# Review

# One year in review 2019: idiopathic inflammatory myopathies

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**ABSTRACT**

*The idiopathic inflammatory myopathies (IIMs) are a rare group of immune, systemic diseases characterised by muscle inflammation and frequently by extramuscular involvement. IIMs are heterogeneous with generally a chronic or subacute onset, which vary from less severe to more serious manifestations, not always easy to diagnose and even less to manage. In the past year, many studies have been published in order to clarify disease pathogenesis and improve patient management and treatment.*

*The purpose of this review article is to provide an overview of the new insights in pathogenesis, serological findings, clinical manifestations and treatment of IIMs, summarising the most relevant studies published over the last year.*

## Introduction

Idiopathic inflammatory myopathies (IIMs) are a heterogeneous group of acquired, autoimmune muscle diseases characterised by muscle weakness, fatigue and inflammation. The most recognised sub-group of IIMs are dermatomyositis (DM), polymyositis (PM), inclusion body myositis (IBM), and overlap myositis, including antisynthetase syndrome (ASSD). Recently, other subsets of IIMs have been defined such as immune-mediated necrotising myopathy (IMNM) and the clinically amyopathic dermatomyositis (CADM) (1).

Extramuscular manifestations are common in IIMs, and the main targets are the skin, lungs, joints, heart and gastrointestinal system, with different degrees of involvement according to the underlying subset of IIMs (2).

By considering the recent advances on IIMs and following a well-established format (3, 4), with this paper we provide an overview of the most important papers focusing on IIMs published in 2018. We performed a Medline search of English language articles published in the PubMed database from 1st January 2018 to 31st December 2018. 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

*Genetic*

The role of genetic polymorphisms as a risk factor for IIM development surely represents a relevant topic of discussion, since they can explain the clinical differences observed in various sub-groups. The high prevalence of HLA-DRB1*03 haplotype has been confirmed in a cohort of 49 Hungarian patients with anti-Jo1 positive ASSD, with a prevalence rate of 68.96%. These patients had also lower CPK levels at diagnosis compared to HLA-DRB1*03 negative anti-Jo1 ASSD, thus potentially linking the genetic background not only to IIMs subtype, but also to disease severity (5). Single nucleotide polymorphisms (SNP) have been associated with IIMs in a cohort of 592 Japanese IIM patients. In particular, SNP rs7919656 of the locus WDFY4 was associated with a subpopulation of 33 clinical amyopathic dermatomyositis (CADM) patients. This polymorphism produced a truncated form of WDFY4 that positively correlated with NF-κB induced by different pattern recognition receptors, such as melanome differentiation-associated gene 5 (MDA5), thus strengthening the role of anti-MDA5 antibodies in CADM occurrence. A control group of European patients did not present this association but with other SNPs (rs11101462 and rs2889697) (6).

Parkers *et al*., reported that HLA-DRB1* 07:01 in DM anti-Mi2 posi-

tive patients and HLA-DQB1*02 in DM anti-TIF-1γ positive patients were negatively associated with latitude, and positively with UV gamma exposure. In the same study, other SNPs positively (for PM: rs2476601, rs4690220, rs7956536) and negatively (for PM: rs17799348; for DM rs4702698) correlated with latitude (7).

IIMs are characterised by inflammatory cell infiltrate that is predominantly of endomysial $Cd8^+$T cells in PM and perymisial $CD4^+$ T cells in DM. Houtman *et al*. speculated that differences between PM and DM in inflammatory cell infiltrate could be explained by different gene expression, especially in $CD8^+$T. In fact, peripheral $CD8^+$T presented 176 differently expressed genes between PM and DM patients, while peripheral $CD4^+$T showed a different expression only for two genes (ANKRD55 and S100B, both increased in PM compared to DM). The authors inferred that these divergences could probably support the hypothesis that PM and DM are sustained by different immune alterations and pathogenic mechanisms (8).

Lastly, Pinal Fernandez *et al*. showed that cancers from paraneoplastic anti-TIF1γ positive patients displayed an overexpression of TIF1γ proteins compared to type-matched control tumours from non-myositis patients and an increased number of somatic mutation (determining a strong activation of immune system) and loss of heterozygosity (LOH) in TIF1 genes compared to paraneoplastic anti-TIF1γ negative myositis patients. This would suggest that mutations in TIF1 genes in cancerous cells might be responsible for the strong immune response against the mutated proteins, thus determining the development of myositis. Otherwise, the high frequency of LOH could explain how tumours escape the immune system attack. (9).

In conclusion, despite the generally low number of evaluated patients, the studies published in 2018 confirmed the association of some HLA and polymorphisms with the occurrence of different IIMs subtypes, also according to latitude (Table I), and possibly their differences in histopathologic findings and cancer association.

*Cytokines and other inflammatory mediators*

Besides the genetic background, also post-transcriptional modifications may influence IIM occurrence. ADAM-17 is a metalloprotease involved in the cleavage of different membrane-anchored cytokines, such as fractalkine/CX3CL1, and cytokine membrane receptors, like the IL-6 receptor. In a study involving 70 IIM subjects (26 PM, 34 DM and 10 clinically amyopathic DM), Nishimi *et al*. demonstrated increased muscular expression and circulating levels of ADAM-17 in PM with interstitial lung disease (ILD) compared to healthy controls and myositis patients without ILD, regardless the clinical phenotype (PM, DM or CADM). Furthermore, ADAM-17 expression was reduced after steroid and/or immunosuppressive therapy and positively correlated with soluble fractalkine/CX3CL1, known to be a surrogate marker of myositis disease activity (10).

Another interesting cytokine is IL-9 which has been found increased in anti-Mi2 positive patients' sera compared to healthy controls (HC) and DM patients with other autoantibodies positivity (anti-TIF1, anti-MDA5 and anti-antisynthetase antibodies [ARS]). This divergence was observed also in $CD4^+$T lymphocytes infiltrating muscle and skin tissue. On the other hand, IL-9 seemed to positively correlate with CPK and aldolase levels, thus indicating the possibility that this cytokine could play a selective pathogenic role in some circumstances (11). Concomitantly, other authors evidenced a similar trend also for hyaluronic acid (HA), in both DM and PM, but in particular in DM (12).

In another study involving 26 CADM patients positive for anti-MDA5 antibodies, serum IL-15 levels were significantly increased in non-survivors, with over time increasing level with respect to survivors (13).

In anti-MDA5 positive patients, IFN-gamma (IFN-γ), IL-1β and IL-12 levels were significantly higher in patients with rapidly progressive ILD (RP-ILD). IFN-γ correlated positively with GG score while serum IL-1β levels correlated negatively with the fibrosis score. Serum IL-6 levels were increased in all IIMs subsets evaluated but not in HC and correlated with disease activity. Furthermore, numerous IL-6-positive plasma cells were found in hilar lymphnodes but not in the lungs. On this basis, IL-6 seems to be important in the immune reactions of DM patients with RP-ILD, but is unlikely involved in local lung injury. (14).

In a study conducted on 26 PM patients, serum levels of macrophage migration inhibitory factor (MIF) (which can induce proinflammatory cytokine such as IL-6 and TNF-α), resulted significantly higher in case of active disease with respect to subjects in remission or to HC. Additionally, IL-6 serum levels were significantly higher in PM patients, both with active disease and remission, compared to HC. Despite both cytokine were elevated in course of active disease, a negative correlation between MIF and IL-6 levels was found (15).

Furthermore, B cell-activating factor (BAFF) and a proliferating-inducing ligand (APRIL) may have a role of IIMs pathogenesis through their action on B-lymphocyte and probably through autoantibodies production. A cross sectional study involving 63 anti-Jo1 positive patients (41 diagnosed as probable or definite PM and 22 as DM) demonstrate a positive correlation between serum levels of BAFF and anti-Jo1. Both are correlated with levels of CPK, myoglobin, AST and C-reactive protein (16). In another study, BAFF levels were increased in IIM patients than in healthy controls, and in children with DM than adults, and among adults, patients with arthritis, weight loss, and pulmonary arterial hypertension (PAH). On the contrary, lower levels were seen in anti-SRP positive patients, suggesting a role for BAFF in development of specific clinical phenotypes of IIMs. (17).

In summary, interesting associations emerged between some molecules and distinct IIMs phenotypes, like ADAM-17 and PM-related ILD, IL-9 and anti-Mi2 DM, IFN-γ and RP-ILD in anti-MDA5 positive DM, BAAF and IIM-related PAH. BAFF, together with MIF, was also found related to muscular and extra-muscular disease activity.

*microRNA*

Micro RNAs (miRNA) are non-coding

**Table I.** Main genetic associations reported in 2018 published papers.

| Genetic polymorphism | Clinical associations |
|---|---|
| HLA-DRB1*02 (05) | Increased prevalence in anti-Jo1 and ASSD, lower CK levels at diagnosis |
| HLA-DRB1*07:01 (7) | Negative correlation with latitude in anti-Mi2 positive DM |
| HLA-DQB1*02 (07) | Negative correlation with latitude in anti-TIF1-gamma positive DM |
| SNP rs2476601, rs4690220, rs7956536 (7) | Positive correlation with latitude in PM |
| SNP rs17799348 (7) | Negative correlation with latitude in PM |
| SNP rs4702698 (7) | Negative correlation with latitude in DM |
| SNP rs7919565, locus WDFY4 | Increased expression in CADM |

ASSD: antisynthetase syndrome; CK: creatine kinase; DM: dermatomyositis: CADM: clinically amyopathic dermatomyositis.

RNA sequences that perform different biological actions by regulating growth processes, cell differentiation and activation by acting on different target genes. The muscular expression of miRNA for vascular factor cysteine-rich protein 61 (Cyr61), connective tissue growth factor (CTGF), and vascular endothelial growth factor (VEGF) resulted significantly higher in 17 PM and 18 DM patients compared to HC, as well as serum levels of Cyr61, CTGF and VEGF, which also resulted significantly reduced after 6 months of therapy (18).

*Liu et al*. assessed the role of miR-381 in the pathogenesis of PM and its effect on high mobility group box 1 (HMGB1), a non-histone nuclear protein involved in PM inflammation. HMGB1 was found increased in both sera and muscle samples from 25 PM patients compared to 10 HC and associated to a negative prognosis, whereas muscular expression of miR-381 was found lower in PM patients than in controls. The possible interaction between these molecules was assessed by a luciferase assays and, interestingly, the authors found that mice macrophages transfected with miR-381 mimics, showed a decrease in HMGB1, IL-17 and ICAM 1 expression, suggestion a possible role of miR381 in reducing inflammation via the downregulation of HMGB1 (19). Another circulating microRNAs (miR-7) showed lower expression in IIMs-ILD patients compared to patients without ILD (20).

Collectively these results show that miR-381 and miR-7 may modulate immune response and reduce the activity and prognosis of IIMs.

*Others*

Neutrophil extracellular traps (NETs) are extracellular structures composed of nuclear DNA, histones and granular antimicrobial proteins, like LL-37, which are formed by neutrophils aimed at killing bacteria. In case of impaired clearance, NETs can induce autoimmune response resulting in type-1 interferon production through Toll like receptor (TLR)-signalling. Peng *et al*. explored the possible relationship between NETs and rapidly progressive ILD (RP-ILD) in MDA5 positive DM patients. Serum cell free-DNA (cfDNA) and LL-37, mostly released by NETs, resulted significantly higher in MDA5+DM, especially when complicated by ILD and RP-ILD, than in MDA5 negative DM patients (less frequently complicated by ILD). Finally, *in vitro* study showed that serum from anti-MDA5 positive patients could induce formation of NETs, evidenced by increased cfDNA levels. Based on these results, the authors hypothesised that during exposure to extracellular pathogens, neutrophils might undergo NETosis. Following this process, LL-37 might be released in extracellular space and, through TLR signalling, could induce the production of interferon which upregulates the expression of MDA5 with the consequent production of specific autoantibodies (21).

The four human neutrophil peptides (HNPs) are α-defensins that perform both an anti-microbial and immune response regulation activity. Elevated HNPs levels in plasma and bronchoalveolar lavage (BALF) were found in systemic sclerosis (SSc) related-ILD. In a study by Sakamoto, HNP levels were significantly higher in 56 patients with IIM related-ILD both in plasma and in BALF compared to 24 HC. HPN levels were correlated with neutrophil amount in BALF (known negative prognostic factor for ILD) but not with severity neither survival. According to these results, the authors hypothesised that NETs, which include HNPs, could be responsible for IIM-ILD, suggesting that, in these conditions, there would be an altered clearance and an accumulation of NETs in the lung and a consequent damage (22).

In the study by Gao *et al*. on 48 DM patients and 16 PM patients compared to 39 HC, the neutrophil serine proteinases (NSPs) as cathepsin (CTSG), neutrophil elastase (NE), and proteinase 3 (PR3) resulted significantly upregulated in both PM and DM patients compared to HC through evaluation of mRNA expression from peripheral blood mononuclear cells (PBMCs), circulating levels and immunochemistry expression at muscle tissue. These NSPs are probably involved in vascular permeability and consequent migration of inflammatory cells as demonstrated by the experiment conducted on human dermal microvascular endothelial cells that were treated with patients' serum (23).

IBM pathogenesis is still controversial. Sachdev *et al*. demonstrated an increased expression of amyloid- (APP) and myostatin-precursor proteins (MstPP, belonging to the class of cytokines TGF beta and capable of inducing muscular atrophy) within the rimmed vacuoles of 20 IBM patients. The accumulation of MstPP induced endoplasmic reticulum (ER) stress and altered release of myostatin resulting in an accumulation of its precursors, leading to the formation of high molecular weight complexes and perpetuating ER stress (24).

Another risk factors for IIMs, as for other autoimmune disease, would be cigarette smoking. In a study on 465 patients (71% Caucasian and 58% affected by PM), Schiffenbauer *et al*. showed that Caucasian ever-smokers were more

likely to have PM, ARS positivity and ILD, with an odds ratio (OR) increasing accordingly to the number of pack-year and the presence of HLA-DRB1*03:01 allele. Conversely, the association was negative in anti-p155/140 autoantibody-positive patients and not significant in Afro-Americans (25).

**Autoantibodies**

Patients with IIMs may present with a broad spectrum of autoantibodies some of which almost exclusively found in IIM patients, defined myositis-specific autoantibodies (MSA). In recent years, some clinical aspects of the ASSD have been further defined like the fact that ASSD-related arthritis resembles RA when occurring from disease onset and, conversely, is very close to a connective tissue disease-related arthritis when occurring during the follow-up (26). Other studies showed that ASSD-related ILD displayed intense lung interstitial inflammation, but a reversible fibrosis and relatively good prognosis (27) and that, in anti-PL12 ASSD, ILD is often the initial manifestation (28).

Recently, a new classification of IIM aggregates IMNM patients in an homogeneous and distinct cluster defined by high CPK levels, necrotic fibres without inflammation on muscle biopsy and anti-SRP or anti-HMGCR antibodies (29). Statin-naive anti-HMGCR antibody-mediated necrotising myopathy may not be rare. Compared with late-onset statin-naive patients (≥50 years old) with anti-HMGCR antibody-mediated necrotising myopathy, early-onset patients (<50 years old) presented more severe clinical features and worse therapeutic responses (30). Coexistence of anti-HMGCR and anti-MDA5 was identified in 4 patients with characteristic rash and ILD, but without muscle weakness and elevated serum CPK levels (31). Some studies suggested that patient-derived anti-SRP+ and anti-HMGCR+ IgG could be pathogenic towards muscle *in vivo* through a complement-mediated mechanism (32). However anti-HMGCR and anti-SRP antibodies are not 100% specific to IMNM: there was no significant association between anti-HMGCR and statin-exposure and between anti-HMCGR or anti-SRP antibodies and muscle symptoms or CPK levels (30).

Autoantibodies to TIF1γ were confirmed to have a strong clinical association with cancers associated-DM and are rarely present in other rheumatic diseases associated cancers (33). Cancers in anti-TIF1γ positive DM were very frequently found close to the time of the DM diagnosis at more advanced stages than anti-TIF1γ negative patients (34).

The clinical characteristics and prognosis of patients with anti-MDA5 autoantibodies are variable. In a recent interesting Brazilian study anti-MDA5 were present in the 14.7% of DM and in the 22.7% of CADM. However, this cohort did not display more ILD or skin involvement compared to anti-MDA5 negative DM, maybe due to the paucity of the sample, with only 52 patients enclosed (35). Furthermore DM-ILD patients with anti-MDA5 positivity were reported to have a worse prognosis, with a shorter survival, compared with DM-ILD patients with anti ARS antibodies (27). A high anti-MDA5 titre (>100 IU/mL) and high levels of ferritin were associated with the development of RP-ILD and a poor outcome in DM-ILD patients in the first 3 months after therapy start; conversely, low titre of anti-MDA5 (<100 IU/mL) and ferritin seemed to be more likely found in patients surviving the first 3 months (chronic phase) who displayed similar outcome to anti-MDA5 negative DM-ILD (36). Besides anti-MDA5 autoantibodies, patients with CADM may have myositis associated autoantibodies (MAAs). Coexistent MAAs could be a marker of favourable prognosis in anti-MDA5-positive patients with CADM (37). In a French series of ASSD and anti-MDA5+ DM with acute respiratory failure, about one-third of patients had no extra-pulmonary manifestations with a similar proportion in the two cohorts, whereas, mortality was higher in anti-MDA+ patients (84% *vs*. 29%) (38). This study is relevant because highlight the need for myositis autoantibodies search also in patients with not otherwise explained acute respiratory distress syndrome, as well as the need for the careful screening of connective tissue disease symptoms, that as previously showed on other settings are not always easy to be detected (39).

Despite previous reports from the US and Italy, calcinosis and malignancy were found to be rare in Chinese adult patients with myositis positive for anti-NXP-2 antibody (40). Yang *et al*. demonstrated a correlation between serum anti-NXP-2 autoantibody levels and disease activity in patients without calcinosis at disease onset, whereas no association was found in patients who presented calcinosis at initial evaluation. The lack of correlation was confirmed also in the sub-group of patients who developed calcinosis during the follow-up, suggesting that the divergence between antibody titre and disease activity at the onset could be a marker for forthcoming calcinosis development (41).

Among MAAs anti-PM-Scl is associated with an IIMs overlap with SSc, with about the 30% of anti-PM/Scl-positive patients that met criteria for SSc: ILD was a presenting feature in just 10% but occurred in 61% of patients during follow-up. No differences were found between patients with only anti-PM/Scl-100 or only anti-PM/Scl-75 autoantibodies (42). On the other hand, anti-Ro52 and anti-Ro60, also included in MAAs, can be found alone or in conjunction with other MSA and can affect the clinical presentation: anti-SS-A/Ro antibody positivity is a risk factor for relapse in patients with PM/DM who achieved disease stabilisation: the association with lower levels of serum complement suggests that anti-SS-A/Ro antibody may affect the pathology through immune complexes (43). Recently, Albayda *et al*. highlighted an association of anti-mitochondrial antibodies (AMA) with a phenotype of a chronic inflammatory myopathy and severe cardiac involvement, in the absence of any MSA and proposed that AMA should be added to the growing list of MAAs (44). In the most recent years, autoantibodies against four-and-a-half LIM domain 1 (FHL1) and poly-U-binding factor 60kDa protein (PUF60), detected in other rheumatic diseases, have been described in IIMs, in particular in DM patients, with anti-PUF60 antibodies presenting higher prevalence of skin ulcerations. Moreo-

ver, longitudinal investigation in eight DM patients with anti-PUF60 antibodies revealed that the antibodies levels decreased with disease remission (45).

**Muscular involvement**

Some papers focused on the pathologic aspects of IIMs, and, among them, Valente de Camargo *et al*. showed that, besides the expected presence of beta-amyloid accumulation and rimmed vacuoles in myofibres of patients with IBM, muscle fibres stained positive for autophagy markers and proteins with post-translation modifications (such as α-synuclein, p62, TDP-43, LC3B) that are typically present in neurons of patients with neurodegenerative diseases These proteins were almost absent in other forms of IIMs, suggesting that these markers may help differentiating IBM from other IIMs (46).

IMNM, on the other hand, is a relatively recent entity, and the pathogenesis of this group of IIMs is still unclear.

Wang *et al*. characterised more in-depth the immunological characteristics of IMNM: many macrophages were observed within the necrotic fibres and in the endomysial tissue, few T cells and no B cells were observed. Both vessels and non-necrotic fibres upregulated MHC class I molecules; membrane attack complex was observed on small vessels and necrotic fibres (47).

Over the last year, additionally, several authors expressed some concerns about clinical and pathologic sets of classification criteria available.

The new EULAR/ACR classification criteria for IIMs (48) have been criticised mainly because of to the lack of MSAs (except anti-Jo1), extra-muscular manifestations (except dysphagia) and IMNM diagnosis from the criteria set (49) and also because of the low sensitivity in diagnosing ADM (50).

On the other hand, Hou *et al*. criticised the European Neuromuscular Centre (ENMC) recommendation for pathology diagnosis of IIMs criteria (51), highlighting their limited reproducibility and poor correlation with clinical phenotypes and, thereon, prognostic value (52).

Finally, Lassche *et al*. proposed an MRI-guided biopsy to increase the accuracy of sampling. The authors show the feasibility of the technique, the advantages (mainly the possibility to target specifically inflamed area of muscle) and the disadvantages (a high rate of symptomatic hematomas compared to traditional needle biopsy was observed) (53).

**Muscle imaging**

MRI has been recent focus of research in the last year, with the aim to implement its role in assisting in the diagnostic process and disease activity assessment of IIMs (54). *Zhao et al*. showed that total fatty infiltration and oedema scores were significantly more severe in IMNM than that in multiple acyl-CoA dehydrogenase deficiency (MADD, the most common subtype of lipid storage myopathy), and this may help to differentiate the two entities (55).

Diffusion-weighted imaging (DWI) is a type of MRI that focuses on measuring the random motion of water molecules within tissues. DWI is routinely employed in cerebral ischaemia and tumour characterisation, where cellular swelling and highly cellular tissues exhibit lower diffusion coefficients. This type of MRI is under investigation by multiple groups to characterise the inflamed muscle in IIMs. To this end, maps of the apparent diffusion coefficient (ADC) may be used to quantify the random motion of water molecules within muscles. Meyer *et al*. showed that ADC positively correlated with IIMs electromyography findings, reflecting muscle fibres loss (56), and CPK and negatively with CRP. Moreover, differences in ADC parameters were also observed between Jo1-positive and Jo1-negative patients (57). Another extension of DWI is diffusion tensor imaging (DTI), commonly used to study white matter of the brain. In a DTI analysis of the proximal lower limbs of DM patients and controls at rest and after exercise, some authors showed that oedema (indicating inflammation) and infiltration (indicated by elevated fat fraction) had a heterogeneous distribution among muscle groups and across patients. Dynamic diffusion measurements showed significantly higher radial and mean diffusion exercise response in IIMs patients compared to controls. Thus static and dynamic diffusion imaging proved to be effective at differentiating IIMs patients from controls (58).

One disadvantage of MRI is that it is time-consuming especially when multiple parameters need to be acquired. Wang *et al*. addressed this issue performing muscle DTI minimises acquisition time through simultaneous multi-slice accelerated echo planar imaging (SMS-EPI-DTI) in patients with IIMs. SMS-EPI-DTI allowed imaging of both thighs within approximately 5 minutes and the analysed parameters were different between IIMs and controls, showing that this modality is clinically feasible (59).

Another imaging modality that has been investigated for its utility in myositis assessment is ultrasonography (US). Sousa Neves *et al*. addressed the applicability of US as a monitoring tool in IIMs. All patients in clinical remission showed a preserved muscle pattern on US assessment. In patients with active myositis, variable degrees of altered ecostructure, muscle atrophy and power Doppler signal were found on US. A single specific US pattern of muscle involvement was not observed in this study (60). Albayda *et al*. focused on the ultrasonographic pattern of muscle involvement in patients with IBM. Patients with IBM had a markedly increased muscle echointensity when compared with controls for all muscles studied. Asymmetry between sides and a heterogeneously increased echointensity was also observed in patients with IBM (61).

Corticosteroids are still the mainstay of the therapy of IIMs, but their prolonged use is associated with significant side effects and among these, steroid myopathy is of particular importance in patients with IIMs (62). Nawata *et al*. studied changes in muscle mass after steroid therapy via cross-sectional computed tomography (CT) in patients with myositis. As controls were used patients with connective tissue diseases other than IIMs that were also treated with equivalent doses of steroids. In both groups, the cross-sectional areas of skeletal muscles decreased; however, in the IIMs group muscular strength and serum muscle enzyme levels improved. These data suggest that, although corticosteroid treatment improved the qual-

ity of muscle and helped regain muscle strength, steroids have a negative effect on muscle volume (63).

**Extramuscular involvement**

In addition to the muscular involvement, IIMs may frequently potentially affect different organs and apparatus (64).

Supporting the importance of extramuscular manifestations in IIMs, the EuroMyositis registry published an analysis of 3067 IIM cases from 11 countries and found that ILD was present in 30% of patients with IIMs, mostly with antisynthetase syndrome. Dysphagia was reported in 39% of patients and cardiac involvement in 9%. Smoking was associated with all the above-mentioned complications. Malignancy was present in 13% of patients, and, as expected, was mostly associated with DM. Malignancy was most commonly diagnosed within 1 month of the diagnosis of IIMs, and the most frequent was breast cancer. Higher disease activity, in terms of muscular strength and limitations of daily functioning, was observed in patients with IBM (65)

Moreover, DM is not always promptly diagnosed thus delaying appropriate therapeutic approach. According to a retrospective study of the 232 patients with confirmed DM, less than half where diagnosed as DM at the onset of the disease and most of the undiagnosed cases were classified as lupus or undifferentiated connective disease. The median delay between original presentation and diagnosis was 15,5 months, and it was even higher in amyopathic forms (66). This data makes clear how important might be to be aware of possible extramuscular manifestation of IIM in order to promptly diagnose this condition.

Unfortunately, an acceptable control of extramuscular manifestation is not always achieved and is associated with a significant negative impact on quality of life (67). According to a prospective study, 38% of the patients with clinically significant skin inflammation achieved clinical skin remission during a 3-year follow-up, despite aggressive therapy. The association with anti-MDA5 autoantibodies was considered a negative prognostic factor for the cutaneous clinical remission, while increasing age or associated malignancy and treatment with mycophenolate mofetil were associated with better outcomes of the skin disease (68).

Contrarily, a retrospective study analysed a heterogeneous cohort of patients with mild to severe skin disease and showed a significant improvement of CDASI (Cutaneous Dermatomyositis Disease Area and Severity Index) in the majority of patients after 2 years of treatment. Interestingly, patients with moderate-severe disease at the baseline had a better outcome compared to patients with mild skin manifestations who mostly tended to remain stable (69). Anti-MDA5 antibody is strongly associated with CADM, and, according to a recent meta-analysis, also with Gottron's sign or papules, mechanic's hand, V rash, skin ulcers, panniculitis, alopecia, arthritis/arthralgia and pneumomediastinum (70).

Cardiac involvement in IIM includes conduction defects, congestive cardiac failure, pericarditis and valvular heart disease. It occurs in up to 75% of patients with IIM, is often subclinical and represents a main cause of morbidity and mortality in these subjects (71). Lilleker *et al*. (72) analysed the potential role of cardiac troponin T (cTnT) and cardiac troponin I (cTnI) in detecting cardiac involvement (determined as per the cardiac domain of MDAAT) in 123 patients and found that it was associated with higher cTnI levels, independently from the overall disease activity. An abnormal cTnI had the highest specificity and positive predictive value for cardiac involvement (95% and 62%, respectively). In those with a normal CK but elevated cTnT or cTnI, an association with increased disease activity scores was observed, confirming the idea that using CK in isolation to assess IIM disease activity can be misleading. Furthermore, they found that serum cTnT correlated with the physician and patient-assessed global visual analogue scales and Health Assessment Questionnaires (HAQ) more strongly than CK or cTnI levels.

Interstitial lung disease (ILD) is one of the most common extra-muscular manifestations of PM/DM, especially in ARS and anti-MDA5 positive forms (73, 74), and is usually associated with poor prognosis (75).

Among anti-ARS autoantibodies, anti PL-12 is the most commonly associated with ILD (28), while the worst prognosis belongs to anti-MDA5 forms, who frequently develop rapidly progressive ILD (RP-ILD) and respond poorly to treatment, showing a five-year survival rates significantly lower (50.2%) than ARS positive patients (97.7%) and Ab negative groups (91.4%) (27, 76–78). Interestingly, lung tip consolidations, at high-resolution computed tomography, were seen exclusively in this group (27). Furthermore, recent studies identified different poor prognostic factors in IIM patient associated with ILD, like clinically meaningful progression of ILD after 3 months, severe infections, delay in diagnosis, heliotrope erythema, Raynaud's phenomenon, anti-ARS Ab positivity and low pulmonary vital capacity at disease onset (79), while high levels of serum Krebs von den Lungen-6 (KL-6) were found to predict ILD relapse in patients with ARS positive DM before treatment initiation and at 6, 12, 18 and 24 month after treatment initiation (80).

**Infections, cancer and other comorbidities**

In a large Swedish cohort of patients with IIMs observed for 10 years, mortality at 1 year after the diagnosis was estimated to be 9% (*vs*. 1% per year mortality of the general population). The main causes of death were malignancies, cardiovascular and respiratory tract diseases. Interestingly, the absolute risks of dying for diseases of the respiratory system and neoplasms were increased in the first year from diagnosis and decreased with disease duration, in contrast to the general population where they kept increasing with age (81). The high mortality burden in patients with IIMs was confirmed also in a Chinese cohort of hospitalised patients with IIMs, with respiratory complications as the main cause, mainly ILD or infections (82). Similarly, in an Iranian cohort of IIMs patients, neoplasia was the most common cause of death, and the presence of pulmonary involvement negatively affected survival. The pres-

ence of neoplasia and dysphagia were associated with poor response to treatment during follow-up (83). Moreover, patients with IIMs are also at increased risk of venous thromboembolism and the risk is particularly high if the patients had neoplasia and are older than 70, posing the problem of considering anticoagulation in a selected group of patients (84). The first year after diagnosis of IIMs is also burdened by the risk of developing opportunist infections (mostly affecting skin and lung). High dose of steroids and escalating immunosuppressive therapy appeared to be the main risk factors thus suggesting that attention should be paid also on treatment related side effects (85). Prior *et al*. retrospectively investigated the frequency and types of infections in 631 patients neuromuscular diseases, 149 with DM. Substantially, the authors showed a similar infection rate in different conditions analysed (19% each) and a correlationship with immunosuppression (eg use of plasmapheresis, mycophenolate mofetil, and corticosteroids) (86).

Regarding the well-known association between cancers and DM, recent studies reported that it seems to be more frequent within the first year after the onset of the DM symptoms. Other risk factors for malignancy are dysphagia and older age (>50) at the time of DM diagnosis. On the other hand, the protective role of ILD for underline malignancy was not confirmed and no differences in incidence of malignancy between classic DM and CADM were found. These data confirm the importance of malignancy screening of dermatomyositis, especially within the first 12 month of the DM onset (87, 88).

The relationship between IIMs and neoplasms has been further analysed since the advent of immune checkpoint inhibitors (ICIs) as anti-tumour drugs. A European study on 10 subjects found that neoplastic patients who developed IIMs after ICIs treatment were negative for MSA/MAA, and presented mostly with myalgia, limb-grindle and axial weakness, diplopia, elevated serum CK, no cutaneous manifestations and a unique histopathologic pattern suggesting a different pathophysiology than primary or paraneoplastic IIMs (89).

Reduced bone mineral density is generally considered a iatrogenic comorbidity in IIM, mainly due to prolonged corticosteroid use. In a recent cross-sectional study by *Gupta et al*., however, asymptomatic vertebral fractures occurred in 46% of patients affected by IIMs or CTD-associated myositis (35 DM, 26 PM, 31 CTD-myositis). The cohort was composed by 82 females with a median age of 35.5 years and a median disease duration of 3 years; interestingly, only 17 patients were post-menopausal women and no correlation was found between number of fractures and gender, age, disease duration, years of corticosteroid intake, body mass index, post-menopause years and myositis damage index. This led the author to suggest the possible existence of additional risk factors for fractures, such as disability (90).

**Treatment**

Although glucocorticoids (GC) are the first-line treatment for myositis, in many cases it is necessary to add an immunosuppressive drug, mainly in case of poor response, relapse after GC tapering or steroid-resistant disease (91).

Knowing that one of the main side effects of steroid therapy is myopathy, it is currently unclear to what extent GC therapy may affects muscle volume and strength. At this regard, a Japanese study found that GC therapy determined an improvement in muscular strength and serum muscle enzyme levels, but a parallel decrease in muscle mass (measured by CT scan), suggesting that the clinical improvement in patients treated with GC in not due to a muscle mass recovery (63).

For the cutaneous involvement of DM patients, one of the most prescribed drug is hydroxychloroquine (HCQ). In a retrospective study, the risk of these side effects seemed to be reduced by the addition of quinacrine. On the contrary the use of chloroquine and association between chloroquine and quinacrine were at higher risk of retinopathy (92).

Conventional immunosuppressive therapy (GC, azathioprine, methotrexate) is associated with a reduction of IL-18 levels in muscle tissue, especially in patients responders to the therapy, indicating a possible pathogenic role of IL-18 in muscle damage (93).

Cyclophosphamide (CYC) has been commonly recognised as an effective drug in the treatment of severe myositis and a recent observational study described an improvement in disease activity scores, MMT8 scores, muscle enzymes and functional assessment scores in patients with refractory disease treated for at least 1 month with oral CYC. In addition, daily glucocorticoid usage steadily decreased, and improvements in pulmonary function tests and cardiac function were observed, despite CYC cardiotoxicity, suggesting that controlling the underlying systemic myositis might have beneficial effects on cardiac function (94).

Among biological DMARDS one of the most used drugs for refractory IIM is rituximab (RTX). Recently, an Italian study evaluated the efficacy and safety of RTX in a monocentric cohort of twenty-six patients with IIM and active refractory disease were treated with RTX (2 infusions of 1000 mg, 2-week apart); after 6 months RTX determined a reduction of CPK, an improved MMT8 and a reduction of the extramuscular activity of the disease, particularly skin rash, arthritis and ILD. Autoantibody positivity (anti-ARS, anti-SRP and antiRo/SSA), and a disease duration <36 months were associated with a better response. Lastly, RTX treatment was also associated with a reduction of the mean daily dose of steroids needed (95). RTX may be useful also in RP-ILD complicating anti-MDA5 positive DM as showed by a study on 4 patients who displayed improvements in respiratory symptoms, PFTs and a drop in the average daily prednisolone (96).

There are few case reports where the off-label use of abatacept in myositis has shown beneficial results. The study of Tjärnlund *et al*. showed that DM and PM patients treated with i.v. abatacept presented a lower disease activity, and increased expression of Foxp3 in repeated muscle biopsies in about 50% of the cases, suggesting a positive effects of treatment on muscle tissue (97).

Tofacitinib, a Janus kinase inhibitor (JAK-i) recently approved for rheuma-

toid arthritis, has been recently tested in anti-MDA5 positive DM with RP-ILD who failed to respond to a triple therapy with GC, *i.v.* CYC and cyclosporine. The addition of tofacitinib helped in controlling disease activity, although complicated by adverse events, including viral, fungal and bacterial infections (98). Another JAK-i, ruxolitinib, showed beneficial effects on facial skin rashes, muscle weakness and CPK levels, and indued a reduction in serum IFN levels and interferon-inducible genes scores, that have an important pathogenic effects in DM (99).

In addition to pharmacological treatment, physical therapies could help in maintaining muscle strength and prevent disability. A small study showed that a 12 weeks of low-load blood-flow restricted resistance (BFR) training did not improve SF-36 or objective physical function, but exerted a preventive (retaining) effect on the disease-related decline in legs' muscle strength, which may aid the long-term preservation of physical function and postpone the need for healthcare assistance (100). A similar study was conducted in 8 patients with IMNM showing that supervised exercise training (aerobic and strength exercises twice a week), increased patients' aerobic capacity, muscle strength and function (101).

## Conclusions

IIMs are rare systemic diseases associated with comorbidity and mortality. Despite having available different effective therapeutic strategies, the diseases are severe with a very high absolute risk of mortality, mainly for malignancies, respiratory and cardiovascular failure, is still high, especially within 1 year of diagnosis. Is therefore crucial that the clinician is aware of the complexity of the disease and in able to manage the patient from the diagnosis of the disease to the choice of the most appropriate therapy and patients should be subjected to a close follow up, especially in the first periods after the diagnosis. Great steps forward our knowledge of the pathogenetic mechanisms of IIMs have been made in the last year and this is may enable widening the therapeutic horizons. In particular, new researches have been made on the pathogenetic role of some of the MSA and on their correlation with some features of the disease, but additional researches are required to expand the link about autoantibodies, clinical manifestations and potential response to the treatments. New imaging techniques, such as ultrasound and diffusion weighted imaging in MRI, appear to be promising, the lack of studies with large number of patients are required in order to propose these techniques for the routinely clinical practice. Alongside traditional therapies, biological drugs, commonly used in arthritis and other connective tissue diseases, are increasingly being used in IIMs with comforting results.

## Key messages

- Different genetic and environmental backgrounds may influences IIM subtypes and autoantibody profile of patients
- Different cytokines and inflammatory mediators could become in short time possible markers of IIMs. They could support a further IIM stratification, in terms of disease manifestation profiling and prognosis. The better definition of these molecules could be also the basis for the identification of new therapeutic targets
- The number of studies showing a possible role of miRNAs and netosis in IIM occurrence is steadily increasing but data for now are not enough to suggest in short time a possible influence in the IIM daily clinical practice
- Myositis autoantibody profile appears to be for now the most useful tool for IIM patients' stratification, able to suggest a different assessment and follow-up according to underlying specificities detected
- Despite the recent classification advances, an additional effort is necessary for the definition of different disease subsets, in particular by considering that muscles represent just one target of IIMs and that lung, joint and skin involvement are not rarely affected in these patients. This need is particularly evident if we consider the large number of new possible therapies available for IIMs

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