods. ParJDMAI includes the following items: 1) parent assessment of skin disease activity (Parent Skin Scale) on a 0–5 Likert scale, by giving 1 point to each of: i) rash on eyelids, ii) rash on nose/cheeks, iii) rash on knuckles, iv) rash on trunk/arms, v) skin ulceration; 2) parent assessment of muscle disease activity (Parent Muscle Scale) on a 0-5 Likert scale, by giving 1 point to each of: i) fatigue/discomfort, ii) muscle weakness, iii) muscle pain, iv) voice change, v) difficulty swallowing; 3) parent assessment of child's fatigue on a 0–10 VAS (0 =no fatigue; 10 = maximum fatigue); 4) parent global assessment of disease activity on a 0–10 VAS (0 = no activity; 10 = maximum activity). To give the 4 components the same weight, the scores of the Parent Skin and Muscle Scales were doubled to a 0-10 scale.

Thus, the total ParJDMAI score ranges from 0 to 40. Initial validation was conducted on a multicentric prospective sample of 213 patients followed in standard clinical care, and on amonocentric sample including 50 patients, all assessed at baseline and 32 also assessed after a median of 3.9 months. Construct validity was assessed in both cohorts (n=263) by calculating the correlations between parJDMAI and: i) physician-centered JDM outcome measures; ii) the global composite DAS for JDM named JDMAI1 and JDMAI2. Responsiveness to change and internal consistency were also evaluated on both samples, whereas discriminant ability was assessed only in the monocentric sample.

Results. Correlations between parJDMAI and physician-centered JDM outcome measures were moderate to high, whereas the ones with JDMAI1 and JDMAI2 were strong. Responsiveness to change was moderate to good and internal consistency was substantial. The discriminant ability of the new instrument was satisfactory.

Conclusion. The new parent-centered composite DAS revealed satisfactory measurement properties and are, therefore, suitable for use in clinical practice and research. The proposed tool should be further tested in different clinical and cultural environments before its widespread use can be recommended.

P-78

CALCINOSIS IN CHINESE JUVENILE DERMATOMYOSITIS ASSOCIATED WITH DIFFERENT MYOSITIS SPECIFIC ANTIBODIES: CLINICAL FEATURES AND LONG-TERM FOLLOW-UP

Xinning Wang[1,2], Jinru Zhang[1], Luyu Liu[3], Xiaolei Wang[1], Xin Yao[1], Yang Yang[4], Ying Chi[1], Yuan Liu[1], Xiaohui Li[2], Jianguo Li[1]

[1]Department of Rheumatology and Immunology, Children's Hospital Capital Institute of Pediatrics, Beijing, China; [2]Children's Hospital Capital Institute of Pediatrics, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China; [3]Department of Ultrasound, Children's Hospital Capital Institute of Pediatrics, Beijing, China; [4]Department of Radiology, Children's Hospital Capital Institute of Pediatrics, Beijing, China

Background. Dermatomyositis (JDM) is the most common inflammatory myopathy in children which is characterized by muscle weakness and cutaneous manifestations. As one of the major complications of JDM and main cause of disability, calcinosis is an important prognostic factor and found in 20–40% of JDM patients. However, much less is known about calcinosis in Chinese JDM patients. The objective of this study is to investigate the clinical characteristics, response to treatment and outcome in the group of patients.

Methods. This is a retrospective, single-center study. Clinical data including gender, age at disease onset and diagnosis, laboratory tests, data on treatment and outcome of disease were collected and analyzed. JDM patients under 18 years between Sep 2016 and Jul 2023 were analyzed.

Results. In total,40 JDM patients (M/F=17/23) with calcinosis were enrolled in this study. There were 17 JDM patients with anti-NXP2 antibody,8 patients with anti-MDA5 patients and 15 patients with negative MSA antibody. In the group of JDM patients with anti-NXP2 (4.5 yrs),the mean age of onset was earlier than those of patients with anti-MDA5 (5.8 yrs) and patients with negative MSA antibody(5.24 yrs).The mean cause of disease of patients with anti-NXP2 (27.4 months) was longer than other groups. Calcinosis occurs mostly in stress areas such as lower limbs, buttocks and hands which distributed in focal form, but also in the chest or abdominal wall and back in diffuse lesion. Different periods and degrees of calcinosis coexist at the same time. Calcium-milk overflow, ulceration and infection can be seen in affected lesions. IgE levels are significantly elevated in most patients. Most patients with calcinosis were treated with combination therapy of multiple immunosuppressants and biological agents. Remission co-existed with new lesions can be seen in some patients with severe and extensive calcinosis. Recurrence remains a common phenomenon.

Conclusion. Anti-NXP2 and MDA5 antibodies are more likely to be associated with calcinosis in Chinese JDM patients. Prolonged disease cause, persistent disease activity and delay in diagnosis and initiation of treatment were significantly associated with increased frequency of calcinosis. Elevated IgE may be an independent risk factor for subcutaneous calcification. Calcinosis is not exactly parallel to disease activity. Early diagnosis and treatment are the key factors to improve prognosis.

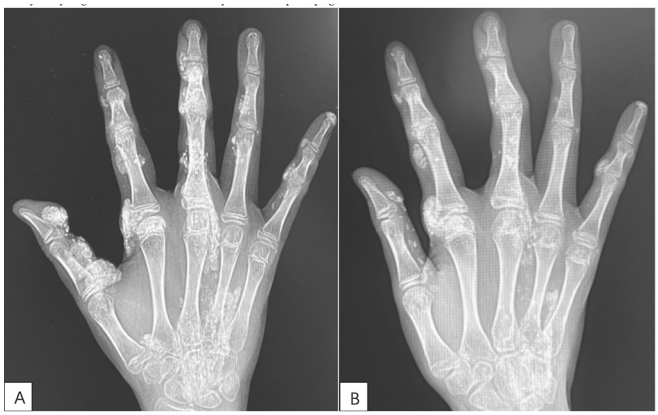


Fig. 1. This is an 11-year-old girl with positive anti-MDA5 antibodies. **A** shows her right hand before treatment; **B** shows significantly reduced calcinosis 8 months after treatment.

P-79

BLOOD DIFFERENTIALS AND WHOLE EXOME SEQUENCING (WES) OF PATIENTS WITH JUVENILE DERMATOMYOSITIS (JDM)

Danlei Zhou, Samantha Coss, Rabheh Abdul Aziz, Katherine Miller, Ohoud Al Ahmed, Vidya Sivaraman, Shoghik Akoghlanian, Edward Oberle, Joanne Drew, Kyla Driest, Stacy P. Ardoin, Charles Spencer, Chack-Yung Yu

Abigail Wexner Research Institute and Division of Rheumatology at the Nationwide Children's Hospital, Columbus, OH and University of Buffalo, New York, USA

Background. JDM is an autoimmune condition characterized by proximal muscle weakness and skin rashes. The mechanism that causes the disease is not well understood but genetic factors appear to play an important role.

Methods. With informed consent, we prepared genomic DNA and plasma samples from JDM patients of European decent recruited at two study sites (Columbus OH, n=58; Buffalo NY, n=8). WES with >100x coverage was performed at our Genome Institute, and sequences of whole human exomes in GnomAD were employed for comparison. We used 2×2 Fisher's exact tests to calculate one-tailed *p*-values and SIFT (Sorting Intolerant from Tolerant) for prediction of deleterious effects. We also put those mutant genes identified through Ingenuity Pathway Analysis (IPA). Verification of mutant sequences were achieved by restriction fragment length polymorphism analyses.

Results. Blood differentials from patients with JDM were compared with those from age matched controls (CTL) of healthy children (n=111). We observed lower levels of red cell hemoglobin (HGB; $p=6.7\text{x}10^{-8}$), but greater variations of RBC distribution width (RDW, $p=1.2\text{x}10^{-10}$) in patients with JDM. There are significantly higher counts of platelets (PLT, $p=1.9\text{x}10^{-12}$) in JDM. The ratios of neutrophils to lymphocytes (NLR), and ratios of platelets to lymphocytes (PLR) in the circulation are convenient biomarkers of inflammation and cardiovascular disorders. Indeed, we observed slightly lower NLR ($p=0.0005$) and robustly higher PLR in patients with JDM than controls ($p=1.9\text{x}10^{-12}$). WES of 51 patients with JDM of European decent were performed to identify novel genetic risk factors. In the order of *p*-values or relative significance, pathophysiologic pathways identified for JDM are mainly engaged in (1) GP6 signaling, (2) dopachrome and eumelanin biosynthesis, and (3) actin cytoskeleton signaling. Specifically, we identified exonic (nonsynonymous) variants with potentially deleterious mutations in 9 genes: TRY, ATP10A, FER1L5, LAMA5, GP6, COL6A6, TTN, DNAH9 and SLC11A1. Of these, three genes (LAMA5, GP6 and COL6A6) have important roles in GP6 Signaling Pathway that is engaged in platelet activations. TYR is of particular interest because its product tyrosinase is an enzyme controlling the synthesis of melanin. Five of our studied patients had autoantibodies against melanoma differentiation-associated protein 5 (anti-MDA5). MDA5 detects long dsRNA and anti-MDA5 is engaged in the production of type 1 interferons. Notedly, all of our patients with anti-MDA5 have a specific TYR mutation at Ser192Tyr ($p=0.02$).

Conclusion. These new data provide guides for innovative studies on pathogenesis of IIM.

P-80

UNDERSTANDING THE LANDSCAPE OF JDM IN AFRICA: A SURVEY OF AFLAR AND PAFLAR MEMBERS

Jessica Perfetto[1], Laura B. Lewandowski[2], Dawn M. Wahezi[1], Kate Webb[3], Christiaan Scott[3], Angela Migowa[4]
[1]The Children's Hospital at Montefiore, Division of Rheumatology, Bronx, NY, USA; [2]Lupus Genomics and Global Health Disparities Unit, Systemic Autoimmunity Branch, National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH, Bethesda, MD, USA; [3]Red Cross War Memorial Children's Hospital, Division of Rheumatology, Cape Town, South Africa; [4]Aga Khan University Medical College East Africa, Nairobi, Kenya

Background. Studies of juvenile dermatomyositis (JDM) in low and middle-income countries (LMIC), including Africa, are few. Many demonstrate high mortality rates, delays to care, and high prevalence of severe manifestations. There is an unmet need for access to rheumatology in Africa, with only 19% of countries with a rheumatologist. Given the morbidity and damage associated with JDM, increasing our understanding of JDM in Africa is critical. Our objectives are to understand the scope of JDM in African countries by exploring prevalence and severity, availability and accessibility of diagnostic tools and medications, and challenges in care.
Methods. A survey, available in English and French, was distributed via WhatsApp to members of the African League of Associations for Rheumatology (AFLAR; n=233) and Paediatric Society of the African League Against Rheumatism (PAFLAR; n=130) from November 2022-January 2023. Topics included respondent specialty, number of JDM patients followed within the past 10 years, severe manifestations, and available diagnostic tools and medications (with and without consideration of cost).
Results. Forty-three (12%) providers started the survey, of whom 37 (86%) met inclusion criteria; of these 37, 4 (11%) partially and 16 (43%) fully completed it. Most were adult and/or paediatric rheumatologists (n=19; 95%). Respondents represented all 5 African regions and described 216 children with JDM within the last 10 years. There was high prevalence of calcinosis and ILD and higher mortality rates in Kenya (n=6; 14%) and Zambia (n=2; 29%) compared to 1–3% mortality reported in studies of high-income countries. Thirteen of 27 diagnostic tools and medications were accessible to ≤50% of respondents after considering cost, mostly in Northern or Southern Africa (n=9; 69%). Despite being cost-free, disease assessment tools and physical exam to assess calcinosis were not reported as universally available or accessible.
Conclusion. This is the first study to explore JDM broadly in Africa. Respondents identified 216 children with JDM seen within the last 10 years, exceeding the reported 196 children with JDM seen within the last 25 years but likely still underestimating prevalence. Our findings align with reports of severe manifestations and poor outcomes in African children with JDM. Access to many diagnostics and medications is limited, and differences in accessibility parallel regional healthcare disparities. The potential differences in JDM severity warrant systematic study and highlight the need to include patients and providers from LMIC in collaborative research efforts to improve our understanding of JDM in a diverse patient population and increase the equity and generalizability of research.

Table I. Clinical outcomes in children with juvenile dermatomyositis in Africa among survey respondents (n=20).

Country (no. of respondents)	Total Patients (n=216)*	Clinically inactive disease†	Remission‡	Calcinosis	Interstitial lung disease	Deaths
Northern Africa (12)						
Egypt (6)	68*	28	13	36	5	2
Libya (3)	55*	18+	39+	12	5+	3
Morocco (1)	19	6 (31.6%)	4 (21.1%)	7 (36.8%)	6 (31.6%)	0 (0%)
Tunisia (2)	3*	6	6	0	4	0+
Eastern Africa (3)						
Kenya (2)	42	15 (35.7%)	12 (28.6%)	13 (31.0%)	8 (19.0%)	6 (14.3%)
Zambia (1)	7	5 (71.4%)	0 (0%)	3 (42.9%)	1 (14.3%)	2 (28.6%)
Central Africa (3)						
Cameroon (2)**	11	6 (54.5%)	5 (45.5%)	3 (27.3%)	2 (18.2%)	0 (0%)
Democratic Republic of the Congo (1)**	3	3 (100%)	1 (33.3%)	3 (100%)	0 (0%)	+
Western Africa (1)						
Nigeria (1)	4	2 (50.0%)	1 (25.0%)	0 (0%)	1 (25.0%)	0 (0%)
Southern Africa (1)						
South Africa (1)	4	1 (25.0%)	1 (25.0%)	2 (50.0%)	0 (0%)	0 (0%)

Number of patients reported as n; (%) also reported when total patients were known.
†Defined as lack of evidence of myositis disease activity as assessed by global and extramuscular assessments, stable muscle strength and function, and normal muscle enzyme levels, per the International Myositis Assessment & Clinical Studies (IMACS) criteria for lack of evidence of active myositis.
‡Defined according to the IMACS 2005 definition: clinically inactive disease while not receiving any drug therapy for a 6-month continuous period.
*At least 1 respondent unsure of total number of patients, therefore number provided is an underestimation and percentages were unable to be calculated; Egypt=3 of 6 respondents unsure about prior patients, Libya=1 of 3 respondents unsure about total current and total prior patients, Tunisia=2 of 2 respondents unsure about total current patients and 1 of 2 unsure about prior patients.
**Respondents answered questions only about current, not prior, patients (Cameroon=1 respondent, Democratic Republic of Congo=1 respondent).
+ Response missing from 1 respondent.

P-81

THE IMPACT OF THE COVID-19 PANDEMIC ON JUVENILE DERMATOMYOSITIS: EXPERIENCES OF A NORTH-EASTERN COHORT

Tresa Ambooken[1], Sangati Kadakia[1], Tara Lozy[1], Brianna Bulbin[4], Suhas Ganguli[2], Dawn M. Wahezi[3], Sivia K. Lapidus[1]
[1]Department of Pediatrics, Joseph M. Sanzari Children's Hospital, Hackensack University Medical Center and Hackensack Meridian School of Medicine, Hackensack, New Jersey, USA; [2]Department of Pediatrics, K. Hovnanian Children's Hospital, Jersey Shore University Medical Center and Hackensack Meridian School of Medicine, Neptune, New Jersey, USA; [3]Department of Pediatrics, Division of Rheumatology, Children's Hospital at Montefiore, Bronx, NY, USA; [4]Department of General Surgery, Hackensack University Medical Center, Hackensack, New Jersey, USA

Background. Juvenile Dermatomyositis (JDM) is theorized to occur in a genetically susceptible individual in response to an environmental trigger. The pathophysiology of JDM has been associated with viruses, with reports of SARS-CoV-2 linked to presentations and flares. Our objective was to investigate the COVID-19 pandemic's impact through evaluating the new JDM diagnoses and flares during the pandemic relative to the 5 years pre-pandemic.
Methods. Biomedical Informatics identified new patients 21 years and younger using the ICD-10 code M33 between June 2015 and December 2022. Data were collected retrospectively comparing manifestations of JDM patients' initial presentations and flares pre-pandemic (6/1/15 to 2/28/20) as well as during the pandemic (3/1/20 to 12/30/22). COVID-19 exposures and infections preceding a flare or initial diagnosis were assessed. Flare episodes were characterized by clinical symptoms, physical exam findings, and medication changes. Exploratory data analysis examined potential relationships between flares pre-pandemic and during the pandemic using summary statistics as well as univariate and bivariate analysis.

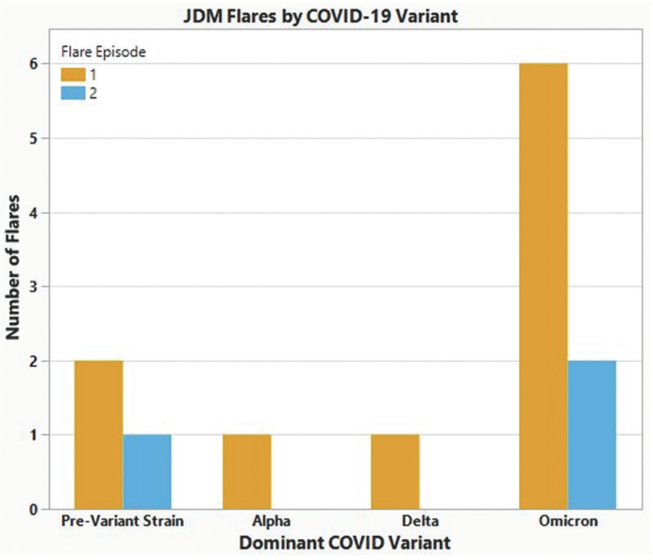


Fig. 1.

Results. Seventeen JDM patients were identified; 8 pre-pandemic and 9 during the pandemic. Fifteen flares were captured from 12 patients, of which 87% (13/15) occurred during the pandemic. Of the 12 patients who flared, 80% flared once and 25% flared more than once during the pandemic. Fifteen percent (n=2) of patients with flare held a medication (methotrexate) for COVID-19 vaccinations (55% of our patients were vaccinated). Two patients had documented COVID-19 infections preceding flare. Most flares occurred during the period when Omicron variants were predominant (12/1/21 to 12/30/2022) (Fig. 1). The majority of flares occurred between in-person office visits. However, 2 patients did have telehealth visits prior to their flares. The median time from visit (any type) to onset of flare was 79 days (IQ range 22.5–181 days).

Conclusion. Over the last 7 years in our center, which was a geographical COVID-19 epicenter, the majority of JDM flares occurred during the COVID-19 pandemic, particularly when the Omicron variant was predominant. Although causality cannot be determined, it may be possible that undocumented or asymptomatic COVID-19 infections may have potentially triggered flares. Holding immunomodulating medications to optimize immune response to COVID-19 vaccination may have also potentially contributed. Use of telehealth did not appear to increase the likelihood of flare. Future investigation in larger cohorts would elucidate correlations between the COVID-19 pandemic and JDM flares. We plan to execute this larger scale analysis using data from the CARRA (Childhood Arthritis and Rheumatology Research Alliance) Registry.

P-82

COMPARISON OF PRE-AND POST-NATAL ENVIRONMENTAL EXPOSURES IN UNITED STATES VS. BRAZILIAN PATIENTS WITH JUVENILE DERMATOMYOSITIS

Tamima Arabi[1], Sylvia Farhat[1], Susan Shenoi[2], Susan Kim[3], Clarissa Carvalho[1], Beatriz Carneiro[1], Lisa G Rider[4], Adriana M. Elias[1]

[1]Pediatric Department, University of São Paulo, São Paulo, Brazil; [2]Seattle Children's Hospital, Seattle, WA, USA; [3]University of California San Francisco, San Francisco CA, USA; [4]National Institute of Environmental Health Sciences, National Institute of Health, Bethesda, MD, USA

Background. The interface of environmental effects on systemic inflammatory diseases is relevant and has grown enormously in recent decades. Inhaled pollutants and tobacco smoking during fetal development were previously demonstrated to be risk factors for juvenile dermatomyositis (JDM) in Brazilian patients in a case-control study. However, no prior studies have assessed differences in environmental exposures among patients diagnosed from Brazil and the United States (U.S.).

Methods. Prevalent patients with probable or definite JDM by Bohan and Peter criteria from 3 centers in the U.S. (n=66) and Brazil (n=36) were enrolled. A questionnaire was used to assess demographic data and environmental exposures during pregnancy (occupational exposure to demolition, chalk, construction and/or quarry dust, paints, varnish, gasoline vapor, and/or battery fluids; stationary sources of inhalable pollution near the mother's home and work); and exposure to tobacco/alcohol.

Results. The mean age at onset of JDM symptoms was 7.12 (SD±4.02) years for U.S. patients and 5.30 (SD±2.52) years for Brazilians (p=0.004). A female predominance was present in both groups (59.3% for U.S. and 54.3% for Brazilian patients). During pregnancy mothers of JDM patients from the U.S. more frequently worked outside the home than mothers of Brazilian patients (65.2% *vs*. 41.2%; p=0.032) (Table 1). U.S. mothers more often worked in offices than Brazilians (51.2% *vs*. 14.3%; p=0.027). Brazilian mothers worked more frequently as teachers in schools compared to American mothers (28.6% *vs*. 4.8%; p=0.029). American mothers commuted to work by subway more frequently than Brazilians (68.3% *vs*. 7.1%; p=<0.01), while Brazilian mothers commuted more frequently by bus (64.3% *vs*. 14.6%; p=0.001). Brazilian mothers were more exposed to dust (42.9% *vs*. 9.5%; p=0.01) and tobacco (50% *vs*. 23.1%; p=0.01). The places where Brazilian mothers worked (35.7% *vs*. 9.1%; p=0.03) and lived (50% *vs*. 10.6%; p=<0.01) during pregnancy were closer to factories and quarries compared to Americans, as well as the place where the child was born (32.3% *vs*. 8.6%; p=0.007). There was no difference in birth weight or frequency of prematurity in U.S. *vs*. Brazilian patients or in gestational exposure to alcohol. After birth, Brazilian JDM patients were more exposed to tobacco, both through their fathers' smoking (26.5% *vs*. 6.2%; p=0.009) and by other residents of the household (36.4% *vs*. 9.2%; p=0.002).

Conclusion. Patients with JDM from Brazil and the United States experienced different environmental exposures during in utero and in postnatal periods regarding type of occupation, maternal transportation to work, distance of mother's home/workplace from factories/quarries, as well as maternal secondhand-smoke exposure. Further studies are needed to determine the role of these exposures in the onset of JDM.

Table I. Prenatal and post-natal exposures in juvenile dermatomyositis patients from United States and Brazil.

Exposure	United States (n=66) n (%)	Brazil (n=36) n (%)	*p*
Mother's occupation during pregnancy - any job	43 (65.2)	14 (41.2)	0.032
Gas station attendant	1 (2.3)	2 (14.3)	0.146
Sales woman or retail	8 (18.6)	1 (7.1)	0.427
Kitchen/ restaurant work	1 (2.4)	2 (14.3)	0.151
Dressmaker	1 (2.4)	1 (7.1)	0.434
Healthcare area	6 (14)	1 (7.1)	0.669
Teacher	**2 (4.8)**	**4 (28.6)**	**0.029**
Office work	**22 (51.2)**	**2 (14.3)**	**0.027**
Distance of mother's workplace from factories and/or quarries less than 500 meters	**4 (9.1)**	**5 (35.7)**	**0.030**
Distance of mother's workplace from gas stations less than 500 meters	25 (49)	9 (64.3)	0.375
Subway commute to work	**28 (68.3)**	**1 (7.1)**	**<0.001**
Bus commute to work	**6 (14.6)**	**9 (64.3)**	**0.001**
Maternal occupational exposures during pregnancy			
Maternal exposure to varnish or paint	3 (7.1)	2 (14.3)	0.590
Maternal exposure to dust	**4 (9.5)**	**6 (42.9)**	**0.01**
Maternal exposure to metals	3 (7.1)	0 (0.0)	0.565
Maternal exposure to batteries	7 (16.7)	0 (0.0)	0.174
Maternal exposure to fluorescent lamps	6 (15.8)	0 (0.0)	0.163
Maternal smoking during pregnancy	7 (10.6)	5 (14.7)	0.536
Smoking and Alcohol			
Intrauterine exposure to cigarettes	15 (23.1)	17 (50)	0.012
Maternal alcohol consumption	2 (3)	0 (0.0)	1.0
Residential exposures			
Distance of mother's house from factories and /or quarries less than 500 meters	**7 (10.6)**	**15 (50)**	**<0.001**
Distance of mother's house from gas station less than 500 meters	20(30.8)	13 (43.3)	0.254
Birth factors			
Prematurity	7 (11.9)	5 (19.2)	0.5
Birth weight <2.5kg	10 (16.1)	2 (7.7)	0.497
Birth weight >2.5 kg	30 (48.4)	10 (52.5)	0.798
Distance of place where the patient was born from factories and /or quarries less than 500 meters	**5 (8.6)**	**10 (32.3)**	**0.007**
Distance of place where the patient was born from gas stations less than 500 meters	17 (29.8)	12 (38.7)	0.478
Postnatal exposure to second hand smoke			
Exposure to maternal smoking	3 (4.6)	3 (8.8)	0.410
Exposure to paternal smoking	**4 (6.2)**	**9 (26.5)**	**0.009**
Exposure to secondhand smoking	**6 (9.2)**	**12 (36.4)**	**0.002**

P-83

THE IMPACT OF DELAY IN JUVENILE DERMATOMYOSITIS: A THREE-PATIENT CASE SERIES AND DEVELOPMENT OF A RETROSPECTIVE DATABASE ON DIAGNOSTIC DELAY

Indira Sriram, Megan Curran
Section of Pediatric Rheumatology, University of Colorado School of Medicine, Aurora, CO, USA

Background. Juvenile dermatomyositis (JDM) is a rare autoimmune disorder causing rash, muscle weakness, fatigue and functional loss. It can be associated with poor long term health outcomes and financial and psychological burdens. Establishing diagnosis early in disease course remains challenging. Due to variable presentations and healthcare provider unfamiliarity, median time from symptom onset to diagnosis is 3.1 months (1). Evidence suggests early identification and aggressive management improves outcomes (2). Conversely, untreated disease duration results in longer time to remission and more complications including uncontrolled skin disease (3). Understanding and mitigating diagnostic delay is required to improve patient outcomes. Diagnostic improvement is a burgeoning medical research area. Here, we describe three patients who experienced diagnostic delay within our medical system.
Methods. Using EPIC Slicer Dicer, we identified 100 JDM patients seen over the last ten years at Children's Hospital Colorado (CHCO). We extracted data from charts of three patients diagnosed with JDM within the last five years who experienced diagnostic delay. All received care from multiple CHCO providers before obtaining their diagnoses. We used the diagnostic error evaluation and research (DEER) taxonomy to code factors leading to delay.
Results. All patients (Table I) are of minority race and had pathognomonic JDM findings that went unrecognized for months to years including facial erythema and Gottron's papules. One patient did not initially present with classic rashes. Through DEER taxonomy coding, we determined that providers in all cases experienced failure in hypothesis generation: there were failures and delays in considering the correct diagnoses. Suboptimal weighing of physical exam findings was also problematic: Gottron's papules were misdiagnosed as eczema in two cases.

Table I. Patient demographics and delay characteristics

Patient	1	2	3
Age at diagnosis (years)	2.4	8.7	7.5
Gender	F	F	F
Race/ethnicity	Hispanic	Hispanic	Hispanic
Symptom duration before first healthcare visit (days)	14	60	10
Number of visits to any provider until diagnosis made	7	19	15
Days from first visit to diagnosis	57	2213	645
Myositis antibody	MDA5	TIF1-gamma	TIF1-gamma

Conclusion. Darker skin tones might have impeded diagnoses, as dermatomyositis rashes can be harder to discern on darker skin. Providers' lack of familiarity with JDM led to diagnostic delay. We are building a retrospective database of juvenile dermatomyositis patients within our system, focusing on describing diagnostic pathways and identifying factors influencing diagnosis using DEER taxonomy. We will then develop educational interventions based on the most commonly identified diagnostic pitfalls.

References

1. NEELY J, SHALEN J, STURROCK H, KIM S; Childhood Arthritis and Rheumatology Research Alliance Investigators: Access to care and diagnostic delays in juvenile dermatomyositis: results from the Childhood Arthritis and Rheumatology Research Alliance Legacy Registry. *ACR Open Rheumatol* 2021; 3(5): 349-54.
2. FISLER RE, LIANG MG, FUHLBRIGGE RC, YALCINDAG A, SUNDEL RP: Aggressive management of juvenile dermatomyositis results in improved outcome and decreased incidence of calcinosis. *J Am Acad Dermatol* 2002; 47(4): 505-11.
3. CHRISTEN-ZAECH S, SESHADRI R, SUNDBERG J, PALLER AS, PACHMAN LM: Persistent association of nailfold capillaroscopy changes and skin involvement over thirty-six months with duration of untreated disease in patients with juvenile dermatomyositis. *Arthritis Rheum* 2008; 58(2): 571-76.

P-84

COMPARISON OF JANUS KINASE INHIBITORS TO BLOCK THE TYPE I INTERFERON PATHWAY IN HUMAN SKELETAL MUSCLE CELLS

Travis B. Kinder[1], James Inglese[1,2]
[1]National Center for Advancing Translational Sciences, National Institutes of Health, Rockville, MD, USA; [2]National Human Genome Research Institute, National Institutes of Health, Bethesda, MD, USA

Background. The family of Janus kinases (JAK1, JAK2, JAK3, TYK2) mediate signal transduction from cytokine receptors through phosphorylation and activation of intracellular signaling pathways and transcription factors. Small molecule antagonists of JAKs (jakinibs) have been developed with varying selectivity for the use in malignancies and immune regulation. There is growing recognition for the effectiveness of jakinibs in autoimmunity of the skeletal muscle called myositis, but which of these drugs is most effective is unknown.
Methods. We have assayed a library of 48 jakinibs for their ability to inhibit the JAK1/TYK2-dependent type I interferon (IFN) - major histocompatibility complex (MHC) class I pathway in human skeletal muscle cells genome-engineered to fuse a pro-luminescent HiBiT peptide to endogenous MHC class I. Results from the top actives were confirmed by RT-qPCR and phospho-STAT1 flow cytometry in primary human myoblasts.
Results. The most potent and effective compounds for blocking IFN signaling over 24 hrs by the MHC class I-HiBit assay were upadacitinib (JAK1/2 inhibitor, FDA approved) with an IC50 of 330 nM and deucravacitinib (TYK2 inhibitor, phase III) with an IC50 of 72 nM.
Conclusion. These active jakinibs warrant further clinical evaluation to show their safety and efficacy in myositis patients.

OP-13

FIBROBLAST GROWTH FACTOR 21 (FGF21) AND GROWTH DIFFERENTIATION FACTOR 15 (GDF15) SERUM LEVELS ARE INCREASED IN PATIENTS WITH JUVENILE DERMATOMYOSITIS (JDM) AT DISEASE ONSET

Maria I. Petrone[1], Emiliano Marasco[1], Giusi Prencipe[1], Ivan Caiello[1], Valentina Matteo[1], Luciapia Farina[1], Fiorella Piemonte[2], Caterina Torda[2], Fabrizio De Benedetti[1], Rebecca Nicolai[1]
[1]Division of Rheumatology, IRCCS Ospedale Pediatrico Bambino Gesù, Roma, Italy; [2]Laboratory of Muscular and Neurodegenerative Diseases, IRCCS Ospedale Pediatrico Bambino Gesù, Roma, Italy

Background. JDM patients show upregulation of interferon (IFN)-stimulated genes and downregulation of several genes related to mitochondrial function. The mitokines GDF15 and FGF21 are induced in situations of muscle stress, particularly mitochondrial myopathies. There is evidence of increased GDF15 levels in serum and muscle of adult patients with idiopathic inflammatory myopathies (IIMs) and in plasma of JDM patients.
The aims of our study were to investigate serum levels of mitokines GDF15 and FGF21 in JDM patients at diagnosis, before start of treatment, and evaluate possible correlations with clinical and laboratory findings, as well as with IFN-related biomarkers.
Methods. We collected muscle biopsy and blood samples of 24 treatment naive JDM patients enrolled at time of diagnosis. Serum levels of FGF21, GDF15, CXCL10, CXCL9 and neopterin were analyzed by ELISA (normal values: 0-200 pg/ml, 200–1000 pg/ml, <300 pg/ml, <150 pg/ml, <1.59 ng/ml respectively); expression of 6 IFN-induced genes (IFI27, IFI44L, IFIT1, ISG15, RSAD2, SIGLEC1) was measured by real-time PCR and used to calculate a type I IFN score in blood and a type I and II IFN score in muscle. For each patient, the following clinical data were recorded: physician's global assessment (PGA) of disease activity VAS (Visual Analogue Scale), Childhood Myositis Assessment Score (CMAS), serum levels of creatine phosphokinase (CK, IU/l), MSA (myositis specific autoantibodies) status. Correlations were determined by the Spearman's rank correlation coefficient. Non-parametric tests were used for comparisons between 2 groups.
Results. Both median FGF21 levels [261 pg/ml (IQR 43.75–617.25)] and median GDF15 levels [1521 pg/ml (IQR 1022-2350)] were increased. Median GDF15 levels tended to be higher in anti-NXP2pos patients (n=4) [3675 pg/ml, (IQR 2535,4645)] when compared to the anti-NXP2neg patients (n=20),

[1430 pg/ml, IQR 883–1888) (p=0.053), and lower in anti-MDA5 positive patients (n=3) [896 pg/ml, IQR 817–1011)] when compared to anti-MDA5 neg patients (n=21), [1704 pg/ml, IQR 1181-2562)] (p=0.08). FGF21 levels showed significant correlation with CMAS (p=0.02, rs= -0.46). GDF15 levels showed significant correlation with CK levels (p=0.004), PGA-VAS (p=0.05), CMAS (p=0.006), and a trend to correlate with blood IFN score (p=0.08).
Conclusion. In our cohort of JDM patients we showed increased levels of FGF21 and GDF15 at disease onset. GDF15 levels, and to a lesser extent FGF21 levels, correlated with disease activity and GDF15 tended to correlate with blood type I IFN score. Our data support the potential use of these mitokines as biomarkers for IMMs.

References

1. DE PAEPE B: Growth differentiation factor-15 as an emerging biomarker for identifying myositis. *Expert Rev Clin Immunol* 2022; 18(2): 115-23. https://doi.org/10.1080/1744666X.2022.2021879
2. DUVVURI B, PACHMAN L, MORGAN G, HERMANSON P, WANG T, LOOD C: Growth and Differentiation Factor 15, an emerging biomarker of mitochondrial dysfunction-associated myopathies: implications for juvenile dermatomyositis. ACR Convergence 2022. November 10-14, 2022. Philadelphia, PA, USA.

OP-14

MYOSITIS OUTCOME IN JUVENILE PATIENTS AFTER TRANSITION INTO ADULTS: ANALYSIS OF A COHORT OF 16 PATIENTS

Ernesto Trallero-Araguás[1], Estefanía Moreno[1], Mireia López-Corbeto[1], Albert Gil-Vila[2,3], Albert Selva-O'Callaghan[2,3]
[1]Rheumatology Department, Vall d'Hebron Hospital, Barcelona, Spain; [2]Systemic Autoimmune Diseases Unit, Internal Medicine Department, Vall d'Hebron Hospital, Barcelona, Spain; [3]Universitat Autónoma de Barcelona, Barcelona, Spain

Background. Inflammatory myopathies are a group of heterogeneous systemic diseases of autoimmune nature. Juvenile myositis (JM) defined at age at onset under 18 years may be severe and life threating. Our objective was to ascertain the adult outcome in patients diagnosed with juvenile form of myositis.
Methods. A total of 16 patients (7 female, median age at onset [IR] 14 years [9.5-15], with a mean [SD] follow up of 18 years [9.9]) who have transitioned from JM to adult were analyzed. Patients belonged to a large cohort of myositis patients diagnosed and followed up in Vall d'Hebron Hospital, Barcelona, Spain from 1989 to 2023. All the patients fulfilled the definitive (>90%) ACR/EULAR criteria for diagnosis. Clinical manifestations, autoantibody profile, and muscle pathology were collected in a myositis data base from the onset of the cohort study. Disease damage and disease activity were retrospectively evaluated at the time of the study by a 10-cm visual analog scale. A global, although subjective, evaluation of the disease outcome in adult was performed by the physician in charge and categorized as satisfactory or not. Quantitative variables were described by mean and standard deviation (SD) if normally distributed and by median and interquartile range (IR) if non-normally distributed. Chi-square and Kruskal-Wallis tests were used to compare qualitative and non-normally distributed quantitative variables among groups. Statistical significance was set at p<0.05.
Results. Patients included in the study were diagnosed with juvenile dermatomyositis (JDM) (9 patients, 2 patients anti-Mi2, 1 patient anti-TIF1g, 6 patients seronegative), overlap myositis (scleromyositis, 3 patients, all anti-PM/Scl+; antisynthetase syndrome, 2 patients, anti-Jo1+), immune-mediated necrotizing myopathy (IMNM) (2 patients, one seronegative and one anti-SRP+). Two patients developed cancer (lung cancer in the ASS after 25 years of activity, cancer-associated myositis -metastatic teratoma- in the seronegative IMNM patient). Our cohort showed that 75% of patients with JM remained asymptomatic in adulthood, 18.8% showed mild symptoms, and 6.3% had an unfavorable course. When compared, age at onset (median, IR) of patients with JDM (11, 8) was significantly lower than patients with overlap myositis (15, 2) (p=0.003) or IMNM 16 (p=0.003). Moreover, JDM patients were those with a higher activity (p=0.048) and a better outcome remaining all asymptomatic or with a satisfactory outcome in adulthood, most receiving a minimum or no therapy.
Conclusion. Juvenile forms of myositis, especially those with severe JDM and lower age at onset have a good outcome after transitioning into adulthood.

Clinical Trials

P-85

DESIGN OF A PHASE 2, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP STUDY OF NIPOCALIMAB IN PARTICIPANTS WITH ACTIVE IDIOPATHIC INFLAMMATORY MYOPATHIES (SPIREA)

Catherine E. Najem[1], Jagriti Craig[1], Lisa Christopher-Stine[2], Federico Zazzetti[3], Wim Noel[4], Christopher Blango Sr.[1], Chetan S. Karyekar[1], Rohit Aggarwal[5]
[1]Janssen Pharmaceutical Company of Johnson & Johnson, Spring House, PA, USA; [2]Medicine and Neurology, Johns Hopkins School of Medicine, Baltimore, MD, USA; [3]Janssen Medical Affairs Global Services, LLC, Buenos Aires, Argentina; [4]Janssen Pharmaceutica, Vilvoorde, Belgium; [5]Division of Rheumatology and Clinical Immunology, Department of Medicine, University of Pittsburgh, Pittsburgh, PA, USA

Background. Idiopathic inflammatory myopathies (IIM) are a rare group of systemic autoimmune diseases characterized by progressive muscular weakness and internal organ involvement, often leading to physical disability and decreased quality of life. Nipocalimab is designed to address the underlying disease pathology by selectively blocking the neonatal Fc receptor to reduce pathogenic autoantibodies. In a phase 2 study of generalized myasthenia gravis (NCT03772587), nipocalimab lowered pathogenic IgG autoantibody levels with significant clinical benefit, acceptable safety, and a favorable benefit-risk profile. SPIREA (NCT05379634) aims to evaluate the efficacy and safety of nipocalimab in patients with IIM.
Methods. SPIREA is a phase 2, double-blind, placebo-controlled, randomized clinical trial enrolling adults (N≈200) with active IIM. The study comprises screening, double-blind treatment, long-term extension, and follow-up periods. Randomized participants are treated every 2 weeks with intravenous nipocalimab or placebo through Week 50. Background oral glucocorticoid (GC) doses will be tapered from Weeks 24–44.
Results. The primary endpoint is the proportion of participants who achieve at least minimal improvement (≥20) in American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) Total Improvement Score (TIS) at Week 52 and on ≤5 mg/day of oral GC from Weeks 44–52. Secondary endpoints include the proportion of participants who achieve ≥20-point improvement in TIS at Weeks 24 and 52.
Conclusion. The ongoing SPIREA study evaluating the safety and efficacy of nipocalimab in patients with IIM will help to validate the ACR/EULAR-TIS endpoint in IIM and the role of nipocalimab as a steroid sparing agent in IIM.
Acknowledgements. This study is sponsored by Janssen Research & Development, LLC. Medical writing support was provided by Panita Maturavongsadit, PhD, of Lumanity Communications Inc., and was funded by Janssen Global Services, LLC.

P-86

RANDOMIZED PLACEBO-CONTROLLED TRIAL TO EVALUATE EFFICACY AND SAFETY OF SUBCUTANEOUS ABATACEPT IN ADULTS WITH ACTIVE IDIOPATHIC INFLAMMATORY MYOPATHY: OUTCOMES FOR JAPANESE STUDY PARTICIPANTS

Rohit Aggarwal,[1] Takahisa Gono,[2] Ingrid E. Lundberg,[3] Yeong-Wook Song,[4] Aziz Shaibani,[5] Victoria P Werth,[6] Michael A. Maldonado[7]
[1]University of Pittsburgh, Pittsburgh, PA, USA; [2]Nippon Medical School Hospital, Tokyo, Japan; [3]Karolinska Institutet, Stockholm, Sweden; [4]Seoul National University, Seoul, Korea; [5]Nerve and Muscle Center of Texas, Houston, TX, USA; [6]University of Pennsylvania Perelman School of Medicine and CMCVAMC, Philadelphia, PA, USA; [7]Bristol Myers Squibb, Princeton, NJ, USA

Background. A randomized, placebo (PBO)-controlled phase 3 trial of subcutaneous (SC) abatacept (ABA) and standard of care (SOC) was conducted in patients with idiopathic inflammatory myopathy (IIM; NCT02971683). 52-week results for the global population were reported (primary endpoint not met)(1). Patients enrolled at Japanese sites were required to complete a 24-week extension; this analysis evaluated efficacy and safety in these patients through 76 weeks of treatment.

P-86 Table I. Endpoints in the DB period (at 24 weeks, ITT analysis population in Japan) and the OLE (at 76 wrrks, OLE-treated analysis population in Japan)[a].

Endpoint	DB period (week 24)			OLE (week 76)		
	ABA n = 11	PBO n = 10	Adjusted mean difference from PBO (95% CI)	ABA n = 11	PBO to ABA switch n = 9	Adjusted mean difference between groups (95% CI)
IMACS DOI, n/N (%)	8/11 (72.7)	5/10 (50.0)	N/A	9/10 (90.0)	7/8 (87.5)	N/A
MRC TIS, adjusted mean (SE)	38.8 (4.9)	41.7 (5.6) *n = 8*	–2.9 (–18.1, 12.3)	46.8 (5.2) *n = 10*	55.3 (5.9) *n = 8*	–8.5 (–23.9, 6.9)
FI-2 (3 score)	1.4 (3.5)	2.6 (4.0) *n = 9*	–1.3 (–12.0, 9.5)	–1.1 (3.2) *n = 10*	6.4 (3.6)	–7.6 (–17.3, 2.1)
HAQ-DI	–0.3 (0.1)	–0.2 (0.1) *n = 9*	–0.1 (–0.4, 0.2)	–0.3 (0.1) *n = 10*	–0.5 (0.1)	0.3 (–0.1, 0.6)
MDAAT	–1.6 (0.3)	–1.6 (0.3) *n = 9*	0.1 (–0.9, 1.0)	–1.7 (0.3) *n = 10*	–2.0 (0.4)	0.4 (–0.6, 1.3)
MMT-8[b]	10.5 (2.8)	15.1 (3.2) *n = 8*	–4.6 (–13.0, 3.8)	19.4 (2.8) *n = 10*	18.8 (3.2) *n = 8*	0.6 (–7.9, 9.1)
Physician Global Assessment VAS[b]	–2.9 (0.5)	–2.9 (0.6) *n = 9*	0.1 (–1.5, 1.6)	–3.5 (0.5) *n = 10*	–3.8 (0.6)	0.4 (–1.2, 1.9)
Patient Global Assessment VAS[b]	–2.3 (1.2)	–3.3 (2.3) *n = 9*	1.1 (–6.9, 9.0)	–2.6 (1.8) *n = 10*	–3.2 (3.1)	0.6 (–10.6, 11.7)
CDASI[b]						
Activity score	–3.5 (1.9) *n = 7*	–5.0 (2.0) *n = 6*	1.5 (–4.6, 7.7)	–8.6 (1.8) *n = 7*	–8.6 (1.9) *n = 6*	0.0 (–5.9, 5.9)
Damage score	–0.9 (0.9) *n = 7*	0.6 (1.0) *n = 6*	–1.5 (–4.4, 1.3)	–1.3 (0.4) *n = 7*	–0.7 (0.5) *n = 6*	–0.5 (–2.0, 0.9)

Data are adjusted mean change from baseline (SE) unless otherwise stated.
[a]In the DB period, primary endpoint IMACS DOI was compared between treatment groups using a logistic regression model; secondary endpoints were assessed using a longitudinal (repeated measures) model. In the OLE, no formal statistical testing was conduced for efficacy analyses.
[b]DB data for these endpoints were for the OLE-treated analysis population in Japan (rather than the ITT analysis population in Japan).
CDASI: Cutaneous Dermatomyositis Disease Area and Severity Index; FI-2: functional index-2; MDAAT: Myositis Disease Activity Assessment Tool; MMT-8: manual muscle test-8; MRC: myositis response criteria; N/A: not applicable; n/N: number of patients meeting IMACS DOI/number of patients in the analysis; TIS: total improvement score; VAS: visual analog scale.

Methods. Adults with active, treatment-refractory IIM received 125 mg weekly SC ABA+SOC or PBO+SOC in the double-blind period (DB; weeks 0–24). In the 28-week open-label period (weeks 24–52, data not shown), patients receiving PBO were switched to ABA+SOC. In the 24-week open-label extension (OLE; weeks 52–76), all patients randomized in Japan continued ABA+SOC. Primary endpoint: proportion meeting International Myositis Assessment and Clinical Studies definition of improvement (IMACS DOI). Secondary endpoints and safety/tolerability were assessed. Here we report results from the full 76-week observation period for the subset of patients at Japanese sites.
Results. Of 148 patients randomized, 21 were from Japanese sites (ABA, n=11; PBO, n=10) and 19/21 completed the OLE. Baseline demographics and disease characteristics were similar to the full study population. IIM disease subtype was similar in both treatment groups (ABA *vs*. PBO: dermatomyositis 7 *vs*. 7, polymyositis 3 vs 3, autoimmune necrotizing myopathy 1 *vs*. 0). Proportions of ABA *vs*. PBO patients achieving IMACS DOI at week 24 were 72.7% *vs*. 50%, and, at week 76, 90% *vs*. 87.5% (Table), demonstrating a sustained benefit of continuing ABA (ABA group) and an improvement after switching to ABA (PBO/ABA group).
Adjusted mean Myositis Response Criteria (MRC) Total Improvement Scores were no different between groups at week 24; at week 76, values were 46.8 and 55.3 in the ABA and PBO/ABA groups, respectively (Table). The proportions of patients with MRC moderate/major responses at week 76 were 70% and 100% in the ABA and PBO/ABA groups, respectively. Improvements were seen in most secondary endpoints when continuing ABA and switching to ABA (Table).
The safety and tolerability of ABA in this subset of patients from Japan were consistent with the full study population.
Conclusion. Throughout the 76-week study, patients in Japan tolerated abatacept well and showed continued clinical responses with abatacept treatment, consistent with findings from the full study population.
Acknowledgements. Study funded by Bristol Myers Squibb, executed by Sandra Overfield and Robin Scully.

Reference
1. AGGARWAL R *et al*.: *Arthritis Rheumatol* 2022; 74 (Suppl 9).

P-87

STUDY DESIGN FOR THE EFFICACY AND SAFETY ASSESSMENT OF DAXDILIMAB SUBCUTANEOUS INJECTION, A SELECTIVE PLASMACYTOID DENDRITIC CELL DEPLETER, IN A PHASE 2 TRIAL OF PATIENTS WITH INADEQUATELY CONTROLLED DERMATOMYOSITIS OR ANTI-SYNTHETASE INFLAMMATORY MYOSITIS

Adina K. Knight, Liangwei Wang, Zhiwen Wang, Annie Lau-Kilby, Nisha Jain
Horizon Therapeutics plc (Now Amgen Inc.), Rockville, MD, USA

Background. Daxidilimab (DAX) is an IgG1λ afucosylated monoclonal antibody specific for immunoglobulin-like transcript 7 (ILT7), a cell-surface protein that is exclusively expressed on plasmacytoid dendritic cells (pDCs). DAX binds to ILT7 on the surface of pDCs, resulting in their depletion via antibody-dependent cellular cytotoxicity.[1] There is an unmet medical need for patients living with dermatomyositis (DM) or anti-synthetase inflammatory myositis (ASIM) as current standard-of-care have significant toxicities, and limitations of use and management of disease.
Methods. This study is a Phase 2, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of DAX in adult participants with DM or ASIM (NCT05669014). The study will enroll 2 idiopathic inflammatory myositis participant populations having a diagnosis of definite or probable myositis according to the American College of Rheumatology/European League Against Rheumatism 2017 criteria. Population #1 will consist of DM participants with definite or probable myositis and a DM rash. Population #2 will consist of ASIM participants with definite or probable myositis and a positive ASIM associated antibody. Up to 96 participants will be randomized by population in a 1:1 ratio (24 participants per group) to receive DAX 300 mg or placebo by subcutaneous injection Q4W. Study endpoints are the same for DM and ASIM, with an independent analysis of the 2 populations. Primary efficacy assessment will occur at Week 24. Safety will be evaluated.
Results. The primary efficacy endpoint is the Total Improvement Score (TIS) at Week 24. Secondary efficacy endpoints include the proportion of participants with improvement of TIS ≥ 40 and without deterioration at 2 consecutive visits at Week 24, proportion of participants with improvement of TIS ≥ 20 and without deterioration at 2 consecutive visits at Week 24, change from baseline in the Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI) activity score at Week 24, proportion of partici-

pants on an oral corticosteroid (OCS) dose ≥ 10 mg of prednisone or equivalent at baseline who achieve a clinically meaningful reduction in the OCS dose: either a 25% decrease or an OCS dose of 7.5 mg/day of prednisone or equivalent at Week 24.

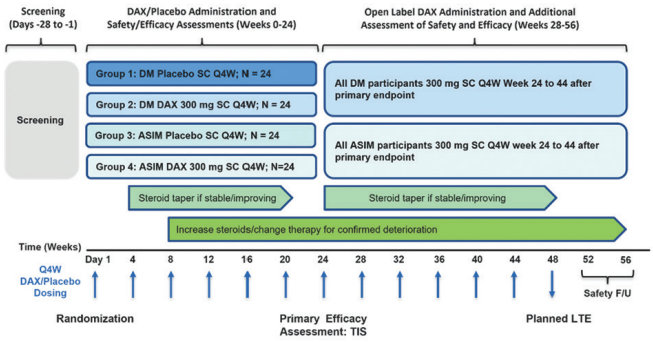


Fig. 1. Study design.

Conclusion. There is a significant unmet medical need to reduce disease activity and improve the quality of life for patients living with DM or ASIM. This study aims to evaluate a new therapy that is novel, fast acting and safe that can fulfil the unmet needs of patients with DM or ASIM.

Acknowledgements. Medical writing support was provided by B. Lujan, PhD, CMPP of Horizon Therapeutics (Now Amgen Inc.).

Funding. This study (NCT05669014) is funded by Horizon Therapeutics (Now Amgen Inc.).

Author COI disclosures. A.K. Knight, L. Wang, Z. Wang, A. Lau-Kilby, and N. Jain are employees of Horizon Therapeutics (Now Amgen Inc.) and own stock.

P-88

DISEASE CHARACTERISTICS AND MEDICATIONS USE IN IDIOPATHIC INFLAMMATORY MYOPATHY: DECENTRALIZED REMOTE VS. TRADITIONAL CLINIC ENROLLMENT

Shiri Keret[1], Raisa Lomanto Silva[2], Tanya Chandra[3], Eugenia Gkiaouraki[3], Nantakaran Pongtarakulpanit[3,4], Shreya Sriram[3], Siamak Moghadam-Kia[3], Chester V. Oddis[3], Rohit Aggarwal[3]

[1]Rheumatology unit, Bnai-Zion Medical Center, Faculty of Medicine, Technion, Haifa, Israel; [2]Internal medicine, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA; [3]Division of Rheumatology and Clinical Immunology, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA; [4]Division of Allergy, Immunology and Rheumatology, department of medicine, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

Background. Idiopathic Inflammatory myopathies (IIM) are a group of rare autoimmune diseases, characterized by heterogeneous manifestations and clinical trajectories. Given its rarity, large IIM clinical trials are scarce. Tele-research modalities could enhance participant enrollment in myositis studies. Our study aims to evaluate disease characteristics, including symptoms, diagnosis delay, medication usage, and work absenteeism in IIM patients throughout the U.S., and compare these parameters between patients recruited remotely versus locally

Methods. "Myositis Patient Centered Tele-Research" (My PACER) is a large multi-center prospective 6-month observational study of U.S. IIM subjects, competitively recruited through traditional in-person clinic visits (Center-Based Cohort [CBC]), and remotely using smartphone technology, wearable devices, and telemedicine principles (Tele-Research Cohort [TRC]). Data collection included baseline demographic and clinical parameters, patient-reported outcomes (PROs) at 6 monthly visits, including myositis core set measures (health assessment questionnaire [HAQ-DI], patient global disease activity, PROMIS physical function), functional tests (six-minute walk, timed up-and-go and sit-to-stand tests), and physical activity monitor. Clinician Reported Outcomes (ClinRO) including myositis core set measures (manual muscle testing [MMT], physician global disease activity, extra-muscular global disease activity, creatine kinase [CK]) were obtained at baseline and 6 months.

Results. A total of 120 IIM patients were enrolled, comprising 82 patients in the TRC cohort and 38 patients in the CBC cohort. The TRC and CBC cohorts were similar in demographics, with a mean age in TRC *vs*. CBC 54.9±13.8 years *vs*. 56.9±12.6 years (p=0.44), 62 (75.6%) *vs*. 28 (73.7%) were females (p=1.0), and 68 (82.9%) *vs*. 29 (76.3%) White (p=0.17), respectively. Overall, 49 dermatomyositis (41%), 32 polymyositis (27%), 28 (23%) anti- synthetase syndrome and 11 necrotizing myositis (9%) patients were enrolled with no significant differences in the prevalence of myositis sub-types observed among the cohorts (p=0.85).

The groups showed similarities in various clinical factors, such as muscle enzymes, diagnosis delay, employment status, several PROs and ClinRO, functional tests, physical activity monitoring, and the frequency of abnormal findings in assessments, including chest CT, pulmonary function tests, and EMG. Notably, patients in the TRC group were treated more frequently with biologics and csDMARDs (Table I).

Conclusion. Remote recruiting using tele-research modalities yielded a patient cohort that is demographically and clinically similar to traditionally recruited patients. These findings indicate the viability and effectiveness of remote recruiting for medical research studies, particularly in rare diseases, offering the potential for robust and diverse patient recruitment across different geographic and ethnic backgrounds.

Table I. Baseline demographic and clinical parameters in the tele-research cohort (TRC) and the center-based cohort (CBC).

	Total (n=120)	Center-Based Cohort (n=38)	Tele-Research Cohort (n=82)	P value
Demographic parameters:				
Age (years) at diagnosis (Mean ± SD)	49.5±14.2	49.3±14.5	49.6±14.2	0.905
Female sex (n, %)	90 (75%)	28 (73.7%)	62 (75.6%)	1.0
Caucasian race (n, %)	97 (80.8%)	29 (76.31%)	68 (82.9%)	0.168
BMI (Mean ± SD)	65.4±18.1	65.1±18.4	65.5±18.1	0.976
Employed (yes, n, %)	68 (56.7%)	21 (55.3%)	47 (57.3%)	0.833
Myositis Disease Subtype				
Dermatomyositis (n, %)	49 (40.8%)	16 (42.1%)	33 (40.2%)	0.845
Polymyositis (n, %)	32 (26.7%)	11 (28.9%)	21 (25.6%)	
Necrotizing Myopathy (n, %)	11 (9.1%)	4 (10.5%)	7 (8.5%)	
Anti Synthetase Syndrome (n,%)	28 (23.3%)	7 (18.4%)	21 (25.6%)	
Clinical parameters:				
Diagnosis delay- years (Mean ± SD)	1.08±2.294	1.55±3.73	0.85±1.10	0.704
CK baseline (Mean ± SD)	455.6±939	681.2±1148	359.0±823	0.151
Positive MSA (n, %)	63 (52.5%)	21 (55.3%)	42 (51.2%)	0.68
Patient-reported outcome measures (PROs)				
PROMIS PF-20 Baseline (Mean ± SD)	42.1±8.8	43.3±9.3	41.5±8.6	0.412
HAQ score baseline (Mean ± SD)	0.8±0.7	0.7±0.6	0.8±0.7	0.379
Patient global disease activity at baseline (Mean ± SD)	3.3±2.4	3.3±2.8	3.3±2.2	0.803
Functional tests:				
Average STS baseline (Mean ± SD)	11.0±4.5	10.9±4.6	11.1±4.5	0.645
Average TUG baseline (Mean ± SD)	12.4±9.4	11.4±5.5	12.9±10.7	0.937
Physical activity measures:				
Average steps per minute (Fitbit) baseline (Mean ± SD)	4.9±3.3	4.7±2.8	5.08±3.5	0.827
Clinician Reported Outcomes (ClinRO)				
MMT8 [0-100] (Mean ± SD)	93.42±15.46	94.80±11.14	92.78±17.14	0.919
Physician global baseline (Mean ± SD)	1.4±1.6	1.6±2.0	1.4±1.4	0.691
Myositis Disease Activity Assessment Tool (MDAAT)				
Muscle disease activity	0.9±1.5	1.3±2.0	0.8±1.3	0.891
Extramuscular global disease activity	0.9±1.3	0.9±1.7	0.9±1.1	0.276
TIS score	9.4±13.7	8.8±12.3	9.6±14.4	0.948
Medications use- ever (n, %)				
Corticosteroids	112 (94.1%)	36 (94.7%)	76 (93.8%)	0.730
csDMARD	111 (93.3%)	32 (84.2%)	79 (97.5%)	**0.013**
IVIg	64 (54.2%)	22 (57.9%)	42 (52.5%)	0.583
Biologics	40 (33.6%)	4 (10.5%)	36 (44.4%)	**<0.001**
Assessments findings:				
EMG consistent with myositis	60 (69%)	20 (62.5%)	40 (72.7%)	0.320
Muscle biopsy consistent with myositis	62 (75.6%)	19 (73.1%)	43(76.8%)	0.716
Abnormal PFT	23 (31.1%)	4 (20.0%)	19 (35.2%)	0.210
Abnormal chest CT	30 (35.3%)	5 (20.0%)	25 (41.7%)	0.057

P-89

PSYCHOEDUCATIVE INTERVENTION AIMED TO IMPROVE HEALTH-RELATED QUALITY OF LIFE IN PATIENTS WITH MYOSITIS: A RANDOMIZED CONTROLLED CLINICAL TRIAL

Imma Armadans-Tremolosa[1], María Palacin Lois[2], Angela Castrechini[1], Susana Sanduvete-Chaves[3], Salvador Chacón-Moscoso[3,4], Mónica Martin-Pozuelo[5,6], Claudia Guasch Capella[7], Ernesto Trallero-Araguás[8], Albert Gil-Vila[6,8], Albert Selva-O'Callaghan[6,9]

[1]Department of Social Psychology and Quantitative Psychology, PsicoSAO-Research Group in Social, Environmental, and Organizational Psychology, University of Barcelona, Barcelona, Spain; [2]Social Psychology and Quantitative Psychology Department, Faculty of Psychology, University of Barcelona, Barcelona, Spain; [3]Department of Experimental Psychology, Universidad de Sevilla, Seville, Spain; [4]Psychology Department, Autonomous University of Chile, Santiago, Chile; [5]Servei Asistencial de Salut, Barcelona, Spain; [6]Universitat Autónoma de Barcelona, Barcelona, Spain; [7]Faculty of Psychology, University of Barcelona, Barcelona, Spain; [8]Rheumatology Department, Vall d'Hebron Hospital, Barcelona, Spain; [9]Systemic Autoimmune Diseases Unit, Internal Medicine Department, Vall d'Hebron Hospital, Barcelona, Spain

Background. Myositis are systemic chronic conditions of autoimmune nature. Involvement of several organs such as lung, joints, skin, and muscles produce suffering to the patients and so affect their quality of life. An intervention aimed to improve the health-related quality of life and wellbeing in patients with myositis was developed.
Methods. A random sample of patients from a large cohort of adult myositis patients attended in our outpatient clinic were contacted by telephone during a 2-month period and invited to participate in the study.

Table I. Psychoeducation intervention

Session 1. Presentation, illness, habits and care
a. Presentation of technical roles of professionals: driving and observation
b. Presentation of the pathology 'Idiopathic Inflammatory Myopathy' (What is the disease, symptoms, evolution, habits and recommended care)
c. Presentation of the patients (a total of 10 in a structured way 2´/per patient)
d. Technique for the identification of healthy and unhealthy habits related to the disease present in the lives of patients (in a structured way using a 2' technique/per participant)
e. Identification of recommended care in the lives of patients, participatory information about driving and participants
f. Patients will commit to care that is made explicit
g. Logout

Session 2. Work activity and emotions
a. Introduction the line of the disease, instruction to perform the technique: incidents during the evolution of your disease
b. Explanation by each participant of the disease line: they are asked to explain those changes in various areas of their life: work, physical and leisure.
c. Identify and select two behaviors that they should perform in each area listed above for their own benefit.
d. Task for the next session: bring photographs of the most important people at the 3 levels (work, leisure and friendship).
e. Logout

Session 3. Family and affective relationships
a. Introduction of the session on the family and its importance in adapting to the disease
b. Explanation of the types of social support (instrumental support, affective or emotional support and material support) and the types of emotional relationships (are they reciprocal/non-reciprocal)
c. Explanation of the selected photograph (task proposed from the previous session) relating it to the types of support and types of emotional relationships (it is done in a structured way using the 5' technique/per participant).
d. Logout

Session 4. Work and society
a. Introduction of the session on the role of work activity and the feeling of social usefulness and adaptation to the disease
b. Explanation of social significance in the lives of patients from the diagnosis of the disease.
c. Explanation of intragroup relationships and the importance of the support network in minority diseases. Explanation of the participants of these networks (in a structured way 2'/per participant)
d. The topic of social understanding will be discussed, and the influence of related social regulations through different areas: social, family, work.
e. Logout

Session 5. Evaluation and assessment
a. Evaluation and assessment
b. Psychometric tests
c. Individual assessment of the psychoeducational group intervention
d. Group Farewell and Closing (carried out in a structured way using a 5' technique/per participant)

Eligibility criteria include 1) diagnosis of definite myositis according to the International Myositis Classification Criteria (score >90); 2) patients able to understand the purpose and procedures of the study, motivated and agree to participate. They were excluded if they had been hospitalized for extremely severe disease, declined participation, require excessive convincing for their participation, or may have a significantly disruptive role in the group. Juvenile subsets, severe psychiatric conditions, or patients with an unfavorable short-term prognosis were also excluded. This randomized controlled trial includes 15 patients (experimental group, 40% women, mean age 51.13, 73.3% diagnosed with dermatomyositis) who participated in the psychoeducation intervention (see table), and 8 participants (62.5% women, mean age 55.13, 62.5% diagnosed with dermatomyositis) who served as a control group. Quality of life (WHOQOL-BREF), well-being (WHO-5), self-efficacy to manage their chronic disease (SEMCD-S) and International Physical Activity Questionnaire (IPAQ) were measured in both groups twice (pre-test and post-test). SPSS version 28 was used to develop statistical analyses (SPSS Software Inc., Chicago, IL). McNemar test was carried out for nominal dependent variables, while repeated measures ANOVA was used for quantitative variables. Eta squared was used as a measure of effect size. Effect sizes values around 0.01 were considered a low effect, around 0.06 medium effect, and around 0.14 high effect.
Results. In the experimental group, scores were higher in the post-test when comparing with the pre-test in quality of life, wellbeing, and self-efficacy to manage the disease. This improvement was more noticeable in the experimental group than in the control group in 70% of the variables studied. Specifically, sedentariness decreased and satisfaction with social relationships increased in post-test in the experimental group in comparison with the control group.
Conclusion. This pilot-study provides preliminary evidence for the effectiveness of an educational intervention for improving HRQoL, wellbeing and self- efficacy to manage the disease in patients with myositis.
Acknowledgements. Vall d'Hebron investigators are supported by the Instituto de Salud Carlos III Grant PI22/00708 co-financed by the European Regional Development Fund (ERDF).

P-90

UPDATE ON PHASE-2 DOUBLE BLIND PLACEBO-CONTROLLLED RANDOMIZED TRIAL IN MYOSITIS: ADD-ON IVIG VS STEROIDS ALONE AS INDUCTION THERAPY: TIME IS MUSCLE

Renske G. Kamperman[1], Sanne W. Evers[1], Johannes A. Bogaards[2], Hannah A.W. Walter[1], Marianne de Visser[1], Corianne de Borgie[3], Jantine C.A. Colen-de Koning[4], Camiel Verhamme[1], Mario Maas[5], Filip Eftimov[1], Ivo N. van Schaik[1,6], Anneke J. van der Kooi[1], Joost Raaphorst[1].

[1]Department of Neurology and Clinical Neurophysiology, Amsterdam UMC, Amsterdam, The Netherlands; [2]Department of Epidemiology and Data Science, Amsterdam UMC, Amsterdam, The Netherlands; [3]Department of epidemiology and Data Science, Amsterdam UMC, Amsterdam, The Netherlands; [4]Department of Clinical Pharmacy, Amsterdam UMC, Amsterdam, The Netherlands; [5]Department of Radiology and Nuclear Medicine, Amsterdam UMC, Amsterdam, The Netherlands; [6]Sanquin Blood Supply Foundation, Amsterdam, The Netherlands

Background. Standard initial treatment for idiopathic inflammatory myopathies (IIM) ('myositis') results in relatively slow improvement of muscle strength. Aggressive treatment of early myositis may induce faster reduction of disease activity and prevent chronic disability due to disease-induced structural muscle damage. Intravenous immunoglobulin (IVIg) in addition to standard glucocorticoid treatment may be promising: we and others have shown that add-on IVIg led to clinical improvement in refractory dermatomyositis patients and that induction monotherapy IVIg improved clinical outcome after 9 weeks, in about half of treatment-naive patients with IIM. Our aim is to investigate whether early addition of IVIg in newly diagnosed IIM patients leads to faster improvement and sustained positive effects, compared to prednisone monotherapy.
Methods. The 'Time Is Muscle' trial is a single-center, phase-2 double-blind randomized clinical trial (RCT), conducted in the Netherlands. We aim to include 48 patients with IIM who will be treated with add-on IVIg or placebo at baseline (within 1 week after diagnosis) and after 4 and 8 weeks, in addition to standard therapy with oral prednisone 1mg/kg/day. The primary clinical outcome is the Total Improvement Score (TIS), a weighted longitudinal score composed of 6 Core Set Measures of the myositis response criteria, measured as the difference of the mean TIS after 12 weeks between intervention and control group. At baseline, 4, 8, 12, 26 and 52

weeks, time to moderate response (TIS≥40), mean daily prednisone dosage, physical activity, health-related quality of life, fatigue and MRI muscle imaging parameters will be assessed as secondary outcomes.
Results. Since September 2021, 21 out of 48 patients (43.8%) have been enrolled and reached their primary outcome, of whom ten patients have completed the one-year study follow-up. Eleven eligible patients declined study participation due to time restraints and travel distance. To date (December 1st, 2023), we have not observed any serious side effects.
Conclusion. In this study, we aim to provide evidence for a clinical effect of add-on IVIg in the first three months after IIM diagnosis. The secondary outcomes may provide useful data for future trials in IIM. The anticipated end date is August 2026.

References

1. LIM J, EFTIMOV F, VERHAMME C *et al*.: Intravenous immunoglobulins as first-line treatment in idiopathic inflammatory myopathies: A pilot study. *Rheumatology* (Bulgaria) 2021; 60(4).
2. JING T, JIESHENG G, JINWEI C *et al*.: Efficacy and safety of the combined treatment with intravenous immunoglobulin and oral glucocorticoid in the elderly with dermatomyositis. *Chinese J Geriatr* 2008; 27: 588-90
3. DALAKAS MC: Update on the use of intravenous immune globulin in the treatment of patients with inflammatory muscle disease. *J Clin Immunol* 1995; 15: 70S-75S. 10.1007/bf01540896
4. AGGARWAL R, RIDER LG, RUPERTO N *et al*.: 2016 American College of Rheumatology/European League Against Rheumatism criteria for minimal, moderate, and major clinical response in adult dermatomyositis and polymyositis: an international Myositis assessment and clinical studies group/Paediatric rheumatology International trials Organisation collaborative initiative. *Ann Rheum Dis* 2017; 76: 792-801. 10.1136/annrheumdis-2017-211400

P-91

A PROSPECTIVE, OPEN-LABEL STUDY EVALUATING THE EFFICACY AND SAFETY OF RESPOSITORY CORTICOTROPIN INJECTION FOR REFRACTORY CUTANEOUS DERMATOMYOSITIS

Anthony P. Fernandez[1,2], Elizabeth Flatley[1,3], Lydia Cassard[1,4], Josh Gallop, Samantha Polly[5], Urmi Khanna[6]
[1]Department of Dermatology, Cleveland Clinic, Cleveland, Ohio, USA; [2]Department of Pathology, Cleveland Clinic, Cleveland, Ohio, USA; [3]Rutgers New Jersey Medical School, Newark, New Jersey, USA; [4]Cleveland Clinic Lerner College of Medicine, Cleveland, Ohio, USA; [5]Department of Dermatology, Duke University, Durham, North Carolina, USA; [6]Department of Dermatology, Albert Einstein College of Medicine, NY, NY, USA

Background. Cutaneous dermatomyositis (DM) is often refractory to multiple medications. Repository corticotropin injection (RCI) is FDA-approved for DM, but little is known about its efficacy and safety for treating cutaneous DM. We conducted a prospective, open-label trial assessing efficacy and safety of RCI for treatment of refractory cutaneous DM.
Methods. DM patients with moderate-to-severe cutaneous activity [Cutaneous Dermatomyositis Disease Area and Severity Index activity (CDASI-A)] >14 despite prior treatment with ³2 systemic agents were enrolled. Patients were required to meet EULAR/ACR idiopathic inflammatory myopathy classification criteria for DM. The other patient met criteria for 'probable' DM diagnosis. Patients were initiated on 80u RCI twice weekly for 6 months and were allowed to continue their current systemic DM treatment regimens at time of starting RCI if they had been on stable doses of medication(s) for ³12 weeks. Primary outcomes included significant decreases in CDASI-A and Physician's Global Assessment (PGA) scores at 6 months.
Results. Of nineteen patients enrolled, fifteen patients (11 females, 4 males) with DM (7 classic, 8 amyopathic) completed 6 months of RCI treatment. Patients were treated with a median 3.0 systemic medications prior to enrollment and were being treated with a median of 2.0 systemic medications at the time of study enrollment. Median baseline CDASI-A score was 19.0 and median PGA activity score was 2.5/10. Only one patient with classic DM had a baseline MMT-8 score <142 felt to be related to active myositis; no patient had elevated CK levels at time of enrollment. For patient-reported outcomes, baseline median patient global skin score (PtGSS) was 3.0/10 and median dermatology life quality index (DLQI) score was 7.0/10. At 6 months, there were statistically significant improvements in multiple outcome measures, including CDASI-A scores (median=10.0), PGA scores (median=0.8/10), PtGSS scores (median=7.0), and DLQI scores (median=2.0). Notably, the median decrease in CDASI-A scores was consistent with clinically meaningful improvements in both cutaneous DM activity and quality of life by 3 months, with further improvement seen at 6 months. Adverse effects were mild and there were no clinically significant laboratory abnormalities.
Conclusion. RCI treatment resulted in statistically significant and clinically meaningful improvement in cutaneous DM activity and quality of life. Our results suggest RCI is an effective, safe, and well-tolerated treatment for patients with refractory cutaneous dermatomyositis.

Extra-Muscular Organ Involvement

P-92

CHARACTERISTICS OF INTERSTITIAL LUNG DISEASE PROGRESSORS IN ANTISYNTHETASE AUTOANTIBODY-POSITIVE POPULATION

Beatrice Panuta[1], Ange Moukam Ngeuleu[1], Juliette Charbonneau[1], Caroline Vo[2], Éric Rich[2], Josiane Bourré-Tessier[1,2], Édith Villeneuve[2], Hélène Manganas[1,3], Andréanne Gauthier[1,3], Julie Morisset[1,3], Sabrina Hoa[1,2], Océane Landon-Cardinal[1,2]
[1]Department of Medicine, Université de Montréal, Montreal, QC, Canada; [2]Division of Rheumatology, Centre Hospitalier de l'Université de Montréal, Montreal, QC, Canada; [3]Division of Respirology, Centre Hospitalier de l'Université de Montréal, Montreal, QC, Canada

Background. Antisynthetase syndrome (ASS) is an autoimmune systemic disease characterized by interstitial lung disease (ILD), myositis, polyarthritis, Raynaud's phenomenon, dermatomyositis-like rash and mechanic's hands. ILD may also present with isolated antisynthetase-specific autoantibodies (AS-aAb) without other clinical features to diagnose ASS. The objective of this retrospective study was to compare the characteristics and evolution of patients with ILD and AS-aAb, with and without systemic manifestations of ASS.
Methods. Patients evaluated at the ILD Clinic with AS-aAb on myositis panel (Euroimmun) were included. Patients were classified as ASS if they had at least 1 other systemic manifestation(s) of ASS; others were stratified as interstitial pneumonia with autoimmune features (IPAF) and non-IPAF, according to 2015 European Respiratory Society/American Thoracic Society (ERS/ATS) criteria. ILD progression was defined according to Outcome Measures in Rheumatology (OMERACT) and ATS/ERS/Japanese Respiratory Society (JRS)/Asociacion Latinoamericana de Torax (ALAT) criteria.
Results. Seventy-one patients were identified, including 16 ASS, 7 IPAF and 48 non-IPAF. Anti-PL12, anti-PL7 and non-anti-PL12/7 aAb were found in 37%, 32% and 31% of patients, respectively. Mean age was 70 years, 86% were Caucasian and mean follow-up duration was 3.0 years. Non-IPAF patients presented more frequently with a usual interstitial pneumonia (UIP) pattern (59% *vs*. 17%, p=0.002) on chest CT scan. Male sex (75% *vs*. 57%), smoking history (83% *vs*. 65%), and moderate-severe ILD (40% *vs*. 33%) on CT scan were numerically higher in non-IPAF patients. Positive anti-Ro52-aAbs were more frequent in ASS patients (63% *vs*. 4%, p=0.0001). Immunosuppressants were used in 87%, 57% and 21% of ASS, IPAF and non-IPAF patients. Non-IPAF patients had more frequent ILD progression (64% *vs*. 33% (ATS/ERS/JRS/ALAT), p=0.03; 59% *vs*. 45% (OMERACT), NS). Oxygen-dependence (43% *vs*. 18%, NS), lung transplant (4% *vs*. 0%, NS) and death of pulmonary cause (11% *vs*. 5%, NS) were numerically more frequent in non-IPAF patients. Time from ILD diagnosis to oxygen-dependence was shorter in non-IPAF compared to ASS patients (4.8 *vs*. 8.1 years). Progressors were more frequently non-IPAF men with UIP pattern and moderate-severe ILD on CT scan.
Conclusion. In this AS-aAb-positive population, ILD progression was more frequent in non-IPAF patients compared to ASS or IPAF patients. Most non-ASS patients did not fulfill the IPAF criteria. Further study is required to identify progression predictors while accounting for treatments effect and confounding by indication.

P-93

SUBCLINICAL MYOCARDIAL INVOLVEMENT IN A COHORT OF PATIENTS WITH ANTISYNTHETASE SYNDROME

Albert Gil-Vila[1], Gemma Burcet-Rodriguez[2], Ernesto Trallero-Araguás[3], Hug Cuellar-Calabria[2], Albert Selva-O'Callaghan[1]
[1]Systemic Autoimmune Diseases, Internal Medicine, Vall d'Hebron University Hospital. Departament de Medicina, Universitat Autònoma de Barcelona, Barcelona, Spain; [2]Cardiovascular Imaging Area, Diagnostic Imaging Department, Vall d'Hebron University Hospital, Barcelona, Spain; [3]Rheumatology Department, Vall d'Hebron General Hospital, Barcelona, Spain

Background. Antisynthetase syndrome (ASS) is an autoimmune disease characterized by inflammatory myopathy, interstitial lung disease, arthritis, fever, mechanical hands, and Raynaud phenomenon. There is an increasing interest in knowing whether patients with ASS may have silent myocardial interstitial involvement. Mapping techniques in cardiac magnetic resonance (CMR) are capable of detecting subclinical myocardial involvement. The purpose of this study was to identify alterations in multiparametric CMR in patients with ASS.
Methods. This is a retrospective cross-sectional study of a cohort of patients with ASS visited in a single Myositis Unit. Patients diagnosed with ASS underwent a CMR along with the standard clinical workup, investigation of specific and associated myositis antibodies, high-resolution chest CT (HRCT) and the standard of care with corticoids and immunosuppressive drugs. The CMR protocol includes routine morphologic, functional, and late gadolinium enhancement sequences in cardiac planes, as well as native T1 and T2 mapping sequences, and repeat T1 sequences 7 minutes after the injection of a gadolinium-based contrast material, which allow for extracellular volume (ECV) calculation.
Results. Twenty-five patients were included in this study (56% women; median age 56,3 years). Three patients were considered in acute phase at the time of inclusion (CMR performed either at time of diagnosis or at the onset of disease flare-up). Eight patients (32%) showed pathological findings in CMR (6 stable disease, 2 acute phase). Elevated T1, T2 and ECV mapping values were found in 20% (5/25), 17% (4/25) and 24% (6/25) of the group, respectively. One stable patient had elevated T1 and T2 values, two patients had elevated T2 and ECV values, and another two had elevation of all three parameters. Two acute phase patients showed myocardial involvement. All patients with elevated ECV values also had T2 elevation. Mean T2 (55ms *vs*. 47.5ms, $p<0.05$) and ECV values (31.3% *vs*. 26.1%, $p<0.05$) were higher in the acute phase group. Overall, multiparametric involvement was more frequent (5/7, 71.4%) than elevation of a single mapping parameter (2/7, 28.6%).

Table I. Population characteristics and CMR values in stable disease and early stage

Variable	Stable disease (n=22)	Acute phase (n=3)	*p*-value (univariate)
Age, median (IQR), years	56,3 (48.6-67.2)	49,1(47.6-69.9)	0.499
CV risk factor, n (%)	8 (36.4)	1 (33.3)	1.000
Years of disease, median (IQR), years	4,5 (2.6-13.4)	1,3 (0-1,9)	0.31
ILD, n (%)	21 (95.5%)	3 (100%)	1.000
MSA			
Jo1, n (%)	17 (77.3%)	1 (33.3%)	
PL7, n (%)	1 (4.5%)	0	
PL12, n (%)	4 (18.2%)	0	
OJ, n (%)	0 (0%)	1 (33.3%)	
EJ, n (%)	0 (0%)	1 (33.3%)	
Ro52, n (%)	18 (81.8)	3 (100%)	1.000
IVS thickness, mean (SD), mm	10,3 (0.5)	11.0 (1.0)	0.604
LV volume, mean (SD), mL	116.0 (7.0)	157.0 (6.8)	**0.047**
LV volume/TBSA, mean (SD), mL/m^2	65.4 (4.2)q	80.0 (1.7)	0.218
LV function, mean (SD), %	64.1 (1.1)	59.3 (3.0)	0.151
RV volume, mean (SD), mL	125.2 (7.3)	179.7 (7.4)	0.013
RV volume/TBSA, mean (SD), mL/m^2	70.6 (4.2)	91.7 (2.0)	0.085
RV function, mean (SD), %	59.2 (1.0)	61.3 (7.7)	0.547
LGE (n=24), n (%)	2 (9.5%)	0 (0%)	1.000
T1, mean (SD), ms	1012.7 (6.6)	1033.3 (13.4)	0.279
Elevated T1 (>1050ms), n (%)	4 (18.2%)	1 (33.3%)	0.504
ECV (n=24), mean (SD), %	26,1 (0.7)	31.3 (1.2)	**0.008**
Elevated ECV (>30%), n (%)	2 (9.5%)	2 (66.7%)	0.061
T2, mean (SD), ms	47,5 (0.8)	55 (4.0)	**0.007**
Elevated T2 (>50ms), n (%)	4 (18.2%)	2 (66.7%)	0.133

In bold: statistically significant.
CMR: cardiac magnetic resonance; CV: cardiovascular; ILD: interstitial lung disease; IQR: interquartile range; IVS: interventricular septum; LV: left ventricle; RV: right ventricle; LGE: Late gadolinium enhancement; ECV: extracellular volume.

Conclusion. This study illustrates how subclinical myocardial involvement in ASS is not uncommon. Although its clinical significance is still not clear, other autoimmune diseases reveal that myocardial involvement led to a poor prognosis. Our results may suggest that immunosuppressive therapy administered for the main manifestations of the disease may benefit the patients avoiding the apparition of clinical manifestations caused by interstitial myocarditis. Whether CMR should be used to screen and monitor ASS patients warrants further study.
Acknowledgements. Vall d'Hebron investigators are supported by the Instituto de Salud Carlos III Grant PI22/00708 co-financed by the European Regional Development Fund (ERDF).

P-94

PROGRESSIVE PULMONARY FIBROSIS IN ANTISYNTHETASE SYNDROME: A SINGLE-CENTER STUDY

Irene Peralta-Garcia[1], Ann Mari Svensson[2], Antonella Notarnicola[1,3], Marie Holmqvist[3,4], Angeles S. Galindo-Feria[1,3], Lara Dani[1,3], Ingrid E. Lundberg[1,3], Maryam Dastmalchi[1,3]
[1]Division of Rheumatology, Department of Medicine, Solna, Karolinska Institutet, Stockholm, Sweden; [2]Department of Radiology, Karolinska University Hospital, Stockholm, Sweden; [3]Medical Unit Gastro, Dermatology and Rheumatology, Karolinska University Hospital, Stockholm, Sweden; [4]Clinical Epidemiology Division, Department of Medicine, Solna, Karolinska Insititutet, Stockholm, Sweden

Background. One of the principal contributors to myositis mortality is interstitial lung disease (ILD), which is the most prevalent manifestation in anti-synthetase syndrome (ASyS). The current treatment for ILD in ASyS (ASyS-ILD) involves high-dose glucocorticoids and immunosuppressants. Despite these, a subset of patients exhibits progression. In 2020 nintedanib, an anti-fibrotic medication, was approved in the context of ILD of progressive phenotype irrespective of etiology. However, the extent to which patients with ASyS-ILD develop progressive pulmonary fibrosis (PPF) remains unknown. The objective of this study was to ascertain the prevalence of PPF in ASyS-ILD.
Methods. We conducted a single-center retrospective study, encompassing individuals diagnosed with ASyS and positive ASyS antibodies (ASyS-Ab): anti-Jo1, anti-PL12, anti-PL7, anti-EJ, and/or anti-OJ. We identified patients classified as ASyS through the Swedish Myositis Network Register.
Results. We extracted information on presence of ASyS-ILD, latest pulmonary function tests, high-resolution thoracic computed tomography (HRCT) scans, and progression of respiratory symptoms from clinical records. For identification of PPF we employed the INBUILD study criteria[1] and the clinical practice guidelines established by international thoracic and respiratory clinical societies (CPG)[2]. An experienced thoracic radiologist reviewed the HRCT scans of individuals meeting the specified criteria to validate the presence of PPF.
We identified 167 patients with ASyS-Ab since 1981. We discarded 81 due to: no ILD (n=25), less than 1 year follow-up (n=21), or missing information (n=35). The final study population comprised 86 patients, 65% women, with a median age at disease onset of 58 years (IQR 20). The median duration from symptom onset to PPF criteria assessment was 6 years (IQR 8). The predominant autoantibody was anti-Jo1(n=61, 71%), followed by PL7 and PL12 (11% and 9% respectively). 41% (n=35) of patients were also positive for anti-Ro52 antibodies (8 of which were anti-Jo-1+). At end of follow-up, most were treated with Mycophenolate mofetil (n=26, 30%), Rituximab (n=9, 10%), or a combination of both (n=23, 27%). 54% of patients (n=41) received glucocorticoids at an equivalent or lower dose than 10 mg/day prednisone.
The predominating radiological findings in the latest CT scans indicated fibrotic changes (n=29, 34%) not conforming to the definition of Usual

Table I.

Characteristics of patients with anti-synthetase syndrome						
	Total	Classified by antibody status				
	n=86	PL7 (n=9)	PL12 (n=8)	Jo1 (n=61)	EJ (n=5)	OJ (n=3)
Women, n (%)	56 (65)	6 (67)	5 (63)	41 (67)	3 (60)	1 (33)
Median age at disease onset, yr (IQR)	58 (20)	57 (26)	61 (19)	56 (19)	72 (22)	61 (19)
Median time since disease onset at fibrosis evaluation, yr (IQR)	6 (8)	9 (19)	4 (3)	6 (8)	2 (10)	4 (6)
Patients meeting criteria for progressive fibrosis, n (%)						
INBUILD criteria	13 (15)	2 (22)	1 (12)	9 (14)	0 (0)	1 (33)
ATS/ERS/JRS clinical guideline	16 (19)	4 (44)	1 (12)	11 (18)	0 (0)	0 (0)
Time since disease onset at evaluation, yr (IQR)	9 (16)	-	-	-	-	

Interstitial Pneumonia followed by inflammatory Non-Specific Interstitial Pneumonia (n=18, 21%).
When applying the PPF classification criteria, 15% (n=13) met the INBUILD criteria and 19% (n=16) met the CPG (see Table I).
Conclusion. In our cohort of ASyS around 17% of patients fulfilled the criteria for PPF at some time during follow up.

References

1. FLAHERTY KR, WELLS AU, COTTIN V *et al.*: *N Engl J Med* 2019; 381(18): 1718-27.
2. RAGHU G, REMY-JARDIN M, RICHELDI L *et al.*: *Am J Respir Crit Care Med* 2022; 205(9): e18-e47.

P-95

EARLY CARDIOVASCULAR DISEASE RISKS IN IDIOPATHIC INFLAMMATORY MYOPATHIES: A TRINETX DATABASE ANALYSIS

Chih-Wei Tseng[1,2], Yi-Ming Chen[1,3,4,5,6,7], Latika Gupta[8,9,10]*
[1]Division of Allergy, Immunology and Rheumatology, Department of Internal Medicine, Taichung Veterans General Hospital, Taichung, Taiwan; [2]Department of Public Health, College of Medicine, National Cheng Kung University, Tainan, Taiwan; [3]School of Medicine, College of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan; [4]Department of Medical Research, Taichung Veterans General Hospital, Taichung, Taiwan; [5]Rong Hsing Research Center for Translational Medicine & Ph.D. Program in Translational Medicine, National Chung Hsing University, Taichung, Taiwan; [6]Department of Post-Baccalaureate Medicine, College of Medicine, National Chung Hsing University, Taichung, Taiwan; [7]Precision Medicine Research Center, College of Medicine, National Chung Hsing University, Taichung, Taiwan; [8]Department of Rheumatology, Royal Wolverhampton Hospitals NHS Trust, Wolverhampton, UK; [9]Division of Musculoskeletal and Dermatological Sciences, Centre for Musculoskeletal Research, School of Biological Sciences, The University of Manchester, Manchester, UK; [10]Department of Rheumatology, City Hospital, Sandwell and West Birmingham Hospitals NHS Trust, Birmingham, UK

Background. Cardiovascular disease (CVD) is the leading cause of mortality and has various presentations from atherosclerotic cardiovascular diseases (ASCVD) to inflammatory heart diseases such as pericarditis and myocarditis. Patients with Idiopathic inflammatory myopathies (IIM) may be at higher CVD risk though this hasn't been accurately substantiated. It is also unclear whether IIM is associated with a higher incidence of inflammatory heart disease.
Using the TriNetX database, we compared early (within 3 years of IIM diagnosis) ASCVD and inflammatory cardiac disease incidence in IIM versus healthy controls (HC) and diabetes mellitus (a CV risk equivalent). We also explored differences in inflammatory heart disease and ASCVD across different IIM subtypes.
Methods. 56,443 IIM cases from 1990 to 2023 were identified from 960,176 records using validated ICD codes, compared against 471,117 HCs and 684,197 diabetes mellitus patients. CVD outcomes included inflammatory heart disease (pericarditis, myocarditis), ASCVD (cerebrovascular complication, ischemic heart disease, peripheral vascular disease), venous thromboembolic disorders (VTE), Major Adverse Cardiovascular Events (MACEs), and mortality.
Results. Incident cardiovascular diseases were calculated using time-to-event analysis with propensity score (PS) matching (30 days to 3 years post-diagnosis) denoted by hazard ratios (HR). Covariates like age, gender, ethnicity, lifestyle (smoking, drinking), socioeconomic status, comorbidities, and laboratory tests were used for matching, focusing on IIM subtype (dermatomyositis-DM, polymyositis-PM, myositis with interstitial lung disease- ILD) differences. (Fig .1: After PS matching for all estimates).
Conclusion. IIMs exhibit significant early risks of CVD morbidity and mortality, with a greater burden of VTE risk, MACE, and mortality in myositis with the ILD group, calling upon stratification of group-specific risks to be a priority agenda for future research. The risks are commensurate or higher than diabetes mellitus, suggesting the need to classify IIM as a CV risk equivalent.

Table 1. CVD risks at 3-year after diagnosis compared with HC and diabetes mellitus

Outcome (3 year after diagnosis)	Hazard ratio (95% CI)		
	IIM vs HC (n=51,226)	Diabetes mellitus vs HC (n=205,581)	IIM vs diabetes mellitus (n=55,980)
(1) Inflammatory heart disease	7.09 (5.61,8.95)*#	2.07 (1.79,2.40)*	3.21 (2.69,3.84)*
(a) Pericarditis	6.86 (5.40,8.71)*#	2.14 (1.84,2.48)*	3.05 (2.55,3.65)*
(b) Myocarditis	15.96 (5.82,43.80)*	1.11 (0.59,2.10)	27.15 (6.65,110.82)*
(2) Arrhythmia	1.84 (1.75,1.94)*#	1.38 (1.34,1.43)*#	1.49 (1.42,1.57)*#
(3) ASCVD	1.97 (1.86,2.09)*#	1.85 (1.79,1.92)*#	1.35 (1.28,1.42)*
(a) Cerebrovascular complication	1.99 (1.84,2.16)*#	1.72 (1.64,1.81)*#	1.40 (1.30,1.50)*
(b) Ischemic heart disease	2.59 (2.35,2.86)*	2.25 (2.12,2.39)*#	1.55 (1.42,1.68)*
(c) Peripheral vascular disease	2.03 (1.85,2.22)*#	2.13 (2.02,2.26)*#	1.30 (1.20,1.41)*
(4) Venous thromboembolic disorder	4.80 (4.21,5.48)*#	1.62 (1.49,1.76)*#	2.92 (2.62,3.27)*#
(5) MACE	2.04 (1.92,2.16)*#	1.87 (1.81,1.94)*#	1.37 (1.29,1.44)*
(6) Mortality	2.49 (2.31,2.69)*#	2.33 (2.22,2.45)*#	1.47 (1.38,1.57)*

Table 2. CVD risks at 3-year after diagnosis compared with HC among different IIM subtypes

Outcome (3 year after diagnosis)	Hazard ratio (95% CI)		
	DM vs HC (n=14,824)	PM vs HC (n=5,801)	Myositis with ILD vs HC (n=2,613)
(1) Inflammatory heart disease	6.39 (4.03,10.11)*	9.52 (4.59,19.76)*	5.78 (3.13,10.67)*
(a) Pericarditis	6.35 (3.96,10.17)*	8.58 (4.12,17.87)*	5.77 (3.12,10.65)*
(b) Myocarditis	5.92 (1.33,26.46)	NA	NA
(2) Arrhythmia	1.80 (1.62,2.00)*#	1.98 (1.70,2.30)*#	3.09 (2.55,3.75)*
(3) ASCVD	1.85 (1.65,2.09)*#	2.21 (1.88,2.60)*	3.22 (2.60,3.97)*#
(a) Cerebrovascular complication	1.80 (1.53,2.11)*	2.50 (1.99,3.14)*	3.58 (2.71,4.73)*
(b) Ischemic heart disease	2.34 (1.92,2.84)*	2.62 (2.00,3.42)*#	4.40 (3.11,6.23)*
(c) Peripheral vascular disease	2.17 (1.81,2.61)*	2.35 (1.81,3.05)*	2.86 (2.07,3.94)*
(4) Venous thromboembolic disorder	4.33 (3.40,5.50)*	7.04 (4.62,10.72)*	7.09 (4.52,11.11)*
(5) MACE	1.87 (1.66,2.10)*#	2.68 (2.28,3.15)*#	3.65 (2.95,4.52)*
(6) Mortality	2.71 (2.34,3.14)*#	3.91 (3.18,4.81)*#	2.59 (2.08,3.23)*#

IIM: idiopathic inflammatory myositis: HC: healthy control; ASCVD: atherosclerotic cardiovascular disease; DM: dermatomyositis; DPM: dermatopolymyositis; PM: polymyositis; ILD: interstitial lung disease; MACE: Major adverse cardiovascular events; CI: Confidence interval; *p<0.001; #proportionality <0.01.
Propensity score matching with age at index, sex, race, social economic status, lifestyles, comorbidities, laboratory in all estimates.
ICD-10 codes for IIM with PPV 88.9% and Sensitivity 84.2% by Hannah et al. 2023.
Inclusion: M33.0, M33.1, M33.2, M33.9, M.36.0, M60.8, M60.9+ ILD (J99.1, J84.9 and J84.1), G72.4
Exclusion: D86.8, M60.0, M63.8, G71.0, G71.3, G72.0, G72.2, G73.7, G72.8, G72.9
ICD-10 codes for DM: M33.0, M33.1, M33.9
ICD-10 codes for PM: M33.2
ICD-10 codes for Myositis + ILD: M60.9+ ILD (J99.1, J84.9, and J84.1)
ICD-10 codes Inflammatory heart disease: Pericarditis: 130, 131, 132, Myocarditis: 140, 141, 151.4
ICD codes Arrhythmia: atrial fibrillation and flutter: 148, tachycardia: R00.0, 147; bradycardia: R00.1, 149.8, 149.5; ventricular arrhytmia: 149
ICD-10 codes ASCVD
Peripheral vascular disease: 170.8, 170.92, 173.89, 170.2, 173.9, 165.2
Aortic aneurysm and dissection: 171
Cardiac arrest: 146.9
Cerebrovascular disease: Stroke: 160-69, Transient ischemic attack: G45
Ischemic heart disease: 124, 121, 122, 125.5, 120
ICD-10 codes Venous thromboembolic disorders pulmonary embolism: 126, deep vein thrombosis: 180.1, 80.2, 181, 182.0, 82.2, 82.3, 82.4, 82.5, superficial vein thrombosis: 180.0, 80.3, 80.8, 80.9, 182.1, 82.6, 82.7, 82.8, 82.9.
ICD-10 codes Major adverse cardiac events (MACEs) myocardial infarction: 121-122, ischemic stroke: 163, 165, 166, 167.89, hemorrhagic stroke: 161-162, heart failure: 150, ventricular arrhythmia: 147.0, 147.2, 149.3, 149.0, sudden cardiac death: 146
All estimates were calculated after PS matching with all covariates. Table I shows the comparison of IIM *vs*. HC and diabetes mellitus while Table II shows the IIM subtypes *vs*. HC across different CVDs.
Expectedly IIM is associated with a higher incidence of inflammatory heart disease, especially myocarditis with a HR of 15.96 for compared to healthy controls (HC), particularly the latter which rises to an HR of 27.15 when compared to diabetes mellitus. Among IIM subtypes, PM exhibited the highest HR for inflammatory heart disease followed by DM and myositis with ILD. In terms of MACE, myositis with ILD had the highest HR (3.22), followed by PM and DM while mortality was highest in PM (HR 3.91). VTEs were higher, more so for PM and myositis with ILD groups (HR 7.04 and HR 7.09 respectively), and arrhythmia was more in myositis with the ILD group (HR 3.09).

P-96

ANTI-SRP IMMUNE-MEDIATED NECROTIZING MYOPATHY-ASSOCIATED INTERSTITIAL LUNG DISEASE

Ana Matas-García, Júlia Barriga i Marín, José C. Milisenda
Muscle Research Unit, Internal Medicine Service, Hospital Clínic de Barcelona, Barcelona, Spain

Background. Immune mediated necrotizing myopathies (IMNM) are a subgroup of idiopathic inflammatory myopathies (IIM) associated to the presence of muscle specific antibodies against signal recognition particle (SRP) and hydroxy-3-methylglutaryl-CoA reductase (HMGCR). SRP-IMNM mainly affects muscles, but extra-muscular involvement seems not to be as rare as previously reported in literature. We aim to describe the clinical characteristics of interstitial lung disease (ILD) in SRP-IMNM of our centre and medical literature.
Methods. We retrospectively analysed patients with SRP-IMNM-associated ILD in a tertiary hospital from May 2010 to May 2023. Reported cases from May 2010 to May 2023 were reviewed through PubMed and Cochrane.
Results. Among our cohort of patients with SRP-IMNM (n=12), three individuals were diagnosed with ILD at the onset, determined through lung imaging. These patients, all around the age of 70, exhibited initial symptoms of exertional dyspnea, symmetrical proximal weakness, and dysphagia, accompanied by elevated levels of serum muscle enzymes. High-resolution computed tomography (HRCT) showed predominant involvement in the lower lobes, with two main radiologic findings including usual interstitial pneumonia (UIP) progressing to nonspecific interstitial pneumonia (NSIP), ground-glass opacities (GGO) accompanied with interlobular septal, pleural thickening and reticulation. Pulmonary function tests (PFTs) indicated a mild to moderate severity of the condition. Following treatment with prednisone, immunosuppressors, and immunoglobulins, respiratory symptoms improved. One patient died during the follow-up period due to a severe pulmonary infection.
Conclusion. ILD in SRP-IMNM seems to be not as infrequent as described in previous studies, especially in older middle-aged patients with dysphagia. Asymptomatic and slowly progressive onset probably contributes to underdiagnosis. Therefore, HRCT and PFT should be performed at diagnosis of SRP-IMNM. The severity is believed to be mild to moderate in most patients. However, further studies are required to elucidate frequency and clinical characteristics of ILD in SRP-IMNM patients.

References

1. PINAL-FERNANDEZ I, CASAL-DOMINGUEZ M, MAMMEN AL: Immune-mediated necrotizing myopathy. *Curr Rheumatol Rep* 2018; 20(4): 21.
2. MARIAMPILLAI K, GRANGER B, AMELIN D *et al*.: Development of a New Classification System for Idiopathic Inflammatory Myopathies Based on Clinical Manifestations and Myositis-Specific Autoantibodies. *JAMA Neurol* 2018; 75(12): 1528-37.
3. ALLENBACH Y, MAMMEN AL, BENVENISTE O, STENZEL W; Immune-Mediated Necrotizing Myopathies Working Group: 224th ENMC International Workshop: Clinico-sero-pathological classification of immune-mediated necrotizing myopathies Zandvoort, The Netherlands, 14-16 October 2016. *Neuromuscul Disord* 2018; 28(1): 87-99.
4. MA X, BU BT: Anti-SRP immune-mediated necrotizing myopathy: A critical review of current concepts. *Front Immunol* 2022; 13: 1019972
5. SUZUKI S, NISHIKAWA A, KUWANA M *et al*.: Inflammatory myopathy with anti-signal recognition particle antibodies: case series of 100 patients. *Orphanet J Rare Dis* 2015; 10: 61.
6. KUSUMOTO T, OKAMORI S, MASUZAWA K *et al*.: Development of necrotizing myopathy following interstitial lung disease with anti-signal recognition particle antibody. *Intern Med* 2018; 57(14): 2045-49.
7. GE Y, YANG H, XIAO X, LIANG L, LU X, WANG G: Interstitial lung disease is not rare in immune-mediated necrotizing myopathy with anti-signal recognition particle antibodies. *BMC Pulm Med* 2022; 22(1): 14.
8. YANG HX, TIAN XL, JIANG W *et al*.: [Clinical and pathological characteristics of immune mediated necrotizing myopathy]. *Beijing Da Xue Xue Bao Yi Xue Ban* 2019; 51(6): 989-95.

P-97

CLINICAL CHARACTERISTIC OF PATIENTS WITH ANTI-SYNTHETASE SYNDROME ASSOCIATED WITH ANTI-Ro52 IN A TERTIARY HOSPITAL, MALAYSIA

Tara Mahadevan, Wendy Lee Wan Hui, Leela Raman, Ravathy Nasadurai, Norliza Zainudin, Malek Faris, Shereen Ch'ng Su Yin, Habibah Mohd Yusoof, Mollyza Mohd Zain
Rheumatology Unit, Hospital Selayang, Selangor, Malaysia

Background. Autoantibodies in inflammatory idiopathic myositis (IIM) are grouped into myositis specific antibodies (MSA) and myositis associated antibodies (MAA). Among the Myositis specific antibodies (MSA), antibodies against aminoacyl-tRNA synthetases (ARS) are related to Antisynthetase syndrome (ASS).
Anti-Ro52 which is among the MAA, has varied clinical significance in several autoimmune diseases including IIM.
Methods. Patients diagnosed with IIM and positive for myositis antibodies were recruited in the myositis cohort from January 2014 till November 2023. Retrospective analysis was performed based on the clinical data and high-resolution CT (HRCT) findings.
Results. Among 51 patients with IIM, 6 patients (11.8%) were positive for ARS autoantibodies. The most common ARS antibody was anti-EJ (n=3) followed by antiJo-1 (n=2). Anti-Ro52 was detected in 5 patients (83%) associated with ARS autoantibodies. Two cases, with positive anti Jo-1 and anti Ro52 presented with respiratory distress symptoms and prominent proximal muscle weakness (CK >1000) thus requiring IV Metylprednisolone 500mg od for three days duration. However, the second case, required cyclical IVIG due to refractory myositis despite a high dose of steroid. HRCT revealed nonspecific interstitial pneumonia (NSIP) pattern (>20%). Two positive anti-EJ cases (one Ro52 positive and another anti PM-ScL-75) showed NSIP Organising Pneumonia (OP) pattern with more than 20% lung involvement and clinical myositis (CK 1000-3500), whereas the third case showed less than 20% NSIP pattern and no associated clinical myositis. All three cases were steroid sensitive. One case of anti PL-12 associated with anti Ro52 showed rapidly progressive interstitial lung disease (ILD), requiring three cycles of IV Rituximab, despite being on an adequate dose of Mycophenolate Mofetil (MMF) and a low dose of steroid. HRCT revealed both NSIP and UIP patterns, thus requiring an antifibrotic agent. Raynaud's phenomenon was its only extra-muscular feature. ILD was commonly detected in this cohort (100%), followed by proximal myopathy (83%). Meanwhile arthritis was less frequently exhibited (1
Conclusion. Within the broad spectrum of antisynthetase syndrome, it is unclear as to what degree serology influences presentation and prognosis. ASS is commonly associated with ILD.
Anti Ro52 antibodies can lead to atypical clinical presentation.

Table I. Characteristics of patients with antisynthetase syndrome at Hospital Selayang.

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Age(diagnosed)	51 (2022)	40 (2014)	41 (2023)	33 (2022)	54 (2023)	23(2021)
Gender	Male	Female	Male	Female	Male	Female
Ethnicity	Punjabi	Malay	Malay	Malay	Chinese	Malay
CK value	1200	2943	1875	3579	336	307
HRCT	OP pattern (>20%)	NSIP pattern (>20%)	OP pattern (>20%)	OP pattern (>20%)	NSIP (<20%)	NSIP & UIP (>20%)
MSA/MAA	Anti Jo-1 Anti Ro52	Anti Jo-1 Anti Ro52	Anti-EJ Anti-Ro52	Anti-EJ Anti PM-SCL75	Anti-EJ Anti Ro52	Anti-PL12 Anti Ro52
ANA	negative	positive	negative	negative	negative	1:640
Steroid	MTP 500mg OD x3/7 → prednisolone tapering dose	MTP 500mg OD x3/7 → prednisolone tapering dose	MTP 500mg OD x3/7 → prednisolone tapering dose	Tapering prednisolone	Tapering prednisolone	MTP 500mg OD x3/7 → prednisolone tapering dose
Immunosuppressants	Azathioprine 100mg od	IVIG ⬇ MMF	MMF 1gm bd	Azathioprine	MMF 750mg bd	MMF 1gm bd ⬇ Rituximab -3 cycles ⬇ Nintedanib April 2024
Clinical myositis	Proximal myopathy	Proximal myopathy	Proximal myopathy	Proximal myopathy	Negative	Proximal myopathy
Arthritis	Yes	No	No	No	No	No
Extra-muscular involvement	ILD Mechanic Hands	ILD	ILD Mechanic hands	ILD	ILD	ILD Raynaud's Phenomenon
Lung Function Test	FEV1: 1.61 (47%) FVC: 1.9 (44%)	FVC: 1.5L (65%) FEV1:1.34L (67%) FEV1/FVC: 110%	-	-	-	FVC: 1.03L (38%) FEV1:1.03L (34%) FEV1/FVC: 100%
Outcome	Alive	Demise - 2019 (TB death)	Alive	Alive	Alive	Alive On LTOT

P-98

CLINICALLY RELEVANT VENOUS THROMBOEMBOLISM EVENTS OCCURING DURING ANTI-SYNTHETASE SYNDROME: A CASE SERIES

Laure Gallay[1,2], Arnaud Hot[1], Margherita Giannini[3], Emilie Berthoux[4], Audrey Gorse[5], Nathalie Streichenberger[2], Lola Lessard[6], Alain Meyer[3], Vincent Cottin[7]

[1]Service de Médecine Interne, Pavillon O, Hôpital Edouard Herriot, Hospices Civils de Lyon, Lyon, France; [2]Service d'Anatomopathologie, Groupement Hospitalier Est, Hospices Civils de Lyon, Lyon, France; [3]Service de Rheumatologie, CHRU de Strasbourg, Strasbourg, France; [4]Service de Médecine Interne, Hôpital Saint Luc Saint Joseph, Lyon, France; [5]Service de Médecine Interne et Maladies Infectieuse, Centre Hospitalier Metropole Savoie, Chambery, France; [6]Service d'Electroneuromyographie et de Pathologies Neuromusculaires, Hôpital Neurologique, GHE, Hospices Civils de Lyon, Lyon, France; [7]Service de Pneumologie, Groupement Hospitalier Est, Hospices Civils de Lyon, Lyon, France

Background. Thromboembolism is a rare complication of inflammatory myopathies and has been scarcely reported in association with dermatomyositis and polymyositis. The present work aims to report a descriptive case series of patients with anti-synthetase syndrome (ASyS) presenting clinically relevant venous thromboembolic events.
Methods. Patients with anti-synthetase syndrome who presented at least one significant venous thromboembolic event (VTE) were identified in the clinical practice of Lyon University Hospital. Inclusion criteria were: ASyS auto-antibodies associated with at least myositis or interstitial lung disease; and at least one VTE attested by dedicated imaging, occurring during the course of the auto-immune disease. Medical records of all included patients were retrospectively reviewed to assess the chronology of such association, collect the VTE characteristics, and the ASyS-associated clinical phenotype.
Results. The present retrospective study reported 7 cases of ASyS patients who had presented VTE during the ASyS course. The mean age of onset of the ASyS was 63 years old; with a male ratio of 0.75. Patient's ASyS antibodies were: anti-Jo1 (n=2), anti-PL7 (n=2), anti-PL12 (n=2), and anti EJ (n=1). The VTE occurred during the initial part of the disease (defined as the first year of ASyS symptoms) for 4 cases, while for the 3 other patients the VTE occurred during a relapse of the disease. Six patients had pulmonary embolism (6/7, 86%), one had proximal venous thrombosis of lower limbs (1/6, 17%). Two patients developed pulmonary hypertension considered as secondary to the pulmonary embolism. Four patients had initially elevated C-reactive protein (CRP), and 3 had abnormal coagulation profile. No other VTE risk factor (obesity, neoplasia, hereditary coagulation disorders, immobility, surgery, hormonotherapy). No patients were currently smoking at time of VTE diagnosis, while 2 had smoked in the past (weaning up to 6 and 15 years). One patient was receiving intravenous immunoglobulins at the time of VTE occurrence.
Conclusion. The present work reports that VTE, and notably acute pulmonary embolism, is an early event during the course of ASyS and seems to be related to the disease activity. This highlights that VTE needs to be investigated at time of diagnosis and in case of ASyS worsening.

P-99

SEVERE INTERSTITIAL LUNG DISEASE IN PATIENTS WITH ANTI-SIGNAL RECOGNITION PARTICLE ANTIBODY: A CASE SERIES

Komal Mushtaq[1], Kinanah Yaseen[1], Sameep Sehgal[2], Aditi Patel[1]

[1]Department of Rheumatology, Cleveland Clinic; [2]Department of Pulmonary Critical Care, Cleveland Clinic, Cleveland, USA

Background. Immune mediated necrotizing myopathy (IMNM) associated with anti-Signal Recognition Particle (SRP) antibody (Ab) is often characterized by severe muscle weakness, muscular atrophy, and dysphagia. Interstitial lung disease (ILD) is an uncommon presentation and is usually mild. This case series reports clinical and serological features of patients with positive anti-SRP Ab and ILD.
Methods. We retrospectively analyzed three patients with positive anti-SRP Ab and ILD, detected in our hospital. We collected demographic, clinical, and treatment date from time of presentation.
Results. Three patients, with a median age of 63 years, presented with severe ILD with positive anti-SRP Ab (Table 1). Patient one presented with hypoxic respiratory failure requiring 10-liters (L) supplemental oxygen (O2), Chest CT demonstrated diffuse ground glass opacities and lower lobe fibrotic changes. Serology was positive for anti-SRP Ab and anti-RNP Ab. No extrapulmonary features or muscle involvement were identified. Her ILD improved with corticosteroids (CS) and mycophenolate mofetil (MMF). Patient two presented with progressive respiratory failure, requiring 10L supplemental 02. Chest CT with fibrotic nonspecific interstitial pneumonitis (NSIP) pattern. Serology with positive ANA, anti-SRP Ab, and Anti-SSb. Despite treatment with CS, MMF and pirfenidone, he developed progressive disease, requiring listing for lung transplantation. No extra pulmonary features or muscle involvement was seen. Patient three presented with myositis with hypoxic respiratory failure and dysphagia. Chest CT with fibrotic NSIP pattern concomitant severe muscle disease and necrotizing myopathy on biopsy. Treated with methotrexate, azathioprine without response eventually started on MMF, intravenous immunoglobulin, and rituximab with clinical improvement. Clinical features and treatment outcomes are listed in Table I.
Conclusion. Severe ILD leading to respiratory failure can be a manifestation of Immune mediated myositis associated with anti-SRP Ab, occasionally without muscle disease.

Table I.

	Patient 1	Patient 2	Patient 3
Age/Sex/Race	42/Female/African American	63/Male/Caucasian	69/Female/African American
Co-morbidities	Pulmonary Hypertension (HTN)	Coronary Artery Disease Pulmonary HTN	Coronary Artery Disease
Presenting symptoms	Dyspnea, myalgias, arthralgia, facial rash	Dyspnea, arthralgia	Muscle weakness, dyspnea, dysphagia
Pulmonary Manifestations			
Chest CT	Bilateral, diffuse, GGO	Bilateral, lower lobe predominant fibrotic changes, with GGO	Bilateral, lower lobe predominant fibrotic changes
Forced Vital Capacity (Lit/% predicted	1.18/34.7%	4.2/50%	1.46/54.1%
DLCO (% predicted)	29.5%	33%	50.8%
Oxigen needs	10 Liters	10 Liters	Mechanical ventilation
Muscle Manifestations	Myalgia	Myalgia	Muscle weakness
Muscle Weakness	No	No	Yes
Peak CK (IU)	206	90	~14000
Concomitant Antibody	Anti-Bibonucleoprotein Ab	Antinuclear antibody and Anti-SS-B (La) Ab	None
Muscle biopsy findings	Not available	Not available	Necrotizing myositis
DLCO-Diffusion Capacity of Lungs for carbon monoxide, GGO-Groud glass opacities.			
Treatment History	MMF, Prednisone	MMF, Pirfenidone and Prednisone	Methotrexate, Azathioprine MMF IVIG, Rituximab and Prednisone
Response to therapy	Yes	No	Yes
Improvement in PETs	Yes	No	Yes
% Change in FVC	+31%	-12%	+19%
Improvement in DLCO	Yes (+18%)	Yes (+4%)	No change
CK improvement	Not applicable	Not applicable	Yes

P-100

ANTI-PL7 IS ASSOCIATED WITH A GREATER EXTENT OF THE FIBROTIC COMPONENT IN PATIENTS WITH INTERSTITIAL LUNG DISEASE

Daphne Rivero-Gallegos[1], Mayra Mejía[1], Héctor I. Rocha-González[2], Juan C. Huerta-Cruz[3], Ramcés Falfán-Valencia[4], Espiridion Ramos-Martínez[5], Heidegger N. Mateos-Toledo[2], María F. Castillo-López[1], Yeimi K. Rodríguez-Torres[1], Valeria Lira-Boussart[1], Jorge Rojas-Serrano[1,6*]

[1]Interstitial Lung Disease and Rheumtology Unit , Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas, Mexico City, Mexico; [2]Postgraduate Studies and Research Section, Escuela Superior de Medicina, Instituto Politécnico Nacional, Mexico City, Mexico; [3]Laboratory of Clinical Pharmacology, Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas, Mexico City, Mexico; [4]HLA Laboratory, Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas, Mexico City, Mexico; [5]Unidad de Investigación en Medicina Experimental, Facultad de Medicina, Universidad Nacional Autónoma de México, Mexico City, Mexico; [6]Program of Masters and PhD in Medical Sciences, School of Medicine, Universidad Nacional Autónoma de México, Mexico City, Mexico

Background. In antisynthetase syndrome (ASSD), the antibody subtype influences clinical phenotype and survival. Anti-PL7 and anti-PL12 antibodies are associated with lower survival rates than anti-Jo1. So far, the cause of the increased mortality in these patients has not been explained. One possible explanation is a higher severity of ILD, with a higher extent of the fibrotic component. Although it has been described that anti-PL7 and anti-PL12 may have a higher degree of the fibrotic component of ILD, a direct comparison of the extent of the fibrotic component between the different subtypes of anti-ARS has not been performed. Due to the background, this study aims to evaluate whether anti-PL7 and anti-PL12 autoantibodies are associated with a greater extent of the fibrotic component of ILD in ASSD patients.

Methods. Patients with ILD-ASSD positive for one of the following autoantibodies: anti-Jo1, anti-PL7, anti-PL12, and anti-EJ were included. Clinical manifestations, CPK, pulmonary function test, and HCRT assessment according to Goh Index were prospectively collected. The fibrotic, inflammatory, and overall extension of the Goh index and DLCO were assessed by multiple linear analyses and compared between ASSD antibody subgroups.

Results. Sixty-six patients were included; seventeen were positive for Jo1 (26%), seventeen for PL7(26%), twenty for PL12 (30%), and 9 (14%) for anti-EJ. The anti-PL7 and anti-PL12 had a more extensive fibrotic component than the anti-Jo1 patients and even a higher frequency of antifibrotic therapy consumption. Anti-PL7 positivity was associated with a 7.8% increase in fibrotic extent and greater severity of ILD with a reduction of 4.46 ml/min/mmHg. These observations were confirmed after adjusting for confounding factors; however, the association between anti-PL12 and fibrosis extent was not statistically confirmed.

Conclusion. Anti-PL7-positive ASSD patients had more extensive fibrosis and severe ILD than the anti-Jo1 subgroup; this information is clinical. This information is clinically useful and has significant implications for managing these patients, suggesting the need for early consideration of concurrent immunosuppressive and antifibrotic therapy.

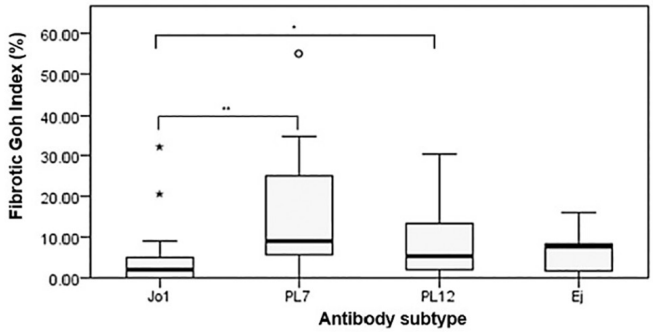


Fig. 1. The fibrotic component according to antibody subtype in antisynthetase syndrome. The boxplot's lower side represents the first quartile,the center lines represent the median, and the upper part of the box represents the third quartile. The lower whisker shows the minimum value of the data, and the upper whisker shows the maximum value. Extreme outlier values between the 95th and 99th percentiles are shows as black asterisks, and extreme outlier values higher than the 99th percentiles are shown as black circles. Statistically different concerning jol with a *p<0.05 or **p<0.01, by Kruskal-Wallis followed by Dunn's test.

References

1. GALINDO-FERIA AS, NOTARNICOLA A, LUNDBERG IE, HORULUOGLU B: Aminoacyl-tRNA synthetases: on anti-synthetase syndrome and beyond. *Front Immunol* 2022 May 13 [cited 2023 Sep 16]; 13.
2. GHIRARDELLO A, DORIA A: New insights in myositis-specific autoantibodies. *Curr Opin Rheumatol* 2018 Nov 1 [cited 2023 Sep 16]; 30(6): 614-22.
3. CAVAGNA L, TRALLERO-ARAGUÁS E, MELONI F *et al*.: Influence of antisynthetase antibodies specificities on antisynthetase syndrome clinical spectrum time course. *J Clin Med* 2019 Nov 1 [cited 2023 Sep 16]; 8(11).
4. OPINC AH, MAKOWSKA JS: Antisynthetase syndrome – much more than just a myopathy. *Semin Arthritis Rheum* 2021; 51(1): 72-83
5. GONZÁLEZ-PÉREZ MI, MEJÍA-HURTADO JG, PÉREZ-ROMÁN DI *et al*.: Evolution of pulmonary function in a cohort of patients with interstitial lung disease and positive for antisynthetase antibodies. *J Rheumatol* 2020 Mar 1.
6. AGGARWAL R, CASSIDY E, FERTIG N *et al*.: Patients with non-Jo-1 anti-tRNA-synthetase autoantibodies have worse survival than Jo-1 positive patients. *Ann Rheum Dis* 2014 Jan.
7. PINAL-FERNANDEZ I, CASAL-DOMINGUEZ M, HUAPAYA JA *et al*.: A longitudinal cohort study of the anti-synthetase syndrome: increased severity of interstitial lung disease in black patients and patients with anti-PL7 and anti-PL12 autoantibodies Rheumatology key messages. *Rheumatology* 2017.

P-101

SURGICAL EXCISION FOR CALCINOSIS CUTIS IN DERMATOMYOSITIS: EXPLORING EFFECTIVENESS, OUTCOMES, AND COMPLICATIONS

Tara Fallah Rastegar[1], Jemima Albayda[1], Adam Levin[3], Andrew L. Mammen[2], Lisa Christopher-Stine[1]

[1]Department of Medicine, Division of Rheumatology, Johns Hopkins University, School of Medicine, Baltimore, Maryland, USA, [2]National Institutes of Health, Bethesda, Maryland, USA, [3]Department of Orthopaedic Surgery, Johns Hopkins University, Baltimore, Maryland, USA

Background. Dermatomyositis is an autoimmune disorder characterized by muscle weakness and skin involvement, including the development of calcinosis. Although various treatment modalities have been attempted, there is limited evidence regarding the optimal medical management of calcinosis in patients with dermatomyositis, and there is a lack of evidence regarding the effectiveness of surgical excision of calcinosis cutis. This case series aims to explore the effectiveness and outcomes of surgical intervention for calcinosis cutis in patients with dermatomyositis.

Methods. We conducted a retrospective analysis of six patients in longitudinal our cohort diagnosed with dermatomyositis and associated calcinosis who underwent surgical excision. The patient selection process was at the discretion of the treating physician, based on the comfort of the patient to pursue surgical removal. Clinical and demographic data were collected, including patient age, gender, duration of disease, extent and location of calcinosis, previous treatments, and autoantibody association. Specifics about the surgical intervention were also provided.

Table I.

Patient	Age	Sex	Disease duration (yrs)	Associated Autoantibody	Current Treatments	No. of surgeries	Surgical site of calcinosis	Postoperative surgical complication	Treatment
1	65	F	27	MDA5	Tofacitinib, Corticosteroids	5	Right elbow, L/R pelvic, L/R thigh	Wound infection and dehiscence, hematoma	Clindamycin, debridement
2	40	F	16	Anti-NXP2	IVIG, Rituximab	3	L/R thigh, Abdomen	Wound infection	Linezolid, Cephalexin, and I&D
3	55	F	9	Anti- NXP2	None	1	Left hip	Hematoma, septic shock	IV antibiotics
4	37	M	34	Anti-Ro	Methotrexate	6	Left elbow L/R thigh Popliteal Left shoulder/ axillary area	None	
5	70	F	17	Anti-NXP2	Corticosteroids, Methotrexate	2	Buttock Right thigh	Wound infection Complex wound closure	Ciprofloxacin
6	47	F	14	Anti-NXP2	IVIG, Corticosteroids Methotrexate	2	Inner thigh and Abdomen	None	

Results. The mean age was 52.3 years, and the patients were predominantly female (5 females and 1 male). The mean duration of dermatomyositis at the time of the surgery was 19.5 years and most were anti-NXP2 positive. Calcinosis removal was performed in multiple sites. The average number of calcinosis surgeries per patient was 3.2. Postoperative wound care consisted of appropriate use of antimicrobial agents and incision and drainage. Complications after surgery were observed in 4 patients. The most common complication was wound infection. (Table I).
Conclusion. In conclusion, surgical excision for calcinosis cutis in dermatomyositis patients showed variable outcomes and notable complications, particularly wound infections. Careful patient selection and close postoperative monitoring are crucial to mitigate risks. Further research is needed, including larger prospective studies to establish evidence-based guidelines for surgical management of calcinosis in patients with dermatomyositis.

P-102

HAND RADIOGRAPHS LESIONS IN ANTISYNTHETASE SYNDROME ARTHRITIS VERSUS RHEUMATOID ARTHRITIS: A MONOCENTRIC CASE CONTROL CROSS-SECTIONAL STUDY

Margherita Giannini[1], Cerise Guillochon-Petitcuenot[2], Thibault Willaume[3], Guillaume Bierry[3], Julien Blaess[4], Giulia Quiring[5], Simone Perniola[6], Julien Campagne[7], Bernard Geny[8], Alain Meyer[9]
[1]Service de Physiologie et explorations fonctionnelles; Centre de Référence des Maladies Autoimmunes Rares, University Hospital of Strasbourg; UR3072, Centre de Recherche en Biomédecine, University of Strasbourg, France; [2]Service de Rhumatologie, Centre de Référence des Maladies Autoimmunes Rares, University Hospital of Strasbourg, France; [3]Service de Radiologie, University Hospital of Strasbourg, France; [4]Service de Physiologie et explorations fonctionnelles, University Hospital of Strasbourg, France; [5]UR3072 Centre de Recherche en Biomédecine, University of Strasbourg, France; [6]Clinical Immunology Unit, Fondazione Policlinico Universitario A. Gemelli-IRCCS, 00168, Roma, Italy; [7]Internal Medecine, UNEOS Metz, France; [8]Service de Physiologie et explorations fonctionnelles, University Hospital of Strasbourg; UR3072, Centre de Recherche en Biomédecine, University of Strasbourg, France; [9]Service de Physiologie et explorations fonctionnelles; Service de Rhumatologie, Centre de Référence des Maladies Autoimmunes Rares, University Hospital of Strasbourg; UR3072, Centre de Recherche en Biomédecine, University of Strasbourg, France

Background. Arthritis occurs in up to 90% of patients with antisynthetase syndrome (ASyS). It is a hallmark of this disease and is associated with poor quality of life. Peculiar hand radiographs patterns have been described in rheumatoid (RA) and psoriasis arthritis. Whether ASyS arthritis is also characterised by typical hands radiographs lesions has been poorly studied. The aim of this study was to assess the hand radiographs findings of ASyS arthritis versus RA.
Methods. A systematic literature review (SLR) was performed to retrieve candidate lesions on hand radiographs. All ASyS patients with arthritis and available hand radiographs were included. Consecutive RA patients of the same centre, matched for age, sex and disease duration, were included as controls. ASyS was defined by Connors' criteria and anti-CCP and rheumatoid factors negativity. RA was diagnosed according to 2010 ACR/EULAR criteria and ASyS antibodies negativity. Arthritis was defined by clinical and/or sonographic synovitis of small joints (with or without large joints involvement). The last available hand radiographs were read by two rheumatologists and one radiologist blinded for the diagnosis. Candidate lesions identified in the SLR (bone erosions, joint narrowing, joint subluxations and capsular calcifications) were quantified on both hands fingers and carpal joints as described by Sharp (1).
Results. Forty ASyS patients (30 females, 75%) and fifty-four RA patients (34 females, 62.3%), age of 55 (±14.1) and 60.4 (±14.1) years respectively (p=0.1), were included. Disease duration at the hand radiographs time was 5.1 (±6.6) and 7.2 (±6.5) years respectively (p=0.1). Hand radiographs lesions were found in 21 ASyS patients (47%) including bone erosions (n=4), joint narrowing (n=16), joint subluxations (n=13) and capsular calcifications (n=13). In ASyS, the capsular calcification score was 7-fold higher than in RA [4 ± 8 *vs*. 0.6±1.4, p=0.003]. The DIP joint of the second and the third fingers were the most frequently involved. Subluxation score was not significantly different [0.9 ± 2.1 *vs*. 1.8±4.3, p=0.2]. In ASyS, subluxations mainly involved the distal joints and the thumb. In contrast, the joint narrowing score was about 7 times lower [3.6±7.4 *vs*. 24.5±28.9, p=0.0001] while bone erosion score was more than 20-fold lower [0.4±1.8 *vs*. 9.2±17.3, p=0.001] in ASyS (Fig. 1).
Conslusion. Capsular calcinosis and joint subluxations of distal joints and thumb are hallmarks of ASyS arthritis supporting it as a peculiar rheumatic disease, part of the syndrome.

Reference

1. SHARP JT *et al*.: How many joints in the hands and wrists should be included in a score of radiologic abnormalities used to assess rheumatoid arthritis? *Arthritis Rheum* 1985; 28(12): 1326-35

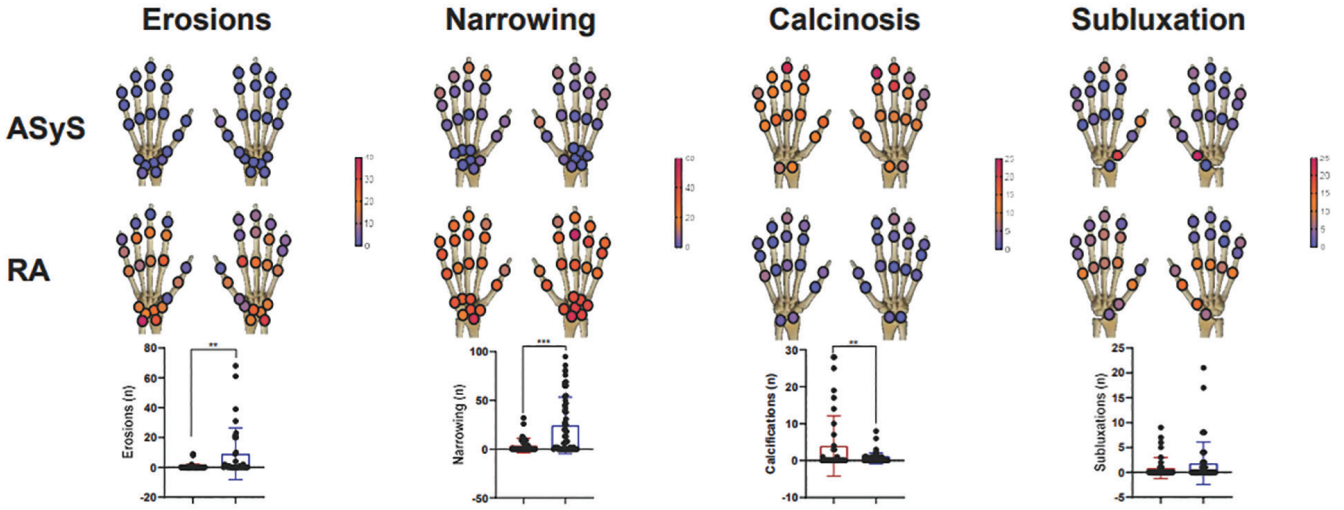


Fig. 1.

P-103

RENAL INVOLVEMENT IN INFLAMMATORY MYOPATHIES: A RETROSPECTIVE ANALYSIS OF A MONOCENTRIC COHORT

Pablo Diaz[1], Jerôme Olagne[2], Laure Gallay[3], Margherita Giannini[4], Alain Meyer[5]
[1]Service de Rhumatologie, Centre de Référence des Maladies Autoimmunes Rares, University Hospital of Strasbourg, France; [2]Département de Néphrologie, University Hospital of Strasbourg, France; [3]Service de Médecine Interne et immunologie clinique, Centre Hospitalier Universitaire Edouard Herriot, Hospices Civils de Lyon, Lyon, France; Laboratoire Cell therapy & musculoskeletal disorders, Université de Genève, Genève, Suisse; [4]Service de Physiologie et explorations fonctionnelles; Centre de Référence des Maladies Autoimmunes Rares, University Hospital of Strasbourg; UR3072, Centre de Recherche en Biomédecine, University of Strasbourg, France; [5]Service de Physiologie et explorations fonctionnelles; Service de Rhumatologie, Centre de Référence des Maladies Autoimmunes Rares, University Hospital of Strasbourg; UR3072, Centre de Recherche en Biomédecine, University of Strasbourg, France

Background. Inflammatory myopathies (IM) are heterogeneous autoimmune diseases affecting skeletal muscle, but also other organs such as lung, joints and skin. Renal involvement, which is widely described in other connective tissue diseases, has been poorly reported in IM.
Methods. Among the 673 patients with IM according to the ACR/EULAR 2017 criteria followed at the Referral Centre for Rare Systemic Autoimmune Diseases in Strasbourg, France, patients with renal involvement (defined as proteinuria >0.3 g/d and/or haematuria >10 red blood cells/mm^3 and/or leukocyturia >10 white blood cells/mm^3 and/or glomerular filtration rate (GFR) <90 ml/min AND abnormalities at renal biopsy) were studied. Patients with renal impairment not related to IM were excluded.
Results. Fifteen patients with IM and renal involvement were identified. Two patients were excluded: 1 with diabetic nephropathy, 1 with AL amyloidosis complicating myeloma. Thus, 13 patients with renal involvement without other causes were included (2%). The sex ratio (F:M) was 7:6 and the median age at IM diagnosis was 57 years [15-74]. Seven patients had muscle weakness, 7 myalgia. The median CK level was 1240 IU/L [123-5700]. All patients had extra-muscle and extra-renal involvement: interstitial lung disease (n=8, 62%), skin rash (n=7, 54%), joint involvement (n=7, 54%), Raynaud's phenomenon (n=7, 54%), neurological involvement (n=3, 23%), dry syndrome (n=2, 15%), pre-capillary pulmonary arterial hypertension (n=1, 8%), gastroesophageal reflux (n=1, 8%). No patient had cancer within 3 years of diagnosis. Most patients (n=8/13, 62%) had IM-associated autoantibodies (anti-PM/Scl n=3, anti-Ku n=2, anti-U1-RNP n=1, anti-MDA5 n=1, anti-Jo1 n=1). The most common subgroup was scleromyositis (n=8, 62%). The other subgroups were dermatomyositis (n=3, 23%), antisynthetase syndrome (n=1, 8%), unclassified myositis (n=1, 8%). The median time from IM diagnosis to renal involvement onset was 1 month [10 years before - 17 years after]. Renal involvement was heterogeneous, with 4 cases of minimal change disease (1 associated to AA amyloidosis), 2 extramembranous glomerulonephritis, 1 IgA nephropathy, 1 isolated AA amyloidosis, 4 thrombotic microangiopathy, and 1 glomerular ischaemia. At diagnosis of renal impairment, proteinuria was > 0.3g/d in 12 cases with a median of 1.91g/d [0.35-6] and GFR was impaired in 9 cases with a median of 29ml/min [12-75]. The prognosis was critical: 7 cases progressing to end-stage chronic kidney disease (6 haemodialysis, 0 renal transplantation) or death.
Conclusion. Kidney involvement is a rare and severe complication of IM. Scleromyositis[1] patients have an increased risk to develop this complication.

Reference

1. GIANNINI M, ELLEZAM B, LECLAIR V *et al*.: Scleromyositis: a distinct novel entity within the systemic sclerosis and autoimmune myositis spectrum. Implications for care and pathogenesis. *Front Immunol* 2023; 13: 974078.

P-104

PREVALENCE AND PROGNOSTIC FACTORS OF CARDIAC INVOLVEMENT ASSESSED BY MAGNETIC RESONANCE IMAGING IN PATIENTS WITH IDIOPATHIC INFLAMMATORY MYOPATHIES

Kateryna Yurchenko[1], Pil Højgaard[2], Redi Pecini[3], Axel C.P. Diederichsen[5], Jesper Lindhardsen[1], Eva Søndergaard[5], Amalie Dahl Haue[3], Kasper Søltoft[4], Sine Søndergaard Korsholm[4], Søren Jacobsen[1], Louise P. Diederichsen[1,4]
[1]COPEACT, Center for Rheumatology and Spine Diseases, Copenhagen University Hospital, Rigshospitalet, Denmark; [2]Department of Internal Medicine, Clinic of Rheumatology, Holbæk Hospital, Denmark; [3]Department of Cardiology, Copenhagen University Hospital, Rigshospitalet, Denmark; [4]Department of Rheumatology, Odense University Hospital, Denmark; [5]Department of Cardiology, Odense University Hospital, Denmark

Background. Cardiac involvement, alongside a higher prevalence of malignancies, is the main cause of mortality in IIM patients. Unfortunately, cardiac symptoms often go unnoticed, leading to delayed diagnosis. Subclinical myocardial inflammation appears to play a central role, contributing to structural changes, myocardial dysfunction, and conduction disturbances. Hence the aim of this study was to investigate myocardial inflammation in established and stable patients with idiopathic inflammatory myopathies (IIM) and its comparison among IIM subtypes and healthy controls using cardiac MRI (CMRI), with an emphasis on T1 and T2 mapping.
Methods. From January 2018 to October 2018, 55 patients with stable IIM were consecutively enrolled in this observational cross-sectional study. All patients underwent clinical examination, blood tests, antibody profiling, electrocardiography, and cardiac MRI. Association analyses were conducted to explore relations between abnormal T1 and T2 values and various cardiac- and IIM-related outcomes. Due to the distinct demographic and clinical features of patients with inclusion body myositis (IBM), CMRI findings were analysed separately for IBM, other IIM types, and healthy controls. A control group of 19 healthy participants underwent CMRI examinations including T1 and T2 mapping. Pathological T1 and T2 values were defined as values exceeding the 95th percentile in the control group, with thresholds of 1055 msec for native T1 and 56.05 msec for T2 mapping.
Results. Abnormal T1 values were observed in 9.1% of IIM patients, displaying significantly higher T1 values compared to healthy controls. Furthermore, T2 values were elevated in 16.4% of IIM patients, with significantly higher values detected among non-IBM patients in contrast to those with IBM. However, association analyses did not identify any apparent correlation between T1 or T2 values and measures related to cardiac or disease characteristics in the present cohort of established and stable IIM patients.
Conclusion. Our study reveals that up to 16.4% of non-IBM IIM patients exhibit pathological T1 and T2 values compared to healthy controls, whereas elevated T1 and T2 values on CMRI are rare in IBM patients. These findings highlight the usefulness of CMRI assessment to detect subclinical heart involvement in IIM patients. However, prospective studies are needed to determine whether CMRI holds any prognostic value regarding cardiac involvement in patients with IIM.

OP-15

INVESTIGATING ESOPHAGEAL INVOLVEMENT IN ANTISYNTHETASE SYNDROME: HOW TO DISCOVER THE SUBMERGED?

Linda Carli[1], Federico Fattorini[1], Chiara Cardelli[1,2], Michele Diomedi[1], Elenia Laurino[1], Simone Barsotti[3], Marta Mosca[1].
[1]Rheumatology Unit, University of Pisa; [2]Department of Medical Biotechnologies, University of Siena; [3]Internal MEdicine Unit, Livorno Hospital, Livorno, Italy

Background. Antisynthetase syndrome (ASS) is an idiopathic inflammatory myopathy, typically characterized from the triad interstitial lung disease (ILD), myositis and arthritis, together with anti-aminoacyl tRNA synthetase (ARS) antibodies (Ab) positivity. Recent data suggested esophageal involvement could commonly occur, being related to a higher risk of pulmonary complications, at first ab ingestis pneumonia, able to significantly worsen the respiratory function of ASS patients and related to a poor prognosis. Esophageal involvement can be assessed using both double-contrast conventional radiology (DCCR) and oro-pharyngeal-esophageal scintigraphy (OPES).

Moreover, DCCR may show the presence of gastrointestinal (GI) pathologies, such as esophagitis, achalasia and hiatal hernia, with a prevalence in Italian population up to 33%, 0.03% and 10% respectively. The first aim of the study is to evaluate the prevalence of esophageal involvement in a monocentric cohort of patients with ASS; secondly, we aimed at comparing DCCR and OPES in highlighting swallowing dysfunctions or GI comorbidities.
Methods. We retrospectively analyzed medical records of consecutive patients with a diagnosis of ASS based on both physicians' clinical diagnosis and ARS Ab positivity, regularly followed at our Myositis Clinic from January 2018 to May 2023. Demographic and clinical data of patients, together with DCCR and OPES results were collected; moreover, patients were asked to fill in MD Anderson Dysphagia Inventory (MDADI) to evaluate their dysphagia. Intergroups comparisons were assessed by using Chi-square, t-test and ANOVA. *p*-values <0.05 were considered significant.
Results. We included 37 patients (21 female, 56.8%) with a mean age of 56,3±7,9 years; 12 (32.5%) reported dysphagia and, on 31 (83.7%) who filled in MDADI, 9 (29%) showed scores corresponding to a swallowing disability, significantly associated to subjective dysphagia ($p<0.001$). Twenty patients (54.1%) performed OPES; up to 5/20 (25%) showed an increased esophageal (E) TT, OP retention index (RI) was increased in up to 17/20 patients (85%) and E RI was increased in up to 12/20 patients (60%). DCCR was performed in 14 patients (37.8%); hypotone and hypokinesis were found in 7/14 (50%); besides, DCCR highlighted the presence of achalasia, esophagitis and hiatal hernia respectively in 7 (50%), 10 and 10 (71.4%) patients.
Conclusion. Less than one third of ASS patients perceive to have dysphagia; however, up to 85% of those who underwent OPES and up to 50% of those who performed DCCR showed a significant swallowing dysfunction. Moreover, DCCR showed a significantly higher prevalence of GI comorbidities in ASS patients than in the general population. To our knowledge, this is the first study analyzing the prevalence of esophageal involvement in ASS through 2 different methods and in comparison with patients' perception of dysphagia. Further studies are needed to confirm our data, but they already could suggest investigating GI involvement and GI comorbidities in ASS, even in asymptomatic patients, with the aim of optimizing their quality of care, also reducing the risk of respiratory complications related to dysphagia.

OP-16

BRACHIO-CERVICAL INFLAMMATORY MYOPATHY, DESCRIPTION OF A GROUP OF 23 PATIENTS

Anna Khelkovskaya-Sergeeva, Lidia Petrovna Ananyeva, Olga Koneva, Liudmila Garzanova, Rushana Shayakhmetova, Alena Kolomeychuk
V.A.Nasonova Institute of Rheumatology, Moscow, Russian Federation

Background. Brachio-cervical inflammatory myopathy (BCIM) is a rare form of autoimmune muscle disease, with unique pattern of muscle weakness- high frequency of axial muscle involvement and drop head syndrome.
Methods. Objective: to observe the course of disease in patients with BCIM. The study included 23 (12%) patients with BCIM in a group of 191patients with inflammatory myopathies. The mean age was 52±14.5 years, there were 16 women (69.6%). The median disease duration was 18[12;48] months. Median follow-up duration was 14 months [5-28].
Results. Among patients with BCIM were 18 (78.3%) scleromyositis, 2(8.7%) myositis and rheumatoid arthritis, 1(4.3%)- myositis and systemic lupus erythematosus and 2 (8.7%) pure BCIM. Clinical features of Sjögren syndrome had 6(25%) pts. Drop head syndrome had 12(52.2%) pts, axial weakness – 18 (78.2%), all pts had proximal muscle weakness in upper extremities and shoulder girdle, in lower extremities- 16(69.6%), 2(8.7%) pts had distal weakness (in finger extensors). The median of manual muscle test was 50 [44-62] (normal range 80). The median creatine kinase level was 1854U/L [600-3100] (normal range 24-195 U), and its levels were normal in 2 patients (8.7%). Moderate dysphagia occurred in 16(69.6%) pts, and in 4(17.4%)-dysphagia was life-threatening. The main skin manifestation was mechanic hand-9(39%), while typical DM-rash in-3(13%) pts, subclinical Gottron's sign-in 4(17.4%) pts. Also 18(78.3%) pts had Raynaud's syndrome and 12(52.2%)- arthritis Interesting, that there was high frequency of organ manifestation – myocarditis in 12(52.2%) pts, arrhythmia in 9(39.1%), interstitial lung disease in12(52%). There were no active neoplasms in this group. 10(43.5%) of pts were positive for anti-PM/Scl, 6(26.1%) for anti – Ku antibodies, for RF 4(17.4%), ACCP2(8.7%) a-Ro60 and/or a-Ro52-6(26%), a-DNA-1(4.3), a-La-2(8.7%); 22(95.7%) of these pts had high titer of antinuclear antibodies HEp-2 – ≥1/640 All patients received systemic oral glucocorticoids, 8(34.8%) - intravenous immunoglobulin in different doses, 18(78.3%) – immunosuppressant's, 16(69.6%)-rituximab. In 8(34.8%) of 20 patients the response to therapy for myositis was good, in 11 (47.8%) it was incomplete, in 1(4.3)-progression. 5(21.7%) patients died (2 died from complications of dysphagia, 1 from heart failure ,1- COVID-19, 1- unknown cause).
Conclusion. BCIM is a unique form of myositis with severe muscle weakness in shoulder girdle, neck extensors, axial muscles, high frequency of dysphagia, heart and lung involvement and incomplete response to therapy. This condition is difficult to diagnose and treat. Often BCIM is a part of an overlap syndrome (especially scleromyositis) with high frequency of anti-PM/Scl, anti – Ku antibodies.

Exercise and Rehabilitation

P-105

QUALITY OF LIFE IS CORRELATED WITH FUNCTIONAL CAPACITY, BODY COMPOSITION AND DISEASE DAMAGE IN PATIENTS WITH MYOSITIS – BASELINE DATA FROM A RANDOMISED CONTROLLED TRIAL

Kasper Y. Jensen[1], Per Aagaard[2], Charlotte Suetta[3,8], Jakob L. Nielsen[2], Henrik D. Schrøder[4], Charlotte Grønset[5], Casper Simonsen[6], Louise P. Diederichsen[1,7,8]
[1]Copenhagen Research Center for Autoimmune Connective Tissue Diseases (COPEACT), Center for Rheumatology and Spine Diseases, Rigshospitalet, Copenhagen, Denmark; [2]Department of Sports Science and Clinical Biomechanics, University of Southern Denmark, Odense, Denmark; [3]Geriatric Research Unit, Department of Geriatric and Palliative Medicine, Copenhagen University Hospital, Bispebjerg and Frederiksberg, Denmark; [4]Department of Pathology, Odense University Hospital, Odense, Denmark; [5]Department of Occupational Therapy and Physiotherapy, Copenhagen University Hospital - Rigshospitalet, Copenhagen, Denmark; [6]Centre for Physical Activity Research, Copenhagen University Hospital - Rigshospitalet, Copenhagen, Denmark; [7]Department of Rheumatology, Odense University Hospital, Odense, Denmark; [8]Department of Clinical Medicine, Faculty of Health and Health Sciences, University of Copenhagen, Copenhagen, Denmark
Trial registration number NCT04486261

Background. Patients with myositis have cardinal traits of muscle weakness (1) and decreased muscle endurance (2) in addition to reduced quality of life (QoL) (3). However, QoL is complex, and factors affecting QoL, are still not fully understood. Knowledge of potential correlations to QoL is important for evoking changes to a better life for patients with myositis. Thus, we investigated the influence of functional capacity, muscle strength, body composition and disease activity and damage on QoL in patients with myositis.
Methods. Measures of functional capacity (functional index 3, 2-minute walk test, timed-up-and-go and 30-s sit-to-stand), muscle strength (5 repetitions maximum strength in leg press, bench press, cable row, knee extension, biceps curl and static handgrip strength; relative to body mass), leg extensor power (Nottingham Power Rig, relative to body mass), body composition (height adjusted appendicular lean mass and total fat mass (%)) and IMACS disease activity and disease damage core set measures were analysed by Spearman's rank correlation to investigate the impact on QoL measured by Short Form 36 questionnaire (SF-36).
Results. All functional capacity measures were correlated with the physical component summary (PCS); functional index 3 (rho=0.44, p=0.012), 2-minute walk test (rho=0.53, p=0.002), timed-up-and-go (rho=-0.44, p=0.011) and 30-sit-to-stand performance (rho=0.43, p=0.013). In muscle strength and power, leg press (rho=0.15, p=0.04), leg power (rho=0.44, p=0.012) Bench press (rho=0.39, p=0.034) and handgrip strength (rho=0.46, p=0.008) showed a positive correlation with PCS. For body composition, total fat mass (%) correlated negatively with PCS (rho=-0.63, p<0.001). In the IMACS measures, Health Assessment Questionnaire (rho=-0.58, p=0.001), Physician Global Damage (rho=-0.47, p<0.006) and Patient Global Damage (rho=-0.70, p<0.001) were negatively correlated with PCS. In contrast, none of the investigated outcome parameters were correlated with the mental component summary of SF-36. See Table 1 for the full list of results.
Conclusion. In this group of Danish patients with myositis, functional capacity and muscle strength were positively correlated with the physical component summary of the QoL, indicating that future interventions should be directed to improve these factors to ultimately improve QoL. The Health Assessment Questionnaire and Patient/Physician Global Assessment of Disease Damage revealed strong correlations with PCS, supporting that both patient-reported outcome measures (PROMs) and clinician-reported outcomes are highly relevant QoL-related monitoring parameters in patients with myositis.

Table I. Functional capacity, muscle strength, body composition and IMACS core set measures vs. Quality of life (Short Form 36 questionnaire).

	Mean (SD)	PCS Spearman's		MCS Spearman's	
		Rho	p-value	*Rho*	p-value
Functional capacity					
FI3 – Percentage	64.40 (29.56)	**0.44**	**0.012**	0.10	0.596
30 STS – Repetitions	15.22 (4.19)	**0.43**	**0.013**	0.06	0.729
TUG – Seconds	6.00 (1.73)	**-0.44**	**0.011**	0.05	0.779
2MWT – Meters	195.91 (32.06)	**0.53**	**0.002**	0.03	0.881
Muscle strength & muscle power					
Leg power – Watt/kg	2.44 (0.96)	**0.44**	**0.012**	0.01	0.969
5RM – leg press* – N/kg	10.21 (4.11)	**0.55**	**0.002**	-0.07	0.703
5RM – Bench press* – N/kg	2.82 (1.06)	**0.39**	**0.034**	0.04	0.814
5RM – Cable row* – N/kg	5.84 (2.72)	0.25	0.191	-0.10	0.590
5RM – Knee ext.* – N/kg	3.84 (2.46)	0.29	0.117	-0.04	0.816
5RM – Bicep curl* – N/kg	0.78 (0.39)	0.24	0.200	-0.09	0.618
Handgrip strength – N/kg	3.88 (1.36)	**0.46**	**0.008**	-0.13	0.481
Body composition					
App. muscle mass – Kilogram/meter^2	7.08 (1.68)	0.10	0.597	0.15	0.398
Total fat – Percentage	37.52 (9.27)	**-0.63**	**<0.001**	<0.01	0.993
Disease activity measures					
PhGA – 0-100	3.75 (4.21)	-0.34	0.058	-0.03	0.861
PtGA – 0-100	7.22 (7.58)	-0.12	0.502	-0.17	0.356
EMGA – 0-100	3.59 (4.44)	**-0.37**	**0.037**	-0.02	0.922
MMT8 – 0-80	76.84 (3.19)	0.04	0.842	0.04	0.822
HAQ – 0-3	0.25 (0.48)	**-0.58**	**0.001**	-0.16	0.388
CK – mmol/L	215 (338)	0.09	0.627	-0.13	0.487
Disease damage measures					
PhGD – 0-100	15.94 (11.18)	**-0.47**	**0.006**	-0.13	0.491
PtGD – 0-100	18.91 (16.30)	**-0.70**	**<0.001**	-0.07	0.687

Data are presented as means and standard deviation in parentheses. PCS: Physical component summary; MCS: Mental component summary; FI3: Functional Index 3; 30 STS: 30-second sit to stand; TUG: timed up and go; 2MWT: 2-minute walk test; 5RM: repetitions maximum strength test; App.: appendicular; PhGA: Physician global activity; PtGA: Patient global activity; EMGA: Extramuscular Global Assessment; MMT8: Manual Muscle testing 8; HAQ: Health Assessment Questionnaire; CK: Creatine Kinase; PhGD: Physician global damage; PtGD: Patient global damage; Bold font means significant. *n=30, 2 patients did not perform the 5RM test. °n=25.

References
1. LUNDBERG IE, FUJIMOTO M, VENCOVSKY J *et al*.: Idiopathic inflammatory myopathies. *Nat Rev Dis Primers* 2021; 7(1): 86. doi:10.1038/s41572-021-00321-x
2. ALEMO MUNTERS L, DASTMALCHI M, KATZ A *et al*.: Improved exercise performance and increased aerobic capacity after endurance training of patients with stable polymyositis and dermatomyositis. *Arthritis Res Ther* 2013; 15(4): R83. doi:10.1186/ar4263
3. POULSEN KB, ALEXANDERSON H, DALGÅRD C, JACOBSEN S, WEILE L, DIEDERICHSEN LP: Quality of life correlates with muscle strength in patients with dermato- or polymyositis. *Clin Rheumatol* 2017; 36(10): 2289-95. doi:10.1007/s10067-017-3706-6

P-106

HIGH-INTENSITY INTERVAL TRAINING VERSUS MODERATE HOME-BASED EXERCISE IN RECENT-ONSET IDIOPATHIC INFLAMMATORY MYOPATHIES: A RANDOMIZED CONTROLLED TRIAL

Kristofer M. Andreasson[1,2], Maryam Dastmalchi[3], Cecilia Leijding[4], Heléne Sandlund[3], Daniel C. Andersson[4,5], Ingrid E. Lundberg[2,3], Helene Alexanderson[1,2]
[1]Karolinska University Hospital, Theme Women's Health and Health Professionals, Medical Unit Occupational & Physical Therapy, Stockholm, Sweden; [2]Karolinska Institutet, Department of Medicine Solna, Division of Rheumatology, Stockholm, Sweden; [3]Karolinska University Hospital, Department of Gastro, Dermatology and Rheumatology, Medical Unit Inflammation and Aging, Stockholm, Sweden; [4]Karolinska Institutet, Department of Physiology and Pharmacology, Stockholm, Sweden; [5]Karolinska University Hospital, Heart, Vascular and Neurology Theme, Cardiology Unit, Stockholm, Sweden

Background. Exercise is a recognized adjunctive therapy for patients with idiopathic inflammatory myopathies (IIM), enhancing physical capacity and reducing inflammation. Primarily, moderate-to-intensive exercise have been studied in established, low-active IIM, hence, effects of intensive exercise in recent-onset, active IIM is less known. This study aims to evaluate tolerance and efficacy of High-Intensity Interval Training (HIIT) compared to clinical standard moderate-intensity home-based training (CT) (Alexanderson *et al*.) in patients with recent onset IIM.

Methods. Between 2017-2023, patients with adult IIM (≤12 months of diagnosis), excluding IBM, aged <70 years, and capable of performing HIIT were recruited. Patients deemed unfit for participation (e.g., severe lung-involvement or active myocarditis) were excluded. Participant's pre- and postintervention investigations included score of disease activity (subset of IMACS disease core set including extra-muscular global assessment, physician's global activity, muscle enzymes and Manual Muscle Test 80 [MMT8]), maximal exercise test (oxygen uptake [peakVO_2] and peak power) on a stationary bike and limb muscle biopsies (done at diagnosis and post-intervention). HIIT included supervised 30-45-second stationary bike intervals (≥85% of maximal heart rate), followed by strength training, thrice weekly. CT followed a home-based exercise regimen (<70% of maximal heart rate) with five sessions weekly. For all participants, intensity and resistance were tailored to individual limitations and heart rate was monitored during exercise. Muscle biopsies were analyzed by Western Blot to study mitochondrial protein expression. Repeated measures ANOVA, paired t-test, and Mann-Whitney U-test was utilized.

Results. 23 patients (5 months average diagnosis duration) were included and randomized, 12 to HIIT (11 completing) and 11 to CT (8 completing). HIIT demonstrated a significant improvement in exercise capacity with higher peakVO_2 (p<0.01), peak power (p<0.01) compared to CT, and in muscle mitochondria protein expression within HIIT (p<0.05). Changes were non-significant in markers of adverse reactions (CK, SR, ASAT, ALAT and LD), MMT8, extra-muscular VAS and physician's VAS for both groups (Table 1). Drop-outs/exclusion were due to time constraints (2), COVID-19 restrictions (1), and IBM re-diagnosis (1).

Table I.

	HIIT		Control	
	Baseline	12-week follow-up	Baseline	12-week follow-up
PeakVO_2, L/min[a]	1.95 (1.77-2.32)	2.24 (1.91-2.74)**	1.55 (1.3-1.86)	1.5 (1.33-1.86)
Peak-power, W[a]	150 (130-176)	190 (160-211)**	120 (92.5-148)	120 (97.5-150)
MMT8[b], 0-80	80 (79.25-80)	80 (79-80)	76.5 (73.25-80)	80 (78-80)
Extra-muscular global assessment VAS, mm[b], 0-100	18.5 (15.75-27.5)	13 (7.5-16.5)	20 (12-30)	10 (8-18)
Physician's global activity VAS, mm[b], 0-100	20 (15.25-24.25)	15 (11-22)	19 (14.25-20)	14 (8-18)
CK[b], µkat/L	1.5 (1.2-1.7)	1.5 (1.3-2.8)	1.2 (0.7-1.5)	1.5 (1.2-2)
SR[b], mm	9 (5-19)	7 (4-13)	6.5 (4-16)	6 (2.5-16.5)
ASAT[b], µkat/L	0.41 (0.33-0.49)	0.44 (0.34-0.5)	0.34 (0.32-0.44)	0.41 (0.36-0.44)
ALAT[b], µkat/L	0.46 (0.33-0.49)	0.4 (0.36-0.58)	0.38 (0.27-0.59)	0.31 (0.26-0.39)
LD[b], µkat/L	3.7 (3.4-4.4)	3.8 (3.3-4.4)	3.7 (3.4-4.5)	3.7 (3.5-3.9)

All data presented in median and interquartile range; a, repeated measures ANOVA between groups; b, Mann-Whitney within groups.
L/min, liters per minute; W, watts; MMT8, manual muscle test 80; VAS: visual analog scale; mm: millimeters, CK: creatine phosphokinase; SR: sedimentation rate; ASAT: aspartate transaminase; ALAT: alanine transaminase; µkat/L: microkatals per liter; normative values male/female: CK 0.8-6.7/0.6-3.5, SR <10/<30, ASAT <0.76/<061, ALAT <1.1/<0.76, LD <3.5/<3.5; **p<0.01.

Conclusion. Supervised HIIT appears to be a safe and effective approach for enhancing exercise capacity compared to moderate home exercise. This study provides novel insights in how to use intensive exercise as an adjunctive treatment in early IIM. Our preliminary data spurs further research in this area that may ultimately change the way we recommend exercise interventions in IIM. The authors extend heartfelt gratitude to the colleagues and patients whose time and commitment made this study possible.

Reference

1. ALEXANDERSON H *et al*.: The safety of a resistive home exercise program in patients with recent onset active polymyositis or dermatomyositis. *Scand J Rheumatol* 2000; 29(5): 295-301. doi:10.1080/030097400447679

P-107

EFFECTIVENESS OF EXERCISE ON INFLAMMATORY MYOPATHIES: A SYSTEMATIC REVIEW

Yasser Salem, Pavit Surii
Hofstra University Hempstead, NY, USA

Background. Inflammatory myopathies, such as dermatomyositis (DM) or polymyositis (PM), are debilitating diseases that involve chronic muscle inflammation and weakness. Numerous studies note exercise may improve strength, aerobic capacity, inflammation, and quality of life (mental, physical, and social function) in patients with myositis. The purpose of this systematic review was to examine evidence regarding the potential benefits and clinical relevance of various types of exercise on myositis patients. Safety, outcomes, and applications are addressed.

Methods. This is a systematic review study. Electronic databases used were PubMed, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), and the Physiotherapy Evidence Database (PEDro). The data searched included all published works to date (November 2023). Studies were included if they met both the criteria of myositis diagnosis and exercise intervention.

Results. This systematic review included 23 studies that met our inclusion criteria. The results from 323 participants with forms of myositis were assessed. Of the 23 studies, there were ten randomized controlled trials, four quasi-experimental designs, five single group designs, one case series report, and three case studies. Sample size ranged from 1-57 patients. Age range of patients was 10-80 years old. Treatment interventions ranged from 3-24 weeks, with frequency of sessions ranging from two times per week to seven times per week, and duration of sessions ranging between 15 to 90 minutes. Five studies performed a follow-up with patients, which ranged from 4-80 weeks. A variety of exercises were implemented to analyze factors such as inflammatory markers, strength, endurance, aerobic capacity, gait, and quality of life. Common outcome measures included muscle biopsies to assess inflammatory markers and/or RNA levels, laboratory analyses to assess inflammation, cardiorespiratory assessments, the MDA assessment tool (MITAX and MYOACT), IMACS myositis response criteria, SF-36, ADL, HAQs, manual muscle tests, Myositis Activities Profile, and FI for myositis.

Conclusion. The evidence suggests that exercise, commonly resistive and non-resistive exercises, either supervised or unsupervised, may be effective in improving muscle strength, endurance, function, fatigue, aerobic capacity, grip strength, gait speed, pain, cardiopulmonary risk, and quality of life in patients with inflammatory myopathies. Importantly, exercise appears to not increase, and sometimes decrease, muscle inflammation in these patients. Additionally, supporting biochemical analyses suggest activation of aerobic, anti-oxidative, and both anabolic and catabolic metabolic pathways. Exercise may reduce disease activity in these patients and augment the ability to perform daily tasks. However, there is significant variability in the design, intervention parameters, and outcome measures of these studies. Nonetheless, a positive correlation between exercise and functional improvements in myositis patients appears to exist. The literature suggests that implementation of exercise regimens have therapeutic implications, with improvements in disease activity, muscle strength, endurance, pain, quality of life.

References

1. BORGES IBP, DE OLIVEIRA DS, MARIE SKN, LENARIO AM, OBA-SHINJO SM, SHINJO SK: Exercise training attenuates ubiquitin-proteasome pathway and increases the genes related to autophagy on the skeletal muscle of patients with inflammatory myopathies. *J Clin Rheumatol* 2021; 27(6S): S224-31. doi: 10.1097/rhu.0000000000001721
2. NADER GA, DASTMALCHI M, ALEXANDERSON H *et al*.: A longitudinal, integrated, clinical, histological and mRNA profiling study of resistance exercise in myositis. *Mol Med* 2010; 16(11-12): 455-64. doi: 10.2119/molmed.2010.00016
3. BOEHLER JF, HOGARTH MW, BARBERIO MD *et al*.: Effect of endurance exercise on microRNAs in myositis skeletal muscle-A randomized controlled study. *PLoS One* 2017; 12(8): e0183292. doi: 10.1371/journal.pone.0183292
4. MUNTERS LA, LOELL I, OSSIPOVA E *et al*.: Endurance exercise improves molecular pathways of aerobic metabolism in patients with myositis. *Arthritis Rheumatol* 2016; 68(7): 1738-50. doi: 10.1002/art.39624
5. ALEMO MUNTERS L, DASTMALCHI M, KATZ A *et al*.: Improved exercise performance and increased aerobic capacity after endurance training of patients with stable polymyositis and dermatomyositis. *Arthritis Res Ther* 2013; 15(4): R83. doi: 10.1186/ar4263
6. ALEMO MUNTERS L, DASTMALCHI M, ANDGREN V *et al*.: Improvement in health and possible reduction in disease activity using endurance exercise in patients with established polymyositis and dermatomyositis: a multicenter randomized controlled trial with a 1-year open extension followup. *Arthritis Care Res* (Hoboken). 2013; 65(12): 1959-68. doi: 10.1002/acr.22068

7. ŠPIRITOVIĆ M, HEŘMÁNKOVÁ B, ORESKÁ S *et al.*: The effect of a 24-week training focused on activities of daily living, muscle strengthening, and stability in idiopathic inflammatory myopathies: a monocentric controlled study with follow-up. *Arthritis Res Ther* 2021; 23(1): 173. doi: 10.1186/s13075-021-02544-5

P-108

EXPLORING WEARABLE TECHNOLOGY ADOPTION IN RHEUMATIC DISEASE PATIENTS: INITIAL INSIGHTS

Alexandre M. dos Santos, Nathalia G.S. Pereira, Samuel K. Shinjo
Division of Rheumatology, Faculdade de Medicina FMUSP, Universidade de Sao Paulo, Sao Paulo, Brazil

Background. Physical inactivity and sedentary behavior are prevalent among patients with rheumatic disease, leading to a reduction in health-related quality of life and worsening disease parameters. Additionally, interpreting and evaluating self-reported physical activity levels pose challenges, hindering the development of strategies for improvement. However, various devices objectively measure physical activity levels, offering potential utility in rheumatic patients. This study aimed to analyze the access to and ability to use these devices in this population.
Methods. Using an electronic survey, we interviewed rheumatic patients from a tertiary center between May and June 2022, adhering to approved protocols for ethical and data security guidelines, using the Research Electronic Data Capture (REDCap). We assessed the access to and the ability to use smartphones and wearable activity trackers. The ability assessments used Likert scales (0-5), with 0 indicating no ability and 5 indicating total ability. Physical activity levels were evaluated using the International Physical Activity Questionnaire Short Form (IPAQ-SF). Quantitative data were described as median and interquartile [25th-75th], and qualitative data as frequency (%).
Results. Thirty-three patients responded to the survey; 76% were women, with an age of 50.0 [37.0-32.9] years and a body mass index of 28.3 [23.3-32.9] kg/m2. Regarding the disease type, 30.3% had dermatomyositis, 27.7% had Takayasu's arteritis, 15.1% had granulomatosis with polyangiitis, 15.1% had antisynthetase syndrome, 6.0% had rheumatoid arthritis, 3.0% had polymyositis, and 3.0% had immune-mediated necrotizing myopathies. All patients reported smartphone access, 97% Internet access, and 36% access to wearables; however, only 15% used wearables. Patients who used smartphones and wearables rated their ability to use them as 4.0 [3.0-5.0] and 4.0 [4.0-4.0], respectively. Finally, only 30% of patients reported a high level of physical activity.
Conclusion. Preliminary data suggest that the main barriers to their use may be education and training regarding the use of wearables and physical activity monitoring apps. Therefore, educational strategies are necessary to monitor and improve physical activity levels in patients with rheumatic diseases.
Acknowledgments. FAPESP #2020/10691-4 (AMS) and #2022/04869-0 (SKS).

OP-17

SPORT AND PHYSICAL ACTIVITY IN PATIENTS WITH IDIOPATHIC INFLAMMATORY MYOPATHIES

Stefanie Glaubitz[1], Stefanie Meyer[1], Mohamed El Aboussi[1], Karsten Kummer[1,2], Denise Rohleder[3], Ina Hunger[3], Lina Hassoun[1], Rachel Zeng[1], Jana Zschüntzsch[1]
[1]Department of Neurology, University Medical Center Göttingen, Germany; [2]Department of Neurology and Pain Treatment, University Hospital of the Brandenburg Medical School Theodor Fontane, Immanuel Hospital Rüdersdorf, Rüdersdorf/Berlin, Germany; [3]Institute of Sport Science, University Göttingen, Germany

Background. Non-pharmacological treatments, such as physical activity, physiotherapy and rehabilitation, are an indispensable component in the treatment of idiopathic inflammatory myopathies (IIM) and should be carried out concomitantly to immunosuppressive therapy. The overall positive benefits of physical activity are well known and its medical safety in IIM has been demonstrated in various studies. However, in depth information covering the level of acceptance of exercise, preferences or reservations regarding physical activity and preferred types of performed physical activities among those affected is still lacking.
Methods. The behaviour of patients with IIM regarding physical activity was assessed using questionnaires specifically targeting sporting activities. In particular, the implementation of low physical activity, such as walking, was surveyed. A questionnaire was used to inquire about the frequency, type, and subjective effects as well as the personal attitude towards physical activity. For most questions, patients could choose between the response options "strongly agree", "mostly agree", "undecided", "mostly disagree" and "strongly disagree". General data on the disease and disease activity were recorded.
Results. A total of 75 patients with IIM participated in the study (f=57%, m=43%). Inclusion body myositis represented the largest group of patients (26.7%), followed by polymyositis (20%), dermatomyositis (17.3%), immune-mediated necrotizing myopathy (16%), overlap myositis (12%) and antisynthetase syndrome (8%).
The most common type of physical activity among patients with IIM was walking, followed by strength training and ergometer training.
A subjectively positive effect of physical activity in general was reported by 75.9% of patients. Interestingly, the majority of patients (74.6%) specifically described a positive effect of physical activity on their mood and the enjoyment of life, whereas only 45.3% of patients reported a subjective improvement in muscular symptoms.
Negative consequences of physical activity were also reported. 14.6% of patients stated that they were worried about physical activity potentially worsening their symptoms and 14% of patients reported avoiding physical activity due to myalgia.
Conclusion. This study emphasizes the positive effects of physical exercise on this patient cohort and provides further evidence on its specific benefits, such as general well-being and quality of life. Therefore, patients with IIM should be encouraged to be physically active and prescription of continuous physiotherapy should be offered. However, the treating physicians need to be aware of the concerns and fears associated to physical activity as well as the possibility of the occurrence of exercise induced myalgias and be able to advise patients accordingly.

Biomarkers and Imaging

P-109

AUTOANTIBODIES AGAINST MYXOVIRUS RESISTANCE PROTEIN 1 ARE ASSOCIATED WITH MYOSITIS AND INTERSTITIAL LUNG DISEASE IN SYSTEMIC LUPUS ERYTHEMATOSUS

Eugene Krustev[1], Marvin .J Fritzler[1], Sasha Bernatsky[2], Evelyne Vinet[2,3], Christian A. Pineau[2], Arielle Mendel[2,3], Fares Kalache[2], Louis-Pierre Grenier[2], Thaisa Cotton[2], Omid Zahedi Niaki[4], May Y. Choi[1]
[1]Department of Medicine, Cumming School of Medicine, University of Calgary, Calgary, AB, Canada; [2]Division of Rheumatology, Department of Medicine, McGill University, Montreal, QC, Canada; [3]Centre for Outcomes Research and Evaluation, McGill University Health Centre, Montreal, QC, Canada; [4]Division of Rheumatology, Department of Medicine, University of Alberta Hospital, Edmonton, AB, Canada

Background. Although inflammatory myopathy and interstitial lung disease (ILD) are uncommon in systemic lupus erythematosus (SLE), they are associated with worse outcomes. The interferon associated protein, Human Myxovirus Resistance Protein 1 (MxA), is a novel sarcoplasm-expressed biomarker in muscle biopsies from patients with dermatomyositis (1). Autoantibodies against MxA (anti-MxA) are expressed in idiopathic interstitial pneumonia (2). We evaluated the frequency of anti-MxA autoantibodies in SLE patients with myositis and/or ILD compared to SLE patients without these disease features.
Methods. McGill Lupus Cohort participants (n=551, 2000-2017) without a history of ILD and/or myositis (ILD/myositis) meeting the 1997 American College of Rheumatology criteria [3] were followed at annual study visits from cohort enrolment until either the date of ILD/myositis diagnosis or December 31, 2017. A case-cohort analysis was performed, comparing all patients who developed ILD/myositis on follow-up with a randomly selected sub-cohort of SLE patients (n=72). Anti-MxA autoantibodies were tested in baseline serum samples (first visit as of Jan 2000 or enrollment visit if later than this date) using addressable laser bead immunoassay with purified recombinant human protein with results expressed as median fluorescent units (MFU).
Results. Thirteen (13/551; 2.4%) SLE patients developed ILD/myositis (ILD alone, 8/551, 1.5%; myositis alone, 3/551, 0.5%; both ILD and myositis, 2/551, 0.4%). There was no significant difference in the proportion of fe-

males (ILD/myositis 85.7% *vs*. control 84.7%; difference in proportion [diff] 0.01, 95% confidence interval [CI] -0.25, 0.15). Among cases, there were non-significant trends for less White race/ethnicity (ILD/myositis 35.7% *vs*. controls 47.2%; diff 0.12, 95% CI -0.16, 0.34) and lower mean age at SLE diagnosis (ILD/myositis 29.5±11.0 years *vs*. controls 33.6±14.2 years, absolute difference 3.8, 95% CI -4.1, 11.6). More patients who developed ILD/myositis were anti-MxA positive at baseline versus controls (46.2% *vs*. 9.7%; crude odds ratio [OR] 8.0, 95% CI 2.1, 30.4) (Table 1). Median baseline anti-MxA titres were significantly higher in ILD/myositis versus controls (161.0 *vs*. 82.8, *p*=0.0004) (Table I). At time of ILD/myositis diagnosis, 11 of 13 patients (84.6%) were anti-MxA positive (ILD alone, 6/8, 75.0%; myositis alone, 3/3, 100.0%; both ILD and myositis, 2/2, 100.0%) (Table I).

Table I. Anti-MxA autoantibody expression in SLE patients withmyositis and/or ILD vs controls (no ILD or myositis).

SLE Disease Subtype	Anti-MxA Positive at Baseline (%)	Median Anti-MxA Titres at Baseline (IQR)	Anti-MxA Positive Near ILD/Myositis Diagnosis (%)	Median Anti-MxA Titres Near ILD/Myositis Diagnosis (IQR)
ILD and/or Myositis (n=13)	6 (46.2%)	161.0 (108.0, 255.0)	11 (84.6%)	222.0 (212.0, 354.0)
ILD Alone (n=8)	5 (62.5%)	233.5 (139, 338.5)	6 (75.0%)	220.5 (204.5, 459.5)
Myositis Alone (n=3)	0 (0.0%)	94.0 (73.0, 108.0)	3 (100%)	222.0 (217.0, 332.0)
ILD and Myositis (n=2)	1 (50.0%)	254.0 (161.0, 347.0)	2 (100%)	288.1 (209.8, 366.5)
Controls (no ILD or myositis) (n=72)	7 (9.7%)	82.8 (64.3, 120.0)		

Anti-MxA titres presented as mean fluorescent units (MFU), upper limit of normal 200 MFU.
ILD, interstitial lung disease; IQR, interquartile range; MxA, Myxovirus Resistance Protein 1; SLE, systemic lupus erythematosus.

Conclusion. These results suggest anti-MxA is an important biomarker for ILD/myositis in SLE. A larger study is underway to confirm these findings and examine associations with other SLE features and other outcomes.

References

1. URUHA A *et al*.: *Neurology* 2017; 88(5): 493-500.
2. HAMANO Y *et al*.: *Sci Rep* 2017; 7(1): 43201.
3. HOCHBERG MC: *Arthritis Rheum* 1997; 40: 1725.

P-110

CONCURRENT QUANTITATIVE ANALYSIS OF ULTRASOUND AND MAGNETIC RESONANCE IMAGING IN PATIENTS WITH MYOSITIS

Yoshida Takeshi[1], Yamazaki Hiroki[2], Matsumoto Yuki[3], Takamatsu Naoko[2], Kanazawa Yuki[3], Kumon Yoshitaka[4], Kawano Hiroshi[5], Nishino Ichizo[6], Nishioka Yasuhiko[5], Harada Masafumi[3], Izumi Yuishin[2]

[1]Department and Rheumatology and Neurology, Chikamori Hospital, Kochi Japan; [2]Department of Neurology, Tokushima University Hospital, Tokushima, Japan; [3]Department of Radiology, Tokushima University Hospital, Tokushima, Japan; [4]Department of Rheumatology, Chikamori Hospital, Kochi, Japan; [5]Department of Respiratory and Rheumatology, Tokushima University Hospital, Tokushima, Japan; [6]Department of Clinical Genome Analysis, National Center of Neurology and Psychiatry, Tokyo, Japan

Background. For the diagnosis of myositis, magnetic resonance imaging (MRI) has been used as the test of choice. On the other hand, muscle ultrasound (US) has received increasing attention for the diagnosis and monitoring of muscle disease, including myositis. Recent literature showed that for the detection of muscle abnormalities compatible with myositis, quantitative US showed lower sensitivity compared with qualitative /semiquantitative US and qualitative MRI short-tau inversion recovery (STIR). On the other hand, US was better detecting treatment response. We sought to evaluate relative efficacy of quantitative MRI and US to detect imaging abnormalities related to myositis and their correlation with various clinical parameters.

Methods. This is an interim data analysis of ongoing multicenter, prospective, observational study that focused on concurrent assessment of skeletal muscle with MRI and US. Muscle biopsy was also performed when clinically indicated. For the quantitative analysis of US images, the mean gray-level (0-255) within the regions of interest along transverse image of left biceps brachii (BB) was measured using ImageJ, an image processing software. For quantitative MRI, STIR signal intensity and fat fraction of left BB were measured from the same slice as US, using Min-Max scaling. Clinical parameters including measures of disease activity (Myositis Disease Activity Assessment Tool (MDAAT)) and damage (myositis damage index (MDI)), manual muscle testing, and creatine kinase (CK) were also collected.

Results. A total of 19 patients (6 patients with inclusion body myositis (IBM), 13 patients with myositis other than IBM (non-IBM)) were included in the current analysis. Patients with IBM showed longer disease duration (84 *vs*. 3 months, *p*=0.001). Also, lower CK (217 *vs*. 1992 U/L, *p*=0.022), lower MDAAT disease activity (3.7 *vs*. 0.9, *p*=0.009), and higher damage (3.7 *vs*. 0.9, *p*=0.009) were revealed. Among non-IBM patients, muscle US of left BB showed significant correlation with MDAAT muscle disease activity (r=0.69, *p*=0.018). However, neither of two MRI sequence did not show significant correlation with clinical parameters.

Conclusion. Quantitative muscle US analysis showed better correlation with clinical disease activity than quantitative MRI in non-IBM patients.

References

1. YOSHIDA T, YAMAZAKI H, NISHIMORI Y *et al*.: Correlation of muscle ultrasound with clinical and pathological findings in idiopathic inflammatory myopathies. *Muscle Nerve* 2023; 68(1): 39-47.
2. WALTER AW, LIM J, RAAPHORST J *et al*.: Ultrasound and MR muscle imaging in new onset idiopathic inflammatory myopathies at diagnosis and after treatment: a comparative pilot study, *Rheumatology* 2023; 62(1): 300-9, https://doi.org/10.1093/rheumatology/keac263

P-111

MYOSITIS AUTOANTIBODIES AS PREDICTORS OF RESPONSE TO IVIG. POST-HOC ANALYSIS OF A LARGE, RANDOMIZED, PLACEBO-CONTROLLED PHASE III TRIAL

Christina Charles-Schoeman[1], Joachim Schessl[2], Elisabeth Clodi[3], Rohit Aggarwal[4], the ProDERM investigators

[1]University of California, Los Angeles, CA, USA; [2]Friedrich-Baur-Institute, Department of Neurology, Ludwig-Maximilians University of Munich, Munich, Germany; [3]Octapharma Pharmazeutika Produktionsges.m.b.H., Vienna, Austria; [4]University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

Background. Two subsets of autoantibodies have been identified in patients with Immune mediated Myopathies (IMM): Myositis-specific antibodies (MSA) and myositis-associated antibodies (MAA). MSA are highly specific for IIMs and represent unique clinical phenotypes and prognosis, MAA are also found in other autoimmune diseases. The ProDERM study demonstrated the efficacy and safety of IVIG in DM patients[1] but the potential effect of autoantibodies on treatment response has not yet been determined. This post-hoc analysis of the ProDERM study investigated the relationship of autoantibody status at baseline to treatment response to IVIG.

Methods. DM patients received 2 g/kg IVIg treatment (n=47) or placebo (n=48) every 4 weeks for 16 weeks. From week 16 onwards eligible patients (n=91) received IVIG for a further 24 weeks. The primary endpoint was a Total Improvement Score (TIS) of at least 20 (=at least minimal improvement) at week 16 and no confirmed deterioration up to week 16.

Results. Serum samples were taken at baseline and analysed for MSA (Jo-1, PL-7, PL-12, OJ, EJ, SRP, Mi-2, TIF-1, MDA5, NXP2, MJ, SUMO) and MAA (PM-SCL, Ku, U1RNP, U2RNP, U3RNP, Ro/SSA) by RNA and protein immunoprecipitations performed by the Oklahoma Medical Research Foundation. Patients were stratified according as MSA-positive (including those also MAA+), MAA-positive only, or no Ab detected (Ab-ve) at baseline. Proportion of patients with minimal (TIS ≥20), or moderate/major (≥40) response were evaluated for all patients (IVIG & placebo group) as well as separately at week 16 and 40.

Table I. Patient demoraphics and baseline characteristics

	MSA positive* (n=49)	MAA positive** (n=13)	No Ab detected (n=33)
Mean (range) age, years	51 (22-79)	54 (33-70)	54 (28-77)
Mean (range) time since diagnosis, years	3.66 (0.16-15.6)	5.04 (0.39-18.4)	5.8 (0.09-48.7)
Sex.n (% female)	39 (79.6)	11 (84.6)	21 (63.6)
Race, n (% White)	42 (85.7)	13 (100.0)	32 (97.0)
Mean BMI, kg/m^2	29.8	27.0 26.5	
Disease severity, n (%)			
Mild	10 (20.4)	4 (30.8)	12 (36.4)
Moderate	31 (63.3)	8 (61.5)	17 (51.5)
Severe	8 (16.3)	1 (7.7)	4 (12.1)
Ranomied treatment			
IVIG	24 (49.0)	4 (30.8)	19 (57.6)
Placebo	25 (51.0)	9 (69.2)	14 (42.4)

*10 patients positive for MSA were also positive for MAA.**MAA-positive group contains only patients with MAA (no MSA).
BMI: body mass index; CDASI: Cutaneous Disease Area and Severity Index; IVIG: intravenous immunoglobulin; MAA: myositis-associated antibodies; MSA: myositis-specific antibodies.

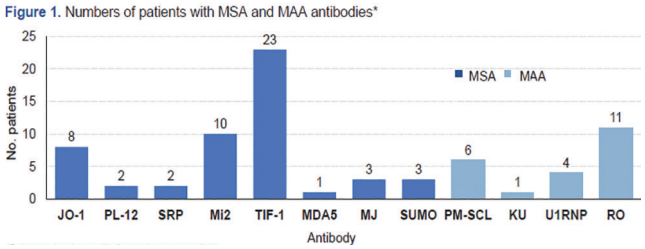


Fig. 1. Numbers of patients with MSA and MAA antibodies*
*Patients may have been positive for more than one autoantibody.
MAA: myositis-associated antibodies; MSA: myositis-specific antibodies.

Conclusion. At baseline, 49 (52%) patients were MSA-positive, 13 (14%) MAA-positive, and in 33 (35%) no Ab were detected. Demographics and AB status of patients are shown in Table 1 and Figure 1. In the MSA+group (both treatment arms), 71% (35/49) of patients had minimal response at week 16, compared to 55% (18/33) in the Ab-ve group (p=0.12) and 38% (5/13) in the MAA+ group (p=0.03). Of the 24 MSA+ patients randomized to IVIG 83% showed TIS response at week 16 compared to 60% of MSA+ patients receiving placebo (p=0.07). In the AB -ve group significantly more patients responded in the IVIG arm than in the placebo arm (p=0.001). A subanalysis of individual autoantibodies showed that only anti-TIF+ patients (n=21) showed significantly more often minimal response compared to anti-TIF-1 -ve patients at week 16 and 40 (p=0.02 and p=0.03 respectively).
The response to IVIG was similar to placebo across the 3 antibody groups, suggesting that IVIG is effective irrespective of myositis autoantibody status.

P-112

SEROLOGICAL TESTING AND ANTIBODY MUTUAL EXCLUSIVITY IN A REAL-WORLD MULTI-CENTRE UK ADULT MYOSITIS COHORT

Xia Lyu[1,2,3], Francisca Bozan[4], Sarah Tansley[5], Patrick Gordon[6], Harsha Gunawardena[7], James B. Lilleker[8], Neil McHugh[5], Janine A. Lamb[3], Hector Chinoy[2,9], MYOPROSP Consortium

[1]Department of Rheumatology, Renji Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China; [2]Division of Musculoskeletal and Dermatological Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, UK; [3]Epidemiology and Public Health Group, School of Health Sciences, University of Manchester, Manchester, UK; [4]Section of Rheumatology, Department of Medicine, Hospital Clínico Universidad de Chile, Santiago, Chile; [5]Department of Pharmacy and Pharmacology, University of Bath, Bath, UK; [6]Southmead Hospital North Bristol NHS Trust, Bristol, UK; [7]King's College Hospital, London, UK; [8]Manchester Centre for Clinical Neurosciences, Salford Royal Hospital, Northern Care Alliance NHS Foundation Trust, Manchester Academic Health Science Centre, Salford, UK; [9]Department of Rheumatology, Salford Royal Hospital, Northern Care Alliance NHS Foundation Trust, Manchester Academic Health Science Centre, Salford, UK

Background. Idiopathic inflammatory myopathies (IIM) are a group of heterogeneous autoimmune diseases comprising different clinic-serological subgroups. Several myositis-specific autoantibodies (MSA) and myositis-associated autoantibodies (MAA) have been identified and play an important role in the diagnosis, management, and prognosis of people with IIM. However, the comparative performance of different autoantibody testing methods, the diagnostic significance of positive results, and the implications of the coexistence of multiple myositis antibodies remain unsolved.
Methods. The MYOPROSP study is a prospective UK-based cohort study that enrolled confirmed adult-onset IIM cases (using EULAR/ACR criteria) from 23 centres from 2016-20. Baseline clinical data, including local autoantibody records, were collected. Baseline serum samples were re-evaluated for MSA/MAAs using standardised methodology in a central lab. The primary method employed was immunoprecipitation (IP), covering antibodies against Jo-1, PL7, PL12, EJ, OJ, KS, Zo, Mi-2, TIF1, SAE, MDA5, NXP2, SRP, Pm-Scl, Ku, U1RNP, Ro60, and La. IP results were compared to local testing, including where available, HMGCR testing. Data was compiled on cases for co-existence of multiple MSA/MAAs.
Results. A total of 233 participants were recruited, and 216 serum samples were evaluated using IP. 97/216 (44.9%) tested had a known MSA/MAA by IP. An additional 16 cases from local testing were positive for anti-HMGCR antibodies. There was an increased number of MSA-positive cases reported locally than detected by IP (SRP: 11 *vs*. 3; TIF1-gamma 8 *vs*. 2; Mi-2 7 *vs*. 0; MDA5 3 *vs*. 0). There were additionally 30 MSA-positive cases by local testing with subsequent negative results by IP. We were unable to differentiate between anti-Ro52 or 60 from local testing. No MSA-positive cases had co-existing MSAs according to IP data (Table I), although three cases were recorded with two co-existing MSAs using local testing.
Conclusion. Less than 50% of the MYOPROSP cohort were IP positive at the time of testing. Local antibody testing identified a higher number of positive MSA/MAAs compared to IP, particularly for anti-SRP, TIF1-gamma, MDA5, Mi-2 antibodies, and also takes into account HMGCR testing. Cases with more than one MSA are infrequent, regardless of the detection method.
Acknowledgments. We express gratitude to all the patients and researchers participating in the MYOPROSP study.

Table I. Co-existing myositis antibodies in IP data (n=216).

Antigen	Positive	Co-Existing Autoantibody (based on IP data)																	
		None	MSA												MAA				
			Jo-1	PL7	PL12	EJ	OJ	ES	ZO	SRP	SAE	TIF1	Mi2	NXP2	MDA5	Ro60	La	PMScl	U1RNP	Ku
Jo-1	43	38														4	2		1	
PL7	5	5																		
PL12	6	6																		
EJ	0	0																		
OJ	0	0																		
KS	0	0																		
ZO	0	0																		
SRP	5	4														1				
SAE	10	9														1				
TIF1	4	4																		
Mi2	0	0																		
NXP2	5	5																		
MDA5	0	0																		
Ro60	9	0	4							1	1						5			
La	5	0	2													5				
PMScl	8	8																		
U1RNP	8	7	1																	
Ku	1	1																		

Positive: number of cases with positive corresponding antibody.
None: number of cases with only one MSA or MAA; IP testing doe not take into account HMGCR r Ro52 positivity.

P-113

DETERMINATION OF TYPE I INTERFERONS AS A BIOMARKER FOR INFLAMMATORY MYOPATHIES

Loïs Bolko[1], Samuel Malartre[2], Paul Breillat[3], Joanna Teran-Gamboa[2], Damien Amelin[2], Céline Anquetil[2], Karim Dorgham[4], Pascale Ghillani-Dalbin[5], Guy Gorochov[4], Olivier Benveniste[6], Yves Allenbach[6]
[1]Rhumatologie, CHU de Reims, France; [2]INSERM U 974, Paris, France; [3]Médecine Interne, Hôpital Cochin, Paris, France; [4]Cimi, INSERM, Paris, France; [5]Département d'immunologie, Hôpital Pitié- Salpêtrière, Paris, France; [6]Département de Médecine Interne et Immunologie Clinique, Hôpital Pitié- Salpêtrière, Paris, France

Background. Idiopathic inflammatory myopathies (IIMs) are a diverse group of multi-system, autoimmune disorders. Dermatomyositis (DM) and anti-synthetase syndrome (ASyS) are distinguished by significant extramuscular manifestations. Evaluating disease activity in DM and ASyS presents challenges due to the lack of biomarkers. Interferons (IFNs) have a crucial role in the pathogenesis of these conditions. This study aimed to validate the efficacy of serum IFN assays in monitoring disease activity in an independent cohort of DM and ASyS patients.
Methods. Single-centre study including DM and ASyS patients defined according to international criteria. Disease activity was measured at the time of serum collection and assessed by muscle testing (MMT8 score 0-150), muscle enzymes (CK and ASAT/LDH/aldolase) and extramuscular assessments via MDAAT for deriving the Physician Global Assessment (PGA) score (0-10). Patients were classified as active if PGA>5. Serum IFNα levels was measured using the single molecule array (SIMOA) technique. Serum IFNβ level was measured by Elisa.
Results. Seventy patients were included in this cohort (DM n=49 and SAS n=21). The mean age was 49 years, with a female-to-male ratio of 3.4 for DM and 5.7 for ASyS. Disease activity was 6 for DM (mean follow-up time 4 years) and 5.8 ASyS (mean follow-up time 7.2 years). The median IFNα level was 0.32 [0.0-3.7] pg/mL in DM and 0.07 [0-0.8] pg/mL in SAS. IFNβ was not detectable in SAS and its median level was 0 [0-31.0] pg/mL in DM. Serum IFNα and IFNβ concentration was significantly correlated with DM activity (R=0.66 [0.5-0.8], p<0.0001 and R= R=0.39 [0.1-0.61]) but not with ASyS activity (R=0.31 [-0.13-0.65], p=0.15).
ROC curves were constructed using data from both cohorts of DM (n=101), separating patients with active (PGA>5) and non-active DM. Patients with active DM exhibited higher median IFNα level (0.49 pg/ml [0.1-3.7]) compared with non-active patients (0.03 pg/ml [0.01-0.07] p<0.05). The area under the curve was 0.90 IC95 (0.76-0.97) p<0.05. For a threshold of 0.1 pg/ml, the sensitivity was 83% and the specificity 81% for determining disease activity. Furthermore, MDA5 patients displayed significantly higher IFNα compared to other antibody groups (6.58 *vs*. 0.14 p<0.005), and NXP2 patients had elevated IFNβ levels relative to those with Tiff1γ antibodies.
Conclusion. Serum IFNα level measured by SIMOA is a biomarker of DM activity. Myositis-specific antibodies appear to be associated with a different secretion profile.

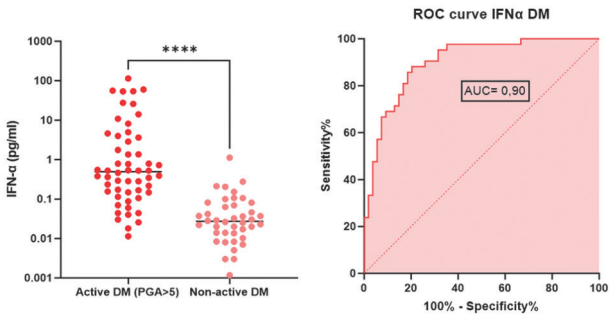


Fig. 1. IFNα as biomarker of disease activity.

P-114

REAL-WORLD PATIENT AWARENESS OF MYOSITIS ANTIBODY STATUS

Raisa Lomanto Silva[1], Shiri Keret[2], Akanksha Sharma[3], Tanya Chandra[4], Siamak Moghadam-Kia[4], Chester V. Oddis[4], Rohit Aggarwal[4]
University of Pittsburgh Medical Center, Department of Medicine Bnai-Zion Medical Center, Faculty of Medicine, Rheumatology, Technion, Haifa, Israel; UPMC Mercy, Department of Medicine University of Pittsburgh Medical Center, Division of Rheumatology and Clinical Immunology, Pittsburgh, PA, USA

Background. Myositis-specific autoantibodies (MSA) represent unique phenotypes in idiopathic inflammatory myopathies (IIM). Myositis-associated antibodies (MAA) most commonly occur in IIM overlap syndromes. MSA and MAA should be evaluated in all IIM patients, but their real-world frequency, distribution, and patient awareness of their antibody status is not well known.
Methods. The Myositis Patient-Centered Tele-Research is a U.S. prospective observational study. Patients were enrolled remotely from anywhere in U.S. through social media and patient organizations and traditionally through myositis centers. Patients completed a pre-screening questionnaire with self-report of MSA and/or MAA status, IIM confirmed diagnosis (by rheumatologist, neurologist, or dermatologist), and on proximal muscle weakness, muscle or skin biopsy, electromyography, muscle enzymes, and/or rashes. A subset of patients had their clinical features, diagnosis and MSA/MAA results confirmed by chart review.
Results. A total of 408 participants completed the pre-screening questionnaire: 317 (77.8%) females, mean age 54.84 (SD ± 13.8), 378 (92.6%) non-Hispanic, and 328 (80.4%) White, 49 (12%) Black, 12 (3.3%) Asian. Most patients (378, 92.6%) met IIM criteria. IIM subtypes were dermatomyositis (195, 51.6%), polymyositis or necrotizing myopathy (183, 48.4%). A total of 177 (46.8%) reported MSA and/or MAA positive, 62 (12.4%) MSA and MAA negative, and 139 (36.8%) were unsure about their antibody status. The most common MSAs were Jo-1 (31.6%), anti-SRP (11.3%), anti-HMGCR (9%), anti-TIF-γ (9%), anti-MI-2 (6.2%), and anti-MDA-5 (5.1%). In terms of MAA, 21 (11.8%) had positive SSA (Ro), 9 (5.1%) anti-PM-Scl. There was no difference in MSA/MAA frequency or distribution by U.S. region or by enrollment method. Significantly higher percentage of patients from the NorthEast were aware of antibody status, and awareness was least in West. Age, gender, ethnicity, and race were not associated with knowledge of antibody status. In a subset of patients, self-report of antibody results was highly consistent with chart confirmation of MSA/MAA antibody positivity (96.4%) and overall awareness of antibody results (91.5%).
Conclusion. In a real-world IIM cohort, anti-Jo1, -SRP, -HMGCR, -TIFγ, -MI-2, -MDA-5, -SSA were the most common MSA/MAA reported by patients. 1/3rd of IIM patients was not aware of their antibody status. There was no difference in antibody frequency, distribution of awareness by patients enrolled remotely *vs*. by expert centers, however, patients enrolled from the NorthEast had significantly more awareness of autoantibody. No demographic differences were seen. Patients' education and awareness of their disease process and key test results is crucial, as they are important allies in the healthcare decision-making process.

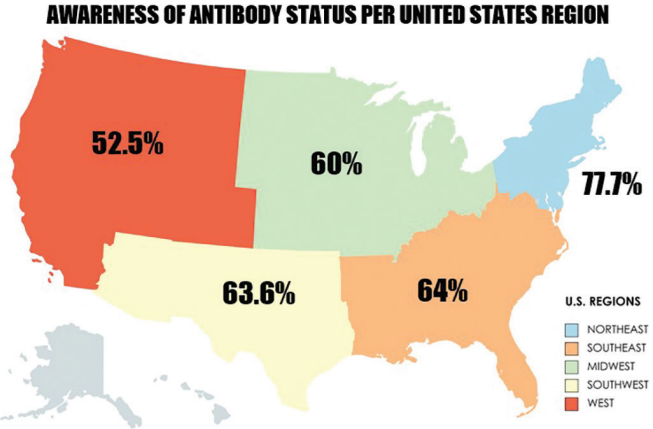


Fig. 1.

P-115

ANTI-RUVBL1/2 AUTOANTIBODIES ARE NOVEL MYOSITIS-ASSOCIATED ANTIBODIES

Ian Langleben[1], Katherine A. Buhler[2], Claudie Berger[3], Meifeng Zhang[2], Océane Landon-Cardinal[4,5], Josiane Bourré-Tessier[4], Yves Troyanov[6], Canadian Inflammatory Myopathy Study, Marvin J Fritzler[2], May Y. Choi[2], Marie Hudson[1,7,8], Valérie Leclair[1,7,8]

[1]Department of Medicine, McGill University, Montreal, Canada; [2]Division of Rheumatology, Cumming School of Medicine, University of Calgary, Calgary, Canada; [3]Research Institute of the McGill University Health Centre, Montreal, Canada; [4]Division of Rheumatology, Centre hospitalier de l'Université de Montréal (CHUM), Montreal, Canada; [5]CHUM Research Center, Montreal, Montreal, Canada; [6]Division of Rheumatology, Hôpital du Sacré-Coeur, Department of Medicine, Université de Montréal, Montréal, Canada; [7]Division of Rheumatology, Jewish General Hospital, Montreal, Canada; [8]Lady Davis Institute for Medical Research, Montreal, Canada

Background. Myositis-specific and associated autoantibodies (MSA/MAA) help define clinical phenotypes, and, in certain cases, can guide management of autoimmune inflammatory myopathies (AIM). Recently, autoantibodies against RuvBL1/2 (a macromolecular complex involved in DNA repair and transcription) were described in patients with scleroderma with and without myositis (1, 2). The aim of this study was to compare the clinical characteristics of AIM patients with and without anti-RuvBL1/2 antibodies in a large AIM cohort.

Methods. The Canadian Inflammatory Myopathy Study (CIMS) is a multicenter research cohort of AIM patients collecting longitudinal standardized assessments, patient-reported outcome measures and biological samples. In CIMS, AIM is classified using an integrated clinico-sero-pathological approach. Sera from consecutive CIMS subjects were tested for anti-RuvBL1/2 by addressable laser bead immunoassays (ALBIA) using full-length human recombinant proteins (Novus Biologicals, Centennial, CO: Cat. NBP1-50845 for RuvBL1 and Cat. H00010856-Q01 for RuvBL2). The ALBIA results were validated by immunoprecipitation. Demographic data, clinical features and known serologies were retrieved from the CIMS database. Chi-square or Fisher exact tests (categorical variables) and Student or median tests (continuous variables) were used to compare AIM patients positive and negative for anti-RuvBL1/2. After Bonferroni correction for multiple comparisons, $p<0.001$ was considered statistically significant.

Results. The study included 141 AIM patients (69% female, mean ± SD age at diagnosis 54±15 years, median disease duration 1.3 years (IQR 0.5-3.4)). The cohort included dermatomyositis (34%), scleromyositis (26%), anti-synthetase syndrome (12%), overlap myositis (7%), immune-mediated necrotizing myopathy (6%), inclusion body myositis (11%) and polymyositis/unspecific myositis (5%) subsets. Of those, 31% (n=43) were anti-RuvBL1/2 positive and anti-RuvBL1/2 antibodies were positive in 5% of patients without other known MSA/MAA. More than half of the anti-RuvBL1/2 positive patients had either dermatomyositis (n=13) or scleromyositis (n=16) (Table I). In the anti-RuvBL1/2 positive group, 35% were positive for at least one other MSA and 63% for MAA. After correcting for multiple comparisons, no statistically significant differences were found between anti-RuvBL1/2 positive and negative patients.

Conclusion. Anti-RuvBL1/2 autoantibodies have been described in scleroderma. Our study demonstrates they are also present throughout the AIM spectrum, though most frequently in dermatomyositis. They are frequent in AIM and were the only autoantibodies present in 5% of subjects. These findings suggest that anti-RuvBL1/2 are myositis-associated autoantibodies and are useful to close the serological gap in seronegative AIM subjects (*i.e.* without known antibodies). Further studies are underway to explore if anti-RuvBL1/2 titers might be helpful to identify specific clinical phenotypes.

Table I. Baseline characteristics of the cohort stratified on anti-RuvBL1/2 status.

	Anti-RuvBL1/2			
Clinical features	Positive N=43	Negative N=98	p-value	Missing
Female, n (%)	33 (77%)	64 (66%)	0.203	1
Age at diagnosis (years), mean (SD)	54.1 (15)	54.4 (14)	0.906	2
Disease duration (years), median (IQR)	2.1 (0.5-5.2)	1.1 (0.5-3.2)	0.180	4
IIM subsets, n (%)				
Dermatomyositis	13 (30%)	35 (36%)		
Anti-synthetase syndrome	2 (5%)	15 (15%)		
Scleromyositis	16 (37%)	20 (20%)		
Overlap myositis	3 (7%)	7 (7%)	0.249	0
Immune-mediated necrotizing myopathy	3 (7%)	5 (5%)		
Inclusion body myositis	3 (7%)	12 (12%)		
Other (polymyositis, unspecific)	3 (7%)	4 (4%)		
Disease severity onset, n (%)				
Mild	12 (28%)	44 (46%)		
Moderate	16 (41%)	36 (38%)	0.067	6
Severe	9 (23%)	16 (17%)		
Extremely severe	2 (5%)	0 (0%)		
Dermatomyositis rashes, n (%)	9 (21%)	32 (33%)	0.158	0
Mechanics hands, n (%)	3 (7%)	13 (13%)	0.278	0
Calcinosis, n (%)	3/42 (7%)	3/95 (3%)	0.370	4
Abnormal nailfold capillaries, n(%)	17 (40%)	35 (36%)	0.665	0
Sclerodactyly*, n (%)	13 (30%)	11/97 (11%)	0.006	1
Raynaud, n (%)	17 (40%)	35 (36%)	0.665	0
Telangiectasias, n (%)	10 (23%)	13/97 (13%)	0.147	1
Puffy fingers, n (%)	3 (7%)	9/97 (9%)	0.654	1
Digital ulcerations, n (%)	4 (9%)	3/97 (3%)	0.120	1
Arthritis, n (%)	6 (14%)	19 (19%)	0.437	0
Dysphagia, n (%)	11 (26%)	30 (31%)	0.545	0
Gastrointestinal reflux, n (%)	19/40 (48%)	38/89 (43%)	0.611	12
ILD, n (%)	13 (30%)	45 (46%)	0.081	0
Myocarditis, n (%)	2 (5%)	1/97 (1%)	0.223	1
Pulmonary arterial hypertension, n (%)	1 (2%)	6 (6%)	0.339	0
Muscle weakness, n (%)	37 (86%)	71/92 (77%)	0.230	6
Proximal	32 (74%)	66 (67%)	0.401	0
Distal	14/42 (33%)	32/97 (33%)	0.969	2
Axial	30 (70%)	48/88 (55%)	0.096	10
Myalgias, n (%)	9 (21%)	28 (29%)	0.342	0
Peak CK (U/L), median (IQR)	850 (307-3735)	673 (156-2722)	0.705	11
Cancer, n (%)	3/42 (7%)	15/97 (15%)	0.180	2
Antinuclear autoantibodies (ANA), n (%)	34 (79%)	68 (69%)	0.237	0
Myositis-specific autoantibodies (MSA), n (%)	15 (35%)	40 (41%)	0.506	0
Myositis-associated autoantibodies (MAA), n (%)	27 (63%)	61 (62%)	0.951	0
No MSA/MAA	7 (16%)	24 (24%)	0.278	0
Mortality, n (%)	6 (14%)	14 (14%)	0.959	0

*After correction for multiple comparison using Bonferroni adjustment, this difference did not remain significant.

References

1. KAJI K, FERTIG N, MEDSGER JR. TA *et al*.: Autoantibodies to RuvBL1 and RuvBL2: a novel systemic sclerosis-related antibody associated with diffuse cutaneous and skeletal muscle involvement. *Arthritis Care Res* 2014; 66(4): 575-84.
2. VULSTEKE J-B, PIETTE Y, BONROY C *et al*.: Anti-RuvBL1/2 autoantibodies in patients with systemic sclerosis or idiopathic inflammatory myopathy and a nuclear speckled pattern. *Ann Rheum Dis 2022*; 81(5): 742-4.

P-116

THE ROLE OF ALDOLASE IN THE DIAGNOSIS AND FOLLOW-UP OF IDIOPATHIC INFLAMMATORY MYOPATHY

Renske G. Kamperman[1], Sanne W. Evers[1], Pinar Özkaynar[2], Anneke J. van der Kooi[1], Joost Raaphorst[1]

[1]Department of Neurology, Amsterdam University Medical Center, Location AMC, Amsterdam, The Netherlands; [2]Department of Neurology, Flevoziekenhuis, Almere, The Netherlands

Background. Muscle enzymes take up an important role in the diagnosis and follow-up of idiopathic inflammatory myopathy (IIM). While serum creatine kinase (sCK) is the most established enzyme, 3-20% of IIM patients present with normal sCK levels (1-3). Another enzyme, aldolase, has limited evidence regarding its role in IIM to date (4-6). This prospective clinical study evaluates the diagnostic value and clinical correlates of aldolase in patients with suspected IIM.

Methods. The current study is a sub-study of the diagnostic ADAPT study in which patients with clinically suspected IIM were included. sCK and aldolase were determined at baseline (treatment naïve) and after six months. The diagnostic accuracy, in terms of sensitivity, specificity and likelihood ratios, of both enzymes was analyzed. A number needed to test (NNT) was calculated, defined as the number of patients requiring testing with aldolase to detect an IIM patient that would otherwise remain undetected. We correlated aldolase levels with muscle strength, functional disability and clinical improvement (Total Improvement Score; TIS).

Results. Seventy-two patients were included of whom two-thirds had IIM (as judged by two clinicians) and one-third had an IIM mimic. The sensitivity and specificity of elevated baseline aldolase levels for an IIM diagnosis was 87% and 61%, respectively, which is comparable to sCK. Six (16%) of the IIM patients had normal sCK levels at baseline, two of whom (both DM) had elevated aldolase levels. Eight patients with normal sCK needed to be tested for aldolase to find one IIM patient (NNT). In five (14%) patients, aldolase was the most elevated enzyme and used as core set measure in TIS. In IIM patients, a significant decrease at follow-up was seen for both aldolase and sCK. In IIM patients with elevated aldolase levels at baseline, 16 out of 19 (84%) had normalization of aldolase levels after six months. Correlations were found between baseline values of aldolase and Manual Muscle Testing (MMT) (r_s -0.446, p=0.005, n=38) and between change in aldolase and TIS (r_s = -543, p=0.016, n=19).

Conclusion. Preliminary data of our prospective diagnostic study show that aldolase has a comparable diagnostic accuracy to sCK in detecting IIM. Clinical correlates between aldolase and both the MMT and TIS were detected. The diagnostic value of aldolase in IIM is modest and seems to be restricted to a subgroup of patients with a normal sCK. The complete data of this sub-study (18 aldolase measurements are pending) will be presented during the conference.

References

1. LEHMANN URBAN D, MOHAMED M, LUDOLPH AC, KASSUBEK J, ROSENBOHM A: The value of qualitative muscle MRI in the diagnostic procedures of myopathies: a biopsy-controlled study in 191 patients. *Ther Adv Neurol Disord* 2021; 14: 1756286420985256.
2. MATHUR T, MANADAN AM, THIAGARAJAN S, HOTA B, BLOCK JA: Serum transaminases are frequently elevated at time of diagnosis of idiopathic inflammatory myopathy and normalize with creatine kinase. *J Clin Rheumatol* 2014; 20(3): 130-2.
3. BOHAN A, PETER JB, BOWMAN RL, PEARSON CM: Computer-assisted analysis of 153 patients with polymyositis and dermatomyositis. *Medicine* (Baltimore) 1977; 56(4): 255-86.
4. NOZAKI K, PESTRONK A: High aldolase with normal creatine kinase in serum predicts a myopathy with perimysial pathology. *J Neurol Neurosurg Psychiatry* 2009; 80(8): 904-8.
5. VOLOCHAYEV R, CSAKO G, WESLEY R, RIDER LG, MILLER FW: Laboratory test abnormalities are common in polymyositis and dermatomyositis and differ among clinical and demographic groups. *Open Rheumatol J* 2012; 6: 54-63.
6. MATHUR T, MANADAN AM, THIAGARAJAN S, HOTA B, BLOCK JA: The utility of serum aldolase in normal creatine kinase dermatomyositis. *J Clin Rheumatol* 2014; 20(1): 47-8.

P-117

EFFICACY AND SAFETY OF ULTRASOUND-GUIDED MUSCULAR BIOPSY IN THE DIAGNOSIS OF IDIOPATHIC INFLAMMATORY MYOPATHIES

Filipa Costa[1,2], Matilde Bandeira[1,2], Eduardo Dourado[2,3,4], Rafael Roque[5], João E. Fonseca[1,2], Raquel C. Marques[1,2], Fernando Saraiva[1,2]

[1]Serviço de Reumatologia, Centro Hospitalar Universitário Lisboa Norte, Centro Académico de Medicina de Lisboa, Portugal; [2]Unidade de investigação em Reumatologia, Instituto de Medicina Molecular, Faculdade de Medicina, Universidade de Lisboa, Centro Académico de Medicina de Lisboa, Portugal; [3]Serviço de Reumatologia, Centro Hospitalar do Baixo Vouga, Aveiro, Portugal; [4]Centro de Investigação em Reumatologia de Aveiro, Centro Académico Clínico Egas Moniz, Portugal; [5]Laboratório de Neuropatologia, Serviço de Neurologia, Centro Hospitalar Universitário Lisboa Norte, Centro Académico de Medicina de Lisboa, Portugal

Background. Idiopathic inflammatory myopathies' (IIM) differential diagnosis frequently requires histological evaluation. Muscle biopsies can be performed surgically or percutaneously. However, since myositis can affect different muscles in the same anatomical region, non-guided methods may provide lower sensitivity. We aimed to assess the safety and efficacy of ultrasound-guided muscle biopsy (UGMB) in obtaining adequate samples for histological analysis and establishing an IIM diagnosis in patients with suspected myositis.

Methods. We included patients followed at the Rheumatology clinic of a tertiary centre with a suspected IIM diagnosis. UGMBs were performed from January 2022 to August 2023. Before the biopsy, a muscle was selected through muscle ultrasound examination. Local anaesthesia was injected up to the muscle fascia under ultrasound guidance. Afterwards, ultrasound was used to guide a 14G biopsy needle to an appropriate biopsy site. Finally, five or more muscle samples were collected, placed in a dry-cooled medium and delivered to the Neuropathology laboratory.

Results. Thirty biopsies were performed, 60% (n=18) to female patients. Almost all (n=27, 90%) samples allowed a thorough histologic evaluation. From all the samples, 37% (n=11) were compatible with myositis, and 27% (n=8) revealed muscle tissue without pathological changes. About 27% (n=8) of the biopsies showed nonspecific muscle alterations. Only 2 samples did not have enough material to perform a complete histologic diagnosis, and 1 presented histological artefacts related to the sample manipulation. A third of the patients with clinically suspected IIM who were not under immunosuppressant treatment (n=12) had a biopsy compatible with that diagnosis. The results were similar amongst the patients under immunosuppressants (n=18), where 38% (n=7) had a biopsy compatible with IIM (Table I). The UGMB was generally well-tolerated, with an average Visual Analogical Scale for pain of 4.5 out of 10 during the procedure. There were no moderate or severe adverse events. One patient reported a mild long-term adverse event (mild pain), which lasted for twelve weeks after the procedure.

Conclusion. UGMB is a safe method to collect muscle samples. To our knowledge, this is one of the first studies analysing the efficacy of the UGMB in IIM. Histological analysis was possible in 90% of the samples, suggesting this is an effective way to collect muscle samples for IIM differential diagnosis.

Table I. Clinical, histological and final diagnosis.

Clinical diagnosis	Indication for biopsy	Histologic diagnosis	Final diagnosis	IMS before biopsy
Suspected inflammatory myopathy	DC	Inflammatory myopathy	Inflammatory myopathy	-
Dermatomyositis	DC	Inflammatory myopathy	Dermatomyositis	PDN
Dermatomyositis	DC	Inflammatory myopathy	Dermatomyositis	-
Suspected inflammatory myopathy	DC	Inflammatory myopathy	Inflammatory myopathy	-
Sjogren's syndrome	DC	Inflammatory myopathy	Inflammatory myopathy	PDN
Antisyntethase syndrome	DC	Inflammatory myopathy	Antisyntethase syndrome	CYC
Dermatomyositis	DC	Inflammatory myopathy	Dermatomyositis	PDN
SLE	DC	Inflammatory myopathy	Inflammatory myopathy	MTX
Dermatomyositis	DC	Inflammatory myopathy	Dermatomyositis	PDN
Dermatomyositis	Diagnostic reclassification	Inflammatory myopathy/ dermatomyositis	Dermatomyositis	PDN, MTX
Polymyositis	DC	Inflammatory myopathy/ polymyositis	Polymyositis	-
Dermatomyositis	DC	Multiple artifacts	Dermatomyositis	PDN, MTX
Suspected inflammatory myopathy	DC	Normal	Non-confirmed IIM	-
Suspected inflammatory myopathy	DC	Normal	Non-confirmed IIM	-
Clinically amyopathic dermatomyositis	DC	Normal	Clinically amyopathic dermatomyositis	MTX
Steroids myopathy	DC	Normal	Steroids myopathy	-
Fibromyalgia with raised CK and inflammatory markers	DC	Normal	Non-confirmed IIM	-
Clinically amyopathic dermatomyositis	DC	Normal	Clinically amyopathic dermatomyositis	PDN, MTX
Dermatomyositis	DC	Normal	Dermatomyositis	AZT
Dermatomyositis	DC	Normal	Dermatomyositis	PDN, MTX
Suspected inflammatory myopathy	DC	Unspecific findings	Non-confirmed IIM	-
Suspected inflammatory myopathy	DC	Unspecific findings	Non-confirmed IIM	-
Necrotising myopathy	DC	Unspecific findings	Necrotising myopathy	PDN, MTX
Antisyntethase syndrome	DC	Unspecific findings	Antisyntethase syndrome	-
Suspected inflammatory myopathy	DC	Unspecific findings	Inflammatory myopathy	AZT
Suspected inflammatory myopathy	DC	Unspecific findings	Non-confirmed IIM	PDN
Suspected inflammatory myopathy	DC	Unspecific findings	Non-confirmed IIM	PDN, MTX
Polymyositis	Diagnostic reclassification	Unspecific findings	Polymyositis	PDN, MTX
Suspected inflammatory myopathy	DC	Insufficient material	Myopathy non-IIM	PDN
Polycythemia with raised CK and positive MSA	DC	Insufficient material	Non-confirmed IIM	-

Abbreviations: AZT: azathioprine; CYC: cyclosporine; CK: creatine kinase; DC: diagnostic confirmation; IIM: idiopathic inflammatory myopathy; IMS: immunosuppressant; MSA: myositis specific antibody; MTX: methotrexate; PDN: prednisolone.

P-118

FABP3 AS A STRONG PREDICTOR OF MUSCLE STRENGTH AND MYOSITIS DISEASE ACTIVITY IN PATIENTS WITH IDIOPATHIC INFLAMMATORY MYOPATHIES

Zoltan Griger[1], Hajnalka Lőrincz[2], Dorottya Szinay[1], Tibor Béldi[1], Henrik Molnár[1], Katalin Szabó[1], Mariann Harangi[2], Melinda Nagy-Vincze[1]

[1]Division of Clinical Immunology, Department of Internal Medicine, Faculty of Medicine, University of Debrecen, Debrecen, Hungary; [2]Division of Metabolism, Department of Internal Medicine, Faculty of Medicine, University of Debrecen, Debrecen, Hungary

Background. Due to the expanding knowledge about the pathogenesis of Idiopathic Inflammatory Myopathies (IIM) there is a pressing need for simple blood-based biomarkers of disease activity and organ involvement. Novel skeletal muscle injury biomarkers that have recently been identified may outperform or add value to the conventional biomarkers like creatine kinase (CK). Fatty acid binding protein 3 (FABP3) is mainly distributed in cardiomyocytes and skeletal muscle cells and is a potential biomarker of musculoskeletal toxicity. Previously it was shown in a small sized myositis cohort that serum level of FABP3 is associated with muscle strength; however, its association with disease activity was not examined. Our aim was to determine FABP3 levels in IIM patients and find correlations between FABP3 and disease activity, CK, muscle strength and other parameters.

Methods. In this cross-sectional study eighty patients with IIM (mean age 56.2±13.4 years, disease duration 9 (5-15) years; 49% (n=39) polymyositis, and 51% (n=41) dermatomyositis) were enrolled. Disease activity was determined using the IMACS core set measures. Muscle strength was measured with manual muscle test (MMT). FABP3 levels were determined using ELISA. Statistical analysis was performed with Statistica v.13.5.0.17 software (TIBCO Software Inc., Tulsa, OK, USA).
Results. Median disease activity was 1 (0-2.15), CK level was 90.5 (62-185) IU/ml. Median FABP 3 level was 1.08 (0.73-1.38) ng/ml. Positive correlation were detected between FABP3 and CK (r=0.42; *p*=0.00009), Physician Global Disease Activity (r=0.28; p=0.013) and C-reactive protein (r=0.35, *p*=0.002), whereas strong negative correlation with MMT (r=-0.39*; p*=0.0005) (Fig. 1). Neither CK, nor CRP showed significant correlation with disease activity, or muscle strength. Stepwise multiple regression analysis confirmed that FABP3 independently correlated with muscle strength ($\beta_{standardized}$=-0.39; *p*<0.01) and physician global disease activity was best predicted by FABP3 ($\beta_{standardized}$=0.28; *p*<0,001) among biomarkers. In addition, when all clinical and patient reported parameters were included, stepwise multiple regression analysis confirmed that the best predictors of Physician Global Activity were the Patient Global Activity ($\beta_{standardized}$=0.83; *p*<0,001) and MMT ($\beta_{standardized}$=-0.36; *p*<0.001).
Conclusion. FABP3 may be a useful biomarker of myositis disease activity, which may predict better muscle strength and Physician Global Activity than CK. Further study of larger myositis patient cohorts with longitudinal data and more diverse activities are required.

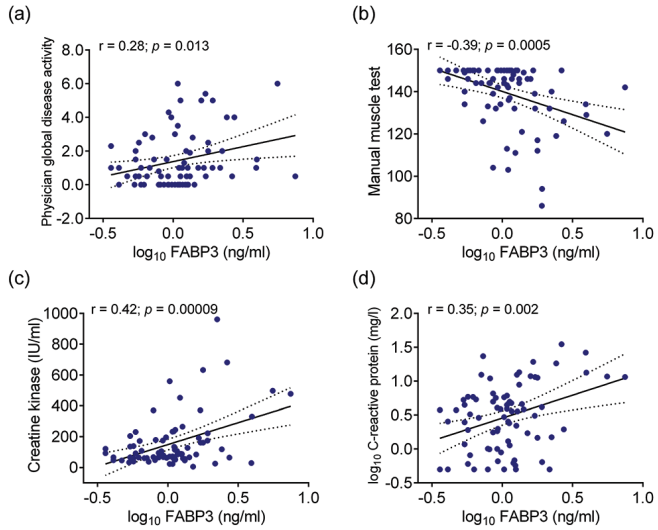


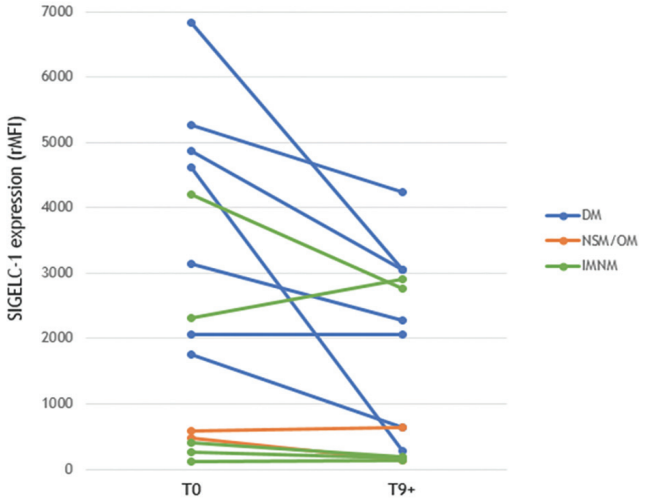
Fig. 1.

P-119

SIGLEC-1, A PROMISING BIOMARKER IN (DERMATO) MYOSITIS

Renske G. Kamperman[1], Saskia R. Veldkamp[2], Sanne W. Evers[1], Annet van Royen[3], Femke van Wijk[2], Anneke J. van der Kooi[1], Marc H.A. Jansen[3], Joost Raaphorst[1]
[1]Department of Neurology, Amsterdam University Medical Center, Location AMC, Amsterdam, The Netherlands; [2]Centre for Translational Immunology, University Medical Center Utrecht, Utrecht, The Netherlands; [3]Pediatric Rheumatology and Immunology, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, The Netherlands

Background. The disease course and response to treatment is variable among patients with idiopathic inflammatory myopathies (IIM). Monitoring disease activity and predicting flares are crucial for treatment optimization. The dermatomyositis (DM) subset of IIM often presents with normal sCK levels. A promising blood-based biomarker is SIGLEC-1, reflecting involvement of type-1 interferon pathway, which correlated well with disease activity in adult IIM and juvenile DM patients and was able to predict treatment response. We aim to investigate the dynamics and relation to clinical response of SIGLEC-1 expression levels in treatment-naive adult IIM patients and after 9 weeks of treatment.
Methods. We used data of IIM patients who completed a prospective phase-2 open-label pilot-study on efficacy of IVIG monotherapy (n=19; 9 DM, 5 immune mediated necrotizing myopathy (IMNM), 5 non-specific/overlap myositis (NSM/OM) and antisynthetasesyndrome (ASS). We assessed SIGLEC-1 expression on monocytes (CD14+), derived from peripheral blood mononuclear cells (PBMCs), at baseline and after 9 weeks of treatment. We compared this among IIM subgroups and healthy controls. Clinical correlates were measured with physician global activity (PhGA), manual muscle testing (MMT) and serum creatine kinase (CK). Treatment response was measured by the Total Improvement Score (TIS).
Results. All IIM patients showed upregulation of SIGLEC-1 expression on monocytes at baseline with a median relative median fluorescence intensity (rMFI) of 2541 (IQR 549-4865) compared to healthy controls (p<0.001), which was most pronounced in DM 4616 (IQR 2575-6052). In DM patients, sCK was normal in 5 patients (55.5%). A decrease of SIGLEC-1 was seen after 9 weeks of treatment, particularly in DM (Fig. 1). SIGLEC-1 correlated strongly with disease activity (MMT and PhGA) in DM, r_s -0.603 and 0.783 respectively. A decrease of SIGLEC-1 expression correlated strongly with the TIS r_s= -0.786, *p*=0.036.



Fig, 1. Decrease of SIGLEC-1 after 9 weeks of treatment.
rMFI: relative median fluorescence intensity; DM: dermatomyositis; NSM/OM: non-specificmyositis/overlapmyositis; IMNM: immune mediated necrotizing myopathy. +; in case of premature end of study, blood is sampled earlier.

Conclusion. Evaluation of early dynamics of SIGLEC-1 in treatment-naïve IIM patients shows highly elevated SIGLEC-1 expression at baseline emphasizing the role IFN type I in this disease. It was followed by a decrease after treatment, in many, but not all patients. SIGLEC-1 correlated strongly with disease activity and treatment response and emerges as a reliable biomarker, mainly in patients with DM with normal sCK levels. Future studies are needed to get more insight in the long-term dynamics of SIGLEC-1 and the ability to predict disease flares.

References

1. LERKVALEEKUL B, VELDKAMP SR, VAN DER WAL MM *et al*.: Siglec-1 expression on monocytes is associated with the interferon signature in juvenile dermatomyositis and can predict treatment response. *Rheumatology* 2021.
2. GRAF M, VON STUCKRAD SL, URUHA A *et al*.: SIGLEC1 enables straightforward assessment of type i interferon activity in idiopathic inflammatory myopathies. *RMD Open* 2022; 8(1).
3. LIM J, EFTIMOV F, VERHAMME C *et al*.: Intravenous immunoglobulins as first-line treatment in idiopathic inflammatory myopathies: A pilot study. *Rheumatology* (Bulgaria) 2021; 60(4).

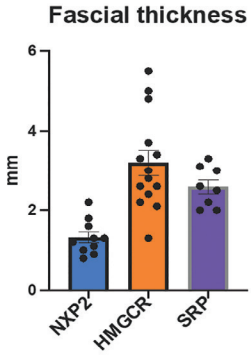
P-120

FASCIAL THICKNESS IN INFLAMMATORY MYOPATHIES

Sandra A. Ogbonnaya-Whittlesey, Iago Pinal Fernandez, Andrew Mammen
Muscle Disease, Unit, National Institute of Arthritis and Musculoskeletal and Skin Disease, National Institutes of Health, Bethesda, MD, USA

Background. Immune necrotizing myopathy (IMNM) is characterized by a paucity of inflammatory infiltrate in the setting of muscle fiber necrosis. Patients usually present with significant proximal extremity weakness and markedly elevated creatine kinase levels and lack cutaneous features associated with dermatomyositis.
Previous analysis of magnetic resonance imaging in patients with IMNM has shown that there is muscle edema predominantly in the posterior compartment of the thigh. We have anecdotally noticed fascial thickening in our patients with IMNM compared to other forms of myositis and wanted to explore if there is a significant difference.
Methods. We determined the fascial thickness on available MRI images of the thighs for 10 patients with anti-NXP2 positive dermatomyositis, 14 patients with anti-HMGCR antibodies, and 7 patients with anti-SRP antibodies.
Results. We detected a mean fascial thickness of 1.32mm (SD 0.46) in patients with anti-NXP2 antibodies, 3.19mm (SD 1.2) in patients with anti-HMGCR antibodies, and 2.58mm (SD 0.51) in patients with anti-SRP antibodies. Patients with anti-HMGCR and anti-SRP positive have significantly greater fascial thickness (both $p<0.01$) compared to patients with anti-NXP2 antibodies.

Fig. 1.



Conclusion. Our initial data suggest that the fascia is significantly thickened in patients with IMNM than in patients with NXP2 dermatomyositis. The mechanism of this finding remains to be elucidated. Additional evaluation is underway to confirm the findings and systematically compare differences across other types of myositis.

Reference

1. PINAL-FERNANDEZ I, CASAL-DOMINGUEZ M, CARRINO JA *et al*.: Thigh muscle MRI in immune-mediated necrotising myopathy: extensive oedema, early muscle damage and role of anti-SRP autoantibodies as a marker of severity. *Ann Rheum Dis* 2017; 76(4): 681-87.

P-121

EVALUATION OF A NOVEL PARTICLE-BASED MULTI-ANALYTE TECHNOLOGY FOR MYOSITIS SPECIFIC ANTIBODY DETECTION IN A LARGE US REFERENCE LABORATORY

Michael Mahler[1], Chelsea Bentow[1], Mary-Ann Aure[1], Tom Martins[2], Lisa Peterson[2,3]
[1]Headquarters & Technology Center Autoimmunity, Werfen, San Diego, CA, USA; [2]ARUP Institute of Clinical and Experimental Pathology, Salt Lake City, UT, USA; [3]Department of Pathology, University of Utah, Salt Lake City, UT, USA

Background. Myositis specific antibodies (MSA) represent important diagnostic and stratification tools in idiopathic inflammatory myositis (IIM) patients. However, the standardization of MSA remains challenging. Consequently, careful evaluation of MSA assays is important and requires reference materials for commutability studies. Recently a novel particle-based multi-analyte technology (PMAT) assay for the detection of MSA has been developed. The aim of the study was to evaluate PMAT for MSA detection.
Methods. A total of 411 samples were collected at ARUP Laboratories (Salt Lake City, UT, USA) selected based on routine testing which included a combination of line immunoassay [(LIA), EUROLINE Autoimmune Inflammatory Myopathies 16 Ag (IgG)], immunoprecipitation (IP), multiplex bead assay (FIDIS, for detection of antibodies against Jo-1) and/or ELISA (QUANTA Lite HMGCR, research use only, Inova Diagnostics). All samples were tested using the novel PMAT MSA assay (research use only) on the Aptiva platform (Werfen, US). A total of 66 healthy individuals were used to assess the specificity of the 12 MSA. Receiver operating characteristic (ROC) and area under the curve (AUC) analyses using the routine method results as binary classifier were used to assess the concordance independent of the PMAT cut-off values.
Results. When the results from the routine method were used as binary classifier in ROC analysis, very high AUC values were obtained for all analytes except OJ (0.638, 95% CI 0.590-0.686) (see Table I). The specificity of all MSA in healthy individuals was 100% except for Jo-1 and NXP-2. One of the 66 (1.5%) control samples was clearly positive for anti-Jo-1 antibodies. For NXP-2, 1/66 (1.5%) was weakly positive.
Conclusion. Our data shows high level of agreement between PMAT and the results obtained at ARUP Laboratories using a highly selected cohort. Further studies are needed to evaluate the agreement using an unselected cohort. Based on the fast turn-around time, PMAT might offer the possibility to improve patient care in patients with IIM.
Acknowledgements. The authors would like to thank the members of the Autoimmune Immunology Laboratories at ARUP Laboratories for technical assistance.

Table I. Method comparison using receiver operator characteristi analysis.

Analyte	No. positive/ total samples	AUC 95% Confidence interval	Comparator
Antisynthetase syndrome			
Jo-1	30/411	0.944 (0.944-981)	FIDIS
PL-7	32/372	0.951 (0.920-0.972)	IP+and/or LIA^{+-}
PL-12	32/380	0.986 (0.975-0.998)	IP+and/or LIA^{+-}
EJ	30/380	0.944 (0.920-0.967	IP+and/or LIA^{+-}
OJ Aptiva	29/381	0.771 (0.728-0.813)	IP
OJ LIA	29/381	0.638 (0.590-0.686)	IP
Dermatomyositis			
MDA5	36/379	0.971 (0.954-0.988)	IP+and/or LIA^{+-}
Mi-2	37/380	0.990 (0.906-1.002)	IP+and/or LIA^{+-}
NXP-2	38/383	0.909 (0.880-0.938)	IP+and/or LIA^{+-}
SAE	32/378	0.999 (0.997-1.002)	IP+and/or LIA^{+-}
TIF1γ	34/380	0.902 (0.873-0.932)	IP+and/or LIA^{+-}
Immune mediated necrotizing myopathies			
SRP	31/380	0.990 (0.980-1.000)	IP+and/or LIA^{+-}
HMGCR	30/41	0.976 (0.929-1.023)	ELISA

OP-18

PATTERN OF MUSCLE INVOLVEMENT IN IMMUNE-MEDIATED NECROTIZING MYOSITIS ON MAGNETIC RESONANCE IMAGING

Kiana, M, Vakil-Gilani, DO MPH, Daniela Ghetie, MD, Nizar Chahin, MD
Oregon Health & Science University, Portland, USA

Background. Inflammatory myopathies are a heterogeneous group of autoimmune diseases characterized by muscle inflammation and various extra-muscular manifestations. Immune mediated necrotizing myopathies (IMNM) are characterized by muscle weakness, elevated CK levels, and positive autoantibodies. Magnetic resonance imaging (MRI) is a key tool in the evaluation of inflammatory myopathies as it accurately shows muscle edema, atrophy, subcutaneous pathology and fatty infiltration. MRIs also demonstrate the distribution of muscle involvement
The aim of this study is to define the distribution of muscle involvement in patients with IMNM as this may provide timely diagnostic information and help guide early treatment options and optimal location for muscle biopsies. Additionally, use of MRI for assessment of muscle inflammation may have a role in longitudinal assessment of therapeutic efficacy.
Methods. We retrospectively collected data on 11 patients with IMNM who were identified from the inter-disciplinary myositis clinic at Oregon Health & Science University from 2016-current. Data collected included: age of symptom onset, list of symptoms, age at MRI, MRI sequence used, muscles involved on MRI, CK level, location of muscle biopsy, biopsy results, antibody positivity, treatment, and outcome. Descriptive analysis of pattern and severity of thigh muscle involvement was completed using the following grading system: Grade 0: under 30%, Grade 1: 31-50%, grade 2: 51-75%, and grade 3: over 75% muscle involvement.
Results. Out of 11 patients (average age at presentation 61.5 ±12.4), 45% had anti-SRP and 54% had anti-HMGCR antibodies. The average CK level was 11894.3 ±6404.7. All biopsied samples (54%) confirmed mild to severe necrosis. MRI analysis showed higher grading of muscle involvement in the semimembranosus (grade 2-3) and the long head of the biceps femoris (grade 1-3) followed by the adductor muscles (grade 0-3) in both anti-SRP and anti-HMGCR groups. There was relative sparing of the semitendinosus and complete sparing of the gracilis muscles in both groups.
Conclusion. In contrast to dermatomyositis (DM) which tends to affect the thigh anterior compartment muscles, we found that the posterior compartment of the thigh muscles is more commonly and severely affected in our cohort of IMNM patients followed by the medial compartment. Both anti-SRP and anti-HMGCR groups had relative sparing of the semitendinosus, and complete sparing of the gracilis muscle. While our data is limited, the timely identification of this MRI pattern as likely IMNM can serve as another noninvasive tool in the diagnosis armamentarium.

OP-19

PATIENTS SEROPOSITIVE FOR MULTIPLE MYOSITIS SPECIFIC AUTOANTIBODIES: EXPERIENCE FROM THE CLASS PROJECT DATABASE

Gianluca Sambataro[1*], Aravinthan Loganathan[2*], Akira Yoshida[3], Eduardo Dourado[4], Giovanni Zanframundo[5], Francisca Bozan[6], Daphne Rivero-Gallegos[7], Iazsmin Bauer Ventura[8], Yasuhiko Yamano[9], Sangmee S. Bae[10], Darosa Lim[11], Sara Faghihi-Kashani[12], Rohit Aggarwal[13#], Lorenzo Cavagna[5#]
[*]Contributed equally and share the first authorship
[#]Contributed equally and share the last authorship
[1]Regional referral center for Rare Lung Disease, Policlinico G. Rodolico-San Marco, University of Catania, Catania, Italy; [2]Royal National Hospital for Rheumatic Diseases, Bath, UK. Department of Life Sciences, University of Bath, Bath, UK. Arthritis Australia, Broadway, Glebe, NSW, Australia; [3]Department of Allergy and Rheumatology, Nippon Medical School Graduate School of Medicine, Tokyo, Japan; [4]Rheumatology Department, Centro Hospitalar do Baixo Vouga, Aveiro, Portugal; Aveiro Rheumatology Research Centre, Egas Moniz Health Alliance, Aveiro, Portugal; Rheumatology Research Unit, Instituto de Medicina Molecular, Faculdade de Medicina, Universidade de Lisboa, Centro Académico de Medicina de Lisboa; [5]Department of Rheumatology, University and IRCCS Policlinico S. Matteo Foundation Pavia, Pavia, Italy; [6]Department of Medicine, Section of Rheumatology, Hospital Clínico Universidad de Chile, Santiago de Chile, Chile; [7]Rheumatology Clinic, Instituto Nacional de Enfermedades Respiratorias, Ismael Cosío Villegas, Mexico City, Mexico; [8]Department of Medicine, Section of Rheumatology, University of Chicago, Chicago, USA; [9]Department of Respiratory Medicine and Allergy, Tosei General Hospital, Seto, Japan; [10]David Geffen School of Medicine Department of Medicine, Division of Rheumatology, University of California Los Angeles, USA; [11]Department of Dermatology, Perelman School of Medicine & Corporal Michael J. Crescenz Department of Veterans Affairs Medical Center, Philadelphia, USA; [12]Stanford School of Medicine, Division of Immunology and Rheumatology, Palo Alto, California, USA; [13]Myositis Center and Division of Rheumatology and Clinical Immunology, Department of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

Background. Myositis-specific antibodies (MSA) are generally considered mutually exclusive. The reference standard for testing is immunoprecipitation; however, this is expensive, time-consuming, and operator-dependent. Due to these limitations, immunoassays such as Line Blot Immunoassay (LIA) are commonly utilized due to its practicality. However, concerns regarding LIA and its tendency to yield multiple positivities for MSAs raise concerns regarding the potential for false positive results and clinical uncertainty in interpreting these findings. This study explores the prevalence of multiple seropositivity testing and its correlation with clinical phenotypes in, to our knowledge, the largest cohort of anti-synthetase syndrome (ASSD) patients from the Classification of Anti-synthetase Syndrome (CLASS) project.
Methods. Data regarding patients positive for Myositis Associated Antibodies (MAA) and/or MSA were extracted from the CLASS project database. To identify the relevance of the antibodies detected in multiple-positive samples, we created three separate groupings: MAA, Antisynthetase Antibodies (ASA) and non-ASA-MSA. Frequency and distribution as well as association with Antinuclear Antibody (ANA) and clinical features were performed among patients with single versus multiple positive antibodies.
Results. Of the seropositive patients (n=2589), 305 (11.8%) exhibited multiple seropositivity for MSA and/or MAA. Patients seropositive for multiple MSA were 176 (6.8%).
Comparing multiple versus isolated positivity, the first group was more tested by LIA (70.5% *vs*. 56%, p=0.0001), the second by ELISA (8.5% *vs*. 14.4% p=0.004). Immunoprecipitation was employed in a similar proportion in the two groups.
Comparing each autoantibody positivity, anti-Pm/scl and anti-Mi2 showed a lower proportion of expected ANA pattern when present in combination versus alone. No other differences were noted for the other antibodies. Patients with multiple positivity involving ASA reported a higher occurrence of mechanic's hands, arthritis and Interstitial Lung Disease.
Those with non-ASA-MSA had a higher prevalence of myositis, Gottron papules or heliotropic rash, whereas those with MAA showed a higher proportion of Raynaud's Phenomenon, scleroderma skin changes.
Since MAA is associated with scleroderma features, ASA with ASSD, and non-ASA-MSA with dermatomyositis, patients with multiple positivity showed a clinical picture coherent with all the autoantibodies reported in 12.1% (see Table 1 for the definitions).

Table I. Classification of the clinical features in the cohort with multiple autoantibody positivity.

Combination	SSc+ DM+ ASSD features	SSc+ DM features	SSc+ ASSD features	DM+ ASSD features	SSc features	DM features	ASSD features
MAA+MSA +ASA (24 pts)	**1***	0	2	0	1	3	4
MAA+MSA (40 patients)	0	**1***	1	1	4	9	2
MAA+ASA (91 patients)	**4***	0	**5***	1	5	3	22
MSA+ASA (63 patients)	**2***	0	4	**3***	2	9	8
o-ASA (39 patients)	**1***	0	1	5	0	2	**9***
o-MSA (34 patients)	0	0	2	6	1	**8***	1
o-MAA (14 patients)	0	0	0	0	**3***	0	0

The table reports the absolute number of patients for each classification.
* Clinical features concordant with the multiple positivity.
ASA: Anti-synthetase Antibody; ASSD: Anti-synthetase Syndrome; DM: Dermatomyositis; MAA: Myositis Associated Antibodies; MSA: Non-ASA-Myositis Specific Antibodies; o: only.
Definitions:
SSc features: Presence of Raynaud's Phenomenon and Puffy Hands or skin fibrosis
DM features: Presence of Myositis and Gottron Papules or Heliotropic Rash
ASSD features: Presence of at least 3 typical features together, including inflammatory arthritis, myositis, Interstitial Lung Disease and Mechanic's hands.

Conclusion. Patients with multiple seropositivity for MSA are at risk of false positivity, however a small proportion of these actually shows a clinical picture coherent with all the autoantibodies together, therefore suggesting a possible overlap syndrome.
Acknowledgements. The study was conducted with the support of the American College of Rheumatology (ACR) and the European Alleance of Associations for Rheumatology (EULAR).

OP-20

AGREEMENT BETWEEN LOCAL AND CENTRAL ANTI-SYNTHETASE ANTIBODIES DETECTION: ANALYSIS FROM CLASSIFICATION CRITERIA OF ANTI-SYNTHETASE SYNDROME (CLASS) PROJECT

Aravinthan Loganathan[1,2,3*], Giovanni Zanframundo[4*], Akira Yoshida[5], Sara Faghihi-Kashani[6], Iazsmin Bauer Ventura[7], Eduardo Dourado[8,9,10], Francisca Bozan[11], Gianluca Sambataro[12], Yasuhiko Yamano[13], Sharon Sangmee Bae[14], Darosa Lim[15], Angela Ceribelli[16,17], Natasa Isailovic[17], Carlo Selmi[16,17], Noreen Fertig[18], Elena Bravi[19], Yuko Kaneko[20], Jose Antonio Pereira da Silva[21], Vega Jovani[22], Javier Bachiller-Corral[23], Jose Cifrian[24], Antonio Mera-Varelam[25], Siamak Moghadam-Kia[18], Veronica Wolff[26], Julien Campagne[27], Alain Meyer[28], Konstantinos Triantafyllias[29], Johannes Knitza[30], Latika Gupta[31], Yair Molad[32], Florenzo Iannone[33], Ilaria Cavazzana[34], Matteo Piga[35], Giacomo De Luca[36], Sarah Tansley[1,2], Francesco Bonella[37], Tamera J. Corte[38,39], Tracey J Doyle[40], David Fiorentino[41], Miguel Angel Gonzalez-Gay[42], Marie Hudson[43], Masataka Kuwana[44], Ingrid Lundberg[45], Andrew L. Mammen[46,47], Neil John McHugh[2], Fredrick W. Miller[48], Carlomaurizio Montecucco[49], Chester Oddis[18], Jorge Rojas-Serrano[50], Jens Schmidt[51], Carlo Scirè[52], Albert Selva O Callaghan[53], Victoria P. Werth[15], Lorenzo Cavagna[4**], Rohit Aggarwal[18**]

[1]Royal National Hospital for Rheumatic Diseases, Bath,UK; [2]Department of Life Sciences, University of Bath, Bath, UK; [3]Arthritis Australia, Broadway, Glebe, NSW, Australia; [4]Division of Rheumatology, University of Pavia and IRCCS Policlinico S. Matteo Foundation, Pavia, Italy; [5]Department of Allergy and Rheumatology, Nippon Medical School Graduate School of Medicine, Tokyo, Japan; [6]Division of Immunology and Rheumatology, Stanford University School of Medicine, Palo Alto, CA, USA; [7]University of Chicago, Department of Medicine, Section of Rheumatology; [8]Rheumatology Department, Centro Hospitalar do Baixo Vouga, Aveiro, Portugal; [9]Aveiro Rheumatology Research Centre, Egas Moniz Health Alliance, Aveiro, Portugal; [10]Rheumatology Research Unit, Instituto de Medicina Molecular, Faculdade de Medicina, Universidade de Lisboa, Centro Académico de Medicina de Lisboa, Lisboa, Portugal; [11]Hospital Clínico Universidad de Chile, Department of Medicine, Section of Rheumatology; [12]Regional Referral Center for Rare Lung Disease, Policlinico "G. Rodolico-San Marco", University of Catania, Catania, Italy; [13]Department of Respiratory Medicine and Allergy, Tosei General Hospital; [14]University of California Los Angeles, David Geffen School of Medicine Department of Medicine, Division of Rheumatology; [15]Department of Dermatology, Perelman School of Medicine & Corporal Michael J. Crescenz Department of Veterans Affairs Medical Center, Philadelphia, United States; [16]Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Italy; [17]Rheumatology and Clinical Immunology, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Humanitas Research Hospital, Rozzano, Italy; [18]Division of Rheumatology and Clinical Immunology, Department of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA; [19]Ospedale Guglielmo da Saliceto, Piacenza; [20]Keio University School of Medicine, Tokyo; [21]Centro Hospitalar e Universitário de Coimbra; [22]Hospital General Universitario of Alicante; [23]Hospital Universitario Ramon y Cajal, Madrid; [24]Hospital Universitario Marques de Valdecilla, IDIVAL, University of Cantabria Santander, Spain; [25]Hospital Clínico Universitario de Santiago de Compostela; [26]Instituto Nacional del Torax; [27]HP Metz, Hopital Belle-Ile, Metz; [28]Centre de Référence des Maladies Auto-immunes Rares, Hôpital de Hautepierre, Hôpitaux Universitaires de Strasbourg; [29]ACURA Center for Rheumatic Diseases, Bad Kreuznach; [30]University of Erlangen; [31]Department of Clinical Immunology and Rheumatology, SGPGIMS, Raebareli Road, Lucknow 226014, India; [32]Rabin Medical Center, Beilinson Hospital, and Sackler Faculty of Medicine, Tel Aviv University; [33]University of Bari; [34]University and AO Spedali Civili, Brescia; [35]University Clinic and AOU of Cagliari; [36]IRCCS San Raffaele Hospital, Vita-Salute San Raffaele University; [37]Center for Interstitial and Rare Lung Diseases, Ruhrlandklinik, University of Duisburg-Essen, Essen, Germany; [38]University of Sydney, NSW, Australia; [39]Royal Prince Alfred Hospital, NSW, Australia; [40]Brigham and Women's Hospital, Harvard Medical School, Boston; [41]Department of Dermatology, Stanford University School of Medicine, Redwood City, CA, USA; [42]Hospital Universitario Marques de Valdecilla, IDIVAL, University of Cantabria Santander, Spain; [43]Jewish General Hospital and Lady David Research Institute, McGill University, Montreal; [44]Nippon Medical School Graduate School of Medicine, Tokyo, Japan; [45]Karolinska Institute, Stockholm, Sweden; [46]National Institute of Arthritis and Musculoskeletal and Skin Disorders, National Institutes of Health, Bethesda, MD, USA; [47]Departments of Medicine and Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, USA; [48]Environmental Autoimmunity Group, Clinical Research Branch, National Institute of Environmental Health Sciences, National Institutes of Health, Bethesda, MD, USA; [49]Interstitial Lung Disease and Rheumatology Units, Instituto Nacional de Enfermedades Respiratorias, Ismael Cosío Villegas, México City, México; [50]Interstitial Lung Disease and Rheumatology Units, Instituto Nacional de Enfermedades Respiratorias, Ismael Cosío Villegas, México City, México; [51]University of Gottingen, Germany; [52]Azienda Ospedaliero Universitaria S. Anna, Ferrara, Italy; [53]Universitat Autònoma de Barcelona, Spain

Background. The recognition and significance of identifying anti-synthetase antibodies as diagnostic and prognostic markers in anti-synthetase syndrome are growing. However, concerns persist regarding the accuracy of these assays, especially when using high-throughput commercial methods like Line blot and ELISA.
Our study assesses the real-world performance of locally reported testing methods against our central definition of positivity for anti-aminoacyl tRNA synthetase antibodies using the CLASS database, which, to our knowledge, is the largest database of anti-synthetase syndrome patients.
Methods. We collected 787 serum samples from participating centers for the CLASS project and their local anti-ARS test results. These samples underwent initial central testing using RNA-IP. Following this, the results were reconfirmed centrally through additional methods, including ELISA, line-blot assay (LIA), and protein-IP in cases of conflicting results. ARS-negative patients were also confirmed using central testing. The sensitivity, specificity, positive likelihood ratio and positive and negative predictive values were evaluated. We also calculated the inter-rater agreement between central and local results using a weighted κ co-efficient.
Results. The final analysis comprised 624 samples, revealing that 47.1% tested positive for an anti-ARS antibody during local testing. However, central testing identified an anti-ARS antibody in 43% of all samples. Regarding anti-Jo1, based on our predefined central definition of positivity, there was strong agreement with LIA, ELISA, IP, and "other" methods (ϰ values of 0.97, 0.97, 1.00, 0.84, and 1.00, respectively).
In contrast, locally reported non-anti-Jo1 exhibited good agreement compared to our central testing results and definition of positivity (ϰ 0.55), with a positive predictive value of 0.61. LIA results reported locally demonstrated good agreement for anti-PL12 and anti-EJ (κ values of 0.68 and 0.63) and moderate agreement for anti-PL7 (κ 0.57). In comparison, locally reported ELISA results showed good agreement for anti-PL12 and anti-EJ (κ values of 0.65 and 0.79) compared to our central definition and centrally performed tests.
Despite these findings, the positive likelihood ratio suggests that local results may remain pertinent and accurate, especially for patients with a high pre-test probability.
Conclusion. Our analysis reinforces the reliability of real-world anti-Jo1 detection methods. In contrast, challenges persist for anti-non-Jo1 identification, particularly anti-PL7 and rarer antibodies such as anti-OJ/KS. Clinicians should exercise caution when interpreting anti-synthetase antibodies, especially when commercial immunoassays test positive for non-anti-Jo1 antibodies. We recommend confirming with the ANA pattern or utilizing another confirmatory test if there is doubt from the clinician about the accuracy of the non-anti-Jo1 immunoassay result.

OP-21

PERFORMANCE OF MUSCLE MRI FOR THE DIAGNOSIS OF IMMUNOTHERAPY-INDUCED MYOSITIS

Claudio Galluzzo[1], Hortense Chassepot[2], Marie Bretagne[3], Adrien Procureur[4], Guillaume Mercy[5], Quentin Monzani[6], Olivier Lucidarme[5], Olivier Benveniste[7], Joe-Elie Salem[8], Yves Allenbach[9]

[1]Unit of Rheumatology, Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia, Italy; [2]Internal Medicine, CHU d'Amiens-Picardie Site Nord, Amiens; [3]Sorbonne Université, INSERM, UNICO-GRECO Cardio-oncology Program, Department of Pharmacology, GRC27, CIC-1901, AP-HP, Hôpital Pitié-Salpêtrière, Paris, France; [4]Sorbonne Université, INSERM, UNICO-GRECO Cardio-oncology Program, Department of Pharmacology, GRC27, CIC-1901, AP-HP, Hôpital Pitié-Salpêtrière, Paris, France; [5]Department of Medical Imaging, AP-HP, Hôpitaux Universitaires La Pitié Salpêtrière-Charles-Foix, Sorbonne Université, Paris, France; [6]Department of Radiology, APHP, Pitié-Salpêtrière University Hospital, Sorbonne University, University Pierre et Marie Curie, Paris, France; [7]Sorbonne Université, INSERM, Department of Internal Medicine, AP-HP, Hôpital Pitié-Salpêtrière, Paris, France; [8]Sorbonne Université, INSERM, UNICO-GRECO Cardio-oncology Program, Department of Pharmacology, GRC27, CIC-1901, AP-HP, Hôpital Pitié-Salpêtrière, Paris, France; [9]Sorbonne Université, INSERM, Department of Internal Medicine, AP-HP, Hôpital Pitié-Salpêtrière, Paris, France

Background. Immune checkpoint inhibitors (ICI) represent a major breakthrough in oncology for treating different types of neoplasms. Yet the frequent occurrence of immune related adverse events (IrAE) poses significant challenges. ICI-induced myotoxicity has the highest mortality rate among IrAE. The diagnosis is based on muscle biopsy but its limited availability

necessitates alternative diagnostic tools. We tested the accuracy of muscular magnetic resonance imaging (MRI) for ICI-induced myositis.
Methods. This single-center retrospective study aimed to assess the diagnostic efficacy of muscle MRI in detecting myositis-ICI. Consecutive patients treated for suspected myotoxicity underwent muscle MRI of the lower and/or upper limbs, including the girdles, within 30 days of muscle biopsy. T2 STIR sequences were analyzed for 146 muscles per patient, using a semi-quantitative score (0-3) to assess hypersignal presence. Blind analysis revealed that patients with hyper STIR signals on at least two muscles bilaterally were classified as MRI-positive. Myositis-ICI diagnosis was confirmed through myopathological examination indicating inflammation.
Results. Out of 126 patients, 31 were included (51.6% male, mean age 67.3 years). Predominant cancers included pulmonary carcinoma (25.8%), renal carcinoma (22.6%), and melanoma (19.4%). ICI usage comprised anti-PD1 (61.3%), anti-PDL1 (16.1%), and anti-PD1 combotherapy plus anti-CTLA4 (22.6%). Clinical signs were present in 71% of patients, including muscle weakness (51.6%), myalgia (38.7%), and other symptoms.
Creatine kinase levels were elevated in 67.7% of patients (2238 IU/L, range 195-11337 IU/L). Additionally, the median time between symptom onset and MRI was 16 days, and between muscle biopsy and MRI was 7 days. Sixty-four percent received corticosteroid therapy for 14.5 days, and 38.7% received ruxolitinib and abatacept for 12 days. MRI and muscular biopsy were positive in 51.6% and 58.1% of patients, respectively. MRI sensitivity and specificity for myositis-ICI diagnosis were 61.11% and 61.54%, with positive and negative predictive values of 68.69% and 75.30%. The positive likelihood ratio was 1.58. Notably, hypersignals on MRI were predominantly found in proximal muscles (88.8%) and axial muscles (88.8%), with distal muscles affected in 11.1% of cases. Furthermore, true positives, with a confirmed diagnosis of ICI-myositis and a positive MRI, represented 61.1%, where false positives represented 38.5%.
Conclusion. This study, though limited by a small sample size, suggests that muscle MRI has moderate diagnostic performance for myositis-ICI. A negative MRI does not eliminate the diagnosis, emphasizing the need for comprehensive evaluation.

Cancer and Myositis

P-122

FROM CLINICAL AMYOPATHY TO SEVERE OROPHARYNGEAL DYSPHAGIA IN PURE DERMATOMYOSITIS: GRADING EXTENT OF MUSCLE WEAKNESS IMPROVES STRATIFICATION FOR CANCER RISK

Hao Cheng Shen[1], Victoria Ivensky[2], Laurence Poirier-Blanchette[1], Yves Troyanov[1,3], Josiane Bourré-Tessier[1], Sabrina Hoa[1], Farah Zarka[2], Jessica Nehme[4], Jean-Paul Makhzoum[2], Anne-Marie Mansour[2], Rosalie-Sélène Meunier[2], Alexandra Mereniuk[5], Darosa Lim[6], Jean-Pierre Raynauld[1], Éric Rich[1], Jean-Richard Goulet[1], Marianne Landry[7], Maude Bouchard-Marmen[8], Valérie Leclair[9], Hugues Allard-Chamard[10], Marie Hudson[9], Erin O'Ferrall[11], Rami Massie[11], Jason Karamchandani[12], Benjamin Ellezam[13], Ira N.Targoff[14], Minoru Satoh[15], Marvin J. Fritzler[16], Jean-Luc Senécal[1], Alain Meyer[17], Océane Landon-Cardinal[1]
[1]Division of Rheumatology, Centre Hospitalier de l'Université de Montréal (CHUM), Montreal, QC, Canada; Department of Medicine, Université de Montréal, Montreal, QC, Canada; [2]Division of Internal Medicine, Department of Medicine, Hôpital du Sacré-Coeur de Montréal, Montreal, QC, Canada; Department of Medicine, Université de Montréal, Montreal, QC, Canada; [3]Division of Rheumatology, Department of Medicine, Hôpital du Sacré-Coeur de Montréal, Montreal, QC, Canada; Department of Medicine, Université de Montréal, Montreal, QC, Canada; [4]Division of Geriatrics, Department of Medicine, Hôpital du Sacré-Coeur de Montréal, Montreal, QC, Canada; Department of Medicine, Université de Montréal, Montreal, QC, Canada; [5]Division of Dermatology, Department of Medicine, Hôpital du Sacré-Coeur de Montréal, Montreal, QC, Canada; Department of Medicine, Université de Montréal, Montreal, QC, Canada; [6]Division of Dermatology, Centre hospitalier de l'Université de Montréal (CHUM), Montreal, QC, Canada; Department of Medicine, Université de Montréal, Montreal, QC, Canada; [7]Division of Internal Medicine, Department of Medicine, Hôpital de LaSalle, Montreal, QC, Canada; [8]Division of Rheumatology, Centre hospitalier Universitaire de Québec-Université Laval, Quebec City, QC, Canada; [9]Division of Rheumatology, Department of Medicine, Jewish General Hospital; Department of Medicine, McGill University, Montreal, QC, Canada; [10]Division of Rheumatology, Department of Medicine, Faculty of Medicine and Health Sciences, Université de Sherbrooke, Sherbrooke, QC, Canada; Centre de Recherche Clinique, Centre Hospitalier de l'Université de Sherbrooke, Sherbrooke, QC, Canada; [11]Department of Neurology and Neurosurgery, Montreal Neurological Hospital, McGill University, Montreal, QC, Canada; [12]Department of Pathology, McGill University and McGill University Health Center, Montreal, QC, Canada; [13]Division of Pathology, Centre Hospitalier Universitaire Sainte-Justine; Department of Pathology and Cell Biology, Université de Montréal, Montreal, QC, Canada; [14]Veteran's Affairs Medical Center, University of Oklahoma Health Sciences Center, Oklahoma Medical Research Foundation, Oklahoma City, OK, USA; [15]Department of Clinical Nursing, University of Occupational and Environmental Health, Kitakyushu, Japan; [16]Department of Medicine, Cumming School of Medicine, University of Calgary, Calgary, AB, Canada; [17]Faculté de Médecine, Université de Strasbourg; Service de Rhumatologie et Centre de Références des Maladies Autoimmunes Rares, Hôpitaux Universitaires de Strasbourg, Strasbourg, France

Background. The risk of cancer is increased in patients with pure dermatomyositis (DM), *i.e.* patients with a DM rash and without an anti-MDA5 syndrome, a suspected or confirmed anti-synthetase syndrome or scleromyositis. The aim of this study was to describe the relationship between the extent of muscle involvement and the prevalence of cancer in serologically-defined subsets of pure DM.
Methods. Patients with pure DM were selected from a retrospective cohort of incident autoimmune myositis (AIM) seen in two rheumatology academic centers between 2000 and 2021. All patients were classified by expert opinion into one of three serologically distinct groups: group 1 (anti-TIF1γ autoantibodies), group 2 (non-anti-TIF1γ autoantibodies) and group 3 (seronegative/not tested). The degree of muscle involvement was stratified in four mutually exclusive categories: clinically amyopathic (CADM), proximal muscle weakness alone, proximal muscle weakness with moderate dysphagia (no aspiration) on videofluoroscopy swallow study (VFSS) and proximal muscle weakness with severe dysphagia (by VFSS or clinical aspiration). A diagnosis of cancer within (±) three years of AIM was recorded.
Results. Of 250 patients with AIM, 64 had pure DM. Anti-TIF1γ autoantibodies were positive in 24 (37.5%) patients, anti-Mi2 in 9 (14.1%), anti-NXP2 in 7 (10.9%) and anti-SAE in 5 (7.8%), while 9 (14.1%) patients were seronegative and 10 (15.6%) untested. Cancer occurred in 29 of 64 (45.3%) patients: 11 of 24 (45.8%) in group 1, 6 of 21 (28.6%) in group 2 and 12 of 19 (63.2%) in group 3.
When stratified by extent of muscle weakness, cancer was seen in 18.8% (n=3/16) of CADM, 41.4% (n=12/29) of patients with proximal muscle weakness alone, 44.4% (n=4/9) of those with moderate dysphagia and 100% (n=10/10) of patients with severe dysphagia (p=0.0003 by Fisher's Exact Test). A statistically significant gradual increase in cancer frequency with incremental extent of muscle weakness was also seen in group 1 (p=0.017). All 3 patients with CADM and cancer survived, whereas all 10 patients with severe dysphagia and cancer died from their cancer.
Conclusion. In pure DM, cancer prevalence within 3 years of AIM diagnosis significantly increases with increasing extent of muscle weakness. Severe oropharyngeal dysphagia combined with proximal weakness is associated with the highest prevalence of cancer and poorest prognosis. Assessing the extent of muscle involvement in pure DM may improve cancer risk stratification.

P-123

IDIOPATHIC INFLAMMATORY MYOPATHIES AND MALIGNANCY SCREENING: A SURVEY OF THE CURRENT PRACTICES AMONGST CANADIAN NEUROLOGISTS AND RHEUMATOLOGISTS

Maria Jekielek[1], Ophir Vinik[2], Rosanne Nisenbaum[3], Charles D. Kassardjian[4]
[1]Division of Neurology, Department of Medicine, University of Toronto, Ontario, Canada; [2]Division of Rheumatology, Department of Medicine, St. Michael's Hospital, Toronto, Ontario, Canada; [3]Division of Biostatistics, Dalla Lana School of Public Health, University of Toronto, Ontario, Canada; [4]Division of Neurology, Department of Medicine, St. Michael's Hospital, Toronto, Ontario, Canada

Background. There is a well-established association between idiopathic inflammatory myopathies (IIM) and malignancy. Although the need for malignancy screening is generally accepted, no evidence-based guidelines exist to guide clinicians on the choice and timing of investigations. Our aim is to better understand and characterize the current gaps and uncertainties amongst Canadian neurologists and rheumatologists with malignancy screening in IIM patients.
Methods. An online survey was created consisting of 18 multiple-choice questions related to IIM malignancy screening practices: respondent characteristics, malignancy screening practices and concerns surrounding these practices. The survey was distributed to adult neurologists and rheumatolo-

gists practising in Canada. Data analysis was both descriptive and quantitative.
Results. The majority of respondents (96%, n=69) performed malignancy screening, however there was variability in practice including delegation and choice of screening tests, influence of patient-specific factors, and time and duration of repeat testing. Only 18% of respondents were confident in their malignancy screening practices. The most significant perceived knowledge gap was lack of consensus or guidelines on choice and frequency of malignancy screening. Between neurologists and rheumatologists, rheumatologists saw a higher proportion of IIM patients, were more likely to consider more patient risk factors and order more investigations, while neurologists were more likely to repeat testing.
Conclusion. Several knowledge gaps and variability exist amongst neurologists and rheumatologists with regards to malignancy screening in IIM patients. There is a lack of consensus and confidence in the choice and timing of investigations, with neurologists and rheumatologists differing in their approach to malignancy screening. Further research is required to better understand the optimal choice of tests and timing of repeat investigations, which may lead to expert-led consensus guidelines.

P-124

IMMUNE CHECKPOINT INHIBITOR USE IN ANTI-TRANSCRIPTIONAL INTERMEDIARY FACTOR 1-GAMMA ANTIBODY-POSITIVE DERMATOMYOSITIS: WALKING ON THIN ICE?

Liang Chen[1], Sabrina Fallavollita[1,2], Lama Sakr[1,3], Michael N. Pollack[1,4,5], Marie Hudson[1,2,5], Valérie Leclair[1,2,5]
[1]Department of Medicine, McGill University, Montreal, Canada: [2]Division of Rheumatology, Jewish General Hospital, Montreal, Canada; [3]Division of Respirology, Jewish General Hospital, Montreal, Canada; [4]Division of Oncology, Jewish General Hospital, Montreal, Canada; [5]Lady Davis Institute for Medical Research, Montreal, Canada

Background. Dermatomyositis (DM) is associated with cancer, especially in the presence of anti-transcriptional intermediary factor 1-gamma antibodies (anti-TIF1γ) antibodies. Immune checkpoint inhibitors (ICI) are associated with a wide range of immune-related adverse events (irAEs), including myositis. Thus, the treatment of cancer patients with paraneoplastic DM who could be candidates for immunotherapy presents an important clinical challenge. We report two cases of anti-TIF1γ positive paraneoplastic DM treated with ICI and a review of the literature.
Methods. Two cases of anti-TIF1γ paraneoplastic DM treated with ICI are described. A literature review was performed using the MeSH terms «dermatomyositis», «myositis», «immune checkpoint inhibitors» and «immune checkpoint blockade» and identified 402 articles, from which two reported on patients with anti-TIF1γ paraneoplastic DM exposed to ICI.
Results. In our first case, an 81-year-old male presented with anti-TIF1γ paraneoplastic DM associated and found to have a non-small cell lung cancer (NSCLC). His DM was treated with prednisone and intravenous immunoglobulins (IVIG). He received chemoradiotherapy for his cancer which was stopped due to febrile neutropenia. While in DM remission, he was initiated on nivolumab as a second line treatment for NSCLC. Although there was a partial cancer response, his DM flared. Still on prednisone and IVIg, he was initiated on hydroxychloroquine, and nivolumab was suspended. He was later rechallenged with nivolumab while on immunosuppression. His dysphagia worsened, possibly due to active DM, and he died from aspiration pneumonia. In our second case, a 32-year-old man presented with anti-TIF1γ paraneoplastic DM and blue cell carcinoma, which was initially treated with chemotherapy while the DM was treated with corticosteroids and IVIG. Due to disease progression on chemotherapy, pembrolizumab was initiated as second line cancer therapy with partial cancer response. He later developed ir-myocarditis and cancer progression and pembrolizumab was stopped. Two cases of anti-TIF1γ paraneoplastic DM exposed to ICI were previously reported (Table I). Both cases were on maintenance immunosuppression at time of ICI initiation and experienced a DM flare after ICI initiation. One of them was successfully rechallenged with ICI and achieved complete cancer remission.
Conclusion. DM flares and new onset irAEs occurred in all 4 patients reported, contributing to at least one death, while one of three cases had a complete cancer response. The decision to treat patients with anti-TIF1g paraneoplastic DM with ICI remains difficult, but can perhaps be guided by activity and treatment of the DM, alternative cancer treatments, and status of the underlying malignancy.

Table I. Summary of anti-TIF1γ paraneoplastic DM cases treated with ICI.

	Case 1	Case 2	Case 3	Case 4
			Sakakida et al. (2020)	Thomas et al. (2021)
Demographic	81M	32M	70M	36F
Past medical history	HTN, DLP, type 2 diabetes, remote bladder tumor	Healthy	NA	NA
Cancer, stage	NSCLC, stage III	Blue cell carcinoma, stage IV	NSCLC, stage NA	Melanoma, stage IIIA
1st line treatment	Chemoradiotherapy	Surgery/radiotherapy		Surgery
ICI	Nivolumab	Pembrolizumab	Atezolizumab	Nivolumab
Clinical DM presentation	Proximal MW, dysphagia, classic DM rashes	Myalgias, dysphagia, classic DM rashes	NA	Proximal MW, classic DM rashes
Max CK (U/L)	17746	120	NA	564
EMG	Myopathic	Myopathic	NA	NA
DM activity at time of ICI initiation	Inactive	Inactive	NA	NA
Immunosuppression at ICI introduction	Prednisone, IVIg 2g/kg/month, HCQ	IVIG 2g/kg/month	Prednisolone	Prednisone, MMF, rituximab
Course of cancer on ICI	Partial response sustained.	Partial response, then cancer progression.	NA	2 ICI cycles then held. After rechallenge, completed 1 year of ICI treatment. Complete response.
Course of DM on ICI	After 3rd cycle, DM flare. Died of aspiration pneumonia.	No DM flare.	DM flare, increased prednisolone and cessation of ICI.	After 2nd cycle ICI, DM flare. Treated with prednisone + 6 months taper then ICI rechallenge. No subsequent flare.

Legend: HTN: hypertension; DLP: dyslipidemia; NA: not available; NSCLC: non-small cell lung carcinoma; MW: muscle weakness; DM: dermatomyositis; IVIG: intravenous immunoglobulins; HCQ: hydroxycloroquine.

P-125

CANCER-ASSOCIATED MYOSITIS BEFORE AND AFTER THE COVID-19 PANDEMIC ONSET – A CHANGING TREND

Filipa Costa[1,2], Bianca Correia[1,2], Matilde Bandeira[1,2], Eduardo Dourado[2,3,4], Ana T. Melo[5], João E. Fonseca[1,2], Sofia C. Barreira[1,2], Raquel C. Marques[1,2]
[1]Serviço de Reumatologia, Centro Hospitalar Universitário Lisboa Norte, Centro Académico de Medicina de Lisboa, Portugal; [2]Unidade de investigação em Reumatologia, Instituto de Medicina Molecular, Faculdade de Medicina, Universidade de Lisboa, Centro Académico de Medicina de Lisboa, Portugal; [3]Serviço de Reumatologia, Centro Hospitalar do Baixo Vouga, Aveiro, Portugal; [4]Centro de Investigação em Reumatologia de Aveiro, Centro Académico Clínico Egas Moniz, Portugal; [5]Unidade de Reumatologia, Centro Hospitalar e Universitário Lisboa Central, Portugal

Background. Cancer associated myositis (CAM) can occur in up to 25% of cases. The COVID-19 pandemic has been linked to a significant delay in cancer diagnosis, potentially impacting the incidence of paraneoplastic conditions. Furthermore, an increased incidence of CAM after the COVID-19 pandemic has been reported in Israel. Therefore, our main goal was to determine the incidence of CAM before and after the onset of the COVID-19 at our department.
Methods. We included Inflammatory idiopathic myopathies (IIM) patients followed at a tertiary Rheumatology Department between June 2016 and June 2023. Patients were divided into two groups: those diagnosed with IIM before the COVID-19 pandemic, and those diagnosed after the onset of the pandemic. CAM was defined as the occurrence of neoplasia within three years (before or after) of the IIM diagnosis.
Results. 133 patients were included, 64% (n=87) diagnosed prior and 36% (n=46) after the start of the pandemic. Demographic data were not statistically different between groups (p=0.680 for age, p=0.500 for sex). For patients diagnosed before the COVID-19 pandemic, the most common IIM

subtypes were dermatomyositis (DM, 27%, n=24) and the most frequent auto-antibody was anti-histidyl tRNA synthetase (anti-Jo1, 19%, n=17). After the COVID-19 pandemic onset, DM remained the most frequent IIM subtype (39%, n=19/46), but with significantly higher relative prevalence (p=0.030), and anti-TIF1γ was the most common auto-antibody, also with a significantly higher relative prevalence (p=0.030). The incidence of CAM was significantly higher after the COVID-19 pandemic (8 *vs*. 1 new case in analogous period, p<0.001). Among the eight patients diagnosed with CAM after the pandemic onset, the most common IIM subtype was DM (75%, n=6), mainly in anti-TIF1γ-positive patients (62%, n=5). Regarding all patients with CAM, they had more frequently anti-TIF1γ-positivity (p<0.001) and an IIM diagnosis occurring after the pandemic (p=0.001) than non-CAM-IIM patients. Anti-TIF1γ-positivity (OR 9.998, 95% CI 1.904-52.500, p=0.007) and diagnosis after the COVID-19 pandemic onset (OR 13.24, 95% CI 1.483-118.261, p=0.021) were independent predictors of CAM among IIM patients.

Table I. Neoplasia and IIM characterization before and after the onset of the COVID-19.

IIM date of diagnosis	Gender	Age	IIM	Neoplasia date of diagnosis	Neoplasia	Antibody
June 2016 – December 2019	M	88	Necrotizing myopathy	2021	Colon	-
January 2020 – June 2023	F	52	AASD	2022	Lung	Jo1
	F	54	Overlap syndrome	2020	Skin	PL12
	F	52	DM	2021	Breast	Mi2b
	F	50	DM	2022	Breast	TIF1γ
	F	87	DM	2019	Colon	TIF1γ
	F	67	DM	2022	Lung	TIF1γ
	M	60	DM	2023	Gastrointestinal – non specified	TIF1γ
	F	50	DM	2023	Breast	TIF1γ

Abbreviations: AASD: antisynthetase syndrome; DM: dermatomyositis; IIM: inflammatory idiopathic myopathy; Jo-l: anti-histidyl tRNA synthetase; PL12: Anti-alanyl tRNA synthetase; TIF1γ: anti-transcription intermediary factor 1-γ.

Conclusion. In our cohort there was a significant increase in the incidence of CAM after the COVID-19 pandemic. Accordingly, DM and anti-TIF1γ positivity became significantly more prevalent. IIM diagnosis occurring after the COVID-19 pandemic is associated with CAM, irrespective of age and sex. This adds to the previously reported increasing CAM incidence observed elsewhere, a worrying trend that may be related to worse management of non-COVID-19-related healthcare conditions, including cancer screening and early diagnosis.

P-126

OUTCOMES OF IMMUNE CHECKPOINT INHIBITOR THERAPY IN MALIGNANCY-ASSOCIATED DERMATOMYOSITIS

Fernandez D.R.[1], Thaler J.[1].
[1]Hospital for Special Surgery, New York, USA

Background. Immune checkpoint inhibitor (ICI) therapy has revolutionized the treatment of many cancers. However, its broad disinhibition of the immune system is associated with a high proportion of immune-related adverse events (irAEs). This is of particular concern in patients with pre-existing autoimmune disease who undergo ICI therapy, as their autoimmune disease may flare.
Methods. Data on outcomes in ICI-treated patients with dermatomyositis are particularly lacking, and critically, very rarely do studies distinguish between patients with malignancy associated-dermatomyositis (m-DM) and those with longstanding disease, who may face different risks from ICI therapy. Clinicians and patients would benefit from more data to help frame decisions about immunotherapy in this specific population Patients with malignancy-associated dermatomyositis seen at Hospital for Special Surgery who underwent ICI therapy between 1/1/2016 and 11/29/2023 were identified by retrospective chart review by DRF and JT.
Results. 5 patients with m-DM undergoing ICI therapy were identified. 4/5 were female. No patients shared the same type of malignancy or the same autoantibody profile. No patients were in remission at the time of ICI initiation. 4/5 experienced disease flares after ICI initiation, usually within weeks. All patients with flares had normal creatine kinase (CK) levels at time of ICI initiation. 3/5 patients experienced severe m-DM flares. One patient's cancer (patient 1) had a complete response to first-line ICI therapy, but the patient suffered repeated flares of dermatomyositis and colitis requiring hospitalization prior to her death. Notably, this patient's only m-DM therapy at the time of ICI initiation was Rituximab, dosed 6 months prior. All other patients were receiving IVIG and steroid therapy at time of ICI initiation. Patient 2 tapered off of IVIG 1 month prior to ICI therapy, and upon ICI treatment developed a severe m-DM flare, refractory to pulse steroids, IVIG, infliximab, and rituximab. Patient 5's treatment is ongoing.
Conclusion. Outcomes varied among m-DM patients following initiation of ICI therapy. 1/5 patients had an excellent cancer response. 4/5 patients experienced substantial flares of m-DM disease activity following immunotherapy. Given this small sample, the precise factors contributing to positive or negative outcomes in any individual are not fully clear; considerations include cancer type, concurrent immunosuppression, type of ICI therapy, and baseline m-DM disease activity. Prospective studies would help to characterize these patients more comprehensively.

P-127

CLINICAL RISK FACTORS ASSOCIATED WITH MALIGNANCY IN TIF1-γ(+) DERMATOMYOSITIS PATIENTS

Lydia A. Cassard[1,2], Elizabeth M. Flatley[2,3], Anthony P. Fernandez[2,4]
[1]Cleveland Clinic Lerner College of Medicine, Cleveland, OH, USA, [2]Cleveland Clinic Department of Dermatology, Cleveland, OH, USA; [3]Robert Wood Johnson Medical School, Rutgers University, Newark, NJ, USA; [4]Cleveland Clinic Department of Pathology, Cleveland, OH, USA

Background. Dermatomyositis (DM) is associated with increased risk of underlying malignancy in patients with autoantibodies to transcriptional intermediary factor 1-γ (TIF1-γ). We aimed to characterize a single-center cohort of TIF1-γ(+)DM patients and identify additional clinical factors associated with malignancy risk.
Methods. TIF1-γ(+) DM patients were identified from our departmental DM registry and our institution's medical records. DM diagnoses were confirmed using 2017 EULAR/ACR criteria. For patients with ³3 years of follow-up after DM diagnosis, we compared demographic, clinical, and serologic variables in those with and without malignancy.
Results. Of 154 TIF1-γ(+) DM patients in our cohort, 116 (75%) were female, median age at diagnosis was 57, and 41% had muscle involvement. The most common cutaneous manifestations were Gottron's papules (85%), poikiloderma (56%), and V-neck erythema (55%). The most common systemic manifestations were dysphagia (23%) and arthralgias/arthritis (24%). Most patients (90%) underwent malignancy screening workups within 3 years of DM diagnosis. The most ordered tests were computed tomography (CT) scans of the chest (64%) and abdomen/pelvis (59%).
Of 110 patients with ≥3 years of follow-up data, 36 (33%) were diagnosed with malignancy, 14 (13%) within 1 year of DM diagnosis and 11 (10%) between 1-3 years from DM diagnosis. The most common cancer types were breast (24%) and lung (16%). Factors associated with malignancy diagnosis within 3 years of DM diagnosis included age >65 (p=0.001), male sex (p=0.002), classic DM (p=0.018), neutrophil-to-lymphocyte ratio (NLR) > 3.82 (p=0.02), and heliotrope rash (p=0.036). In addition to these, ANA titer <1:160 (p=0.027) and dysphagia (p=0.03) were also associated with malignancy diagnosis within 1 year of DM diagnosis.
Of patients with <4 of these risk factors, 8/81 (9.9%) developed cancer within 3 years of DM. Of patients with ³4 risk factors, 17/29 (58.6%) developed cancer within 3 years of DM (p<0.0001). Presence of each additional risk factor is associated with twice the risk of cancer within 3 years of DM (OR 2.12 [95% CI: 1.52, 2.97], p<0.0001).
Conclusion. In TIF1-γ(+) DM patients, male sex, age >65, muscle involvement, heliotrope rash, dysphagia, low ANA titer, and elevated NLR are associated with underlying malignancy risk. Our results suggest that TIF1-γ(+) DM patients with ³4 clinical risk factors have a sufficiently high probability of underlying cancer to support that benefits of extensive malignancy screening work-ups outweigh the risks.

Other

P-128

HEALTHCARE COSTS AND RESOURCE UTILIZATION ASSOCIATED WITH LONG-TERM MEDIUM-TO-HIGH DOSE USE ORAL CORTICOSTEROID USE IN PATIENTS WITH DERMATOMYOSITIS OR POLYMYOSITIS

Daniel D. Labson[1], Qian Cai[1], Concetta Crivera[2], Evo Alemao[2], Federico Zazzetti[3]

[1]Janssen Global Services, Global Market Access RWE, Spring House, PA, USA; [2]Janssen Global Services, Immunology Market Access, Horsham, PA, USA; [3]Janssen Global Services, Immunology Medical Affairs, Horsham, PA, USA

Background. Dermatomyositis (DM) and polymyositis (PM) are rare autoimmune conditions primarily characterized by muscle weakness and inflammation. Real-world evidence on economic outcomes of patients with DM or PM who used oral corticosteroids (OCS) is limited. This study investigated the association between duration and dose of OCS and annual healthcare costs and resource utilization among patients with DM or PM.

Methods. Adults who had ≥2 medical claims of DM/PM 30-365 days apart between 1/1/2016-12/31/2022 and ≥1 diagnosis code associated with a physician specialty of interest (*e.g.* rheumatologist) were selected from the IBM MarketScan® database. Patients were required to have ≥1 pharmacy claim for OCS (index date) on or after the diagnosis date; ≥12 months pre- and 12 months post-index continuous enrollment; and should not have a diagnosis of inclusion body myositis during the study period. Patients were classified as long-term (LT) users if they had continuous OCS use for ≥3 consecutive months within the 12-month post-index period; otherwise, they were classified as short-term (ST) users. Patients were classified into the medium/high-dose (MHD) group if they had an average daily dose >7.5mg/day within the 12-month post-index period; otherwise, they were classified into the low-dose (LD) group.

Results. A total of 2,280 patients [mean (±SD) age: 53 (±13.4) years; female: 74.6%] were included, of which 1,313 (57.6%) were in the LT and 1,592 (69.8%) in the MHD group. Compared with the ST or LD groups, LT or MHD OCS users had increased odds for all-cause inpatient admission (LT *vs*. ST: adjusted odds ratio [aOR]=1.66, 95% CI, 1.28-2.15; MHD *vs*. LD: aOR=1.67, 95% CI, 1.27, 2.20), and positive association with disease-related inpatient admission (LT *vs*. ST: aOR=3.78, 95% CI, 2.30-6.21; MHD *vs*. LD: aOR=2.07, 95% CI, 1.27-3.36) after baseline covariates adjustment. On average, LT users incurred higher adjusted total all-cause costs by $21,310 ($p$<0.01), and higher adjusted disease-related costs by $18,334 ($p$<0.01) compared with ST users. MHD users incurred higher adjusted total all-cause costs by $17,638 ($p$<0.01) and higher adjusted disease-related costs $9,562 ($p$=0.01) compared with LD users.

Conclusion. Patients with LT or MHD OCS incurred substantially higher economic burden. These findings provide insights to inform clinical care and support the development of advanced therapy that can reduce OCS use among patients with DM or PM.

Acknowledgements. This study was supported by Janssen Global Services, LLC. Editorial support was provided by Panita Maturavongsadit, PhD, of Lumanity Communications Inc. and funded by Janssen Global Services, LLC.

P-129

HIGH PREVALENCE OF CHRONIC FATIGUE AND POOR HEALTH-RELATED QUALITY OF LIFE IN PATIENTS WITH IDIOPATHIC INFLAMMATORY MYOPATHIES AND SYSTEMIC VASCULITIS: A BRAZILIAN MULTICENTER CROSS-SECTIONAL STUDY

Alexandre Moura dos Santos[1], Jucier Gonçalves Júnior[1,2,3], Romão Augusto Alves Filgueira[4], Talita do Nascimento Silva[5], Daniel Brito de Araújo[6], Estelista Lima Cândido[4], Samuel Katsuyuki Shinjo[1]

[1]Division of Rheumatology, Faculdade de Medicina FMUSP, Universidade de Sao Paulo, Sao Paulo, Brazil; [2,3]School of Medicine, Universidade Federal do Cariri (UFCA), Ceará, Brazil; [4]Division of Rheumatology, Hospital Universitário Walter Cantídio, Universidade Federal do Ceará (UFC), Ceará, Brazil; [5]Division of Rheumatology, Hospital Geral César Carls (HGCC), Ceará, Brazil; [6]Division of Internal Medicine, Universidade Federal de Pelotas (UFPel), Grande do Sul, Brazil

Background. Recent studies have explored fatigue and health-related quality of life (HRQoL) in various systemic autoimmune diseases (SAD) such as idiopathic inflammatory myopathy (IIM) and primary systemic vasculitis (PSV). However, to our knowledge, no studies have simultaneously examined these parameters in IIM and PSV or their subtypes, prompting this current study.

Methods. This multicenter cross-sectional study included adult patients with IIM and PSV from five Brazilian tertiary centers who were diagnosed according to the ACR/EULAR criteria. The patients were age-, sex-, and body mass index (BMI)-matched with individuals without SAD (CTR). Chronic fatigue and HRQoL were assessed using the Fatigue Severity Scale (FSS) (range: 9–63) and EQ-5D (range: -0.6–1.0), respectively. Additionally, the visual analog score (VAS) for fatigue (range: 0–10) and weekly metabolic equivalents (using the IPAQ-SF questionnaire) were assessed.

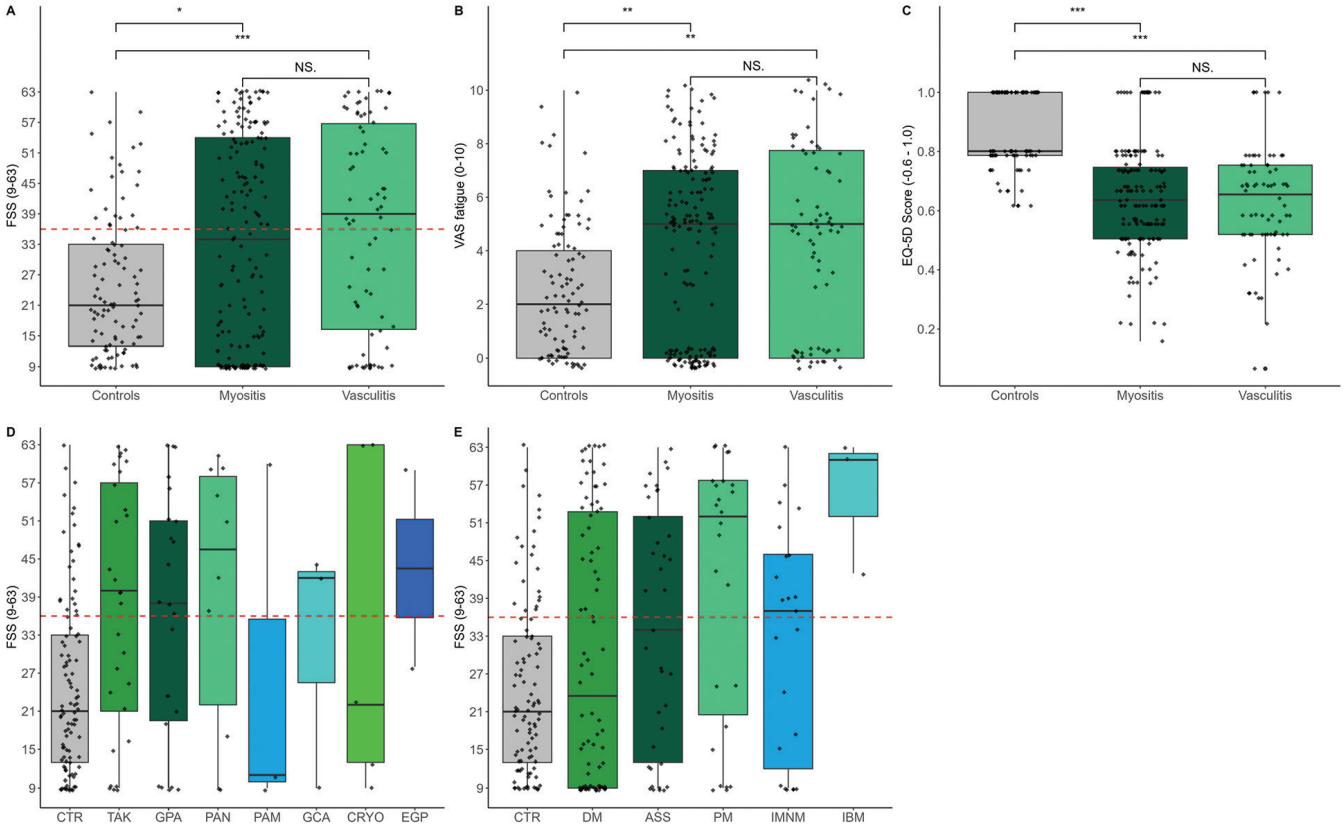
Results. We included 171 adult patients with IIM [82 with dermatomyositis (DM), 37 with antisynthetase syndrome (ASS), 26 with polymyositis (PM), 23 with immune-mediated necrotizing myopathy (IMNM), and three with inclusion body myositis (IBM)], and 74 patients with VSP [27 with Takayasu arteritis (TAK), 22 with granulomatosis with polyangiitis (GPA), 10 with polyarteritis nodosa (PAN), three with giant cell arteritis (GCA), five with cryoglobulinemic vasculitis (CRYO), three with microscopic polyangiitis (PAM), and two with eosinophilic granulomatosis with polyangiitis (EGP)], and 99 with CTR. The median age was comparable among IIM, PSV, and CTR [51.0 (42.0-61.0), 48.0 (42.0-61.7), and 46.0 (37.5-58.0) years, respectively; p>0.05], with a predominance of females. BMI was also similar among the groups [28.3 (24.1-31.7), 27.1(23.8-31.8), and 25.9 (23.5-28.7) kg/m^2; p>0.05]. Patients with IIM and PSV experienced more significant fatigue (Fig. 1A-B) and reduced HRQoL (Fig. 1C) than those with CTR did. To discriminate, Figures 1D and 1E show FSS according to subtypes of IIM and VSP, respectively. Finally, FSS and EQ-5D scores were negatively correlated (Spearman correlation: rho=-0.505; p<0.001).

Conclusion. Patients in the IIM and PSV groups exhibited chronic fatigue and diminished HRQoL compared to those in the CTR. Further studies are needed to explore the potential triggers of chronic fatigue and identify treatments contributing to its reduction, thereby enhancing overall HRQoL.

Acknowledgments. FAPESP #2020/10691-4 (AMS) and #2022/04869-0 (SKS).

References

1. DAVIES K, DURES E, NG WF: Fatigue in inflammatory rheumatic diseases: current knowledge and areas for future research. *Nat Rev Rheumatol* 2021; 17(11): 651-64.
2. DOS SANTOS AM, MISSE RG, BORGES IBP *et al.*: High prevalence of fatigue in patients with Takayasu arteritis: a case-control study in a Brazilian centre. *Rheumatol Adv Pract* 2022; 6(2): 1-9.
3. RICCI G, FONTANELLI L, TORRI F, SCHIRINZI E, SICILIANO G: Fatigue as a common signature of inflammatory myopathies: clinical aspects and care. *Clin Exp Rheumatol* 2022; 40(2): 425-32.



P-129 Fig. 1. Chronic fatigue and health-related quality of life.

P-130

MULTIMORBIDITY AND PATIENT-REPORTED OUTCOMES IN IDIOPATHIC INFLAMMATORY MYOPATHIES: INSIGHTS FROM THE COVAD STUDY ANALYSIS

Marco Fornaro[1], Vincenzo Venerito[2], Florenzo Iannone[3], Naveen R[4], Elena Nikiphorou[5], Mrudula Joshi[6], Ai Lyn Tan[7], Sreoshy Saha[8], Samuel Shinjo[9], Vishwesh Agarwal[10], Nelly Ziade[11], Tsvetelina Velikova[12], Esha Kadam[13], Marcin Milchert[14], Ioannis Parodis[15], Abraham Edgar Gracia-Ramos[16], Lorenzo Cavagna[17], Masataka Kuwana[18], Johannes Knitza[19], Ashima Makol[20], Dey Dzifa[21], Carlos Enrique Toro Gutierrez[22], Carlo Vinicio Caballero[23], Oliver Distler[24], Jessica Day[25], Hector Chinoy[26], Vikas Agarwal[4], Rohit Aggarwal[27], Latika Gupta[28], on behalf of COVAD Study Group

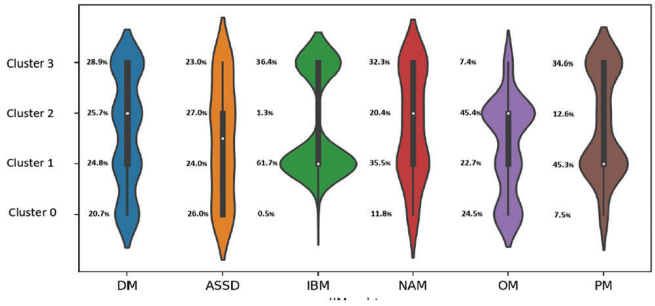
[1]Rheumatology Department, Università degli Studi di Bari, Bari, Italy; [2]Rheumatology Department, Università degli Studi di Bari, Bari, Italy; [3]Rheumatology Unit, Department of Precision and Regenerative Medicine and Ionian Area, University of Bari "Aldo Moro", Bari, Italy; [4]Sanjay Gandhi Postgraduate Institute of Medical Sciences (SGPGIMS), Lucknow, India; [5]King's College London, London, UK; [6]Byramjee Jeejeebhoy Government Medical College and Sassoon General Hospitals, Pune, India; [7]University of Leeds, Leeds, UK; [8]Mymensingh Medical College, Faridpur, Bangladesh; [9]Faculdade de Medicina FMUSP, Universidade de Sao Paulo, São Paulo, Brazil; [10]Mahatma Gandhi Missions Medical College, Lucknow, India; [11]Saint-Joseph University, Beirut, Lebanon; [12]Department of Clinical Immunology, Medical Faculty, University Hospital Lozenetz, Sofia University St. Kliment Ohridski, Sofia, Bulgaria; [13]Seth Gordhandhas Sunderdas Medical College and King Edwards Memorial Hospital, Mumbai, India; [14]Department of Internal Medicine, Rheumatology, Diabetology, Geriatrics and Clinical Immunology, Pomeranian Medical University in Szczecin, Szczecin, Poland; [15]Karolinska Institutet, Stockholm, Sweden; [16]Department of Internal Medicine, General Hospital, National Medical Center La Raza, Instituto Mexicano del Seguro Social, Av. Jacaranda S/N, Col. La Raza, Del. Azcapotzalco, C.P. 02990, Mexico City, Mexico; [17]Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; [18]Nippon Medical School Graduate School of Medicine, Tokyo, Japan; [19]Department of Internal Medicine 3 Rheumatology and Immunology, Friedrich-Alexander-University Erlangen-Nürnberg, University Hospital Erlangen, Erlangen, Germany; [20]Mayo Clinic, Rochester, MN, Rochester, MN; [21]Department of Medicine and Therapeutics, University of Ghana School of Medicine and Dentistry, College of Health Sciences, Korle-Bu, Accra, Ghana; [22]Centro de Estudios de Reumatología y Dermatología SAS, Cali, Colombia; [23]REUMACARIBE IPS, Barranquilla, Colombia; [24]Department of Rheumatology, University Hospital Zurich, University of Zurich, Zurich, Switzerland; [25]Walter and Eliza Hall Institute, Melbourne, Australia; [26]The University of Manchester, Sale, UK; [27]University of Pittsburgh, Pittsburgh, PA; [28]Royal Wolverhampton Trust, Wolverhampton/University of Manchester, UK

Background. Global data on the burden of comorbidities and its impact on health outcomes and QoL in vulnerable groups such as Idiopathic inflammatory myopathies (IIMs) are scarce.

Methods. We studied the prevalence, distribution and clustering of comorbidities and multimorbidity among patients with IIM, other autoimmune rheumatic disease (AIRDs) and healthy controls (HCs) and its impact on health outcomes, utilizing data from the COVAD 2 study, a global patient-reported e-survey. Basic multimorbidity (BM) /Complex multimorbidity (CM) were defined as the co-occurrence of ≥2 non-rheumatic comorbidities and ≥3 non-rheumatic chronic conditions affecting ≥3 different organ systems respectively. Human Development Index (HDI) of their country was taken as a surrogate marker for socioeconomic status. PROMIS global physical health (PGP), mental health (PGM), fatigue 4a (F4a) and physical function short form (SF10) were analysed using descriptive statistics and linear regression models. Hierarchical Clustering on Principal Components was performed to outline the grouping.

Results. Among 10740 respondents, 1558 IIMs, 4591 other AIRDs and 3652 HCs were analysed. IIMs comprised mainly of DM (30.2%) and IBM (24.1%) whilst AIRDs comprised 2450 inflammatory arthritis (53.4%), 2050 CTDs (44.6%) and 235 systemic vasculitis (5.1%). Individuals with IIMs exhibited high burden of any comorbidity(OR: 1.62 *vs*. AIRDs and 2.95 *vs*. HCs, $p<0.01$), BM (OR 1.66 *vs*. AIRDs and 3.52 *vs*. HCs, $p<0.01$), CM(OR: 1.69 *vs*. AIRDs and 6.23 *vs*. HCs, $p<0.01$), and mental health disorders(MHDs) (OR 1.33 *vs*. AIRDs and 2.63 *vs*. HCs, $p<0.01$). IIM patients with comorbidities(and MHDs) had worse physical function(low PGP, PGM, SF10 and higher F4a scores, all * $p<0.001$). Worse physical function (PGP, SF10a, F4a) and mental health (PGM) was predicted by age, active disease, BM, and MHDs. Worse SF10a and F4a scores were also associated with female gender and country HDI, respectively.
4 distinct clusters were identified among IIMs (Fig. 1A):

Cluster 0: lower comorbidity burden and good health status
Cluster 1: older patients with higher comorbidity burden and poorer health status
Cluster 2: patients with higher prevalence of MHDs, lower PGP, PGM and higher F4a scores
Cluster 3: older patients with average comorbidity burden and good health status.
DM, Anti-synthetase syndrome and necrotizing autoimmune myopathy were similarly represented in all clusters; IBM and PM were more predominant in clusters 1 (61.7% and 45.3%) and 3 (36.4% and 34.6%), while overlap myositis was more represented in clusters 2 (45.4%) (Fig. 1B).
Conclusion. Patients with IIMs have a higher burden of comorbidities that adversely impact physical and mental health, calling for optimized approaches for holistic patient management.



	Cluster 0 (n. 219)	Cluster 1 (n.564)	Cluster 2 (n. 318)	Cluster 3 (n.422)
Female, n. (%)	189 (86.3)[a]	358 (63.5)[b]	288 (90.6)[a]	258 (61.1)[b]
Age, mean ± SD	44 ±13[a]	66 ±10[b]	45 ±12[a]	66 ±9[b]
BM, n. (%)	10 (4.6)[a]	330 (58.5)[b]	44 (13.8)[c]	156 (37)[d]
CM, n. (%)	4 (1.8)[a]	153 (27.1)[b]	27 (8.5)[c]	31 (7.3)[c]
MHDs, n. (%)	39 (17.8)[a]	241 (42.7)[b]	176 (55.3)[c]	61 (14.5)[a]
PROMIS Global Physical health, mean	15.8 ±2.1[a]	10.2 ±1.9[b]	10.5 ±2.3[b]	14.5 ±1.7[c]
PROMIS Global Mental Health, mean	15.4 ±2.7[a]	11.2 ±2.7[b]	10.8 ±3.0[b]	15.2 ±2.4[a]
PROMIS Physical function SF10a, mean	45.8 ±4.5[a]	25.6 ±8.5[b]	34.3 ±8.6[c]	36.4 ±9.5[d]
PROMIS Fatigue 4a score, mean	7.2 ±2.4[a]	13.7 ±3.2[b]	13.8 ±3.3[b]	8.0 ±2.3[c]

Each superscript letter indicates a subset of the 4 groups analyzed for which the means or proportions showed no difference at a significance level of .05.

Fig. 1. A: Distribution of myositis subset in different clusters. B: Cluster characteristics in idhiopatic inflammatory myopathies.

P-131

MUSCLE PATHOLOGY IN PATIENTS WITH PRIMARY BILIARY CHOLANGITIS

Jose Milisenda[1,3,4,5], Iago Pinal-Fernandez[1,2], Katherine Pak[1], Maria Casal-Dominguez[1,2], Yaiza Duque-Jaimez[3], Gloria Garrabou[3,4,5] ,Sandra Munoz-Braceras[1], Mariona Guitart-Mampel[3,4,5], Jiram Torres-Ruiz[1], Ester Tobias[3,4,5], Maria Dolores Cano[3,4,5], Iban Aldecoa[3,4,5], Josep Maria Grau[3,4,5], Andrew L. Mammen[1,2,6]
[1]Muscle Disease Unit, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD, USA; [2]Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, USA; [3]Muscle Research Unit, Internal Medicine Service, Hospital Clinic, Barcelona, Spain; [4]Barcelona University, Barcelona, Spain; [5]CIBERER, Barcelona, Spain; [6]Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Background. Primary biliary cholangitis (PBC) is a chronic autoimmune liver disease that primarily affects middle-aged women. It is characterized by elevated serum alkaline phosphatase levels, the presence of antimitochondrial antibodies (AMAs), and cholangiopathy on liver pathology. Fatigue is a common symptom experienced by up to 80% of patients at the time of diagnosis and during follow-up. Unfortunately, current treatments have not been effective in alleviating fatigue. The objective of this study is to evaluate fatigue and investigate any potential muscle involvement in PBC patients.
Methods. We conducted a single-center, cross-sectional study involving 50 patients who suffered from both PBC and fatigue. Muscle biopsies were performed to whom presented muscle weakness. Histopathological analysis was made and also RNA sequencing was performed on muscle biopsies (n=10) as well as 33 normal muscle biopsies. Muscle biopsies were stained for human immunoglobulin and PDC-E2.
Results. Abnormal accumulation of mitochondria in the subsarcolemal region was observed in both optical and electron microscopy. A significant set of immunoglobulin genes was specifically found to be overexpressed in CBP, while over 50 genes related to mitochondrial function were predominantly underexpressed. In muscle biopsies positive for AMA-M2, immunoglobulins were localized in the cytoplasm and colocalized with PDC-E2.
Conclusion. Based on these findings, we can conclude that there is muscular involvement in PBC, and we hypothesise it is likely mediated by AMA-M2 antibodies.

References

1. WANG X, WEI Y, YANG Y *et al*.: Animal models of primary biliary cholangitis: status and challenges. *Cell Biosci* 2023; 13(1): 214. doi: 10.1186/s13578-023-01170-9
2. XU Q, ZHU W, YIN Y: Diagnostic value of anti-mitochondrial antibody in patients with primary biliary cholangitis: A systemic review and meta-analysis. *Medicine* (Baltimore) 2023; 102(45): e36039. doi: 10.1097/md.0000000000036039

P-132

DETERMINING PATIENT AND CARER PRIORITIES IN MYOSITIS: A CONSUMER-LED ACTION RESEARCH STUDY

Kevin L. Austin[1,2], Bill E Hawkins[2], Kelly A.L. Beer[1,3], Merrilee Needham[1,3,4,5]
[1]Centre for Molecular Medicine and Innovative Therapeutics, Murdoch University, Perth, Australia; [2]Enzyme Group, Sydney, Australia; [3]Perron Institute for Neurological and Translational Science, Perth, Australia; [4]Department of Neurology, Fiona Stanley Hospital, South Metropolitan Health Service, Perth, Australia; [5]School of Medicine, University of Notre Dame, Australia, Perth, Australia

Background. Myositis is a rare group of diseases that can be extremely challenging for patients, carers and families. There is a paucity of research directed towards understanding the relative priorities of myositis patients and their carers. The purpose of this Australian study was to discover challenges and their relative priority as seen through the eyes of myositis patients and carers, and to measure their perception of their ability to cope.
Methods. This consumer-led study was conducted in phases. An initial discovery phase was conducted with a small cohort of IBM patients and carers (n=32) to discover challenges and issues. Thematic analysis through affinity diagramming identified key themes, which were reviewed and validated by participants. These themes informed a subsequent quantification phase, where a larger group of myositis patients and carers across Australia (n=200) participated in an online survey to prioritise the themes and self-rate their current level of coping within each theme. Participants were able to add additional challenges if required.
Results. During the Discovery phase, 10 key themes of inter-related challenges and priorities were identified. Within the quantification phase, the relative importance of these themes was determined using forced binary trade-off. Two hundred valid responses were received, from 163 patients and 37 carers. Ninety-five percent of total importance came from 7 themes: (1) Uncertain future: disease progression, housing needs & loss of independence; (2) Coping with daily frustrations; (3) Lack of cure, treatment and understanding; (4) Impact on carer's capabilities & own needs; (5) Change of roles and relationships; (6) Getting information, education & support when we need it and (7) Significant impact on our mental health. The other themes identified were: (8) Financial impact; (9) Issues with National Disability Insurance Scheme and myagedcare (Australian Health Policy programmes); (10) Concern not covered by voluntary euthanasia. Participants scored their personal ability to cope with each theme on a scale of 0 to 10 (0=not coping, 10=coping well), with a mean 'coping score' emerging of less than 5 across all themes.
Conclusion. This study suggests that myositis patients and carers are finding it difficult to cope. The themes that emerged identified gaps in care, education and support. Alongside practical challenges associated with functional disability, a significant impact on mental health was identified. Understanding the priorities of myositis patients and carers is critical in delivering collaborative, consumer-centered care and support.
Acknowledgements. This research study was partially funded by Myositis Association Australia.

P-133

FROM THE BACK SEAT TO THE DRIVER'S SEAT: OUR JOURNEY TO CO-PRODUCTION

Kelly A.L. Beer[1,2], Merrilee Needham[1,2,3,4], Myositis Research Consumer Panel[1,2,5,6]
[1]Centre for Molecular Medicine and Innovative Therapeutics, Murdoch University, Perth, Australia; [2]Perron Institute for Neurological and Translational Science, Perth, Australia; [3]Department of Neurology, Fiona Stanley Hospital, South Metropolitan Health Service, Perth, Australia; [4]School of Medicine, University of Notre Dame, Australia, Perth, Australia; [5]Myositis Association of Australia, Sydney, Australia; [6]Consumer and Community Involvement Program, Perth, Australia

Background. Increasingly the clinical research community is understanding the value and significance of consumer involvement in research. The field of consumer involvement is rapidly evolving, with dedicated advocates, exemplar practices and increasing literature and resources to guide practitioners. However, within this emerging specialty area, it can be challenging to find genuine and meaningful ways to involve consumers, particularly within rare disease areas and with limited research budget and resource. Within our rare disease area (myositis), we sought to establish a consumer involvement strategy that would facilitate co-production of research, as well as improving research and health literacy of consumers. We aimed to make our research team and projects relevant, accessible, and collaborative.
Methods. In 2019 our team partnered with the Myositis Association of Australia (MAA) to establish a national 'Myositis Research Consumer Panel'. We worked with the Consumer and Community Involvement Program (CCIP) to formalise and guide the panel. The panel meets online 2-3 times per year, with a membership of around 15 consumer members and 5 research members. The panel's remit has been flexible, allowing for changes of scope and direction, and facilitation of consumer-led research.
Results. Since the panel's inception, members have meaningfully contributed to numerous research projects. The panel has added considerable value to research activities, including providing critical consumer perspectives, revisions and advocacy that resulted in award of a AU$1.8M government grant for a clinical trial in Inclusion Body Myositis (IBM). However, the most exciting impact of the panel has been the enablement of consumer-led research. We have recently completed two research projects on topics championed by consumers and are currently undertaking an important consumer-led project investigating patient and carer priorities in myositis.
Conclusion. Providing a forum to partner with consumers, where ideas are shared and traditional clinician/patient barriers removed, has opened opportunities not only for improved research outcomes, but also true co-design and co-production. A willingness to learn from each other and adapt the panel's activities and direction to support consumer-led projects has been key. The panel is an invaluable part of our myositis research programme, providing an environment for consumers and clinician/researchers to partner in research and clinical initiatives.

P-134

MUSCLE IMMUNOPROFILING OF A VIETNAMESE MYOSITIS COHORT

Yue-Bei Luo[1,2], Léo Heinon[3], Nham Pham Minh[4], Thuy Nguyen Thi Phuong[4], Begum Horuluoglu[2], Ingrid I.E. Lundberg[2]
[1]Depart of Neurology, Xiangya Hospital, Central South University, Changsha, China; [2]Division of Rheumatology, Department of Medicine, Solna, Center for Molecular Medicine, Karolinska Institutet, Stockholm, Sweden; [3]Faculté de Médecine, Maïeutique et Sciences de la Santé, Université de Strasbourg, Strasbourg, France; [4]Rheumatology Department, Bach Mai Hospital, Hanoi, Vietnam

Background. The discovery of myositis-specific antibodies (MSAs) enables better delineation of myositis patient subgroups. These auto-antibodies are found in 50-80% of patients with myositis, with various composition among different ethnic groups. In previous studies of our group, we have depicted the genetico-clinico-serological picture of a Vietnamese myositis cohort. In this pilot study, we aimed to further explore the immunopathological changes of this cohort and their correlation with MSAs.
Methods. Thirty-six patients that fulfilled the Bohan and Peter criteria for myositis were included in this study. MSAs were tested for all patients. Immunohistochemistry using primary antibodies targeting CD3, CD4, CD8 for T cells, CD20 for B cells, CD68 and CD163 for macrophages, CD31 for endothelial cells, C5b-9 for complement attack complex, and MHC-I was performed. The QuPath software was used for quantification of the area of immunopositivity. Sections were reviewed in three to six randomly selected field under x40 magnification. Immunoreactive area was defined as the percentage of immunoreactive area to whole muscle section area of interest. An overall pathology score was estimated according to general changes including muscle necrosis/regeneration, fiber variation and rimmed vacuoles.
Results. Nineteen patients were tested positive for MSAs. The most common MSA in this cohort was SRP, Jo-1 and MDA5 antibodies (n=4 for each). EJ (+) patients had the highest density of CD4+ T cells (0.319%), while TIF1-γ (+) patients had the lowest (0.013%). The PL-12 (+) group showed the highest levels of CD8+ T cells as well as CD163+ macrophages (0.207%, 4.080%). Compared with T cells, there were very few infiltrating B cells. There was no significant difference in the levels of any of the lymphocyte subtype between MSA subgroups. The infiltration of CD3, 4, 8, 68 and 163 was correlated with the overall pathology score, with CD163 showing the strongest correlation (r^2=0.625). The densities of CD3 and CD4 were correlated with Physician Global Activity scores (p=0.002, 0.006 respectively), while those of CD68 and CD163 were correlated with CK levels (p=0.029, 0.046 respectively). MHC-I staining was positive in muscle fibers of all patients. The staining pattern was perifascicular in one Jo-1 (+), one EJ and one MDA5 (+), as well as three seronegative patients. C5b-9 was positive on the capillaries in 25% of SRP (+) (1/4) and 25% of MDA (+) (1/4) patients.
Conclusion. CD163+ macrophages were the predominant immune cells in muscles from all MSA groups. Patients with DM had more CD4+ than CD8+ T cells. No correlation between the pathological changes or immune infiltrate and MSAs was identified, possibly due to the small sample size. A larger number of patients is needed to validate the present findings.

P-135

PREGNANCY OUTCOME IS INFLUENCED BY INTERNAL ORGAN INVOLVEMENT AND NUMBER OF PREGNANCIES IN MYOSITIS PATIENTS

Melinda Nagy-Vincze[1], Sarolta Molnár[2], László Balkay[3], Tibor Béldi[1], Zoltán Griger[1]
[1]Division of Clinical Immunology, Faculty of Medicine, University of Debrecen, Debrecen, Hungary; [2]Pathology Institute, University of Debrecen, Debrecen, Hungary; [3]Department of Medical Imaging, Division of Nuclear Medicine, University of Debrecen, Debrecen, Hungary

Background. Data about pregnancy outcome in patients suffering from myositis are scarce. Probably due to later onset, there is a lack of consensus guideline for planning and managing patients' pregnancy. Previously published articles stated that the activity of maternal disease could lead to worse pregnancy outcome. A former multicentre study suggested that anti-Jo1 antibody positivity and joint involvement could distinguish a more vulnerable group considering pregnancy complications. Our aim was to find prognostic factors among clinical symptoms at disease onset and autoantibody profile for identifying a high-risk group for unfavourable pregnancy outcome.
Methods. Clinical data of myositis cohort of Division of Clinical Immunology, University of Debrecen, Hungary were reviewed retrospectively. IIM diagnosis was made by Bohan and Peter's criteria or EULAR/ACR diagnostic criteria. Disease activities were evaluated based on physician opinion. Normal labor was defined when healthy, >2500 g weight new-born was delivered after 37 weeks of pregnancy. Stillbirth was defined when the pregnancy ended between gestational week 28 and 37. Abortion was defined when the pregnancy ended before 28 weeks, not specified as spontaneous or induced. Early abortions revealed in the first, late abortion in the second trimester.
Results. Reviewing clinical data of overall 763 patients (542 women and 221 men) revealed that 5.2% (28/542) of female patients had 60 pregnancies after myositis onset. 71.4% (20/28) of the mothers suffered from Polymyositis (PM) and 28.6% (8/28) from Dermatomyositis (DM)). Their mean age at myositis diagnosis was 25.28 years and the average time between myositis diagnosis and first pregnancy was 55.4 months (-6-300 months). Maternal complications were preeclampsia in one case and pregnancy induced myositis in 25% (7/28) of cases. All pregnancy induced cases improved after immunosuppressive treatment. Early or late foetal loss was detected in 41.7% of the pregnancies (25/60), stillbirth in 18.3% (11/60) of labours. Although complications seemed more frequent in PM form, logistic regres-

sion analysis confirmed that multiple pregnancies could be independent risk factor of foetal complications (OR=4.19; CI:[1.39, 12.69]; *p*=0.0112) and the presence of interstitial lung disease of maternal complications (OR: 12; 95% CI: 1.48-97.18; *p*=0.02).
Conclusion. Besides maternal disease activity, internal organ involvement and number of pregnancies could influence pregnancy outcome in myositis patients. Patients' family planning should have to be well organised and counselled by myositis experts. Prospective, multicentre collaborations needed to preciously identify high-risk groups and state managing guidelines.

P-136

BURDEN OF DISEASE IN IDIOPATHIC INFLAMMATORY MYOPATHIES: FIRST PERSPECTIVES FROM A PATIENT-LED RESEARCH STUDY

Manuel Lubinus[1], Karen Cheng[1], Yuan Pai Hu[1], Lynn Wilson[1], Jerry Williams[1], Abhiram Bhashyam[2], Salman Bhai[3]
[1]Myositis Support and Understanding, Patient-Centered Research, Lincoln, DE, USA; [2]Massachusetts General Hospital, Boston, USA; [3]University of Texas Southwestern Medical Center, Neurology, Dallas, USA

Background. Idiopathic Inflammatory Myopathies (IIM) are a heterogenous group of autoimmune diseases causing proximal muscle weakness and other extra-muscular features, such as skin rashes, interstitial lung disease, arthritis, and gastrointestinal tract involvement. Much has been written about the clinical diagnosis and treatment of IIM, but the effect of IIM on patients' quality of life remains understudied. For this reason, we performed a prospective cross-sectional survey study to assess the physical, emotional, social and financial challenges of patients with IIMs.
Methods. An anonymous online survey to assess biosocial disease burden in IIM patients was developed by Myositis Support and Understanding (MSU), a non-profit patient-led advocacy organization and the University of Texas Southwestern (UTSW). The survey was distributed via RedCAP to MSU members worldwide, to assess information about demographics, diagnostics, and physiological and psychological effects of IIM from a patient's perspective.
Results. Demographics: 583 patients (71% female, 29% male; 88% white/Caucasian; age range: 18 to 90) responded to the survey conducted in May 2022.
Self-reported diagnosis: Inclusion Body Myositis (40%), Dermatomyositis (26%), Polymyositis (11%), Anti-Synthetase Syndrome (10%), Immune-mediated necrotizing myopathy (7%) and others (6%).
Medical Care: Rheumatologists care for 50% of these patients, along with neurologists, neuromuscular specialists, pulmonologists, dermatologists and immunologists. For diagnosis, 69% had muscle biopsies, and 36% had antibody testing. 63% were diagnosed after 1 year, and 52% travelled further than 20 miles for treatment despite 44% requiring mobility aids.
Mobility: More than 50% had difficulty doing household chores, carrying groceries, or climbing a flight of stairs. About 25% were unable or had much trouble dressing and toileting.
Emotional & Financial Burden: 38% felt isolated and a third expressed negativity and lacked confidence to maintain relationships. More than 30% had financial difficulty that necessitated reducing routine expenses and using savings.

Scan for data infographics

Fig. 1. Scan for data infographic.

Musculoskeletal: 46% experienced 5 or more falls, 24% had a fracture since diagnosis, and 33% had fractures that required orthopedic surgery. 51% needed pain medications, with 37% experiencing joint pain for more than 5 years.
Conclusion. In this study, we provide a holistic view of the burden of disease in patients with IIM in terms of social, financial, physical and psychological effects. Addressing this burden may be alleviated through early diagnosis, targeted therapies, mental health interventions, and comprehensive support services. Overall, a comprehensive multidisciplinary care approach is likely essential to improve patient outcomes.
Acknowledgements. MSU & UTSW acknowledge the support of our patient community, without whom this work would not be possible.

References
1. Access to MSU Myositis Journey and Burden of Disease Infographics: https://sites.google.com/view/msupatientledresearchresources/myositis-journey-and-burden-of-disease-infographics?authuser=0
2. CAMPAR A, ALVES I, MARTINS DA SILVA A, FARINHA F, VASCONCELOS C: Idiopathic inflammatory myopathies – The burden of disease: Cohort analysis focusing on damage and comorbidities,*Autoimmun Rev* 2023; 22(12): 103455. https://doi.org/10.1016/j.autrev.2023.103455

P-137

ANTI-MDA5 DERMATOMYOSITIS PATIENT-LED RESEARCH SURVEY: UNVEILING SYMPTOMS, TREATMENTS AND TRIAL ATTITUDES

Tim Kaniecki[2], Benita Moyers[1], Manuel Lubinus[1], Yuan-Pai Hu[1], Lynn Wilson[1], Stephen Moore[1], Jerry Williams[1], Lisa Christopher-Stine[2]
[1]Myositis Support and Understanding (MSU), Patient-Centered Research, Lincoln, DE, USA; [2] John Hopkins Myositis Center, Johns Hopkins Division of Rheumatology, Baltimore, MD, USA

Background. Dermatomyositis (DM) with the anti-MDA5 antibody poses distinct challenges due to its aggressive nature and rapid disease progression. Patients afflicted with this subset often confront heightened severity and varying clinical courses, warranting specialized support. This observational survey conducted by Myositis Support and Understanding (MSU), sought to understand the characteristics of anti-MDA5 DM by collecting meaningful data from this patient cohort and creating an anti-MDA5 DM profile that could be useful in determining more successful management, treatment, and clinical trial design.
Methods. MSU adapted the survey design from a study conducted on Juvenile Dermatomyositis (1). The online survey was fielded across MSU's support groups, completing 46 responses between December 8, 2022, and January 11, 2023. Participants had a clinical DM diagnosis and tested positive for the anti-MDA5 DM autoantibody. Data analysis excluded three participants who had a DM diagnosis but tested negative for anti-MDA5 autoantibodies.
Results. Forty-three individuals with DM and positive anti-MDA5 autoantibodies were part of the analysis. Symptoms observed at diagnosis encompassed common issues like skin problems (93.0%), muscle weakness (74.4%), pain (72.1%), ulcers (58.1%), and arthritis (55.8%).
Less common symptoms included lung issues such as Rapidly Progressing-Interstitial Lung Disease (RP-ILD) (16.3%) and ILD (30.2%).
Post-diagnosis, persisting skin issues included rashes (88.4%), heliotrope rash (76.7%), mechanics' hands (74.4%), Gottron's papules (67.4%), itching (62.8%), nail fold capillary changes (60.5%), and ulcers (53.5%). Extra-muscular concerns comprised pain (67.4%), arthritis (55.8%), and non-rapidly progressive ILD (46.5%). Fatigue (88.4%) and exercise intolerance (55.8%) were also reported.
Muscle symptoms were measured using the VAS scale**,** majority rated muscle compromise as ≤5 on a 0-10 scale (83.7%). Patients were under a variety of treatments, more than half were taking steroids (53.3%) and most were taking three or more medications (63%).
Not participating in a clinical trial was largely due to reluctance towards receiving a placebo (53%) or health risks associated with changing medications (44%).
Conclusion. To our knowledge, this dataset represents the first to gather patient insights regarding disease manifestations, clinical evaluations, and perspectives on clinical trial participation within a single MSA cohort. Thus, the results highlight the importance of patient-centricity in addressing the needs of specific disease phenotypes, despite variable disease management

strategies across healthcare providers. Further education and disease awareness of the characteristics of this DM subtype can potentially enable earlier diagnoses, targeted therapeutic interventions, and monitoring of progression for better patient outcomes.

Reference

1. McCANN *et al*.: *Pediatric Rheumatology* 2014; 12: 31.

P-138

PATIENT-REPORTED PHYSICAL FUNCTION, MENTAL HEALTH, AND TREATMENT PATTERNS IN DERMATOMYOSITIS

Lisa Christopher-Stine[1], Julie J. Paik[1], Brendan M. Johnson[2], Alexandra S. Goriounova[2], Jolie Feldman[2], Taryn Smith[2], Paul N. Mudd Jr[2]
[1]Johns Hopkins School of Medicine, Baltimore, MD, USA; [2]Priovant Therapeutics, Durham, NC, USA

Background. Dermatomyositis (DM) is characterized by painful, itchy skin rash and proximal muscle weakness that can significantly impact daily activities. Additional life-threatening manifestations include interstitial lung disease and increased risk of malignancy. The profound impacts of DM and treatment patterns on patient quality of life (QoL) are not yet well-characterized in the literature.
Methods. To capture adult patient perspectives on the impact of DM and frequently used medications on patients' QoL, a 60-question survey was developed via focus groups and adaptations from existing tools. Members of The Myositis Association with a self-reported diagnosis of DM, 18–75 yrs of age, and onset of symptoms ≥1 yr were invited to complete the online survey. Responses were collected per several Likert scales.
Results. Respondents (n=195) predominantly lived in the US (97%), were female (88%), white (82%), with a median age of 57 yrs; 53% and 35% experienced DM symptoms for 3 to 10 yrs or >10 yrs, respectively. Arithmetic mean QoL impact scores (out of 5) for patients with mild, moderate, or severe/very severe disease, respectively, were 1.9, 2.7, and 3.6 when asked if DM limits their ability to do things they enjoy; 2.3, 2.6, and 3.2 when asked how often they worry their disease will worsen; and 1.8, 2.4, and 3.4 when asked how often they worry about their disease will limit their ability to carry out daily activities. Across all QoL endpoints, more than 50% of participants said their social life and relationships are at least somewhat negatively impacted by DM, and that DM limits their ability to perform daily activities (65%) and the ability to climb stairs (63%). Immunosuppressants were most commonly used (72%), then over-the-counter NSAIDS (56%) and oral corticosteroids (48%). 84% of respondents use more than 1 medication for DM. Use of steroids increased as disease worsens (35%, 44%, and 65% of mild, moderate, and severe/very severe respondents, respectively). There was also increased use of opioids in respondents with severe/very severe disease (32%), compared to mild/moderate disease (<10%). Patients using more medications also reported greater impact of their disease on QoL.
Conclusion. This survey highlights the physical limitations and high emotional burden in patients living with DM. The survey also suggests an unmet need for additional steroid-sparing therapies and novel treatments that address disease pathogenesis. The self-reported use of opioids in the most severely affected patients living with DM has not previously been appreciated.

P-139

IS THE ACR/EULAR TOTAL IMPROVEMENT SCORE RESPONSIVE TO CHANGE IN PATIENT-REPORTED OUTCOMES IN AUTOIMMUNE INFLAMMATORY MYOPATHIES?

Valérie Leclair[1,2,3], Claudie Berger[4], Canadian Inflammatory Myopathy Study, Marie Hudson[1,2,3]
[1]Department of Medicine, McGill University, Montreal, Canada; [2]Division of Rheumatology, Jewish General Hospital, Montreal, Canada; [3]Lady Davis Institute for Medical Research, Montreal, Canada; [4]Research Institute of the McGill University Health Centre, Montreal, Canada

Background. The ACR / EULAR Total Improvement Score (TIS) is increasingly used in research but its ability to reflect how autoimmune inflammatory myopathies (AIM) patients feel and function is largely unknown. We aimed to assess the TIS responsiveness to change in patient-reported outcomes (PROs).
Methods. Adult AIM subjects with active disease at baseline visit and a 1-year follow-up were identified from a multi-center research cohort. Standardized assessments and self-administered questionnaires were longitudinally collected including the IMACS core set measures (i.e. physician/patient global assessments (PhGA/PtGA) and extramuscular assessments (numerical rating scales; range 0–10), manual muscle testing (MMT8; range 0–150), Health Assessment Questionnaire (HAQ; range 0–3), and creatine kinase levels). Fatigue was measured using the Functional Assessment of Chronic Illness Therapy (FACIT; range 0-52, lower scores representing more fatigue). Depressive symptoms using the Patient Health Questionnaire (PHQ-9; range 0–27, higher scores representing worse symptoms). The PROMIS Short Form v.1.0 – Fatigue 8a and the Medical Outcomes Trust Short Form-36 (SF-36) were used to assess sleep quality and health-related quality of life (HRQoL), respectively with mean scores of 50 and standard deviations (SD) of 10 (PROMIS, higher scores representing worse sleep quality; SF-36, lower scores representing worse HRQoL). Multivariable linear regression models were generated to determine the absolute change in PROs for each increase of 20 units in the absolute TIS.
Results. We included 82 AIM subjects (70% female, mean age at diagnosis 52 years, median disease duration 3 years) with dermatomyositis (43%), scleromyositis (15%), anti-synthetase syndrome (13%), overlap myositis (9%), immune-mediated necrotizing myopathies (6%), inclusion body myositis (9%) and polymyositis or unspecific myositis (6%). At baseline, mean±SD PhGA was 3.4±1.9 and PtGA 5.1±2.8. Longitudinal PRO scores are presented in Table I. At year-1, there was significant mean±SD absolute change in FACIT scores (4.0±9.2, p=0.001), SF-36 physical (PCS; 2.8±8.5, p=0.01) and mental component score (MCS; 2.6±9.9, p=0.05). In multivariable linear regression models adjusted for age, sex and AIM subsets, each increase of 20 units in the absolute TIS was associated with a statistically significant and clinically meaningful improvement in pain, fatigue, and the SF-36 PCS, but not in the PHQ-9 scores or the SF-36 MCS.

Table I. Longitudinal PRO measures and adjusted parameter estimates in the change in PROs for each increase of 20 units in the absolute TIS.

				Δ in scores for 20 units	
Measures	n	Baseline	Year-1	increase in TIS‡ β (95% CI)	p-value
Lower scores, better					
Pain, median (IQR)	59	3 (0-7)	3 (0-6)	-1.8 (-3.1, -05)	0.008
PROMIS-fatigue†, mean ± SD	62	57±10	55±11	-3.4 (-6.5, -0.3)	0.034
PHQ-9, median (IQR)	62	5 (2-11)	3 (1-11)	0.2 (-1.3, 1.8)	0.770
Higher scores, better					
FACIT, median (IQR)	62	28 (19-41)	38 (24-44)	3.6 (0.4, 6.8)	0.027
SF-36 PCS†, mean ± SD	60	35±12	38±13	3.4 (0.0, 6.8)	0.051
SF-36 MCS†, mean ± SD	60	46±10	48±11	0.9 (-3.4, 5.3)	o.665

PCS: physical component score, MCS: mental component score.
†T-scores.
‡Adjusted for age, sex and AIM subset.

Conclusion. Improvement measured by the TIS corresponded to improvement in pain, fatigue, and physical HRQoL. However, the TIS was not associated with changes in mood and mental HRQoL. These findings are helpful to inform researchers on the ability of the TIS to reflect PROs in future studies.

P-140

DEVELOPMENT OF AN INITIAL PREDICTIVE MODEL FOR ANTI-JO-1 ANTIBODY IDENTIFICATION IN IDIOPATHIC INFLAMMATORY MYOPATHIES: ADVANCES FROM THE BRAZILIAN REGISTRY REMAS

Alexandre M. Santos[1], Fernando H.C. de Souza[1], Renata Miossi[1], Lorenza R.S. Silva[1], Marlise S.M. Mendes[1], Daniel B. de Araújo[2], Luiz Felipe A. Sousa[3], Juliana A. Vieira[3], Dawton Y. Torigoe[3], Jean M. Souza[4], Simone Appenzeller[4], Marília P.S. Santos[4], Ana C.D. Oliveira[5], Luiz S.G. Machado[5], Samuel K. Shinjo[1]

[1]Division of Rheumatology, Faculdade de Medicina FMUSP, Universidade de Sao Paulo, Sao Paulo, Brazil; [2]Division of Internal Medicine, Universidade Federal de Pelotas (UFPel), Grande do Sul, Brazil; [3]Division of Rheumatology, Faculdade de Medicina da Santa Casa de Sao Paulo, Sao Paulo, Brazil; [4]Division of Rheumatology, Faculty of Medical Sciences, Universidade Estadual de Campinas UNICAMP, Campinas, Brazil; [5]Rheumatology Division, Universidade Federal de São Paulo UNIFESP, São Paulo, Brazil

Background. Idiopathic inflammatory myopathies (IIMs), or systemic autoimmune myopathies, notably antisynthetase syndrome, present formidable diagnostic challenges, particularly in underserved areas. Timely detection of anti-Jo-1 antibody plays a pivotal role in early identification, facilitating more efficacious therapeutic interventions. This study aimed to address this gap by formulating a robust initial predictive model for anti-Jo-1 antibody identification, leveraging data from the Brazilian Registry of Systemic Autoimmune Myopathies (REMAS). Prioritizing traditional variables and specific details regarding initial signs and symptoms, we aspire to create a decision-support tool catering to rheumatologists.

Methods. Data were compiled for 191 patients diagnosed with IIMs, according to EULAR/ACR 2017 classification criteria. Employing an innovative approach, we integrated advanced machine learning libraries, including Boruta and RandomForest, to construct a predictive model. Boruta, specializing in variable selection, and the RandomForest algorithm, renowned for classification efficacy, were strategically chosen to optimize model robustness. Cross-validation procedures were implemented to ensure model generalizability of the model, In addition, we employed a training-to-testing data split of 70% to 30% for the model.

Results. The predictive model demonstrated exceptional performance, yielding a Brier Score of 0.036, signifying noteworthy consistency between the predictions and actual labels. The area under the curve (AUC) achieved a maximum value of 1.000 (Fig. 1A), emphasizing the exceptional ability to discriminate between positive and negative cases. An accuracy of 1.000 reflects the model's proficiency in identifying true positives, with a recall of 0.778, denoting a robust capture rate of positive instances. The F1-Score of 0.875 underscores the effective balance between precision and recall. The confusion matrix (Fig. 1B) provides a detailed description of the performance of the model across different classes.

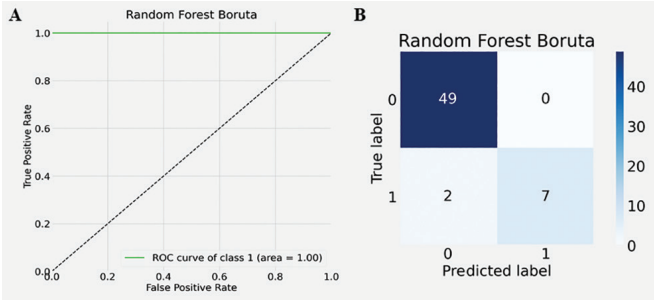


Fig. 1. The area under the curve and confusion matrix.

Conclusion. This pioneering study, which focused on the development of a predictive model for anti-Jo-1 antibody identification in IIMs, underscores its potential clinical significance. Acknowledging this as an initial step, we advocate for a comprehensive exploration of machine-learning algorithms to enhance and validate their effectiveness. Future investigations should encompass diverse algorithms and substantially enlarge the patient cohort, which is critical for solidifying and augmenting the clinical utility of the model. This endeavor targets its pivotal role in early anti-Jo-1 antibody identification in IIMs, constituting an indispensable decision-support tool for rheumatologists.

Acknowledgments. FAPESP #2020/10691-4 (AMS) and #2022/04869-0 (SKS).

References

1. GENG Q, CAO X, FAN D *et al.*: Diagnostic gene signatures and aberrant pathway activation based on m6A methylation regulators in rheumatoid arthritis. *Front Immunol* 2022; 1-13.
2. BETTERIDGE Z, MCHUGH N: Myositis-specific autoantibodies: an important tool to support diagnosis of myositis. *J Intern Med* 2016; 280(1): 8-23.

P-141

DERMATOMYOSITIS ASSESSMENT OF RASH VIA TELEMEDICINE

Nantakarn Pongtarakulpanit[1,2], Tanya Chandra[1], Sedin Dzanko[1], Eugenia Gkiaouraki[1], Shiri Keret[3], Raisa L. Silva[4], Shreya Sriram[1], Didem Saygin[1], Vladimir M. Liarski[1], Dana P. Ascherman[1], Chester V. Oddis[1], Siamak Moghadam-Kia[1], Rohit Aggarwal[1]

[1]Division of Rheumatology and Clinical Immunology, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA; [2]Division of Allergy, Immunology and Rheumatology, Department of Medicine, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand; [3]Rheumatology, Bnai-Zion Medical Center, Faculty of Medicine, Technion, Haifa, Israel; [4]Internal medicine, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA

Background. Recent advances in telemedicine have enabled greater patient access to medical care. This study investigates the feasibility of telemedicine in evaluating dermatomyositis (DM) skin rash compared to traditional in-clinic assessments.

Methods. DM patients, according to the 2017 European League Against Rheumatism/American College of Rheumatology classification criteria, were prospectively enrolled in an observational study called DART, or "Dermatomyositis Assessment of Rash via Telemedicine". Each patient underwent evaluations by two independent rheumatologists (MD1 and MD2) for both in-clinic and telemedicine visits (2-4 weeks post-clinic evaluation). The Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI) were scored during these assessments. Telemedicine visits were done through a Health Insurance Portability and Accountability Act (HIPAA) -secured platform and aided by patient self-photographs obtained via a mobile application (SkinIO) on the patient's smartphone. In addition, patients were asked to complete a modified CDASI developed for the patient's self-assessment of the rashes. The patient also completed a Patient-Reported Outcome questionnaire called Skindex to evaluate the patient's skin quality of life simultaneously. We compared the telemedicine CDASI with in-clinic CDASI.

Results. A total of 23 DM patients underwent evaluation, resulting in 30 sets of visits (1–2 sets per patient; 1 set of visits comprised of 1 in-clinic visit and 1 telemedicine visit). Most of the patients were female (82.6%), with a mean age of 48.6 ± 17.4 years and a median (Q1-Q3) disease duration of 38.0 (9.5–88.0) months. Their median CDASI activity at baseline visit was 4.5 (2.0–17.5). Telemedicine CDASI had strong correlations with in-clinic CDASI, patient CDASI, and Skindex, indicating good convergent validity. The intraclass correlation coefficient (ICC) for inter-rater reliability for telemedicine CDASI was excellent for MD1 and MD2 (ICC=0.97). The ICC for intra-rater reliability between the same rater in-clinic and telemedicine was 0.97 and 0.96 for MD1 and MD2, respectively.

Conclusion. Our results demonstrate favorable validity, inter-rater reliability, and intra-rater reliability of telemedicine CDASI in evaluating DM patients with skin rashes remotely.

Table I. The correlation between in-clinic CDASI, telemedicine CDASI, patient CDASI, and Skindex.

Spearman rank correlation coefficients	Clinic MD1 CDASI Activity	Clinic MD2 CDASI Activity	Tele MD1 CDASI Activity	Tele MD2 CDASI Activity	Patient CDASI	Patient Skindex
Clinic MD1 CDASI Activity	1.00	0.89*	0.92*	0.91*	0.74*	0.84*
Clinic MD2 CDASI Activity	0.89*	1.00	0.83*	0.80*	0.68*	0.77*
Tele MD1 CDASI Activity	0.92*	0.83*	1.00	0.89*	0.68*	0.82*
Tele MD2 CDASI Activity	0.91*	0.80*	0.89*	1.00	0.68*	0.71*
Patient CDASI	0.74*	0.68*	0.68*	0.68*	1.00	0.66*
Patient Skindex	0.84*	0.77*	0.82*	0.71*	0.66*	1.00

CDASI: Cutaneous Dermatomyositis Disease Area and Severity Index; Clinic MD1: in-clinic evaluation by MD1; Clinic MD2: in-clinic evaluation by MD2; Tele MD1: telemedicine evaluation by MD1; Tele MD2: telemedicine evaluation by MD2.
*p-value <0.001.

P-142

FOCAL MYOSITIS: FROM GLOBAL ENTITY TO DISTINGUISHED SUBGROUPS

Laure Gallay[1,2], Lola Lessard[3], Clara Baverez[1], Yves Allenbach[4], Tanguy Fenouil[2], Philippe Petiot[5], Arnaud Hot[1], Nathalie Streichenberger[2]
[1]Service de Médecine Interne, Pavillon O, Hôpital Edouard Herriot, Hospices Civils de Lyon, Lyon, France; [2]Service d'Anatomopathologie, Groupement Hospitalier Est, Hospices Civils de Lyon, Lyon, France; [3]Service d'Electroneuromyographie et de Pathologies Neuromusculaires, Hôpital Neurologique, GHE, Hospices Civils de Lyon, Lyon, France; [4]Service de Médecine Interne, Hôpital de la Pitie Salpetriere, Paris, France; [5]Consultation Neurologique, Clinique Medicina, Lyon, France

Background. Focal myositis (FM) is a rare inflammatory muscle disease considered as benign. The origin is unknown, but occasionally, FM has been described in association with disorders such as radiculopathies, as well as infectious and autoimmune diseases. The prevalence of these associations remains unknown. Given the heterogeneity of its clinical phenotype, it remains unclear whether FM should be considered as a syndrome associated with other conditions or as a full-fledged entity. The present work aims to further define the clinicopathological specificity of FM when associated with Behçet's disease (BD) or neoplasia.
Methods. This retrospective study included FM patients with FMSS ≥2 associated with either BD or neoplasia. Cases of FMSS <2 and ocular myositis during Grave disease, known as a distinct entity, were excluded. Cases were collected in the MYOLYON database, and additional cases were retrieved through the French muscular rare disease network. For all cases, medical, biological, morphologic, and electrophysiologic data were retrieved. Pathologic specimens were analyzed for all cases. Standard patient consents, human biological samples and associated data were obtained from Cardiobiotec Biobank (CRB-HCL Hospices Civils de Lyon BB-0033-00046).
Results. This work identified two distinct FM subgroups: FM with BD or FM with neoplasia. On one side, 10 patients had FM occurring during BD (FM BD+ group), the median [IQR] age at BD diagnosis was 25 [16–35] years, and at FM diagnosis, it was 30 [26–42] years. The sex ratio was 1. The diagnosis of BD preceded FM in most cases (n=8/10). FM occurrence was associated with BD flare-ups in 3 cases. Histological analyses identified relatively preserved muscle tissue, associated with vasculitis (n = 5/6). All patients required treatment; most patients relapsed (n=9/10). On the other side, 14 FM patients were associated with neoplasia (FMneo+ group). The latter had a median age of 55 [45.8-71.3] years, and a sex ratio of 0.4. FM diagnosis preceded that of neoplasia in 71.4% of patients by a median of 6 [2-8] months. Neoplasia were solid tumors in 10 patients (71.4%), and hematologic malignancies for 4 (28.6%). Patients with FM associated with neoplasia had a lower sex ratio, an older median age, atypical locations, systemic symptoms, and marked necrosis on histology, as compared to FM patients without associated diseases.
Conclusion. While FM has long been considered a harmless disorder, the results of the present studies highlight the potential severity of this disease, particularly regarding the associated conditions. Regarding these 2 subgroups of FM patients, the in-depth analysis of clinical and muscle histological data identified specific patterns, useful hallmarks that may warn both the clinician and the pathologist.

P-143

CAREGIVER BURDEN AMONG IDIOPATHIC INFLAMMATORY MYOPATHY (IIM) CAREGIVERS

Manuel Lubinus[1], Yuan-Pai Hu[1], Lynn Wilson[1], Jerry Williams[1], Abhiram Bhashyam[2], Salman Bhai[3]
[1]Myositis Support and Understanding (MSU), Patient-Centered Research, Lincoln, USA; [2]Massachusetts General Hospital, Surgery, Boston, USA; [3]University of Texas Southwestern Medical Center (UTSW), Neurology, Dallas, TX, USA

Background. Idiopathic inflammatory myopathies (IIMs) often lead to severe impairments in quality-of-life related to physical and emotional burdens. While the healthcare delivery burden in patients with specific types of IIMs has been explored (1), little is known about caregivers' burden, especially in rare diseases (2).
Myositis Support and Understanding (MSU), a non-profit patient-led advocacy organization for IIMs, distributed a survey to its members to better understand caregiver burden. The aim of this study was to evaluate the association between caregiver burden by IIM subtype and factors that impact caregiver wellbeing.
Methods. Data Source: An anonymous survey was distributed via RedCAP to MSU members worldwide. A total of 120 caregivers (age range: 30–89) responded to the survey over the course of 4 weeks.
Survey. Demographic, diagnostic information, and disease duration data was collected from participants and their caregivers. The Zarit Burden Interview (ZBI), a validated instrument for a diverse range of patients and caregivers, was used to determine caregiver burden, testing domains including health, mental well-being, personal relationships, physical overload, social support, and home environment (3).
Statistical analysis. Pearson chi-square test was performed to assess the association between duration of caregiving, myositis type, and caregiver age on the social well-being of caregivers. Regression analysis was also conducted to identify risk factors for increased caregiver burden. Significance was set at $p<0.05$.
Results. Most of the caregivers in this study were responsible for the care of participants with inclusion body myositis (IBM, 64%) followed by dermatomyositis (DM, 22%). Caregivers reported that 74% of IIM patients under their care had moderate to severe difficulties with mobility and required help some or most of the time. A total of 102 caregivers completed the ZBI: reported burden was mild to moderate in 44%, moderate to severe in 25%, and severe in 4% of caregivers. There was a high degree of at least moderate severity burden in IBM (33%), DM (25%), and polymyositis (25%).
Conclusion. Caregivers face a high degree of burden, most evident in IBM. Burden positively correlated with disease duration with an inflection time of 6 years, thereafter caregivers reported increased burden. The domains that were most impacted include personal strain, social and family life, role strain, and loss of control over one's life. Insights from this study can help create specific emotional coping strategies for myositis patients and their caregivers.
MSU and UTSW acknowledge the support of our caregiver community, without whom this work would not be possible.

References

1. CHRISTOPHER-STINE L, WAN GJ, KELLY W, MCGOWAN M, BOSTIC R, REED ML: Patient-reported dermatomyositis and polymyositis flare symptoms are associated with disability, productivity loss, and healthcare resource use. *J Manag Care Spec Pharm* 2020; 26(11): 1424-33.
2. YANG G, CINTINA I, PARISER A *et al*.: The national economic burden of a rare disease in the United States in 2019. *Orphanet J Rare Dis* 2011; 17: 163. https://doi.org/10.1186/s13023-022-02299-5
3. BACHNER YG, O'ROURKE N: Reliabiity generalization of responses by care provides to the Zarit Burden Interview. *Aging Ment Health* 2007; 11(6): 678-85. https://doi.org/10.1080/13607860701529965

P-144

FACTORS ASSOCIATED WITH FATAL OUTCOME IN IDIOPATHIC INFLAMMATORY MYOPATHIES

Aleksandra Opinc-Rosiak, Ewelina Kulesza, Agnieszka Mikosińska, Olga Brzezińska, Joanna Makowska
Department of Rheumatology, Medical University of Lodz, Lodz, Poland

Background. Idiopathic inflammatory myopathies (IIM) is a group of connective tissue diseases associated with one of the highest mortality rates among autoimmune disorders. According to the literature, malignancy, cardiac and pulmonary involvement, older age at the time of diagnosis, fever and specific serological profiles are among the most commonly identified predictors of fatal outcome. The aim of the study is to analyse the mortality rate and causes of mortality in the cohort of patients from the Department of Rheumatology, Medical University of Lodz.
Methods. Patients diagnosed with IIM were identified among the patients hospitalized at the Department of Rheumatology, Medical University of Lodz within the period of 03.2017-06.2023. Electronic medical records were analysed. Data on demographics, course of the disease and clinical symptoms, results of serological tests including the presence of muscle-specific and muscle-associated antibodies (assessed by immunoblot), administered treatment, concomitant diseases and disease outcome were collected. Data was analysed statistically with STATISTICA 13 software, factors associated with the risk of fatal outcome were identified.
Results. 81 patients with IIM were identified. The mean age at the diagnosis was 56.79±14.40 years. The average diagnostic delay reached 21.01±37.04 months, ranging from the immediate diagnosis to even 17 years. The most

frequently diagnosed subtypes were antisynthetase syndrome in 32.10% (n=26) and dermatomyositis in 30,86% (n=25). Polymyositis was diagnosed in 18.52% of the cohort (n=15), cancer-associated dermatomyositis in 9.88% (n=8) and immune-mediated necrotizing myopathy in 8.64% (n=7). 11.11% (n=9) of the patients died, including 8 fatal outcomes due to infectious complications (88.89% of all deaths). Mean time till death was, respectively, 46 months (median=24 months) from the disease onset and 23 months (median=16 months) from the disease diagnosis. 11.11% of the patients had a history of malignancy, including CADM in 8 of them, however, none of the deaths reported was caused by malignancy. Cardiac involvement (OR=4.44, *p*=0.046), treatment with mycophenolate mofetil (OR=6,25; *p*=0.0135), and concomitant autoimmune diseases such as rheumatoid arthritis, Sjögren's syndrome, type 1 diabetes, autoimmune hepatitis and autoimmune labyrinthitis (OR=5.50; *p*=0.0390) were significantly associated with higher risk of death.

Conclusion. Patients with IIM and cardiac involvement as well as patients with overlapping myositis were found to be at higher risk of fatal outcome. A high percentage of deaths due to infections highlights the urging need to attract more attention to latent infection screening, infection prevention and rational immunosuppression in IIM patients.

P-145

PATIENT BURDEN OF MULTIMODALITY DIAGNOSTIC TESTING IN PATIENTS SUSPECTED OF AN IDIOPATHIC INFLAMMATORY MYOPATHY: DATA FROM THE ADAPT STUDY

Hannah A.W. Walter[1], Renske G. Kamperman[1], Sanne W Evers[1], Johannes H.T.M. Koelman[1], Wouter V. Potters[1], Robert Hemke[2], Frank F. Smithuis[2], Eleonora Aronica[3], Ester M.M. van Leeuwen[4], Paul A. Baars[4], Marianne de Visser[1], Ivo N. van Schaik[1,6], Patrick M.M. Bossuyt[5], Camiel Verhamme[1], Joost Raaphorst[1], Anneke J. van der Kooi[1]

[1]Department of Neurology and Clinical Neurophysiology, Amsterdam University Medical Centre, University of Amsterdam, Amsterdam Neuroscience, Amsterdam, The Netherlands; [2]Department of Radiology and Nuclear Medicine, Amsterdam University Medical Centre, Amsterdam Movement Sciences, Amsterdam, the Netherlands; [3]Department of (Neuro)Pathology, Amsterdam University Medical Centre, Amsterdam Neuroscience, Amsterdam, The Netherlands; [4]Department of Experimental Immunology, Amsterdam institute for Infection & Immunity, Amsterdam UMC, Amsterdam, The Netherlands; [5]Department of Clinical Epidemiology, Biostatistics and Bioinformatics, Amsterdam University Medical Centre, Amsterdam Neuroscience, Amsterdam, The Netherlands; [6]Sanquin, Amsterdam, The Netherlands

Background. Various diagnostic tests can be employed to reach an idiopathic inflammatory myopathy (IIM) diagnosis, but the burden of these tests has not been investigated systematically. We performed an over-complete diagnostic accuracy study in patients with proximal muscle weakness and a clinical suspicion on IIM, and asked patients to assess the burden of the ancillary investigations.

Methods. One-hundred patients suspected of an IIM were included prospectively. All patients underwent venipuncture, also including myositis specific (MSA) and myositis associated (MAA) antibodies testing, whole-body (WB-)MRI, muscle ultrasound (US), EMG and open muscle biopsy (Bx), in the same order. Patient burden of the different diagnostic modalities was evaluated using a 4-point Likert scale: 1 = 'not burdensome at all', 2= 'little burdensome', 3= 'quite burdensome' and 4= 'very burdensome'.

Results. Ninety-four patients completed the questions, of whom 55% were female. Mean age was 59.3 years (SD 13.8). Median scores of the Likert scales concerning venipuncture, WB-MRI, US, EMG and Bx were 1, 1, 1, 2 and 3 respectively. Most patients (73.1%) ranked EMG as not or little burdensome, and nearly half of the patients (47.9%) rated muscle biopsy similarly (Table I).

Table I. Frequency table of the burden of ancillary investigation on 4-point Likert scale

	Not burdensome	Little burdensome	Quite burdensome	Very burdensome
Venipuncture; n (%)	73 (77.7)	14 (14.9)	4 (4.3)	3 (3.2)
WB-MRI*; n (%)	58 (62.4)	22 (23.7)	10 (10.8	3 (3.2)
Ultrasound; n (%)	86 (91.5)	7 (7.4)	0 (0)	1 (1.1)
EMG*; n (%)	17 (18.3)	51 (54.8)	16 (17.2)	9 (9.7)
Muscle biopsy; n (%)	5 (5.3)	40 (42.6)	26 (27.7)	23 (24.5)

WB-MRI: whole-body magnetic resonance imaging; US: ultrasound (nine muscles bilaterally); EMG: electromyography (ten muscles were tested unilaterally; Bx: open muscle biopsy.
*data was missing for one person.

Conclusion. Patients rated venipuncture, WB-MRI and US less burdensome than EMG and muscle biopsy. However, most patients did not consider EMG as burdensome. Though muscle biopsy caused more discomfort, nearly half of the patients reported little to no burden. It would be preferred if IIM can be diagnosed accurately with a combination of tests which are rated less burdensome.

Trial registration number: Netherlands trial register NL8764.

P-146

GENERAL FEATURES OF PATIENTS WITH IDIOPATHIC INFLAMMATORY MYOPATHIES: A BRAZILIAN MULTICENTER REGISTRY (REMAS)

Daniel B de Araujo[1], Fernando HC de Souza[2], Renata Miossi[2], Alexandre M dos Santos[2], Lorenza RS Silva[2], Marlise SM Mendes[2], Luiz FA de Sousa[3], Juliana A Vieira[3], Dawton Y Torigoe[3], Jean M de Souza[4], Marilia PS dos Santos[5], Simone Appenzeller[5], Luiz SG Machado[6], Ana CD Oliveira[6], Samuel K Shinjo[2]

[1]Departamento de Clínica Médica, Faculdade de Medicina, Universidade Federal de Pelotas, Pelotas, Brazil; [2]Division of Rheumatology, Faculdade de Medicina FMUSP, Unviersidade de São Paulo, São Paulo, SP, Brazil; [3]Division of Rheumatology, Faculdade de Medicina da Santa Casa de São Paulo, SP, Brazil; [4]Division of Internal Medicine, Faculty of Medical Sciences, Universidade Estadual de Campinas (UNICAMP), Campinas, Brazil; [5]Division of Rheumatology, Faculty of Medical Sciences, Universidade Estadual de Campinas (UNICAMP), Campinas, Brazil; [6]Division of Rheumatology, Universidade Federal de São Paulo (UNIFESP), São Paulo, SP, Brazil

Background. The Brazilian Registry of Systemic Autoimmune Myopathies (REMAS) was established in September 2022, with the support of the Brazilian Society of Rheumatology.

Methods. It aims to establish a comprehensive and updated registry of patients with IIM in Brazil, collecting and storing detailed clinical data including information on symptoms, medical history, laboratory and imaging tests, activity, and clinical outcomes.

Results. In November 2023, the REMAS had eight Brazilian centers and included 194 patients with complete and analyzed data.

The median age was 52.3±16.1 years, with 75% women. Regarding ethnicity, 44%, 37%, 16%, and 2.1% of participants were white, mixed-race, black, and yellow, respectively. Ninety-seven patients had dermatomyositis, 45 had antisynthetase syndrome, 21 had clinically amyopathic dermatomyositis, 19 had polymyositis, 10 had immune-mediated necrotizing myopathies, and two had inclusion body myopathy.

In terms of initial/cumulative clinical manifestations, fever was present in 13.9% of the cases, heliotrope rash in 36.6%, Gottron's sign in 31.4%, Gottron's papules in 32.5%, dysphagia in 33.5%, upper limb weakness in 79.4%, lower limb weakness in 82%, joint involvement in 30.9%, Raynaud's phenomenon in 25.3%, lung involvement in 35.1%, and cardiac involvement in 1.5%. Muscle biopsy and electroneuromyography were performed in 25.3% and 58.8% of the patients, respectively. Autoantibodies were positive in 85.1% of the patients, with anti-Jo-1 being the most frequently detected antibody (16.5%). Regarding treatment, 82.5% of patients received glucocorticoids, whereas 33.5%, 33.5%, and 19.6% of patients received intravenous methylprednisolone, immunoglobulin, and cyclophosphamide, respectively. The use rates of methotrexate, azathioprine, cyclosporine, leflunomide, mycophenolate mofetil, and tacrolimus were 53.1%, 52.1%, 20.6%, 8.2%, 16%, and 0.5%, respectively.

Regarding cardiovascular diseases and their risk factors, 37.1%, 26.3%, 18.6%, 2.6%, and 0.5% had arterial hypertension, dyslipidemia, diabetes mellitus, a history of myocardial infarction, and a history of stroke.

Moreover, 12.4%, 12.4%, 10.3%, and 2.6% of patients had hypothyroidism, depression, fibromyalgia, and a history of neoplasia. Smoking and alcoholism were present in 9.3% and 2.6% of the patients, respectively.

Conclusion. To our knowledge, this is the first study to demonstrate the general profile of Brazilian patients with IIM. The proposal is to continue increasing with new samples and new centers, and even allow comparison with the IIM population of other international centers.

Funding. this study was supported by the Brazilian Society of Rheumatology, FAPESP #2020/10691-4 (A.M.S.), and FAPESP #2022/08896-2 (S.K.S.).

P-147

INTEGRATING LARGE LANGUAGE MODELS IN MEDICINE: A STUDY OF CLAUDE 2'S PERFORMANCE IN MDAAT SCORING FOR IDIOPATHIC INFLAMMATORY MYOPATHIES

Marco Fornaro[1], Vincenzo Venerito[1], Sara Sabbagh[2], Shounak Ghosh[3], Hector Chinoy[4,5,6], Latika Gupta[5,7,8] on behalf of MyoLLM investigators

[1]Rheumatology Unit, Department of Emergency and Organ Transplantation, Bari, Italy; [2]Division of Rheumatology, Department of Pediatrics, Medical College of Wisconsin, Milwaukee, WI, USA; [3]Department of Rheumatology, Calcutta Medical Research Institute, Kolkata, India; [4]Division of Musculoskeletal and Dermatological Sciences, Centre for Musculoskeletal Research, School of Biological Sciences, Faculty of Biology, Medicine and Health, Manchester Academic Health Science Centre, The University of Manchester, Manchester, UK; [5]National Institute for Health Research Manchester Biomedical Research Centre, Manchester University NHS Foundation Trust, The University of Manchester, Manchester, UK; [6]Department of Rheumatology, Salford Royal Hospital, Northern Care Alliance NHS Foundation Trust, Salford, UK; [7]Department of Rheumatology, Royal Wolverhampton Hospitals NHS Trust, Wolverhampton, UK; [8]City Hospital, Sandwell and West Birmingham Hospitals NHS Trust, Birmingham, UK

Background. The role of Artificial Intelligence (AI) and large language modules (LLMs) in medicine is becoming more precise with every passing day (1). AI-generated scientific abstracts have been deemed comparable to content created by humans (2). We aimed to use AI to assess the severity of disease in idiopathic inflammatory myopathies (IIM) and to compare its assessments with those made by human evaluators as this may have commercial utility in trial recruitment.

Methods. The open-access LLM "Claude 2" was embedded with a document denoting the Myositis Disease Activity Assessment Tool Visual Analog Scale (MDAAT-VAS) scores along with 30 clinical cases of IIM curated by multiple clinicians. Claude 2 was asked to score a VAS score for each of the 9 organ systems mentioned in the MDAAT score (Constitutional, Cutaneous, Skeletal, Gastrointestinal, Pulmonary, Cardiovascular, Muscular, Extramuscular, Global), independently, using the following prompt: "Please only score MDAAT-VAS, autonomously, based on how detrimental those involvements are for everyday life and workability, considering that VAS 10 = almost death". Three independent rheumatologists, two being experienced in IIM research (>3 years) also scored the MDAAT-VAS for each of these 30 cases, and average Intraclass Correlation Coefficent (ICC) with a two-way random effects model and Pearson's correlation coefficient were calculated to check the inter-reader variability between Claude and each of the assessors on Stata 18.

Results. Thirty training cases and the MDAAT-VAS scores given by Claude 2 and assessors were analysed. Considering each MDAAT-VAS as a separate rating, ICC was 0.89 (n.270 targets, n.3 raters). In 29 out 30 cases (97%) average ICC was >0.75, demonstrating good reliability between human assessors and Claude. Table I presents the detailed inter-reader reliability results between Claude and the three independent assessors, showcasing the individual and average ICC for each specific case. In the context of this study, Claude's assessments demonstrated significant consistency with human evaluators. Pearson's correlation coefficients for the "Global assessment" score highlighted a strong positive correlation between the mean MDAAT Global VAS scores provided by Claude 2 and those by expert assessor 1 (r=0.88, $p<0.001$) and 2 (r=0.78, $p<0.001$), while a moderate positive correlation was observed with less experienced assessor 3 (r=0.53, $p=0.002$) (Fig. 1).

Conclusion. Claude 2 has demonstrated excellent consistency with expert human scoring in clinical cases of patients suffering from IIM, with performance better than naive assessors. Its potential future uses are broad, ranging from clinical training for MDAAT scoring to the creation of clinical cases for use in trial recruitment, or trial screening of electronic medical records.

Table I. Inter-reader reliability results between Claude 2 and human assessors.

Case No	A/G	Subtype	Individual ICC	Average ICC
1	47/F	DM	0.68	0.89
2	57/M	IMNM	0.90	0.97
3	53/F	ASSD	0.75	0.92
4	19/F	DM (amyo)	0.72	0.91
5	39/M	ASSD	0.77	0.93
6	34/F	DM	0.72	0.91
7	48/M	IMNM	0.50	0.80
8	45/F	JDM	0.31	0.64
9	29/F	DM	0.88	0.97
10	73/M	CAM	0.95	0.99
11	56/F	ASSD	0.69	0.90
12	15/M	JDM	0.93	0.98
13	73/F	ASSD	0.83	0.95
14	24/F	DM	0.84	0.95
15	69/F	IMNM	0.67	0.89
16	51/F	DM	0.84	0.95
17	19/F	JDM	0.47	0.78
18	66/M	IBM	0.69	0.90
19	52/M	DM	0.92	0.98
20	28/F	DM	0.74	0.92
21	54/M	CAM	0.89	0.97
22	55/M	IMNM	0.78	0.93
23	60/F	DM	0.63	0.87
24	34/M	DM	0.89	0.97
25	15/M	JDM	0.66	0.89
26	10/M	JDM	0.92	0.98
27	48/M	DM	0.84	0.95
28	50/F	ASSD	0.82	0.95
29	55/F	DM	0.90	0.97
30	71/F	CAM	0.91	0.97

Abbreviations: A/G: age/gender; ASSD: anti-synthetase syndrome; CAM: cancer associated myopathy; DM: dermatomyositis; F: female; IBM: inclusion body myositis; ICC: intraclass Correlation Coefficent; IMNM: immune mediated necrotizing myopathy; JDM: juvenile dermatomyositis; M: male.

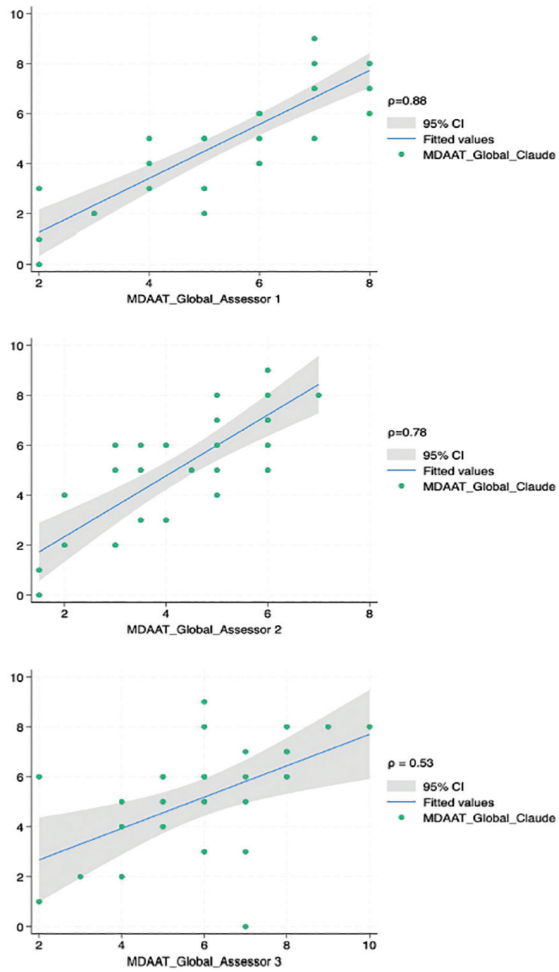


Fig. 1. Relationship between the mean MDAAI Global VAS scores provided by Claude 2 and Assessors 1, 2 and 3.

References

1. VENERITO V, PUTTASWAMY D, IANNONE F, GUPTA L: Large language models and reumatology: a comparative evaluation *Lancet Rheumatol* 2023; 5: e574-8.
2. DUNN C, HUNTER J, STEFFES W *et al*.: Artificial intelligence-derived dermatology case reports are indistinguishable from those written by humans: A single-blinded observer study. *J Am Acad Dermatol* 2023 Apr 11.

P-148

VALID MEASURES OF PHYSICAL FUNCTION IN IDIOPATHIC INFLAMMATORY MYOPATHIES

Tanya Chandra[1], Raisa L. Silva[2], Shiri Keret[3], Runjia Li[4], G.K. Balasubramani[5], Akanksha Sharma[6], Dana P. Ascherman[1], Chester V. Oddis[1], Siamak Moghadam-Kia[1], Rohit Aggarwal[1]
[1]Division of Rheumatology and Clinical Immunology, University of Pittsburgh, Pittsburgh, Pennsylvania, USA; [2]Internal medicine, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA; [3]Rheumatology, Bnai-Zion Medical Center, Faculty of Medicine, Technion, Haifa, Israel; [4]Department of Biostatistics, School of Public Health, University of Pittsburgh, Pittsburgh, Pennsylvania, USA; [5]Department of Epidemiology, School of Public Health, University of Pittsburgh, Pittsburgh, Pennsylvania, USA; [6]UPMC Mercy Hospital, Pittsburgh, Pennsylvania, USA

Background. Idiopathic inflammatory myopathies (IIM) can cause significant impairment in physical function and quality of life. Sit to Stand (STS) and Timed Up and Go (TUG) are quick, operator-independent measures of physical function. We conducted an evaluation to assess the baseline and longitudinal relationship of STS and TUG with patient- reported outcomes as well as data from physical activity monitors (PAMs).
Methods. The data from a 6-month prospective observational study on IIM known as the Myositis Patient Centered Tele-Research Study (My PACER) was analyzed. Patient reported assessments and functional assessments (STS and TUG) were collected monthly over 6-months. PAM data was collected by subjects wearing a Fitbit® for at least 10 hours a day, ≥7 days/month. The STS measures the number of times a patient can stand from a seated position and sit down in 30 seconds. TUG is the time taken to rise from a chair, walk 3 meters, return to the chair and sit down.
We evaluated the association of STS and TUG at baseline with Health Assessment Questionnaire Disability Index (HAQ-DI), HAQ Pain, Patient Global Visual Analog Scale (VAS), PROMIS- PF 20, PAM data. We used Spearman to determine the strength of the correlation. The relationship of STS and TUG with these variables was further assessed using a linear mixed model, adjusting for covariates age at enrollment, gender, race, BMI and sub-type of IIM (DM, PM or NM), as well as patient-level random effects.
Results. 120 patients (75% female, 80.8% Caucasian, mean age of 55.5±13.43 years, 39.2% PM, 51.7% DM, 9.1% Necrotizing Myopathy [NM]) participated in this study.
There was a strong test-retest reliability at baseline and month 1 for both STS (r=0.8) and TUG (r=0.87), $p<0.01$.
At baseline, both STS and TUG were found to have the highest correlation with HAQ-DI and PROMIS-PF 20 which implies a significant association with overall functional status of IIM patients. Out of the remaining measures, STS was found to have a stronger correlation with PAM data whereas TUG was more associated with Patient Global VAS (Table I). Considering longitudinal repeated measures at all visits, STS and TUG were strongly associated with PROMIS-PF 20 and HAQ-DI, controlling for age, gender, race, BMI and IIM subtype.

Table I. Association of STS and TUG with various Patient Reported Outcomes and Physical Activity Monitor Data (*: $p<0.05$; *: $p<0.01$; ***:$p<0.001$).

Baseline [Spearman correlation co-efficient]						
	HAQ-DI	HAQ Pain	Patient Global VAS	PROMIS-PF 20	Average Steps/min	Average Peak Cadence
STS	-0.7***	-0.29**	-0.47***	0.7***	0.58***	0.58***
TUG	0.67***	0.34***	0.51***	-0.68***	-0.5***	-0.44***
Longitudinal [Co-efficient of regression (95% confidence interval)]						
	HAQ-DI	HAQ Pain	Patient Global VAS	PROMIS-PF 20	Average Steps/min	Average Peak Cadence
STS	-2.19 (-3.03,-1.45) ***	-0.4 (-0.83,0.02)	-0.13 (-0.26,0) *	0.14 (0.08,0.21) ***	-0.02 (-0.17,0.15)	0 (-0.01,0.02)
TUG	3.17 (1.92,4.58) ***	1.59 (0.83,2.4) ***	0.41 (0.17,0.67) **	-0.24 (-0.34,-0.15) ***	-0.29 (-0.59,0)	-0.03 (-0.07,0) *

Conclusion. The strong correlation between STS and TUG with various functional PROs, particularly HAQ-DI and PROMIS PF-20, makes them highly effective tools for assessing the overall functional status of patients.

P-149

LUNG TRANSPLANTATION OUTCOMES IN PATIENTS WITH IDIOPATHIC INFLAMMATORY MYOPATHY-RELATED INTERSTITIAL LUNG DISEASE

Sarah L. Khan, Pali D. Shah, Sonye K. Danoff
Division of Pulmonary and Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Background. Interstitial lung disease (ILD) occurs frequently in patients with idiopathic inflammatory myopathy (IIM) and accounts for up to 80% of mortality in affected patients. Lung transplantation can be a lifesaving intervention, but the data on post-transplant outcomes for IIM-ILD are limited.
Methods. We conducted a retrospective cohort study of patients with IIM-ILD who underwent lung transplantation at Johns Hopkins Hospital between January 2015 and February 2023. We compared their outcomes with patients with non-myositis connective tissue disease-related ILD (NM-ILD) and idiopathic pulmonary fibrosis (IPF).
Results. Eight patients underwent lung transplant for IIM-ILD with a median lung allocation score of 46.0 (IQR: 39.5-60.1). All eight patients were taking low doses of prednisone before transplant and all but one were on at least one other immunosuppressant. All eight patients had pulmonary hypertension diagnosed by right heart catheterization and the median mean pulmonary artery pressure was 29.5 mmHg (IQR: 27–32.5). Four patients were prescribed pulmonary vasodilator therapy. At the time of transplant, four patients were already admitted to the hospital for hypoxic respiratory failure. After transplant, five patients had uneventful courses and were discharged after one to three weeks. The other three patients were hospitalized for four to seven months with courses complicated by prolonged respiratory failure, cardiac arrests, venous thromboembolic events, and renal failure. Each of these patients survived their index admissions but died within 16 months. One other patient died two and a half years after transplant due to metastatic malignancy. IIM-ILD had a hazard ratio for death of 5.61 (95% CI 1.03, 30.69, p-value 0.047) after adjusting for age at the time of transplant. Comparatively, the hazard ratio for death was 0.60 for NM-ILD (95% CI 0.14, 2.47, p-value 0.477) and 0.27 for IPF (95% CI 0.03, 2.30, p-value 0.231). These associations were attenuated after adjusting for pulmonary hypertension.

Table I. Comparison of IIM-ILD, and IPF patients who underwent lung transplantation. Continuous variables are presented as median (interquartile range). Categorical variables are presented as n (%).

	IIM-ILD (n=8)	NM-ILD (n=33)	IPF (n=41)
Age at time of transplant (years)	51 (38.5 - 60.5)	62 (56 - 67)	64 (61 - 69)
Female	6 (75.0%)	20 (60.6%)	12 (29.3%)
Race			
White	3 (37.5%)	20 (60.6%)	36 (87.8%)
Black	5 (62.5%)	6 (18.2%)	3 (7.3%)
Asian	0	2 (6.1%)	1 (2.4%)
Other	0	5 (15.2%)	1 (2.4%)
Lung allocation score	46.0 (39.5 - 60.1)	42.8 (38.6 - 74.2)	46.1 (39.3 - 51.5)
Immunosuppression			
Prednisone	8 (100%)	26 (78.8%)	12 (29.3%)
Other	7 (87.5%)	30 (90.9%)	8 (19.5%)
PH diagnosis	8 (100%)	22 (66.7%)	27 (65.9%)
mPAP	29.5 (27 - 32.5)	22 (17 - 33)	23 (19 - 28)
Pulmonary vasodilators	4 (50%)	11 (50%)	10 (43.5%)
Bilateral transplant	5 (62.%)	28 (84.8%)	31 (75.6%)
PGD grade at 72 hours			
0	0	1 (3.0%)	1 (2.4%)
1	5 (62.%)	19 (57.6%)	21 (51.2%)
2	0	5 (15.2%)	10 (43.5%)
3	3 (37.5%)	6 (18.2%)	2 (4.9%)
Post-operative complications			
Prolonged respiratory failure	3 (37.5%)	4 (12.1%)	10 (43.5%)
Cardiac arrest	3 (37.5%)	2 (6.1%)	1 (2.4%)
Renal replacement therapy	3 (37.5%)	3 (9.1%)	7 (17.1%)
Significant bleeding	0	2 (6.1%)	4 (9.8%)
Wound healing complications	0	6 (18.2%)	0
Length of post-op hospital stay (days)	22.5 (9 - 163.5)	16 (10 - 25)	13 (9 - 33)
Incidence of ACR within 1 year	1 (12.5%)	8 (24.2%)	4 (9.8%)
New DSA	4 (50%)	10 (30.3%)	21 (51.2%)
Time to DSA (days)	73 (12 - 1452)	10 (7 - 21)	21 (7 - 141)
Number deceased	4 (50%)	5 (15.2%)	4 (9.8%)

Conclusion. The eight patients with IIM-ILD who underwent lung transplantation at our institution were younger and had higher mean pulmonary artery pressures than patients with NM-ILD and IPF. After transplant, their overall post-operative courses were similar, but the mortality rate among IIM-ILD patients reached 50% within two years. Other studies have reported different findings including a European cohort which found similar post-transplant survival between their IIM-ILD patients and international registries (1). A smaller Chinese cohort reported decreased survival (2). It is difficult to draw meaningful conclusions from any one of these cohorts and more work is needed, with collaboration across institutions, to provide further clarity.

References

1. RIVIÈRE A, PICARD C, BERASTEGUI C *et al*.: Lung transplantation for interstitial lung disease in idiopathic inflammatory myositis: a cohort study. *Am J Transplant* 2022; 22(12): 2990-3001. doi:10.1111/ajt.17177
2. YANG X, WEI D, LIU M *et al*.: Survival and outcomes after lung transplantation for connective tissue disease-associated interstitial lung diseases. *Clin Rheumatol* 2021; 40: 3789-95. doi:10.1007/s10067-021-05704-9/Published.

P-150

CHARACTERIZATION OF MYOSITIS-SPECIFIC ANTIBODY-POSITIVE PATIENTS AMONG US VETERANS BETWEEN 2011-2021

Vladimir M. Liarski
VA Pittsburgh Health Care System, University Drive Campus, Pittsburgh, PA, USA, and University of Pittsburgh, Division of Rheumatology and Clinical Immunology, Pittsburgh, PA, USA

Background. The rare frequency and number of Myositis-Specific Antibodies (MSAs) makes studying Idiopathic Inflammatory Myopathy (IIM) subsets extremely challenging. We leveraged the Veterans Affairs Corporate Data Warehouse to identify MSA-positive patients and examine associations with clinical diagnoses of interstitial lung disease (ILD) and dermatomyositis (DM), and all-cause mortality.
Methods. Patients who underwent MSA testing between 1/1/2011 and 12/31/2021 were selected. Positive results were identified with date of first test positivity inferred to be the date of IIM diagnosis. A minimum of 2 outpatient ICD-9 or ICD-10 visit codes from Neurology, Rheumatology, Pulmonary, or Dermatology clinics occurring at least 30 days apart were used to confirm clinical diagnoses of smoking, ILD, and DM. Due to the large number of Jo-1 cases, all-cause mortality was compared to all non-Jo-1 individuals with Cox proportional hazard modelling identifying factors influencing survival. Mortality data for this study was right censored as of 12/10/2023.
Results. We identified 4260 individuals testing positive for a singular MSA of which 4084 (95.9%) were Jo-1 (see Table 1). For all MSAs, men exceeded women, in line with the general VA patient population. OJ antibodies were associated with the youngest mean age at diagnosis (54.8 years) as opposed to HMGCR, which was associated with the oldest (mean 70.9 years). Patient racial makeup was similar across all antibody groups. All MSAs were associated with elevated CK levels with the lowest seen with TIF-1g (mean 623) and highest with HMGCR (mean 10279). The frequency of MSA positivity and incidence of concurrent ILD, clinical diagnosis of DM, and smoking status are shown in Table 1**.** Based on Kaplan-Meier analysis, the worst all-cause mortality was observed in MDA5 while the most favorable outcomes were seen with Jo-1. Cox proportional hazard modelling identified presence of ILD (mean HR 1.67, 95% CI 1.51–1.84, $p<0.001$), clinical DM (mean HR 1.57, 95% CI 1.21–2.03, $p<0.001$), and non-Jo-1 MSA (mean HR 5.91, 95% CI 4.94–7.07, $p<0.001$) as being associated with increased mortality. Male sex was identified as mildly increasing survival (mean HR 0.88, 95% CI 0.80–0.97, $p=0.01$) but this was likely influenced by our cohorts' male and Jo-1 predominance. Race, smoking status, or age at diagnosis did not influence mortality risk.
Conclusion. To our knowledge, this is the first comprehensive MSA-based classification of IIM in US veterans. Patients were overwhelmingly positive for Jo-1, which exhibited best overall survival. Poor prognostic factors included female sex, presence of ILD, clinical DM presentation, and non-Jo-1 MSA positivity.

P -150 Table I.

		JO-1	HMGCR	SRP	MDA5	PL-7	PL-12	EJ	MJ	OJ	Mi-2	TIF1-γ	Statistic
N		4084	27	41	7	41	29	12	8	12	46	12	
Mean Age at Dx, yrs (±SD)		59.0 (±14.1)	70.9 (±9.0)	67.1 (±11.3)	68.5 (±12.3)	66.6 (±10.6)	60.0 (±12.7)	65.2 (±11.5)	68.3 (±13.6)	54.8 (±17.5)	67.9 (±10.0)	58.6 (±11.8)	$p=2.5*10^{-11}$
Sex	*Male*	3493	27	38	5	35	24	12	8	10	43	11	
	Female	591	0	3	2	6	5	0	0	2	3	1	$\chi^2=0.19$
Race	*White*	2309	18	28	5	22	21	8	5	4	34	7	
	Black	1336	5	10	2	13	6	4	3	6	9	3	
	Asian	51	0	2	0	1	1	0	0	0	0	1	$\chi^2=0.34$
	AI/AN	34	2	1	0	3	0	0	0	0	0	1	
	NH/OPI	53	0	0	0	0	0	0	0	0	0	0	
Mean CK_{max} (±SD)		2124 (±7192)	10279 (±7109)	2186 (±3282)	2579 (±4012)	5681 (±16794)	1089 (±1910)	1498 (±2413)	3214 (±6983)	1701 (±2280)	1024 (±1507)	623 (±1243)	$p<2*10^{-16}$
ILD	*Present*	3246	25	21	4	26	21	9	4	6	32	3	
	Absent	838	2	20	3	15	8	3	4	6	14	9	$p<2.2*10^{-16}$
Dermato-myositis	*Present*	73	2	2	1	1	6	0	0	0	10	3	
	Absent	4011	25	39	6	40	23	12	8	12	36	9	$p<2.2*10^{-16}$
Smoking	*Current/ Prior*	922	1	11	0	14	12	3	1	1	10	4	
	Never	3162	26	30	7	27	17	9	7	11	36	8	p=0.03
Deaths (%)		1465 (35.9)	4 (14.8)	17 (41.5)	1 (14.3)	16 (39.0)	8 (27.6)	7 (58.3)	1 (12.5)	2 (16.7)	17 (37.0)	3 (25)	χ^2=0.12

P-151

AUTO-ANTIBODIES AFFECTING SARCOLEMMA REPAIR PROTEINS COMPROMISE MEMBRANE INTEGRITY AND CONTRIBUTE TO THE PATHOGENESIS OF IDIOPATHIC IMMUNE MYOPATHIES

Hannah Bulgart, Shane Bruckner, Kassidy Banford, Kevin McElhanon, Ana Capati, Nicholas Young, Brian J. Paleo, Eric X Beck, Rohit Aggarwal, Chester Oddis, Noah Weisleder, Wael Jarjour
Department of Physiology and Cell Biology, and Division of Rheumatology and Immunology, The Ohio State University Wexner Medical Center, Columbus, OH; Pfizer Inc., Cambridge, MA; Division of Rheumatology and Clinical Immunology, University of Pittsburgh, Pittsburgh, PA, USA

Background. Idiopathic immune myopathies (IIM) are a group of disorders involving chronic inflammation of skeletal muscle due to an uncontrolled autoimmune response. The pathogenesis of IIM is not well understood. Our previous work generated a robust model of inflammatory myositis by com-

bining a mouse with impaired sarcolemmal membrane repair synaptotagmin VII (SytVII)$^{-/-}$ with a mouse with a regulatory T cell deficiency FoxP3$^{-/Y}$. The sarcolemmal membrane repair response is a conserved response necessary to restore membrane integrity in myocytes in a variety of muscle diseases. Previous work helped identify TRIM72/MG53 and dysferlin proteins as critical components of the membrane repair process. Our current studies address if antibodies against TRIM72/MG53 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 ELISA. Membrane repair function was determined using mechanical glass bead wounding or multi-photon infrared laser microscopy to damage the cell membrane of muscle fibers and live cell imaging to record the entry of fluorescent FM4-64 dye. We also measured membrane integrity *in vivo* through the use of IgG immunostaining of muscle histology sections. Additionally, we injected exogenous antibodies against membrane repair proteins into myositis mice and determined changes to the myositis phenotype *in vivo*.

Results. In this study we use a robust model of IIM combining knock-out of Syt VII with a FoxP3 mutation resulting in a mouse with impaired membrane repair and regulatory T-cell deficiency. Adoptive transfer of lymphocyte preparations isolated from this mouse to recombination-activating gene 1 (RAG-1) null mice results in severe skeletal muscle inflammation. We show that while a deficiency in T-regulatory cells is not sufficient to induce sarcolemma fragility, purified antibodies against critical proteins facilitating sarcolemma repair is sufficient to reduce membrane integrity in vitro. We also demonstrate that sarcolemma integrity is reduced in distal muscles in the absence of inflammation. We have established by direct ELISA that autoantibodies against a critical protein involved in sarcolemma repair are elevated in IIM patient sera and find that exogenous delivery of IIM positive patient serum compromises sarcolemma repair in healthy skeletal muscle. Moreover, the injection of exogenous antibodies against membrane repair proteins can increase muscle pathology in this adoptive transfer mouse model of IIM.

Conclusion. These findings represent a novel mechanism contributing to the pathogenesis of IIM when decreased sarcolemma integrity induces a vicious cycle of antigen presentation that directly contributes to the pathophysiology of idiopathic immune myopathies.

P-152

COLLABORATIVE RESEARCH IN MYOSITIS-RELATED DISORDERS: MIHRA A GLOBALLY SHARED COMMUNITY MODEL

Helene Alexanderson[1], Mazen Dimachkie[2], Floranne Ernste[3], Pedro Machado[4], Elie Naddaf[3], Julie Paik[5], Lesley Ann Saketkoo[6], Barbara Shafranski[7], Latika Gupta[8], Christopher Mecoli[5], Didem Saygin[9], Jemima Albayda[5], Pari Basharat[10], Jessica Day[11], Malin Regardt[1], Antonia Valenzuela[12], Alejandro Benitez[13], Lisa Christopher-Stine[5], Bianca Lang[14], Christian Lood[15], Chester V. Oddis[9], Annet van Royen[16], Jiri Vencovsky[17], Victoria Werth[18], Hector Chinoy[19], David Isenberg[4]

[1]Karolinska Institutet, Stockholm, Sweden; [2]University of Kansas, Kansas City, KS, USA; [3]Mayo Clinic Rochester, Minnesota, USA; [4]University College, London, UK; [5]Johns Hopkins Medical Institute, Baltimore, Maryland, USA; [6]Louisiana State University and Tulane University Schools of Medicine, New Orleans, Louisiana, USA; [7]Patient Research Partner, New Jersey, USA; [8]Royal Wolverhampton Hospitals and NHS Trust, Manchester, UK; [9]University of Pittsburgh, Pittsburgh, Pennsylvania, USA; [10]Western University, Ontario, Canada; [11]Walter and Eliza Hall Institute for Medical Research, Melbourne, Australia; [12]Pontificia Universidad Catolica de Chile, Santiago, Chile; [13]Universidad de Buenos Aires, Buenos Aires, Argentina; [14]Dalhousie University, Halifax, Nova Scotia, Canada; [15]University of Washington, Seattle, Washington, USA; [16]Universiteit Utrecht, Utrecht, Netherlands; [17]Institute of Rheumatology, Prague, Czech Republic; [18]University of Pennsylvania, Philadelphia, Pennsylvania, USA; [19]University of Manchester, Manchester, UK

Background. The IIM research community ignited over 25 years ago to engage in collaborative research projects to investigate critical concepts in adult and pediatric IIM care and research. During this a tremendous amount had been achieved with sparse funding but unusual force of unity in a growing community. The community's collaborative projects have become increasingly complex but able to be accelerated on many fronts with newer technologies and capabilities. Further, advocacy from within the expert community has been desired but lacking a formal representative vehicle.

The authors sought to address the growing needs of the research community, examining through iterative examinations of models, how best to meet the holistic needs of the community and sustain its rate of growth as well as continued rate of complexity.

Methods. Members of the IIM research community investigated organizational components that would allow for feasible, sustainable and economically viable growth that would provide increasing value to the IIM research community, accelerate global clinical trial readiness and strengthen partnerships with other professional societies, patient organizations and industry. This was approached in a many tiered process via interviews with multiple organizations in rare diseases, discussions with partners and stakeholders, close examination of processes and procedures related to operational models, and iterative exercises to gain consensus on identifying critical community values.

Results. Consensus was achieved in recognizing that a non-profit charitable organization based in the US, would provide financial latitude to support community research as well as to assist in supporting goals and operations of partner organizations.

The members identified through iterative exploratory exericse, content examination, and consensus methodology:

A **vision** to 'create a world where we can cure myositis together.'

A **mission**

- To optimize the health & well-being of people living with myositis worldwide.
- To cultivate global expertise and promote synergy across myositis endeavours.
- To secure future research and clinical care through mentorship programs and education.
- To drive international collaborative research and clinical trial readiness in myositis.

Values: global inclusivity, community-driven leadership, proactive mentorship, prioritization of collegial-compassion.

A **name** reflecting the community's scope of engagement and intent: Myositis International Health and Research Collaborative Alliance

An **acronym** reflecting the community's spirit: **MIHRA** with linguistic roots across many languages meaning kindness, community, goodness and peace.

5 organizational cores that operate as critical drivers of global collaborative research:

1. Clinical Trial Readiness
2. Database Harmonization
3. Education,Mentorship and Career Enhancement
4. Excellence in Clinical Care
5. Global Equity

Conclusion. A non-profit charitable research organization, MIHRA, incorporated in October 2023, has been established to foster accelerated work of the pediatric and adult myositis research community and the work of their partner organizations.

P-153

SELF-REPORTED FATIGUE AND PHYSICAL ACTIVITY AND ITS ASSOCIATIONS TO ANXIETY AND DEPRESSION IN PATIENTS WITH IDIOPATHIC INFLAMMATORY MYOPATHIES

Kristofer M Andreasson[1,2], Fabricio Espinosa-Ortega[1,3], Heléne Sandlund[3], Helene Alexanderson[1,2]

[1]Karolinska Institutet, Department of Medicine Solna, Division of Rheumatology, Stockholm, Sweden; [2]Karolinska University Hospital, Theme Women's Health and Health Professionals, Medical Unit Occupational & Physical Therapy, Stockholm, Sweden; [3]Karolinska University Hospital, Department of Gastro, Dermatology and Rheumatology, Medical Unit Inflammation and Aging, Stockholm, Sweden

Background. Patients with inflammatory diseases such as rheumatoid arthritis exhibit reduced levels of physical activity (PA) compared to the normative population and suffer from anxiety and/or depression. PA at a health-enhancing level can help alleviate these symptoms and other co-morbidities. The aim was to evaluate the relationship between PA, anxiety, and depression, as well as patient- and physician reported registry data.

Methods. All adult patients registered at the rheumatology clinic at Karolinska University Hospital in Stockholm, Sweden (during 2019–2022) were eligible to participate. Questionnaires measuring anxiety, depression (Hospital Anxiety and Depression Scale [HADS]), and PA (International Physical Activities Questionnaire [IPAQ]) were provided during yearly check-up or by mail due to reduced in-person visits amid the COVID-19 pandemic. IPAQ categorizes PA as low, moderate, or high. Registry data: demographics, Short Form Health Survey – Mental Health (SF36-MH), Manual Muscle

Test 80 (MMT8), pain and fatigue (0-100 visual analog scale [VAS]), patient and physician's global disease activity (PtGA & PhyGA), health assessment questionnaire (HAQ), creatine-kinase (CK), functional index-2 (FI2), and global organ damage, was obtained from Swedish Rheumatology Quality Registry. Multivariate logistic regression analysis and χ^2 were utilized.
Results. Of the 488 invited patients, 336 agreed to participate, and 246 completed the questionnaires. Median age was 64 years, median disease duration five years and two-thirds were women. Notably, 82% reported moderate/high level of PA. Probable anxiety and depression were experienced by 25% and 14%, respectively, similar to general population in Sweden (1). Moderate/high level of PA was associated with a 70% lower risk of depression (p<0.001), and each millimeter worsening in fatigue increased the risk of anxiety or depression by 2 and 3%, respectively. Anxiety, depression, and low PA were associated with worse health (SF36-MH and fatigue), worse muscle- and physical function (MMT8 and HAQ) (p<0.05 - p<0.001). Anxiety and depression were associated with low PA (IPAQ), higher pain and poorer patient-reported disease activity (PtGA) (p<0.05 - p<0.001). Depression and low PA were associated with higher global organ damage (≥20/100 VAS) (p<0.05). Low PA was associated with anxiety and depression (HADS), poorer FI2 and higher age (p<0.05 - p<0.001).

Table I.

	HADS Anxiety		HADS Depression	
	Yes n=62 (25%)	No N=184 (75%)	Yes n=34 (13%)	No N=212 (87%)
Sex				
Women n=154	46 (59)	108 (74) *	23 (68)	131 (62)
Men n=92	16 (41)	76 (26)	11 (32)	81 (38)
Age				
≥64 years (n=128)	30 (52)	98 (47)	18 (47)	110 (48)
<64 years (n=118)	32 (48)	86 (53)	16 (53)	102 (52)
Disease duration, years	4.1 (1.9, 11.4)	5.7 (2.4, 11.0)	4.05 (1.4, 14.3)	5.3 (2.4, 11)
Dermatomyositis 84/246	22 (35)	62 (34)	10 (29)	74 (35)
No dermatomyositis, 162/246	40 (65)	122 (66)	24 (71)	138 (65)
PhyGA, VAS 0–100, n=141	12 (0, 21)	4 (0.0, 11)	8 (0, 18)	5 (0, 15)
PtGA VAS 0–100, n=165	41 (26, 56)	13 (2.8, 32,8) ***	47 (31, 60)	14 (3, 35) ***
MMT8 0–80, n=148	77.5 (70.3, 80)	80 (78, 80) **	76 (71, 79)	80 (77, 80) *
HAQ 0 – 3.0, n=165	0.94 (0.38, 1.5)	0.25 (0.0, 0.63) ***	1.0 (0.63, 1.65)	0.25 (0.0, 0.63) ***
CK mcat/L, n=163	1.4 (1.1, 3.6)	1.6 (1.2, 2.9)	1.4 (1.0, 4.1)	1.6 (1.2, 3.0)
FI2, 0–00 (n=115)	44.5 (22, 61.5)	49 (26, 69)	34 (12, 51)	49 (27, 69)
IPAQ				
Level 2+3 (203)	45 (73)	158 (86) *	20 (59)	183 (86) ***
Level 1 (43)	17 (27)	26 (14)	14 (41)	29 (14)
Global Damage (n=206)				
Damage high (≥20/100), n=74	22 (47)	52 (33)	16 (62)	58 (32) **
Damage low (<20/100), n=132	25 (53)	107 (67)	10 (38)	122 (68)
Pain VAS 0–100, n=176	31.5 (15.3, 60.8)	9 (1.3, 22.8) ***	22 (8.3, 50.8)	12 (2, 28) *
Fatigue VAS 0–100, n=176	50.5 (36.3, 66.5)	14 (3.0, 41.8) ***	51.5 (38.8, 65.8)	15.5 (3.0, 42) ***
SF36-MH, n=137	56 (42, 60)	84 (72, 92) ***	44 (38, 60)	80 (64, 92) ***

*<0.05, **0.01, ***<0.001
PhyGA: Physician Global Assessment; VAS: visual analog scale; PtGA: Patient Global Assessment; MMT8: Manual muscle test 8 groups; HAQ: Health Assessment Questionnaire; CK: creatinkinase; mcat/L: microkat per liter; FI2: Functional index-2; IPAQ: International Physical Activities Questionnaire; SF36-MH: Short Form Health Survey – Mental Health.

Conclusion. Most patients reported being physically active (moderate/high IPAQ). The results highlight the potential influence of PA on mental health and its role in mitigating risks associated with depression and fatigue among IIM-patients. It underscores the importance of PROMs, and their role in understanding and improving healthcare interventions. Further, more research is needed to uncover causes and confirm these connections.

Reference

1. LOVIK A, GONZÁLEZ-HIJÓN J, KÄHLER AK *et al*.: (2023). Mental health indicators in Sweden over a 12-month period during the COVID-19 pandemic – Baseline data of the Omtanke2020 Study. *J Affect Disord* 2023; 322: 108-17. https://doi.org/10.1016/j.jad.2022.11.004

P-154

EFFICACY AND SAFETY OF TOCILIZUMAB IN THE TREATMENT OF SEVERE JUVENILE DERMATOMYOSITIS

Ying Chi, Jian-guo Li
Department of Rheumatology and Immunology, Children's Hospital Affiliated to the Capital Institute of Pediatrics, Beijing, China

Background. To explore the efficacy of tocilizumab in the treatment of severe juvenile dermatomyositis (JDM) compared to cyclophosphamide (CTX).
Methods. 18 children with JDM treated with tocilizumab (group T), who were hospitalized in our department from March 2022 to June 2023, were collected, and compared with 18 age-matched children with CTX pulse (group C) during the same period. Every 4 weeks, the children's rash, muscle strength and laboratory indicators were analyzed
Results. In group T, 11 males and 7 females, with a mean age of 7.04±3.17 yrs. All children were severe JDM without treatment. They were treated with tocilizumab and glucocorticoids. In group C, 8 males and 10 females, mean age 7.34±3.02 yrs. They were treated with CTX (500-1000mg/m^2/every month), glucocorticoids and IVIG. Both groups were followed up from 6 to 15 months. After treatment, the rash and muscle strength in both groups improved. The muscle strength improvement in group T is faster, but there is no statistically significant difference. In the first 3 months, serum CK, CKMB, LDH, and HBDH in group T decreased significantly compared with those in group C (p-values <0.05). The hormone dosage in group T was significantly lower than that in group C. One case in group T relapsed in muscle MRI after stopping the drug and four cases in group C relapsed after stopping the drug. No intolerable side effects were found.
Conclusion. Compared with CTX, tocilizumab has similar effects in terms of muscle strength and rash, and can decreased serum muscle enzyme levels more quickly. The hormone dosage was significantly less than that of CTX group.

P-155

GERMAN PATIENT-BASED REGISTRY FOR TRIAL READINESS IN IBM: 8 YEAR INTERIM REPORT OF FUNCTIONAL PARAMETERS RELEVANT FOR CLINICAL STUDIES AND DISEASE PROGRESSION

K. Kummer[1], S. Thiele[2], S. Krause[2], M. Heidemann[2], A.K. Güttsches[3], M. Vorgerd[3], M.C. Walter[2] J. Schmidt[1,4,5]
[1]Department of Neurology and Pain Treatment, Neuromuscular Center, Immanuel Klinik Rüdersdorf, University Hospital of the Brandenburg Medical School, Rüdersdorf bei Berlin, Germany; [2]Friedrich Baur Institute, Department of Neurology, Munich, Germany; [3]Department of Neurology, Neuromuscular Center Ruhrgebiet, Bochum, Germany; [4]Faculty of Health Sciences Brandenburg, Brandenburg Medical School Theodor Fontane, Rüdersdorf bei Berlin, Germany; [5]Department of Neurology, Neuromuscular Center, University Medical Center Göttingen, Germany

Background. Inclusion body myositis (IBM) is a relentlessly progressive inflammatory myopathy for that no effective treatment is available so far. Patients suffer from muscle weakness of knee extensors and finger flexors and display varying degrees of dysphagia. Novel therapeutic strategies are developed and several clinical trials have been started or are planned. The German patient-based registry for IBM was developed in 2015 to obtain data on epidemiology and the natural course of the disease, to study standards of care and to achieve trial readiness for this disease. Based on standardized clinical and histopathological findings (revised ENMC criteria), the registry is expected to provide a longitudinal, harmonized dataset of German patients diagnosed with IBM.
Methods. A harmonized dataset including clinical data and muscle biopsy reports was recorded since 01/2016 using a dual patient and professional online report system (www.ibm-register.de). The registry entry was entirely patient-based. Automated questionnaires were distributed to all patients once per year. National legislation, data protection laws and ethical recommendations were strictly adhered to. The registry collected longitudinal data of German IBM patients over 8 years.
Results. The registry was designed to evaluate longitudinal data on the disease course. Apart from demographical information such as age, sex, and onset of disease, the data included disease specific symptoms such as weakness of arms and legs, impairment of walking, swallowing abnormalities, antibody

status, medication, biopsy findings and patient reported outcomes concerning quality of life and various well established scales that capture swallowing impairment, walking and IBM specific functional scores of daily living activities. An updated 8-year interim report will be presented on all available data.
Conclusion. Data from patient-based registries can be instrumental in generating real world data with relevance to the evaluation of novel treatment strategies. This German IBM registry has already demonstrated the much needed trial-readiness and may serve as a blueprint for the design of patient-based registries in IBM and other myositis subsets. It is envisaged to expand the registry beyond geographical and language boundaries and make it a global resource. In the future, this would help to improve patient care and provide trial-readiness at a global scale. These measures would foster the design and assessment of novel treatment strategies for IBM and beyond.

P-156

INCIDENCE AND PREVALENCE OF DERMATOMYOSITIS, AND POLYMYOSITIS, IN ADULTS LIVING IN THE UNITED STATES. A STUDY IN THE MERATIVE™ MARKETSCAN® DATABASE

Caroline Foch[1], Jan Feifel[1], Luisa Henkel[1], Deborah Denis[2], Andrew Bender[2], Jeffrey M. Muir[3]
[1]the healthcare business of Merck KGaA, Darmstadt, Germany; [2]EMD Serono, Rockland, USA; [3]Health Economics & Outcomes Research, Cytel, Inc., Toronto, Canada

Background. Incidence and prevalence data for dermatomyositis (DM) and polymyositis (PM) in the United States are limited and outdated, with few estimates published since the 2017 introduction of the European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) criteria. This study provides updated incidence and prevalence data derived from a large commercial insurance database in the United States.
Methods. Adult (aged ≥18 years) patients with ≥1 inpatient or ≥2 outpatient diagnoses (30-365 days apart) of DM (DM: ICD-10: M33.1x, M33.9x) or PM (ICD-10: M33.2x) between 01 Jan 2015 and 30 Jun 2021 were selected from the Merative™ Marketscan® medical claims database. Incidence and prevalence were estimated during 2015-2021, as was monthly incidence of disease/disease flares during 2018-2021 (algorithm combining treatment, and hospitalization). Additional analyses investigated the sensitivity in definitions of DM and PM in claims (all practitioners *vs*. specialist). We also investigated whether seasonal influenza impacted incidence or prevalence
Results. DM incidence during 2018-2021 was 2.16 (95% confidence interval [CI]: 1.99-2.35) per 100,000 patient-years (PY); prevalence was 11.1 (95% CI: 10.7-11.4) per 100,000 persons. Following introduction of the 2017 EULAR/ACR reclassification incidence was 2.24 in 2018-19 *vs*. 2.85 in 2015-16; prevalence was 10.26 in 2018-19 *vs*. 11.11 in 2015-16 (Fig. 1). PM incidence during 2018-2021 was 1.92 (95% CI: 1.76-2.09) per 100,000 PY; prevalence was 8.5 (95% CI: 8.2-8.8) per 100,000 persons. A similar pattern to that seen with DM was seen in the changes in PM incidence (3.35 *vs*. 2.33) and prevalence (10.17 *vs*. 8.12) following the 2017 reclassification. In the sensitivity analysis, DM incidence was 1.88 (95% CI: 1.72-2.05) per 100,000 PY (specialists) *vs*. 2.16 (all practitioners), while PM incidence was 1.61 (95% CI: 1.47-1.77) per 100,000 PY (specialists) *vs*. 1.92 (all practitioners).
No patterns in the monthly incidence rates of DM/PM according to the influenza season were seen (Fig. 1).
Conclusion. The data indicate numerical decreases in PM incidence and prevalence since introduction of the new EULAR/ACR criteria. There was no evidence of a seasonal pattern in DM/PM incidence coinciding with the early/peak influenza season(s). Potential limitations include lack of generalizability to other insured or non-insured populations, and the potential for errors in coding or missing data. This study provides an important update to DM and PM incidence and prevalence in the United States.
Acknowledgements. The healthcare business of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945) sponsored this study and editorial support by Bioscript Group Ltd.

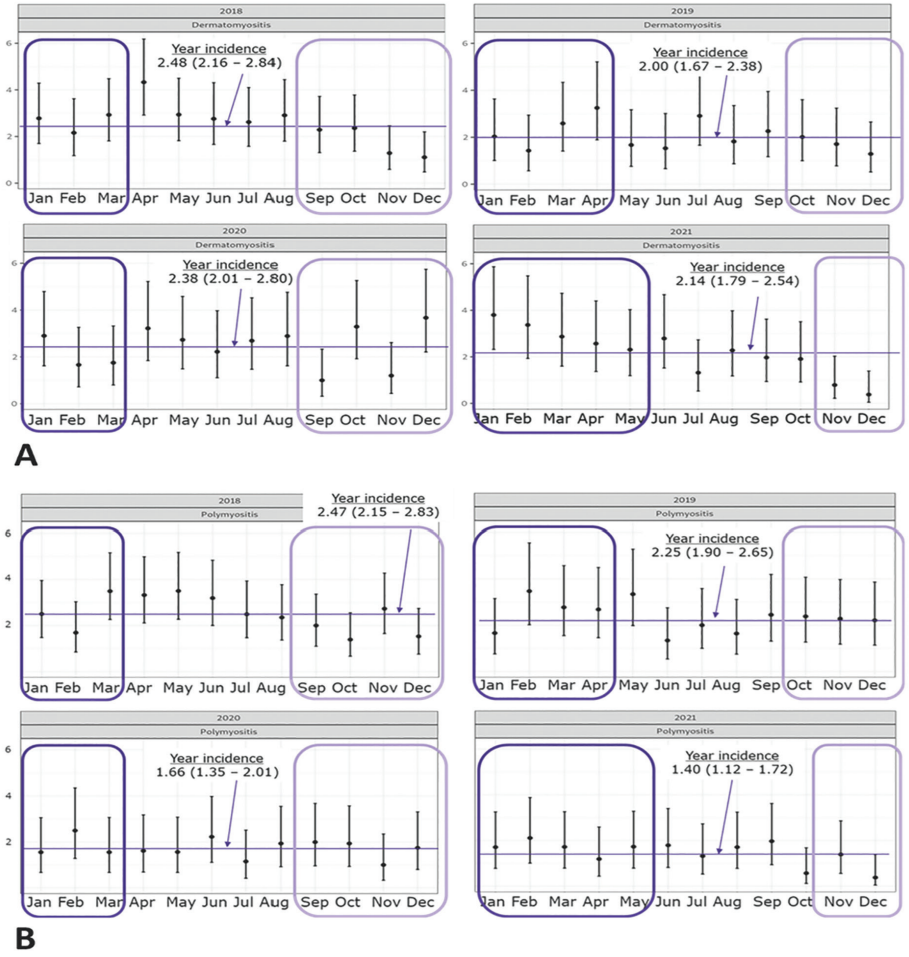


Fig. 1. Monthly incidence of DM (**A**) and PM (**B**) per 100,000 person-years, compared with seasonal flu. High flu season is denoted by dark purple outline; low flu season is denoted by light purple outline.

OP-22

POSTURAL ORTHOSTATIC TACHYCARDIA SYNDROME IN THE SETTING OF DERMATOMYOSITIS: A CASE SERIES

Lillian Xie[1,2], Caroline J. Stone[1,2], Daniella Forman[1,2], Lais Lopes Almeida Gomes[1,2], Victoria P. Werth[1,2]
[1]Department of Dermatology, Corporal Michael J. Crescenz VA Medical Center, Philadelphia, PA; [2]Department of Dermatology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

Background. Postural orthostatic tachycardia syndrome (POTS) is an autonomic disorder characterized by orthostatic intolerance and tachycardia in the absence of hypotension (1). While its etiology remains unknown, there are several underlying pathophysiologic mechanisms, including sympathetic hyperreactivity, autonomic neuropathy, and autoimmunity (2). Despite its heterogeneous presentation, POTS shares many overlapping features with autoimmune disease (3). Our case series proposes an association between POTS and dermatomyositis (DM), an autoimmune connective tissue disorder with hallmark cutaneous findings often accompanied by muscle weakness.
Methods. In a retrospective chart review of patients from the Penn Dermatomyositis Database, five patients were identified with POTS and DM.
Results. Case 1: 37-year-old female was diagnosed with classic DM after workup demonstrated elevated creatine kinase, positive anti-Jo-1 titer, and signs of ILD and thigh muscle edema on imaging. Five years later, she developed intermittent tachycardia and orthostatic lightheadedness. Cardiac workup confirmed POTS.
Case 2: 46-year-old female previously diagnosed with classic DM in 2019 and Sjögren's in 2020 experienced intermittent orthostatic tachycardia three years later. Subsequent tilt table testing confirmed the diagnosis of POTS.
Case 3: 48-year-old female with a history of polyarthralgia, gastroparesis, and fibromyalgia was concomitantly worked up for POTS and classic DM. Hemodynamic changes on tilt-table testing were consistent with POTS. Muscle weakness, nailfold changes, and rash in the DM distribution prompted antibody testing. Despite a negative myositis panel, her skin biopsy showed interface dermatitis, supporting a diagnosis of classic DM considering her muscle symptoms.
Case 4: 22-year-old female with hypothyroidism was diagnosed with POTS at age 15. Symptoms improved with treatment with fludrocortisone and a beta-blocker. From a young age, she had a persistent rash involving the nasolabial folds, chronic myalgias, and baseline arthralgias. A positive myositis panel (anti-Mi-2 and anti-centromere autoantibodies) and elevated ANA ultimately led to a diagnosis of juvenile DM overlapping with mild CREST symptoms.
Case 5: 38-year-old female previously diagnosed with POTS at age 25 started to experience violaceous periorbital swelling, recurrent rashes, and facial swelling. Workup revealed a negative myositis panel, positive ANA (1:80, homogeneous), and positive SSA.
Her clinical findings were overall consistent with amyopathic DM.
Conclusion. A previous study found that 16–20% of POTS patients have a coexisting autoimmune disease (4). Another study reported up to 85% of POTS patients display at least one dermatologic manifestation (5). Given the prevalence of comorbid autoimmunity and cutaneous findings in POTS, these cases underscore the need for further research on the incidence and etiology of POTS in the setting of DM.

References

1. LOW PA, SANDRONI P, JOYNER M, SHEN WK: Postural tachycardia syndrome (POTS). *J Cardiovasc Electrophysiol* 2009; 20(3): 352-8.
2. SEBASTIAN SA, CO EL, PANTHANGI V *et al*.: Postural orthostatic tachycardia syndrome (POTS): an update for clinical practice. *Curr Probl Cardiol* 2022; 47(12): 101384.
3. VERNINO S, STILES LE: Autoimmunity in postural orthostatic tachycardia syndrome: current understanding. *Auton Neurosci* 2018; 215: 78-82.
4. ABOSEIF A, BIRELEY JD, LI Y, POLSTON D, ABBATEMARCO JR: Autoimmunity and postural orthostatic tachycardia syndrome: Implications in diagnosis and management. *Cleve Clin J Med* 2023; 90(7): 439-47.
5. HUANG H, DEB A, CULBERTSON C, MORGENSHTERN K, DEPOLD HOHLER A: Dermatological manifestations of postural tachycardia syndrome are common and diverse. *J Clin Neurol* 2016; 12(1): 75-8.

OP-23

INTESTINAL INFECTION MIGHT A RISK FACTOR FOR GASTROINTESTINAL INVOLVEMENT IN ANTI-NXP2 ANTIBODY-POSITIVE JUVENILE DERMATOMYOSITIS

Xin Yao[1,2], Xinning Wang[1], Jianguo Li[1]
[1]Department of Rheumatology and Immunology, Children's Hospital Capital Institute of Pediatrics; [2]Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China

Background. To investigate the clinical characteristics, risk factors, and prognosis associated with gastrointestinal involvement in children with juvenile dermatomyositis (JDM).
Methods. We conducted a retrospective analysis of clinical data from 13 JDM patients with gastrointestinal involvement admitted to our hospital between 2016 and 2022. 13 JDM patients without gastrointestinal involvement, matched for myositis-specific autoantibodies, were randomly chosen as controls. The differences in clinical characteristics between these two groups were analyzed, and the risk factors associated with gastrointestinal involvement in children diagnosed with JDM were further explored.
Results. In the group with gastrointestinal involvement, there were 9 female and 4 male participants, with an average age of 5 years. All 13 patients tested positive for anti-nuclear matrix protein 2 (anti-NXP2). Potential triggering factors included intestinal infection (12 cases; one case not examined), malnutrition (10 cases), unhygienic dietary habits (5 cases), and overeating (2 cases). JDM patients with gastrointestinal involvement, symptoms comprised fever (10 cases), abdominal pain (12 cases), diarrhea (7 cases), vomiting (5 cases), thickened gastrointestinal walls (12 cases; one case not examined), gastrointestinal ulcers with bleeding (9 cases), and gastrointestinal perforation (7 cases). Predominant perforation sites were the duodenum (4 cases), colon (2 cases: 1 case individually and 1 case concurrent with duodenal perforation), and cecum (1 case). Of the 7 perforation cases, 5 underwent intestinal repair surgeries (3 concurrently underwent intestinal fistulation), while 2 received conservative treatment. Of these, 4 cases were fatal, leading to a 57% mortality rate due to intestinal perforation. Comparatively, there were no significant differences in gender and age between the groups with and without gastrointestinal involvement. Individuals with gastrointestinal involvement seemed to exhibit characteristics such as edema, skin infections, and challenges in achieving clinical remission in contrast to those without such involvement. Additionally, BMI, albumin levels, lymphocyte count, NK cell count, and γδT cell count appeared lower in the group with gastrointestinal involvement than in the non-gastrointestinal involvement group.
Conclusion. JDM patients experiencing gastrointestinal involvement are predominantly those with anti-NXP2 antibodies. Intestinal infection emerges as a significant and potentially inducing factor. Malnutrition, along with edema, infections, and lymphopenia, may contribute as high-risk factors. Timely detection and proactive intervention can lead to clinical remission in JDM cases involving the gastrointestinal system. However, the mortality rate remains notably high among patients experiencing gastrointestinal perforation.
Acknowledgements. Thanks to all the participants for their involvement in the study.

OP-24

FEMALES AND MALES WITH IDIOPATHIC INFLAMMATORY MYOPATHIES: CLINICAL DIFFERENCES, BUT SHARED UNMET NEEDS

Linda Carli[1], Chiara Cardelli[1,2], Elenia Laurino[1], Claudia Alia[3], Federico Fattorini[1], Michele Diomedi[1], Simone Barsotti[4], Marta Mosca[1]
[1]Rheumatology Unit, University of Pisa; [2]Department of Medical Biotechnologies, University of Siena; [3]Neuroscience Unit, CNR, Pisa; [4]Internal Medicine Unit, Livorno Hospital, Livorno, Italy

Background. It is well known that connective tissue diseases (CTD) are more frequent in women; many studies have investigated gender-related differences among patients with CTD, but only a few of them have analyzed idiopathic inflammatory myopathies (IIM). This work aims to clarify whether gender may determine clinical, functional, or emotional differences among IIM patients.
Methods. We retrospectively analyzed the clinical charts of patients with a diagnosis of IIM according EULAR/ACR 2017 criteria, followed at the Myositis Outpatient Clinic of our Unit, belonging to ERN-reconnect network, from January 2018 to May 2023, collecting epidemiological and clinical data. Patients' Quality of Life (QoL) and productivity were investigated through the following: Patient Reported Outcomes (PROs): Short Form 36 (SF36), Hospitality Anxiety and Depression Scale (HADS), FACIT-Fatigue and Work Productivity and Impairment Activity Index (WPAI). Statistical significance was assessed using Mann-Whitney U-test, t-test, Chi-square test and Fisher test, as appropriate. The level of significance was set at $p<0.05$.
Results. A total of 176 patients [117 (66.5%) women], with a mean age at diagnosis of 58.8±15.4 years and a mean disease duration of 9.4±6.9 years were enrolled. No significant gender-related differences emerged with regard to clinical subset, or organ involvement. Anti-OJ antibodies were more frequent in men ($p=0.05$), while sicca syndrome was prevalent in the female sex ($p=0.008$). Among comorbidities, women showed a higher risk of developing osteoporosis (OP) and fragility fractures ($p=0.004$), fibromyalgia (FM) ($p=0.02$) and thyroid dysfunctions ($p=0.00002$), in particular thyroiditis, multinodular goiter and hypothyroidism ($p<0.04$). Hyperuricaemia, on the contrary, was more frequent in men ($p=0.04$). PROs were administered to 88 (50%) patients; they showed significantly worsened values of both FACIT and SF-36 Body Pain item in women ($p=0.04$); no differences in WPAI emerged. While the multivariate analysis confirmed the significance of all clinical variables (except for fragility fractures) with p-values <0.03, it could not corroborate the associations between gender and QoL parameters after correcting for FM.
Conclusion. Our data showed that women less frequently had anti-OJ positivity and HU than men. On the contrary, female patients with IIM were at a significantly higher risk of developing OP, thyroid dysfunctions, sicca syndrome and FM. Intringuingly, after correcting for FM diagnosis, no significant gender-related differences emerged in QoL parameters; this unexpected data highlights how IIM are able to affect both the functional and emotional sphere also in males. These results suggest a gender-guided approach in assessing IIM patients, particularly for comorbidities, which could help rheumatologists improve quality of care and underline that optimization of QoL and WA still represents an unmet need of IIM patients, independently of sex differences.

Author Index