# Review

# One year in review 2020: idiopathic inflammatory myopathies

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**ABSTRACT**

*The study of idiopathic inflammatory myopathies (IIMs) is acquiring growing importance among systemic autoimmune diseases and every year several articles are published about this group of diseases. Despite this growing interest, the management of IIMs is still critical due to the relative rarity of the condition. The availability of up-to-date knowledge of the evidence on this subject is essential to correctly understand this condition and provide the best care for the patients. The purpose of this review is to provide an overview of the most relevant literature contributions published in the last year.*

## Introduction

Idiopathic inflammatory myopathies (IIMs) are a group of rare autoimmune diseases, mainly involving the muscles, the skin and lungs. The recent advances in identifying myositis-specific and -associated antibodies (MSAs, and MAAs) and specific clinical and histopathological patterns, are profoundly changing the way to diagnose, classify and treat these diseases. With the purpose of providing an overview of the most important papers focusing on IIMs published in the last year and following a well-established format, we performed a Medline search of English language articles published in the PubMed database from 1st January 2019 to 31st December 2019. The following key words were used: "idiopathic inflammatory myopathies", "myositis" (MeSH terms and semantic search), "pathogenesis", "diagnosis", "clinical manifestations", "therapy".

All the articles were critically reviewed in order to select the most relevant contributions.

## Pathogenesis

The pathogenesis of IIMs is characterised by activation of the immune system by environmental triggers in genetically predisposed subjects. Chen *et al*. analysed the association between single nucleotide polymorphisms (SNPs) of BANK1 (B cell scaffold protein with ankyrin repeats 1) which is involved in B cell activation and only SNP rs3733197 was found to be associated to a Chinese population of polymyositis (PM)/dermatomyositis (DM) patients especially in those that presented interstitial lung disease (ILD) (1). A genome-wide association study (GWAS), performed in a Vietnamese cohort showed that HLA-DRB1*13 could be considered a possible risk factor for PM but not for DM. On the other hand, HLA-DRB1*07 was less expressed in both PM and DM patients, and HLA-DRB1*09 appeared to be protective for DM development (2). Acosta-Herrera *et al*. performed a meta-analysis of different GWAS studies involving patients with autoimmune diseases and healthy controls (HC). The assumption underlying this analysis consisted in the presence of overlapping clinical manifestations and pathogenetic mechanisms between these diseases, thus making it possible to speculate on shared risk genes. This study allowed the identification of 5 risk loci, 4 of which were associated with the risk of developing IIMs not identified in previous studies (Table I) (3).

Wu *et al*. evaluated the role of elastase released from activated polymorphonuclear (PMN) leukocytes, in IIMs. Elastase is a serine proteinase that would increase the permeability of vascular endothelial cells promoting migration and muscle damage from inflammatory cells. The authors confirmed that elastase and the PMN elastase-to-neutrophil ratio, positively correlate with the disease activity of IIMs (4). In previous studies on pulmonary fibrosis both monocyte chemoattractant

**Table I.** Results of a genome-wide meta-analysis by Acosta Herrera *et al*. (3).

| SNP | GENE | OR (95% CI), Meta-analysis *p*-value | Autoimmune diseases associated | Pathogenetic pathway |
|---|---|---|---|---|
| rs744600 | NAB1 | 0.88 (0.85 to 0.92) $p=7.07\times10^{-11}$ | IIMs, RA, SLE, SSc | Interferon signalling |
| rs112846137 | KPNA4-ARL14 | 1.27 (1.17 to 1.37) $p=1.42\times10^{-08}$ | IIMs, RA, SLE, SSc | involved in cytoskeleton dynamic |
| rs13101828 | DGKQ | 1.27 (1.17 to 1.37) $p=1.42\times10^{-08}$ | IIMs, RA, SLE, SSc | Activation of epidermal growth factor signalling |
| rs76246107 | PRR12 | 1.28 (1.14 to 1.43) $p=3.36\times10^{-08}$ | IIMs, SLE, SSc | Involved in fibrinogen signalling involved in vascular inflammatory diseases |

SNP: Single nucleotide polymorphism; OR: odds ratio; IIMs: idiopathic inflammatory myopathies (IIMs); RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; SSc: systemic sclerosis.

protein-1 (MCP- 1) and transforming growth factor-β1 (TGF-β1) had been identified as a fundamental mediator of inflammation and fibrosis. Another recent study demonstrated that the serum levels of both these chemokines are significantly more elevated also in the case of ILD in the course of IIMs compared to HC and pulmonary infection (5).

Andrés Cerezo and colleagues explored the role of S100A11, a member of S100 family of calcium-binding proteins recently identified as a possible mediator of inflammation. S100A11 resulted to be elevated in serum and expressed in regenerating and necrotising myofibres of both DM and PM samples, in particular around the inflammatory infiltrates of the muscle fibres in the case of PM and in the perivascular fibres in the case of DM. Furthermore, stimulation with S100A11 induced interleukin-6 (IL-6) secretion by peripheral blood mononuclear cells (PBMCs) isolated from IIMs patients, supporting its role in inflammatory reaction and muscle damage (6).

Matrix metalloproteinases-9 (MMP9) is a member of zinc-ion-dependent proteinases, which through degradation of basement membrane and tight junction (TJ), mediate immune cell migration during autoimmune disease. In the study by Liu *et al*., MMP9 mRNA levels were significantly higher in myositis compared to HC and associated to ILD. Serum MMP9 was significantly higher in patients with anti-Jo1 antibodies compared to patients with anti-melanoma differentiation-associated gene 5 (anti-MDA5), antibody-negative and HC. These results led the author to suggest that MMP9 could promote invasion of muscle fibres by $CD8^+$ T lymphocyte in anti-Jo1 positive subjects (7).

The study by Pinal-Fernandez *et al*. demonstrated that type I Interferon (IFN-1) and type 2 Interferon (IFN-2) inducible genes were more expressed in muscle samples from DM, anti-synthetase syndrome (ASSD), inclusion body myositis (IBM) and immune-mediated necrotising myopathy (IMNM) patients than in HC and displayed different activation levels based on different type of myositis. Particularly, IFN-2 pathway was highly activated in DM, ASSD and IBM but not in IMNM. Since IFN is involved in JAK/STAT pathway activation, the authors eventually suggested a possible future employment of JAK inhibitors in DM, IBM and ASSD but not in IMNM (8). An increased IFN-1 signature was also demonstrated in a population of anti-MDA5 positive patients and was strongly correlated with skin lesion secondary to vasculopathy (9). Additionally, Rigolet *et al*. confirmed the lack of IFN signature in IMNM (suggesting autoantibody and complement mediated myofibre damage) and also found an increased IFN2 signature in ASSD and IBM, as suggested by the myofibre expression of MHC-2 in proximity to $CD8^+$T cells (10).

Another study showed that muscle damage could be mediated by perimysial microarteriopathy in DM patients with positivity of anti-nuclear matrix protein-2 antibodies (anti-NPX-2). The damage of these perimysial arterioles is probably mediated by IFN-1 (as suggested by the expression of Myxovirus resistance protein A in endothelial cells) associated with an impaired neoangiogenesis (suggested by low expression of vascular endothelial growth factor (VEGF) in endomysial neo-vessels), and may be responsible for intense muscle ischaemia found in anti-NPX-2 positive DM patients (11).

Gao *et al*. evaluated whole expression of miRNA and mRNA in DM and PM muscle tissue compared to HC and found specific alterations in pathological samples. Significantly, miR-196a-5p was down-regulated in PM resulting in the over-expression of carboxypeptidase M (CPM), involved in the degradation of extracellular proteins and cancer cell migration. Similarly, miR-193b-3p was negatively correlated with NECAP-2 in both PM and DM. NECAP-2 is involved in endosome recycling and its role in PM/DM pathogenesis is yet to be clarified (12).

Many studies focused on abnormal T lymphocyte activity in IIMs pathogenesis. The study by Feng *et al*. confirmed the previous observations according to which at the basis of autoimmune diseases, including PM and DM, there may be an imbalance between effector T-cells and regulatory T lymphocytes (Treg). The results of this study also suggested that the administration of low dose IL-2 could have a role in the treatment of IIMs through the reconstitution of adequate levels of Treg (13).

Zhou *et al*. explored the role of T cells that, through tumour necrosis factor-related apoptosis-inducing ligand (TRAIL), would induce muscle cell death. The two forms (membrane bound and soluble) of TRAIL were indeed upregulated in PM and DM patients compared to HC, and positively correlated with disease activity (evaluated as MYOACT) and presence of

dysphagia, whereas it was negatively correlated with anti-Jo1 positivity. The authors suggest a possible role of TRAIL as a marker of disease activity or therapeutic target (14).

Another subpopulation of T lymphocyte, the follicular T helper (Tfh) and its associated cytokine (IL-21), may be dysregulated causing loss of immune tolerance of B-cells. Zhang *et al*. found increased levels of circulating Tfh cells precursors in IIMs patients compared to HC suggesting a possible pathogenetic role in myositis as previously demonstrated in other autoimmune diseases (15). T-cells could also be involved in specific manifestations as ILD. Specifically, $CD4^+CXCR4^+$ T cells isolated from peripheral blood and bronchoalveolar lavage fluid (BALF) were significantly more elevated in IIMs-ILD patients than controls (idiopathic pulmonary fibrosis, ILD secondary to RA, ILD secondary to SSc, community acquired pneumonia, IIMs alone and HC). Moreover, high peripheral $CD4^+CXCR4^+$ T-cells levels correlated with ILD severity and seemed to be an independent risk factor for mortality. In clinically amyopathic DM (CADM)-ILD, they also induced *in vitro* proliferation of pulmonary fibroblast and production of TGF-β, a-SMA and collagen I, supporting the hypothesis of a pro-fibrotic effect of this subtype of T-cells in ILD-IIMs (16). Galindo-Feria *et al*. showed a greater activation of $CD4^+$ T lymphocytes isolated from peripheral blood and BALF of IIMs/ASSD patients after stimulation with histidyl-transfer RNA synthetase (HisRS) compared to controls (sarcoidosis patients and HC). This data, together with the finding of an increased level of anti-Jo1 (anti-HisRS) antibodies in BALF and in pulmonary germinal centres, suggested a direct activation of T-lymphocytes against HisRS in the lung (17).

In a study performed on DM patients, the lymphocyte subset may vary according to disease activity, showing a reduction of transitional B cells and an increase in memory B cells after remission induction. Untreated DM patients also displayed higher levels of naïve $CD4^+$ T cells and B cells compared to HC, whereas naïve $CD8^+$ Tcells and differentiated B and T cells were fewer. These differences with HCs appeared more pronounced when considering DM patients with ILD (18).

Greenberg *et al*. suggested that the involvement of a specific subpopulation of T-cells also in IBM pathogenesis. Highly differentiated cytotoxic lymphocyte, not responsive to steroids and conventional immunosuppressive drugs, would be the reason of refractoriness to therapy of this particular myositis (19). This aspect was also confirmed by an analysis on PBMCs with a mass cytometry where IBM patients showed higher levels of $CD8^+$ T cells expressing T-bet (T-box expressed in T cells, a transcription factor driving differentiation in cytolytic and in memory cells) than HC. Moreover, $CD8^+$T-$bet^+$ cells from patients displayed a unique activated and non-senescent profile, revealing a continuous proliferative capacity and effector functions. The authors suggested that $CD8^+$T-$bet^+$ cells could be used as a biomarker for IBM (20). Huntley *et al*. investigated a possible role of the accumulation within muscle fibres of TAR DNA-binding protein 43 (TDP-43) as another possible actor in IBM pathogenesis. Compared with HC, IBM patients had a colocalisation of TDP-43 with mitochondria, being probably responsible for their dysfunction (21). In addition to TDP-43, other proteins such as p62, lysine (Lys) 63-linked ubiquitin, and LC3 are accumulated in sporadic IBM muscle cells, promoting the autophagy of ubiquitinated protein aggregates and consequent activation of NF-κB signalling pathways. Cylindromatosis (CYLD) enzyme performs a deubiquitinising function and consequently regulates this pathway. In a study by Yamashita *et al*., CYLD was co-expressed with pTDP-43, phosphorylated p62, and Lys63-linked ubiquitin in IBM, suggesting that a CYLD dysfunction could contribute to muscle damage (22). Mitochondrial dysfunctions in IBM are also well known and extensively described in literature. In the last year, however, Bhatt *et al*. found that also a depletion of mitochondrial DNA (mtDNA) in muscle cells could be a marker of IBM, since a significant reduction was found in IBM biopsies from 9 patients compared to samples from IMNM and HCs (23).

Liu *et al*. explored the protective role of NF-E2-related factor 2 (Nrf2) in IIM pathogenesis. Nrf2 is a transcription factor that promotes anti-oxidative enzymes expression with consequent inhibition Reactive Oxygen Species (ROS)-mediated damage. In this study, a muscle sample from DM and PM patients showed a higher expression of CD163 macrophages and of pro-inflammatory factors compared to HC, and lower expression of Nrf2. Furthermore, CD163 macrophages isolated from an experimental autoimmune myositis (EAM) rat model, after transfection with Nrf2, showed a significant increased expression of oxidative stress inhibitors, reduction of pro-inflammatory factors (MCP-1, TNF-α, and IL-6) and a reduction of migration ability (24). A summary of the novelties in the pathogenesis of IIM is provided in online Supplementary Table S1.

**General and muscular involvement**

In IIMs, the positivity of specific autoantibodies is associated with distinct clinical patterns. The study by Casal-Dominguez *et al*. showed that anti-U1RNP positive patients were more likely to have sclerodactyly, Raynaud phenomenon (RP), mechanic's hands, ILD and arthritis compared to DM. Conversely, when compared with ASSD, they displayed ILD less frequently. Moreover, glomerulonephritis and pericarditis were almost exclusively found in anti-U1RNP group. Interestingly, despite their clinical diversity, anti-U1RNP patients and IMNM, showed surprising similarities in muscle biopsies (25). Otherwise, IMNM has characteristic histopathological features but is indistinguishable from non-necrotising myositis by clinical manifestations, serology, or laboratory findings (26).

In the evaluation of disease activity and treatment outcomes, patient-reported outcome measures (PROM) are of fundamental importance. The OMERACT Myositis Special Interest Group (SIG) identified the domains fatigue, level of physical activity, muscle symptoms,

pain and adverse events to be assessed mandatorily in all trials, while the domains lung, joint and skin symptoms only in specific circumstances (27). In addition to PROMs, also muscle function tests play an important role; assessment of selected proximal muscle groups (deltoids/psoas) combined with functional tests (Barré/Mingazzini/chair rise, squatting and leg-crossing capacity) is a simple and time-saving way to assess IIM patients in clinical practice. Assessment of deltoids and psoas, and interestingly also the Barré test showed the strongest responsiveness to change (28). Manual muscle testing (MMT), a measure of isometric muscle strength, is considered as a surrogate of muscle function but it may be insufficient to describe muscle dysfunction completely and, particularly in patients with high baseline strength or complaints of fatigability, the addition of Myositis Functional Index-2 (FI2) proved to be very useful (29).

*Classification and disease activity criteria*

Bohan and Peter classification criteria are the most widely used, although in 2017 new criteria were proposed by European League Against Rheumatisms/American College of Rheumatology (EULAR/ACR). The performance of the two criteria sets was similar in the absence of muscle biopsy, but Bohan and Peter criteria had higher sensitivity when biopsy is present (30). Moreover, the EULAR/ACR criteria showed a high sensitivity in identifying IIMs, but correlated poorly with expert opinion in IIM subtype assignment, possibly because it is impossible to include clinically relevant information and organ involvement (31). To this end, the inclusion of an extended panel of MSA, magnetic resonance imaging (MRI) and histologic evidence of myofibre invasion, seemed to improve ACR/EULAR performance, thus increasing the accuracy of IIM diagnosis, especially for non-anti-Jo1 patients (32, 33). Moreover, minor modifications of the items, such as including the presence of ILD as variable, could increase the possibility of correctly classifying more patients (34).

*Histology*

Muscle biopsy remains one of the pillars for a correct diagnosis of the IIM subtypes. Nevertheless, the variability in interpreting and scoring individual biopsy abnormalities was found to be very high amongst experts, thus suggesting that standardisation would be necessary (35).

Attention should be given to granulomatosis-associated myositis since, in a small European cohort, almost half of these patients matched the sIBM criteria. This group of patients, interestingly, was more likely to be unresponsive to myopathy treatment (36).

The sarcoplasmic expression of myxovirus resistance protein A (MxA) may be considered a sensitive and specific pathological hallmark of DM; in particular anti-MDA5 autoantibody-positive DM showed a scattered distribution pattern of MxA-positive fibres (37).

*Muscular imaging*

IIM muscle biopsy could be affected by false negative results, due to patchy inflammation and therefore, MRI could be helpful in targeting muscle biopsy. Moreover, detection of specific MRI patterns of muscle involvement could help also in IIM subtyping.

With this aim in mind, Day *et al*. found that IMNM patients in early phases showed severe and extensive muscle oedema (ME), fatty replacement (FR) and atrophy, mainly in the lower limbs (pelvic muscles and adductors), whereas IBM was characterised by marked anterior thigh involvement which stabilised or progressed at follow-up imaging. Inter-rater reliability for atrophy and FR assessment was higher than for oedema. Disease activity tests, such as MMT8, MDAAT and VAS scales, did not significantly correlate with MRI findings (38). In addition to the currently used T1 and STIR sequences, new protocols are being developed: diffusion-weighted imaging (DWI) and readout-segmented echo-planner imaging (rs-EPI) DWI detected more ME than STIR sequences, being a valuable add-on in early active phases of IIM, while T2 maps identified the severity of damaged muscles better than rs-EPI DWI (39, 40). Wang and colleagues developed an accelerated T2 mapping technique, called GRAPPATINI that shortened the examination time, allowing the acquisition of both thighs from hips to knees in only 2 min and 18 s, making T2 mapping feasible in clinical practice (41). A Swedish group performed a study on IBM muscle biopsies and MRI scans and found a correlation between muscle weakness and extension of atrophic changes. Conversely, inflammatory changes did not show any correlation with muscle weakness or degenerative changes, being present in all examined muscles at every stage of disease. This makes it difficult to understand whether the degenerative changes could be considered exclusively as an evolution of inflammation (42).

In the last year, also neuromuscular ultrasound (US) emerged as a useful tool in detecting active myositis, particularly IBM, showing high sensitivity among experienced clinicians (43). Texture analysis of sonographic muscle images was able to differentiate between IIM and non-inflammatory myopathies, such as myotonic dystrophy (44). Moreover, shear wave elastography (SWE), a relatively new US-based technique, allowed the identification of reduced thigh muscle stiffness which correlated with muscle weakness and MRI signs of oedema and atrophy (45).

Fluorine-18 fluorodeoxyglucose ($^{[18F]}$-FDG) positron emission tomography (FDG-PET), routinely performed for neoplastic screening, could be useful also for muscular activity assessment, thus avoiding the systematic need for biopsy. IIM muscles had greater FDG uptake than healthy muscles, whether they presented disease activity or not. Maximal standardised uptake values (mSUVmax) threshold of 0.66 differentiated high from low or absent muscle disease activity with excellent accuracy. Accordingly, the serum creatine kinase level was positively correlated with mSUVmax (46). A study by a French group showed that the SUVPROX/SUVMLT ratio >1.73 (SUVPROX= maximum SUV in proximal muscles, SUVMLT= maximum SUV in musculus longissimus thoracis) seems to be a solid diagnostic criterion of active myositis due to its relatively high specificity in DM patients (47).

In addition, recent data evidenced that both PET and CT could differentiate IMB from other IIMs. IBM globally showed a higher muscular standardised $^{[18F]}$florbetapir uptake value ratio (amyloid-PET), if compared with PM, while quantitative CT imaging analysis revealed that IBM displayed a characteristic anterior muscle degeneration involving quadriceps femoris, medial gastrocnemius and tibialis anterior, unlike PM or amyopathic lateral sclerosis (48, 49).

Needle electromyography (EMG) is another important tool in the diagnosis of IIM. In the last year, EMG changes usually considered typical for IIM, such as short-small motor unit potentials (MUPs) have been furtherly studied. De Carvalho *et al*., indeed, found that the first recorded MUP showed similar firing rates in IIM and HCs, whereas the second MUP displayed lower variability in IIM patients, thus suggesting an adaptation mechanism in IIM muscles (50). According to another study, fibrillation potentials and short duration MUP were the most frequent abnormalities found in IIM and could help to predict histological findings of muscle fibre necrosis, splitting, and/or vacuolar changes (51). Moreover, electrical impedance myography (EIM), which measures the passive electrical characteristics of muscles, could help differentiate IBM from healthy patients, also showing a correlation with clinical outcome scales (52).

Multifibre muscle velocity recovery cycles (MVRC) is a relatively new neurophysiological technique that provides an indirect measure of sarcolemmal excitability and resting membrane potential. In IBM, MVRC showed a prolonged muscle relative refractory period (MRRP) and reduced early supernormality (ESN) compared to HC. This could be due to amyloid deposition that determined a relative depolarisation of the resting membrane potential. MVRC parameters, however, did not correlate with disease severity or duration (53).

**Autoantibodies**

Patients with IIMs may present with a broad spectrum of autoantibodies. In detail, MSAs are almost exclusively found in IIM patients and they include: antisynthetase autoantibodies (or anti-aminoacyl-tRNA-synthetase, ARS), anti-Mi-2, anti-signal recognition particle (SRP), anti-MDA5, anti-nuclear matrix protein 2 (NXP2, previously anti-MJ), anti-p155/140 (anti-TIF1-γ), anti-small ubiquitin-like modifier-1 activating enzyme (SAE), and anti-HMG CoA reductase (statin-related necrotising myopathy). MAAs, conversely, can be found in other systemic autoimmune rheumatic diseases and they include anti-PM/Scl, anti-Ku, anti-U1/U2/U3Anti-U1-ribonucleoprotein (RNP), anti-SSA, and anti-SSB (54). Although myositis subsets have been traditionally determined clinically, autoantibodies offer valuable information about prognosis, patterns of organ involvement, and treatment response (55). Concerning specific clinical features, ILD is known to have a correlation with distinct MSA (56), while the association between ILD and MAA, including anti-Ro52, is less established. Sclafani *et al*. performed a retrospective cohort study of 73 adults with ILD and a positive anti-Ro52 antibody and they found that the majority of patients with ILD and anti-Ro52 had no established connective tissue disease (78%), and one-third had no rheumatologic symptoms. Forty-five patients had organising pneumonia (OP) pattern at HRCT and thirteen patients (17.8%) required intensive care unit (ICU) admission for respiratory failure. Of the 73 subjects, 85.7% had a negative SS-A, and 49.3% met criteria for idiopathic pneumonia with autoimmune features (IPAF). The 50 patients with anti-Ro52 alone were indistinguishable from those with anti-Ro52 plus an MSA. Coexistence of rheumatologic symptoms or ANA ≥1:320 was associated with better outcomes (57).

Besides their diagnostic utility, MSAs may also help to stratify patients into subsets with peculiar clinical features, treatment responses, and disease outcome. Consequently, standardisation of MSA detection is of the outmost importance. Immunoprecipitation (IP), currently used as a detection method in many laboratories, is of difficult standardisation, thus implying the need for reliable alternatives. In a recent study by Cavazzana *et al*., 54 sera samples from patients with IIM were tested using three methods: IP, line immunoassay (LIA) and a novel particle-based multi-analyte technology (PMAT). The analysis focused on antibodies against EJ, SRP, Jo-1, NXP-2, MDA5, TIF1-γ, and Mi-2. Significant variations were observed among all methods. In detail, the novel PMAT seemed to be a potential alternative to IP and other diagnostic assays showing a slightly better correlation with IP, although the kappa agreement was strongly dependent on the antibody tested. When the results obtained from IP were used as a reference for receiver operating characteristic (ROC) curve analysis, good discrimination and a high area under the curve (AUC) value were found for PMAT, which were significantly better than those found for the LIA method. However, additional studies based on larger cohorts are needed to fully assess the performance of this novel system (58). Moreover, a study by Espinosa-Ortega *et al*. compared IP and LIA in a cohort of 110 patients with IIM. The overall concordance rate between the two assays was 78% with moderate agreement. In detail, very good agreement was found for anti-SRP, anti-Ku and anti-SAE1, and good agreement for anti-Jo-1. Agreement for anti-PmScl, anti-MDA5, and anti-TIF1γ was moderate (59).

**Extra muscular involvement**

The burden of IIM-related ILD is acquiring growing importance also among pneumologists, since a correct diagnosis may mean avoiding futile diagnostic procedures and starting adequate treatments, thus improving patients' prognosis. A summary of the novel findings about IIM extramuscular involvement is reported in Table II.

Fidler *et al*. found that about 27% of patients (44/165) previously diagnosed with idiopathic ILD, displayed positivity for MSAs or MAAs; this led to a diagnosis change in 8.4% of cases. Anti-Ro52 (11%), anti-PM/Scl75 (8%) and ARS antibodies (9%) were the most frequently detected. Current smoking and lower DLCO showed a correlation with the presence of MSA/

**Table II.** Summary of the extra muscular involvement reported in articles published in 2019.

| | Main findings |
|---|---|
| Lung involvement | MSA/MAA might be positive in about 30% of patients with idiopathic pulmonary fibrosis (60)<br>Organising pneumonia pattern is frequently associated with anti-Ro52 (57, 62)<br>KL-6 might be a useful marker of presence, severity and response to therapy (64–68)<br>BAAF levels seem to be associated with ILD and reduce after therapy (70)<br>$CD4^+CXCR4^+$ T cells are high only in ILD related to IIM and a serum percentage >30% could be a risk factor for mortality (16)<br>Other markers of ILD in anti MDA5: neopterin, sIL-2R, ferritin, YKL-40 (71) |
| Skin | Epidermal/Inflammatory histologic changes are more frequent in ASSD, while vascular alterations are commonly found in anti-MDA5 positive patients (72, 73)<br>Skin disease activity score relates to quality of life scores only in high disease activity (75) |
| Microcirculation | IIMs display the highest rate of nailfold videocapillaroscopy (NVC) alterations, after SSc (76)<br>NVC alteration are more common in anti-MDA5 and anti-TIF1γ than in ASSD (78)<br>NVC abnormalities in IIM could be reversible with adequate treatment (78, 79) |
| Heart | Subclinical involvement could be found in 50% of PM/DM (82)<br>Coronary heart disease seems to be more frequent in IIMs than in general population (84) |
| Malignancy | Skin rash, distal muscle weakness, older age, ANA negativity, could be considered risk factors (85, 86)<br>Anti-TIF1γ titre could precede cancer onset up to five years (88)<br>$^{18}$F-FDG PET/CT did not provide any advantage in early diagnosis of IIM-associated cancer (89) |
| Gastrointestinal | Dysphagia might be due to pharyngeal and tongue muscles weakness and shorter UES opening (90)<br>Liver dysfunction has been described in anti-MDA5+ myositis (93) |
| Antisynthetase syndrome (ASSD) | ASSD seemed to have common evolution regardless ARS specificity (94)<br>ASSD-arthritis could be very similar to RA, even at US, and misdiagnosed with it (95, 96) |

MAA, whereas patient-reported CTD symptoms did not, which prompted the author to propose routine detection of MSA/MAA in ILD patients (60). On the other hand, a Chinese study showed that anti-MDA5 and anti-Ro52 antibodies performed better than other MSA/MAAs in identifying PM/DM patients with ILD, although anti-Ro52 poorly discriminated IIMs from other CTDs (LR+ 1.1 *vs*. 28.46 of anti-MDA5). On the other hand, anti-NXP2 and anti-TIF1γ seemed to be more frequent in PM/DM patients without ILD (61). The role of anti-Ro52 was further investigated by Chen *et al*. who focused on rapid progressive ILD in DM patients. They retrospectively screened 491 patients with PM/DM-ILD and selected all proven cases of isolated anti-Ro52-associated rapidly progressive-ILD (RP-ILD). Among 20 PM/DM patients with Ro52-isolated-ILD, 5 of them had a rapidly progressive form. These 5 patients had typical rashes including Gottron's sign (80%), heliotrope rash (80%) and mechanic's hands (100%), but only a few patients (20%) had arthralgia and muscle weakness. All patients had elevated levels of serum ferritin and decreased counts of $CD3^+$ T cells. The HRCT patterns of these patients showed organising pneumonia (OP), thus determining a better response to GC and survival compared to anti-MDA+ and anti-ARS+ patients (80% *vs*. 42% and 58%, respectively), who often developed NSIP-ILD (62).

Concerning clinical features of ILD in anti-U1-RNP patients, Lhote *et al*. reviewed chest CT scans of 544 patients with anti-RNP antibody and found that 26% of them had radiological features of ILD. The presence of ILD was significantly associated with dyspnea, crackles, arthritis, RP, myositis and sicca syndrome. The most frequent pattern was NSIP (81%). Among patients with ILD, 35% had a radiological pattern consisting of cysts and ground-glass attenuation not fulfilling the lymphoid interstitial pneumonia (LIP) criteria (63).

Several studies reported the usefulness of different serum markers in detecting or monitoring the course of IIM-related ILD.

Serum Krebs von den Lungen-6 (KL-6) levels were found to be higher in 165 CTD-ILD patients (including 56 IIMs) compared to CTD patients without ILD, showing a negative correlation with DLCO and FVC and a positive one with CT extension of ILD (64). Accordingly, a Japanese study on 110 IIMs (68% with ILD) found higher baseline KL-6 levels in PM/DM/CADM patients with ILD than in patients without ILD as well as in relapsing compared to non-relapsing patients, with serum levels fluctuating accordingly to disease activity. The presence of anti-ARS antibodies was also associated with a higher rate of relapse (65). Other studies confirmed the association between KL-6 levels and ILD occurrence in PM/DM patients, as well as with neopterin, sIL-2R, ferritin and anti-MDA5 titre in anti-MDA5 positive patients. Interestingly, the level of serum markers tended to reduce only after 6 months from the beginning of remission-induction therapy (66, 67). Serum KL-6 also correlated positively with ILD extension at HRCT and lung US and negatively with DLCO and total lung capacity (68).

An interesting association between ANA, RP and a disproportional reduction of DLCO compared to FVC, was found by Park *et al*. in 103 IIM patients. It should be noted, however, that pul-

monary arterial hypertension was assessed only in a few patients (69).

Serum B-cell activating factor (BAFF) has also been studied as an ILD marker in DM. Matsushita *et al*. found that BAAF levels were significantly higher in ARS+ and anti-MDA5+ patients than in HC and correlated with ILD and RP-ILD occurrence. Furthermore, in anti-MDA5+ patients, BAAF seemed to reduce after 9 months of therapy, together with anti-MDA5 titre. Interestingly, BAAF levels of DM patients with other MSAs (anti-Mi2, anti-TIF1γ) did not significantly differ from HC. These findings suggested a possible role for BAAF in the pathogenesis of ILD and possibly as a potential target for treatment (70).

Other markers associated with poor prognosis have been identified: YKL-40 levels (a chitinase-like protein secreted by macrophages, neutrophils and certain epithelial cells) >80 ng/ml correlated with RP-ILD and poor 6-months prognosis in an anti-MDA5+ cohort (71).

Cutaneous involvement is a hallmark of DM and efforts have been made in order to improve our histopathological knowledge of DM-related skin lesions. A large study on 288 DM skin biopsies revealed that 95% of samples displayed epidermal/inflammatory changes (interface dermatitis, dermal mucin deposition or perivascular inflammation) and only 27% vessel damage/thickening. These 2 patterns did not significantly overlap within the same sample, suggesting that they were caused by different pathways (72). Moreover, psoriasiform dermatitis, eczematous reactions and interface dermatitis with dyskeratotic cells were found frequently in anti-ARS+ patients, whereas anti-MDA positive patients showed vascular injury and MxA expression (absent in anti-ARS group) (73).

It has also been reported that CTD inflammatory lesions could be related to severe itching, especially in DM. (74). Furthermore, a retrospective study on 171 DM, found that the correlation between the index of cutaneous disease activity in DM (CDASI) and standardised indexes of quality of life in dermatology (Skindex-29 and DLQI) was very poor for low values of CDASI, suggesting that total skin clearance might not be a meaningful outcome for these patients (75).

Nailfold videocapillaroscopy (NVC) is a useful tool to assess vascular alterations in systemic sclerosis (SSc) and has been studied also in IIMs patients, who showed the highest incidence of scleroderma pattern among non-SSc CTDs, irrespectively of the presence of RP (76). In a small cross-sectional study, vascular disorganisation, avascular zones and giant capillaries were found more frequently in DM and overlap myositis (OM) than in ASSD and IMNM and only OM displayed scleroderma pattern (77). Kubo *et al*. also found that anti-MDA5+ and anti-TIF1γ+ patients were more prone to showing NVC alterations (about 90% of cases) whereas in anti-ARS+ patients the frequency was only 27%. Interestingly, NVC abnormalities disappeared in most cases after 1 year of treatment (78), although in another study, only rituximab seemed to be able to achieve this result (79). In a very large cohort of 190 patients with ASS, NVC abnormalities, included a reduction of capillary number, giant capillaries, microhaemorrhages, and avascular areas, were observed in 62.1% of the patients, while a clear scleroderma pattern in 35.3% with an association with anti-Jo1 antibodies, independently of the presence of RP (80).

Subclinical cardiac involvement is possible in IIMs, as identified by Barsotti *et al*. in a multiparametric study (81). Moreover, Khoo *et al*. found cardiac MRI alterations (late gadolinium enhancement and elevated native T1 suggesting inflammation and/or fibrosis) in about 50% of asymptomatic DM/PM patients (82). MRI relaxometry showed excellent performance of naïve T1 sequences in discriminating IIM patients from HC in the myocardium, while they were less discriminant in skeletal muscles (83). In addition, PM and DM patients from a large Taiwanese cohort seemed to be more prone to developing also coronary heart disease compared to the general population, with HR of 2.21 and 3.73, respectively (84).

Several studies analysed IIM characteristics potentially associated with cancer, revealing that skin rash, distal muscle weakness, older age and, interestingly, ANA negativity, could be considered risk factors (85, 86). The high prevalence of anti-TIF1γ among IIM-related cancer was confirmed, with the clinical course apparently related to cancer activity and antibody titre possibly preceding cancer onset by up to five years (87, 88)

The role of $^{18}$F-FDG PET/CT was studied for the early diagnosis of IIM-associated cancer, but did not show any advantage compared to conventional cancer screening (89).

An interesting study found that IIM-related dysphagia could be due to shorter duration of upper oesophageal sphincter (UES) opening and poor pharyngeal/tongue contraction, rather than reduced UES diameter. This suggested a possible role for swallowing exercises in the treatment of this condition (90).

The study of oesophageal function may be challenging in patients with IIMs, but oro-pharyngeal-oesophageal scintigraphy may open new possibilities for the quantification of swallowing dysfunction of this frequent extramuscular involvement (91).

Primary biliary cirrhosis (PBC) was found in a minority of IIMs patients displaying anti-mitochondrial antibodies (AMA) positivity (2/7 AMA+ patients). The prevalence of AMA+ was about 5% and was associated with a low frequency of MSA positivity and atypical (asymmetrical, distal) muscle involvement (92).

Moreover, Nagashima *et al*. found liver dysfunction occurring in 10/50 observed DM patients, all of whom displaying anti-MDA5 positivity. Steatosis and hepatocyte ballooning were the most commonly detected bioptic alterations (93).

Despite the well-known heterogeneity of ASSD, involving several extra-muscular manifestations, Cavagna *et al*. stated that the clinical course of ASSD is not relevantly affected by ARS specificity since most patients developed, over time, a complete form of ASSD with similar survival. Interestingly, ILD was the most common onset manifestation in anti-PL7, anti-PL12 and anti-EJ patients, while anti-Jo1 mostly started with arthritis (94). In a small

retrospective study, US findings seen in ASSD-related arthritis were synovial hypertrophy with active Doppler, tenosynovitis and erosions (95), further confirming that ASSD-related arthritis could be very similar to rheumatoid arthritis, and possibly confused with it: in a study on anti-Jo1+ cohort, the time to achieve a correct diagnosis ranged from 3 to 20 years (96). ASSD patients also seemed to display reduced aerobic capacity compared to HC (unlike DM patients), despite comparable disease activity, lung involvement and concurrent cardiovascular diseases (97).

## Treatment

*Pharmacologic therapies*

Glucocorticoids (GCs) remain the first-line treatment for PM/DM as stated by a multidisciplinary consensus of rheumatologists, neurologists and dermatologists. According to this study, oral GC should be used for systemic manifestation of IIM whereas iv pulse therapy should be reserved for life-threatening manifestations (*e.g.* myocarditis or RP-ILD). Association with immunosuppressants is advisable in order to reduce GC dosage or in relapsing diseases (98). Although GC monotherapy is the first choice of treatment, approximately 50% of patients with IIM fail to maintain remission when the GCs are tapered. Moreover, steroid-related side effects are common and disabling. For these reasons, immunosuppressants are often associated to GCs since disease onset, as confirmed by a recent retrospective study of 63 patients with PM/DM. In this cohort, azathioprine (AZA) was the preferred drug as first-line therapy followed by methotrexate (MTX) and GC monotherapy; both therapies allowed the reduction of GCs over time (99). Further immunosuppressive agents commonly used in IIM are calcineurin inhibitors (CNIs), including cyclosporine A (CsA) and tacrolimus (TAC), cyclophosphamide (CFX) and mycophenolate mofetil (MMF). These agents can be used in monotherapy in combination with steroids or in combination with each other in refractory cases. Hanaoka *et al*. analysed retrospectively the efficacy and tolerability of MMF alone or in combination with CNIs in 19 patients with IIM refractory to conventional immunosuppressive therapy. They found that the combination of MMF and CNIs was more effective in decreasing CK levels than MMF alone, whereas neither of these treatments yielded an improvement in ILD over a short-term observation period (100).

Other studies focused on ILD treatment. Suzuka *et al*. reported the efficiency of TAC plus GCs in eleven patients with DM-ILD, although with an increased risk of infectious and renal side effects (101). Huapaya *et al*. evaluated the specific effects of AZA and MMF in two different groups of patients with IIM-related ILD; both treatments were associated with FVC% improvement and prednisone dose reduction. Patients treated with AZA also showed DLCO improvement and lower dose of GCs after 36 months, although with a higher rate of adverse events (102). Ning *et al*. focused on the effects of plasma-exchange in refractory cases of acute ILD in PM/DM/CADM patients, reporting an improvement in about 60% of cases (103). High levels of ferritin and subcutaneous/mediastinal emphysema were found to be negative prognostics factors of response to therapy. However, this data could be limited by the paucity and inhomogeneity of the cohort, giving a lack of a complete MSA assessment (103). Moreover, Tsuji *et al*. conducted a very interesting multicentric prospective study on early combined immunosuppressive therapy with high-dose GCs, TAC, and CFX in 29 anti-MDA5 positive DM/CADM patients with RP-ILD. At the end of the follow-up (52 weeks), anti-MDA5 titre, serum ferritin level, VC% and high-resolution tomography scores improved and, after six months, patients treated with combined immunosuppressive therapy had higher survival rates than patients treated with conventional therapy (104).

Regarding the treatment of IMNM, de Souza *et al*. published a study conducted on thirteen patients with active IMNM treated with intravenous human immunoglobulin (IVIg) and/or methylprednisolone pulse therapies, as first-line therapy. This early and aggressive approach led to the achievement of clinical response (according to IMACS definition) in 10/13 patients after a median time of 2.5 months and to a better functional and radiological (MRI) muscular outcome in the long term (105). Another study analysed the efficacy of TAC plus GCs in patients who failed the first-line therapy with GC monotherapy. The retrospective analysis revealed that patients precociously treated with combination therapy showed substantial improvement in muscle strength and reduction in GC dose (106).

In the past year some studies have been published about the treatment of patients with IBM, for which there is not yet a proven effective therapy. Among these a phase IIb/III double-blind, placebo-controlled multicentre study named RESILIENT (NCT01925209) was completed and published. The aim of the trial was to assess the safety, efficacy, and tolerability of bimagrumab – a fully human monoclonal antibody that binds to activin type 2 receptors on skeletal muscle fibres – in subjects with IBD. Bimagrumab was found able to induce muscle growth in cell culture and mice. A total of 251 IBM patients were recruited to the study. Unfortunately, the study failed to reach the primary end-point at 52 weeks, represented by a significant change in 6-min walking distance (6MWD) (107). Additionally, another study showed no improvement in five IBM patients treated with the monoclonal antibody against IL-1β (canakinumab) (108).

Biological drugs are generally reserved for refractory cases of IIM patients who do not respond to conventional therapy. Rituximab (RTX), a chimeric murine/human monoclonal antibody targeting CD20 expressing cells, is one of the most used biological agents. A retrospective study published in the past year investigated the effect of RTX in anti-synthetase antibody (ARS-ab)-positive patients compared to ARS-ab-negative patients. At the end of the study both groups showed moderate/major improvement after RTX, but a significant GC-sparing effect was only observed in the ARS-ab positive group (109).

On the contrary, RTX use in patients with anti-HMGCR IMNM has rarely been reported. In one retrospective analysis, nine patients with refractory

anti-HMGCR IMNM were treated with RTX: one-third responded to treatment, while RTX was clearly ineffective in two-thirds (110).

A further biological drug that has been used in refractory IIM patients is abatacept, a fusion protein synthesised from the Fc portion of IgG1 and the extracellular domain of cytotoxic T-cell lymphocyte-associated protein 4. In 2018, a randomised, phase IIb trial with abatacept in 20 refractory IIM patients was published, named ARTEMIS. With a delayed treatment design, half of the patients started abatacept at week 0 and the other half at week 10. Comparisons between the two arms showed significant improvement in the treatment arm over the delayed arm at both 3 and 6 months (111). In 2019, a sub-study of the ARTEMIS trial, conducted on twelve patients, failed to identify treatment-related changes in peripheral T cell phenotypes, although a positive correlation between the CD4/CD8 ratio (both at baseline and after treatment) and improved muscle endurance was found, thus emerging as a possible marker of treatment efficacy (112). Another open-label study was conducted with tofacitinib, a Janus Kinase inhibitor, in patients with early stage anti-MDA5-positive CADM-ILD. Patients precociously treated with tofacitinib showed a higher survival rate 6 months after ILD onset compared with controls (treated with conventional immunosuppressive agents). Furthermore, the study group showed improvements in ferritin level, findings in high resolution CT, FVC and DLCO values. Tofacitinib was successfully used even in four treatment-refractory DM patients who showed improvement in cutaneous manifestations and inflammatory arthropathy (113).

*Non-pharmacologic treatments*

In addition to medical therapy, physical exercise, supervised by physical therapist, is now recommended by experts and has become part of routine management of patients with IIM (114). In this regard, a randomised single-blinded phase II trial showed that a 12-week aerobic training programme is safe, feasible and able to improve aerobic capacities in people with IBM (115). Similar results have been reported even on IMNM patients, for whom supervised exercise training seemed to be safe and effective, but also capable of increasing aerobic capacity, muscle strength and function, suggesting that this could be a novel potential coadjutant therapy in IMNM (116).

## Conclusion

In 2019 a great number of significant contributions have been provided about pathological phenotyping of IIMs and their clinical management. Also according to what was presented in the previous editions of this review (117, 118), genetic polymorphisms seem to play a role as risk factors for specific subsets of IIMs. The same aspect could be observed also for other molecular marker of IIMs and specific subsets of the disease may differ from each other in terms of mRNA expression for specific molecules. Moreover, T lymphocytes have been extensively studied this year, thus confirming their central role in IIM pathogenesis. Some subpopulations of T-cells have been identified as correlating with specific clinical manifestations, as seen for $CD4^+CXCR4^+$ T cells and ILD (16). Novel data have been published also about specific clinical patterns, and additionally for pulmonary and cardiovascular involvement, which represent the main causes of death in these patients.

These differences in the pathogenesis and in the clinical phenotype could explain the heterogeneity that these diseases manifest in clinical practice and could also affect the response to treatment, therefore IIMs should be considered as a group of different diseases and not as a single disease. With the availability of new targeted therapies, it appears reasonable that the choice of treatment should be based both on specific clinical patterns and internal organ involvements, thus leading to a personalised medicine and a personalised therapeutic approach. In this context, MSA determination and/or muscular biopsy should be performed in IIM patients in order to correctly diagnose the subset of the disease, allow a prognostic stratification and predict the response to a specific treatment. The clinical picture may be misleading thus leading to the wrong diagnosis and consequently ineffective therapies, as in the case of IMNM (105) or IBM.

In conclusion, we believe that these recent findings highlight the importance of being aware that not all IIMs are the same. Clinicians should be aware that every IIM case requires a detailed assessment including the detection of MSAs and possible extra-muscular manifestations, in order to correctly identify the disease of the single patients and propose the right treatment for the individual patient.

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