Review

Idiopathic inflammatory myopathies: one year in review 2023

E. Conticini[1], E. Dourado[2], F. Bottazzi[3], C. Cardelli[4,5], L. Bruno[6], J. Schmidt[7], L. Carli[4], L. Cavagna[3], S. Barsotti[8]

[1]Department of Medicine, Surgery and Neurosciences, Rheumatology Unit, University of Siena, Italy;
[2]Rheumatology Department, Unidade Local de Saúde da Região de Aveiro; Aveiro Rheumatology Research Center, Egas Moniz Health Alliance; and Rheumatology Research Unit, Instituto de Medicina Molecular, Faculdade de Medicina, Universidade de Lisboa, Centro Académico de Medicina de Lisboa, Portugal;
[3]Department of Internal Medicine and Therapeutics, Università di Pavia, and Division of Rheumatology, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy;
[4]Rheumatology Unit, University of Pisa, Italy;
[5]Department of Medical Biotechnologies, University of Siena, Italy;
[6]Rheumatology Unit, Department of Medicine and Surgery, University of Perugia, Italy;
[7]Department of Neurology and Pain Treatment, Immanuel Klinik Rüdersdorf, University Hospital of the Brandenburg Medical School Theodor Fontane, Rüdersdorf bei Berlin, and Department of Neurology, Neuromuscular Centre, University Medical Centre Göttingen, Germany;
[8]Rheumatology Outpatient Clinic and Internal Medicine, Livorno Hospital, Italy.

Edoardo Conticini, MD
Eduardo Dourado, MD
Francesca Bottazzi, MD
Chiara Cardelli, MD
Lorenza Bruno, MD
Jens Schmidt, MD, FEAN, FAAN
Linda Carli, MD
Lorenzo Cavagna, MD
Simone Barsotti, MD

Please address correspondence to:
Simone Barsotti
Reumatologia e Medicina Interna,
Ospedali Riuniti di Livorno,
Viale Alfieri 34, 57124 Livorno, Italy.
E-mail: simone.barsotti.pisa@gmail.com

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ABSTRACT

Idiopathic inflammatory myopathies are a group of rare, autoimmune, diseases typically involving striate muscle and also variously affecting several other systems or organs, such as joints, skin, lungs, heart and gastrointestinal tract. IIM are mainly characterised by subacute onset and chronic course and are burdened by significant morbidity and mortality. Despite the rarity of these conditions, several efforts have been undertaken in the last years to better understand their pathogenesis, as well as to achieve a more precise classification and to define the optimal therapeutic approach. The aim of this review is to provide an up-to-date digest of the most relevant studies published on this topic over the last year.

Introduction

Idiopathic inflammatory myopathies (IIM) make a heterogeneous group of autoimmune, rare diseases affecting several organs and systems. Striate muscle is the most commonly involved organ, typically leading to proximal weakness and fatigue, but also joints, skin, lungs, heart and gastrointestinal tract can be affected, with a various degree of severity. IIM usually have a chronic course and are associated to a relevant morbidity, as well as to a higher risk of malignancy and to an increased mortality (1, 2).

According to the most recent and accepted classifications, IIM are furtherly subdivided into dermatomyositis (DM), juvenile dermatomyositis (JDM), clinically amyopathic dermatomyositis (CADM), polymyositis (PM), inclusion body myositis (IBM), immune-mediated necrotising myopathy (IMNM) and anti-synthetase syndrome (ASS). Each condition is characterised by peculiar clinical features and differs from the others for presentation, outcome and response to treatment.

In light of the increasing number of studies carried out in the last years, aim of this review was to provide the reader an up-to-date overview of the most recent papers in the field of IIM. Following a well-established format, we conducted a Medline search of English-language articles published in PubMed database from July, 1st, 2022 to, June, 30th, 2023. 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 study of the pathogenetic mechanisms of IIM represents an intriguing, yet poorly understood, aspect of these conditions.

In particular, the interplay between genetic predisposition (namely HLA-DRB1*03:01 allele in anti-Jo-1 positive ASS) and environmental factors (such as viruses or statins in the case of IMNM) seem to play a crucial role, as well the activation of both innate and adaptive immune systems and non-immune mechanisms, including autophagy, hypoxia and endoplasmic reticulum stress.

Some studies have been, therefore, carried out in order to assess genetic factors associated with the risk of suffering from IIM and the development of certain clinical features. A wide Swedish study has highlighted that first-degree relatives of patients with IIM first carry a higher odd of having any relative affected by other autoimmune, rheumatic and non-rheumatic, diseases. These findings suggest that IIM may share genetic susceptibility with several other autoimmune disorders, such as thyroiditis and coeliac disease

(3). Moreover, an association between male relatives of patients suffering from DM and liver and haematological malignancies has been described (4).

Many studies have been conducted on identifying specific cytokines whose over-expression may be associated with development, prognosis and clinical manifestations of IIM and most of them focused on the IFN pathway. In particular, an upregulation of IFN-I signature has been observed not only in IIM patients when compared to controls, but also in anti-MDA5 positive DM rather than in patients displaying other myositis specific autoantibody (MSA) positivity (5-7). IFN-I signature appears to be a valuable tool to predict mortality and monitor disease activity in these patients. Moreover, IFN-I score seems to positively correlate with serum IFN-α and ferritin concentration and disease severity in anti-MDA5 DM, negatively correlating with survival rate and therefore making it a suitable prognostic biomarker (6); in this subset of patients, serum levels of IFNγ-induced protein 10 (IP-10) are higher than in controls and their levels decrease upon treatment, strictly correlating with IFN-α2 (7).

An hyperexpression of IFN pathway, through the upregulation of cGAS-STING, has been assessed in muscle biopsies from IMNM and DM patients, in which cGAS-STING pathway may be involved in the development of necrosis and muscular atrophy both in IMNM and DM (8). In the latter, the mechanisms behind the occurrence of typical perivascular atrophy remain quite unclear but it may be mediated by the upregulation of IFN and NF-κB (9).

Immune system has a pivotal role in the pathogenesis of IIM, but the exact mechanisms leading to the activation of T and B cells remains partly obscure. RNA-sequencing analysis has evidenced the key role of iron in the glucose metabolism and differentiation of T helper cells (10). Among T helper cells subsets, their proportion may vary according to disease features: in particular, Th1 and Th2 decrease and increase, respectively, in case of interstitial lung disease (ILD), particularly in anti-MDA5 DM and in non-specific interstitial pneumonia (NSIP) pattern (11, 12). At the same time, in this subset of disease, $CD8^+$ cells appear less expressed; nevertheless, their frequency, as well as that of $CD4^+$ cytotoxic cells, positively correlate with ferritin levels and disease severity in anti-MDA5 DM with rapidly progressive (RP) ILD (12). However, several pathological mechanisms are linked to the onset of RP-ILD in anti-MDA5 DM: in this regard, low albumin and sCD40L levels, as well as an increase of D-dimer are associated with higher mortality and poorer outcome (13).

In IIM, B cells are crucial in the pathogenesis and clinical expression of the disease (14). Humoral response seems to play a role also in IBM, in which plasma cells display unique features, different from those seen in DM and PM (15). Specifically focusing on patients positive for any MSA, a reduction of memory B cells was assessed in active patients, counterbalanced by an increase of plasma cells, particularly in anti-MDA5 DM (14). Conversely, in ASS patients, regardless from MSA specificity, a tissue-specific subpopulation of $CD138^+$ plasma cells and $CXCL12^+/CXCL13^+CD20^+$ B cells has been identified. Such a prominent B-cells and plasma-cells activation is associated with activation of mesenchymal fibroblasts and macrophages and may explain the self-maintenance of inflammatory process in ASS (16).

Adaptive response may also vary according to the occurrence of concomitant viral infections: in this regard, a Chinese study aimed at comparing DM patients affected by EBV and/or CMV with DM without detectable viremia and healthy controls. The infection group displayed a significant decrease in levels of B, T, NK and Th17 cells, while the administration of IL-2 led to a re-increase of both Th17 and Treg; such findings make IL-2 a potential suitable treatment for restoring immunodeficiency in DM patients with concomitant infections (17). The pivotal role of Th17 and Treg cells has been also investigated in a retrospective Italian study aiming at comparing sarcoidosis with rheumatic autoimmune diseases, such as IIM: the latter, distinguished by sarcoidosis and ANCA-associated vasculitis, through cluster analysis, were characterised by a significantly reduction of both Th17 and Treg and by a lower percentage of immature B-cells (18).

Although typically overlooked in IIM, innate immune system seems to carry an important role in their pathogenesis. In particular, macrophages, NLRP3, caspase-1 and IL-1β are hyper-expressed in muscle biopsies from PM patients; consequently, and more importantly, the inhibition of NLRP3 through MCC950 or siRNA leads to an overall attenuation of muscle inflammation, as well as of serum myonecrosis biomarkers (19). Similar evidence has been found for IBM, in which the evidence of the upregulation of the IL-1 axis could potentially pave the way for novel treatments (20). On the contrary, another study from a Mexican cohort seems to suggest the expression of myeloid-derived suppressor cells (MDSCs) and programmed cell death ligand 1 (PD-L1) is strictly correlated with disease activity and damage accrual, as well as with pulmonary involvement and the onset of opportunistic infections (21).

Finally, it is well known that complement-mediated microangiopathy has a paramount role in the pathogenesis of IIM, through the deposition of C5b-9 membrane attack complex in muscle and skin and the positive feedback loop with IFN system. In this regard, two studies conducted in two different, wide, international cohorts, have investigated the role of serum complement factors in IIM: both studies have displayed that C4A gene copy number appears downregulated not only in systemic lupus erythematosus and primary Sjögren's syndrome but also in IIM (22), particularly in DM (23) rather than in PM, IBM and JDM; low C4 serum levels also correlate with the presence of anti-SSA/SSB (22), anti-Jo1 and anti-PM/Scl antibodies (23) rather than with specific clinical features.

Scanty evidence is conversely available about the role of environmental factors: in this regard, a Chinese study employing 16S rRNA gene sequencing, enzyme-linked immunosorbent

assay (ELISA) and metabolomics evidenced the strict correlation between microbiota dysbiosis and the increase of inflammatory cytokines in IIM (24). A Chinese group identified by RNA sequencing 193 IMNM-related differentially expressed genes (DEGs) aberrantly upregulated in the IMNM population compared to the control group. Among these, LTK, MYBPH, and MYL4 were further confirmed by quantitative real-time polymerase chain reaction (qRT-PCR) as potential key molecules for IMNM, playing a role in the autophagy-lysosome pathway and muscle inflammation (25). In this condition, a paramount role is also carried out by mitochondria, whose dysfunction seems associated with muscle fibres damage in patients displaying anti-HMGCR positivity (26). Surprisingly, although muscle specimens of IMNM and DM display a reduced cross-sectional area, in both these conditions higher levels of serum irisin, a protein physiologically involved in muscle metabolism, have been assessed, particularly when compared with healthy controls. Such finding was counterbalanced by a lower expression of FNDC5, precursor of irisin, and elevated mRNA levels of ADAM10, which activates cleaving FNDC5 and whose dysregulation could be potentially involved in the pathogenesis of IMNM and DM (27).

On the contrary, in IBM, metabolomic and transcriptomic analyses focused on specific metabolite changes, such as the pathways of histamine and chondroitin sulfate biosynthesis, which results upregulated and infiltrate muscle tissues, while carnitine and creatine metabolism pathways appear downregulated (28).

An impaired regenerative potential in IBM is well known, but the cause has remained elusive. A recent paper identified the senescence of non-myogenic resident cells in the muscle, fibro-adipogenic progenitors. The cells displayed an enhanced inflammatory milieu and various classical pathways of aging. These mechanisms may help to find an answer on how a presumed pre-degenerative condition in IBM could contribute to the disease cause (29).

Take-home messages

- IFN pathway has a crucial role in the pathogenesis of IIM, particularly in MDA5 DM (5, 6).
- A decrease of Th1, counterbalanced by an increase in Th2, has been assessed in IIM with concomitant lung involvement (11, 12).
- Aging in skeletal muscle can be a key element of the interplay between inflammation and degeneration in IBM (29).

General aspects and muscular involvement

Classification criteria

Classification of IIM patients is surely important, and to define sensitivity and specificity of existing criteria is important, to define which improvements are necessary for the most adequate classification of patients. The 2017 European Alliance of Associations for Rheumatology (EULAR)/American College of Rheumatology (ACR) IIM classification criteria had a sensitivity of 0.86 and a specificity of 0.85 for DM and a sensitivity of 0.73 and a specificity of 0.87 for PM compared to expert physician's diagnosis in a cohort of patients from Latin America (30). The EULAR/ACR criteria identified more patients with probable or definite IIM than the Bohan & Peter criteria, however the sensitivity for PM was slightly lower than that of the Bohan & Peter criteria (30). These data suggest that all efforts should be undertaken by IIM experts to make a reliable diagnosis and to use the best available criteria.

Confirming previous reports, a recent article identified, in a South Indian cohort, a weak agreement between physician's opinion and EULAR/ACR criteria in the subclassification of patients with DM (31). The authors suggested that an ethnic/geographic variation in the prevalence of classic DM cutaneous features included in the EULAR/ACR criteria (heliotrope rash and Gottron's papules and sign) could justify that discrepancy (32) is also supported by data obtained in the derivation cohort from the EULAR/ACR criteria (31). Although classic DM skin rashes were among the most common in Asian and Caucasian patients, almost 10% of the DM patients in the derivation cohort had none of the three classic DM skin rashes (31). Adding myositis-specific antibodies (MSA) and perifascicular atrophy on muscle biopsy to the EULAR/ACR criteria improved the agreement between the physician and EULAR/ACR criteria (32).

Disease activity

The EULAR/ACR Myositis Response Criteria (MRC) were developed as a composite measure using absolute percentage change in six core set measures. A recent study was performed to validate the MRC using data from adult IIM patients in rituximab, etanercept, and abatacept trials (33). Of patients with at least minimal improvement, almost all had improvement in muscle-related measures, and a vast majority had improvement in patient-reported outcomes measures (PROMs) (33). Patients with minimal improvement had worsened in a median of one core set measure, and most patients with moderate-major improvement had no worsening core set measures. Finally, physician assessment of change generally agreed with MRC improvement categories (33).

Patient-reported global disease activity (PGA) is included in the MRC measures; however, disagreements between physician and patient perception of disease activity may negatively impact shared decision-making. A study examining the discordance between PGA and physician-reported global disease activity (PhGA) in IIM, found that the two measures were discordant in almost a third of the assessments (34). Physical function and fatigue measures mainly contributed to PGA, while PhGA was primarily driven by muscle disease activity (34). A recent study showed the test-to-retest reliability and construct validity of the PROM Information System (PROMIS) Pain Interference (6av1.0), Fatigue (7av1.0), and Physical Function (8bv2.0) instruments using a large international cohort of IIM patients (35). The internal consistency of these instruments was excellent, and a ceiling effect was noted only for the Pain Interference instrument (35).

Myostatin is a negative regulator of muscle mass and has been proposed as

a disease activity marker. IIM patients had lower circulating myostatin protein levels and gene expression than healthy controls (36). In particular, active DM and ASS patients had lower myostatin levels than inactive ones, while IMNM patients had persistently low myostatin levels (36).

Histology

Data on muscular ultrastructure was scarce in IIM patients (37) and mainly limited to IBM. A recent study analysed muscular biopsy with scanning electron microscopy (SEM), showing more evident ultrastructural changes (porosities, sarcolemma irregularities, perforations, and even loss of muscle morphology) in the muscle fibres of patients with lower muscle strength, but no association between ultrastructural findings and the presence of autoantibodies, nor myositis phenotype (38). The muscle fibres were cylindrical, with a diameter of approximately 50 μm, parallel to each other, surrounded by collagen fibres forming the endomysium. The most common finding in IIM patients was myofibre surface irregularities (90%), followed by altered muscle morphology (60%), non-linear muscle fibres (60%), cellular infiltrates (50%), and myofibre surface porosities (30%) (38).

Another study included patients with IIM and with muscular involvement in other connective tissue diseases (CTDs) with muscular weakness and prominent B cells aggregates on muscle pathology, thus showing B cells may represent a morphological biomarker against a diagnosis of sporadic IBM (39).

Muscular imaging

Muscular MRI is an important tool for the study of muscular aspects in IIM. In a retrospective study using MRI in IMNM patients, the percentage of STIR-positive muscles was higher in untreated patients and in those who performed the exam earlier, particularly in pelvic muscles (40). About a quarter of the STIR-positive muscles showed fat replacement progression at a second MRI (40). These results suggest that muscle MRI is a sensitive biomarker for monitoring disease activity in IMNM, especially when performed early in the disease course, and could represent a supportive outcome measure and early prognostic index (40).

A prospective observational IBM cohort study with quantitative MRI assessments at baseline and one year later, suggesting as reduction of thigh muscle volume ed increase of inter/intramuscular adipose tissue correlate with decrease function of the quadriceps (41). Muscular MRI may also have an important role in the differential diagnosis between IIM and muscular dystrophies (MD). In a monocentric large cohort of patients with IIM and MD, the difference in patterns of distribution of muscular oedema, atrophy and intramuscular adipose changes in pelvis and lower limbs were evaluated. Oedema was more prevalent in IIM compared with MD while adipose infiltration/substitution and muscular atrophy were more prevalent in MD. These results highlighted the different distribution of muscular involvement between IIM and MD and suggests that muscular MRI may be useful in the differential diagnosis of the two groups of disease (42).

A recent report suggests that an automatic deep learning (DL) method based on a pre-trained neural network may be helpful in differentiating IIM patients from controls with high sensitivity and specificity (43). These automatic tolls, may also be helpful for differential diagnosis, discriminating between type 1 facioscapulohumeral dystrophy (FSHD1) and IIM with similar performances to those achieved by two experienced radiologists (44).

B-mode ultrasound and shear wave elastography (SWE) may be helpful in the diagnosis of IIM. In a prospective cross-sectional study, increased muscle echogenicity correlated with fatty infiltration/atrophy on MRI (45). Ultrasound or SWE measures of fascial thickness and muscle bulk showed poor discrimination characteristics (45). Power Doppler measures of vascularity correlated poorly with the presence of oedema on MRI or inflammation or fatty infiltration on biopsy (45).

Take-home messages

- Adding MSA and histologic findings seems to increase the diagnostic accuracy of ACR/EULAR criteria (31, 32).
- Myostatin could be considered a promising biomarker, as low serum levels can be found in active IIM (36).
- MRI has confirmed its usefulness in distinguishing IIM from non-inflammatory myopathies (42).

Extramuscular manifestations

Extramuscular manifestations are common in patients with IIM and may affect both skin and internal organs, such as heart, lungs and oesophagus (Table I).

Pulmonary involvement

Pulmonary involvement, and in particular ILD, has been extensively studied in myositis, and it is associated with a worse outcome. In clinical practice lung involvement is mainly assessed with high-resolution chest CT (HRCT) and pulmonary function tests (PFTs).

Several studies have dealt with new methods to deepen the characteristics of lung involvement and their clinical implications. The role of the automatic quantitative scoring on lung HRCT in evaluating ILD has been confirmed by Roncella *et al*. (46). By applying the CALIPER software in a cohort of patients with different subsets of IIM, the authors found an inverse correlation between the quantitative score obtained with the CALIPER software, and the Warrick score, and the DLCO alterations. These alterations proved to be greater in patients with ASSD than in patients without myositis-specific autoantibodies.

Although ILD is a common manifestation of myositis, RP-ILD occurs with high frequency in MDA5 patients. RP-ILD is the most severe lung involvement as it is burdened by an acute onset and rapid evolution towards respiratory failure with a high mortality rate. Chen *et al*. (47) described radiological and pathological features of ILD in MDA5 patients: the most common HRCT radiographic patterns were organizing pneumonia (OP), non-specific interstitial pneumonia (NSIP) and NSIP+OP (with the poorest prognosis together with diffuse alveolar damage), while the predominant histological patterns were NSIP and NSIP+OP.

Early identification of RP-ILD may be crucial for the patient's prognosis. In a retrospective study by Zhang *et al*. (48)

Table I. Summary of the extra muscular involvement reported in the reviewed articles.

Lung involvement	There is an inverse correlation between the degree of imaging alterations quantified by the automated software CALIPER quantitative scores and the score of Warrick, and the DLCO alterations (46). FDG PET/CT and HRCT is a useful method to stratify the risk of developing RP-ILD (48). In MDA5 patients the most common HRCT radiographic patterns of ILD are OP, NSIP and NSIP+OP (47). Spontaneous pneumomediastinum is associated with higher mortality rate and occurs more frequently in MDA5 patients (49).
Heart involvement	A lower manual muscle testing score, dysphagia, and anti-SRP can be predictors of cardiac involvement (51). Cardiac involvement can be found in IMNM patients: arrhythmia, myocardial ischemia, acute coronary syndrome, left ventricular hypertrophy, pericardial effusion, decreased left ventricular ejection fraction and decrease in left ventricular diastolic function, myocardial oedema (52). In MDA5 patients' cardiac involvement may be an independent prognostic factor for death in addition to RP-ILD (53). CEST creatine mapping detects subclinical myocardial changes and it can be a valuable screening for detect early-stage heart involvement with negative late gadolinium enhancement (54). Myocardial damage progresses subclinically if the course of the disease is characterised by multiple flares (55). IIM patients, especially if anti-Mi2 e anti-PL7 positive, present more frequently a prolonged QTc compared with healthy controls (56). Higher serum levels of YKL-40 can be predictors of myocarditis (57).
Oesophagus	IBM dysphagic patients can be older, have a stronger knee extension, and less fatty infiltration of the limb muscles (58).
Skin	In DM, more frequent are mechanic's hands, Gottron's sign and Gottron's but also poikiloderma, tufted hair, telangiectasias and erythema on the scalp. Gingival cobblestones, gingival telangiectasias, and palatal telangiectasias can be found on the oral cavity (59).
Microcirculation	In DM can be found capillary dilations and tortuosity, cuticular haemorrhage and hyperkeratosis, avascular areas (59). TIF1-γ patients have more enlarged and reduce capillaries (60).
Malignancy	Cancer development occurs in the first three years before or after myositis diagnosis in TIF1-γ, later in MDA5 patients (61). The tumours associated with TIF1-γ are mainly ovarian and breast (62).

the combination of FDG PET/CT and HRCT has been used to stratify the risk of developing a RP-ILD by the development of a risk score based on PET score, HRCT score and MDA5-positivity.

Although ILD is the most frequent lung involvement, also other pulmonary complications may occur in IIM, such as spontaneous pneumothorax or pneumomediastinum. Abe *et al*. (49), comparing MDA5 positive and MDA5 negative patients, noticed that spontaneous pneumomediastinum was associated with higher mortality rate and occurred more frequently in MDA5 patients.

ILD may also occur in other CTDs, but few studies have focused on comparing the characteristics of ILD in IIM and other CTDs. The study of Nurmi *et al*. (50) focused on identifying the characteristics of ILD that are more typically manifested in myositis than in other CTDs. The results showed that IIM-ILD often develops acutely and that in most patients ILD was diagnosed before or simultaneously with myositis, unlike what usually happens in patients with CTD.

Heart

In IIM, cardiac involvement is considered rare, and it is mostly subclinical, however, it can generate severe complications and must therefore always to be sought due to its influence on prognosis. A Portuguese multicentre study by Bandeira (51) analysed the characteristics of IIM patients with cardiac involvement (clinically evident myocarditis, conduction abnormalities, dilated cardiomyopathy, pericarditis, premature coronary artery disease) compared with IIM patients without cardiac involvement. Patients with cardiac involvement had a lower manual muscle testing score, a higher prevalence of dysphagia, and anti-SRP positivity.

Cardiac involvement has not been studied much in IMNM, as this subset of disease is considered to have a prevalent peripheral proximal muscle involvement. Liu *et al*. (52) described cardiac involvement in a IMNM cohort (56.1% with anti-SRP, 21.1% anti-HMGCR and 22.8% seronegative): 52.6% presented with varying degrees of cardiac involvement (arrhythmia, myocardial ischemia, acute coronary syndrome, left ventricular hypertrophy, pericardial effusion, decreased left ventricular ejection fraction and decrease in left ventricular diastolic function, myocardial oedema) without significative difference between patients with different subtypes of IMNM. Cardiac involvement is also possible in MDA5 patients, and it may be an independent prognostic factor for the death of anti-MDA5 patients, in addition to RP-ILD (53).

Traditionally, myocarditis is diagnosed by echocardiography and cardiovascular magnetic resonance. Cardiovascular magnetic resonance chemical exchange saturation transfer (CEST) creatine mapping can detect subclinical myocardial changes and Fan *et al*. (54) found that this method can be a valuable screening for detect early-stage heart involvement with negative late gadolinium enhancement in IIM. Confirmation of the impact of myocardial involvement, even subclinical, in the long term, is evidenced by Peter's study (55). Cardiac function of patients with myositis has been monitored by echocardiography over the course of two years and it has been found that myocardial damage progressed subclinically, if there were multiple disease flares; systolic and diastolic dysfunctions were found in asymptomatic patients.

Electrocardiographic alterations have been poorly characterised in myositis. Korsholm *et al*. (56) identified QTc

interval alterations in a multicentre cohort: IIM patients, especially if anti-Mi2 e anti-PL7 positive, presented more frequently a prolonged QTc (> 450 ms) than healthy controls. Monitoring ECG is therefore helpful, to avoid dangerous ventricular arrhythmias to which prolonged QTc predisposes.

In addition to imaging methods, biomarkers were searched for early detection of cardiac involvement. Although serum YKL-40 is not specific for myocarditis, as it is secreted by local inflammatory cells in inflamed tissues, higher levels of it were found to be associated with and to predict myocarditis in patients with IIM (57).

Dysphagia, skin and vascular alterations

Involvement of the swallowing muscles is a debilitating complication of myositis, capable of worsening quality of life and increasing the risk of aspiration pneumonia. This year's studies focused on the characterisation of dysphagia in IBM. Taira *et al*. (58) noted that dysphagic patients were older, and they had stronger knee extension, and had less fatty infiltration of the limb muscles. The swallowing problems highlighted in IBM (58) were mostly tongue base retraction and residual pharyngeal pooling, as highlighted in video swallow.

It is known that capillaroscopic and cutaneous alterations exist in patients with DM, however, abnormalities at the level of the scalp and oral mucosa have been explored only at a limited extent, also because they are usually less frequent and less visible. Salguiero *et al*. (59) conducted the first study that compare trichoscopic, oral and periungual findings between DM and healthy patients. Obviously, in DM were more frequent mechanic's hands, Gottron's sign and Gottron's papules as well as capillary dilations and tortuosity, cuticular haemorrhage and hyperkeratosis, avascular areas. In DM patients, poikiloderma, tufted hair, telangiectasias and erythema were found on the scalp, while gingival cobblestones, gingival telangiectasias, and palatal telangiectasias on the oral cavity. An observational cohort study compared the nailfold videocapillaroscopy (NVC) findings at baseline and follow-up in IIM patients with different MSAs. The frequency of dilated capillaries at baseline was higher in patients with anti-TIF1γ antibodies compared to those with anti-synthetase antibodies, and reduced capillary density was also more prevalent in anti-TIF1-positive patients compared to those with anti-MDA5 or anti-synthetase antibodies (60). Both dilated capillaries and reduced density improved after disease stabilisation in patients with anti-MDA5 antibodies (60), but not in patients with anti-TIF1γ or anti-synthetase antibodies (59). A significant reduction in haemorrhages was observed in all three groups (60). In a cross-sectional study, the presence of capillary dilation or tortuosity, avascular areas, cuticular haemorrhage, or cuticular hyperkeratosis in periungual folds were associated with a higher Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI) activity score (59). A preliminary study (60), carried out considering a small number of patients, noted a correlation between specific autoantibody positivity and greater capillaroscopic alterations. Particularly in anti-TIF1γ patients were found more enlarged and reduced capillaries.

Malignancies

IIM patients have a higher risk of developing cancer than the general population and many studies have investigated the risk associated with specific autoantibody positivity. Anti-TIF1-γ antibodies are the most frequently associated with malignancies, so scrupulous screening is mandatory.

Izuka *et al*. (61) retrospective cohort study evaluated the long-term risks of malignancy in patients with anti-aminoacyl-tRNA synthetase, anti-MDA5, anti-Mi-2, and anti-TIF1-γ: although the risk compared to the general population was higher in all patients, cancer development occurred in the first three years before or after myositis diagnosis in anti-TIF1-γ, later in anti-MDA5 patients.

These data are also confirmed in the study by Mecoli *et al*. (62), which reveals that the tumours associated with anti-TIF1-γ are mainly ovarian and breast and showed a higher standardised prevalence ratio in anti-Mi-2, anti-SAE, anti-NXP-2, while patients with anti-synthetase, anti-MDA-5, or anti-HMGCR antibodies had the same cancer risk as the general population.

Take-home messages

- Spontaneous pneumomediastinum seems to be associated with higher mortality rate and occurs more frequently in DM with anti-MDA5 antibodies (49).
- Cardiac involvement can be assessed in up to 50% of patients affected by IMNM, particularly in those carrying anti-SRP positivity (51).
- Malignancies more frequently associated with TIF1-γ are breast and ovarian carcinomas (62).

Particular subsets of IIM

Inclusion body myositis

IBM is the most common form of IIM over 50 years of age (63) and represents an important risk factor for aspiration pneumonia, PEG tube placement, falls, and sepsis (64).

Initial misdiagnosis is frequent, since although a biopsy is performed, less than half of the patients had all three pathologic hallmarks (endomysial inflammation, mononuclear cell invasion, and rimmed vacuoles) (65). Black patients had significantly greater weakness in several muscle groups, while female had stronger finger flexors and knee extensors than their male counterparts (65); although the overall response to therapy remains poor in IBM, this heterogeneity might influence the response to treatment.

The typical clinical symptoms of IBM including weakness of hand grip and knee extension are well known. Atypical presentations are less common and often lead to a delayed or wrong diagnosis. Recent evidence supports previous notions that impairment of ventilator muscles (69) as well as camptocormia and dropped head can occur in IBM (70).

The frequency of $CD8^+CD57^+$ T-cell large granular lymphocytes (T-LGLs) was high in 40% of an Australian cohort of IBM patients, although most of these patients showed only a slight expansion of these cells and in rare cases a diagnosis of T-LGL leukaemia was made (66). These changes in the CD8+

T-lymphocyte milieu appear to exacerbate the immune dysregulation and to increase the disease burden in this subgroup of IBM patients, who in the Australian cohort were more likely to require mobility aids, implying greater disease severity.

Immune-mediated necrotising myopathy

IMNM is an entity characterised by severe proximal muscle weakness and prominent necrotic fibres without inflammatory cell infiltration at histology, with an unclear pathogenesis.

Anti-3-hydroxy-3-methylglutaryl CoA reductase (anti-HMGCR) antibodies showed a strong positive predictive value for HMGCR-IMNM in a cohort of Australian patients, who typically present with proximal limb weakness, dysphagia and markedly elevated serum creatine kinase (CK) values (67). Despite multiple immunosuppressive therapies, a significant number of patients of this cohort presented with persistent biochemical myositis. Anti-HMGCR antibodies do not appear to correlate with CK levels at diagnosis and, although their titre tends to decrease with treatment, they remain positive in most patients (67).

Anti-synthetase syndrome

ASS is characterised by the typical clinical triad of myositis, arthritis and ILD, but the clinical picture can be heterogeneous and these phenotypic features are not always expressed as they can also occur separately; in particular, it seems that different autoantibodies positivity is expressed with different initial symptoms (68). Moreover, it appears that the association with anti-Ro52 positivity constitutes a more severe disease phenotype, with not infrequent development of rapidly progressive ILD (RP-ILD) (68).

A Japanese study on muscle biopsies from ASS patients showed necrotising myopathy was the most common myopathological pattern, with prominent myopathy in anti-OJ compared to non-OJ ASA (69). Furthermore, except for IBM, HLA-DR expression was markedly more frequent in ASS than in the other entities (DM, IMNM, possible mimic myositis), with the prevalent expression pattern being the perifascicular localisation (69). Similarly, da Silva *et al*. found the necrotising pattern to be the most frequent in muscle biopsies from patients with anti-Jo1+ ASS (70).

Take-home messages

- In less than 50% of IBM patients, typical findings can be assessed at muscle biopsy (65).
- In IMNM, anti-HMGCR titre do not correlate with CK levels at diagnosis and tends to decrease with treatment (67).
- Necrotising pattern is the most common in biopsies of patients affected by ASS with anti-Jo-1 antibody (69).

Autoantibodies

MSAs are found in most patients with IIM, being present, for instance, in 88% of a large cohort of patients from China (71). Jiang *et al*. investigated the long-term outcomes and prognosis of IIM patients according to MSAs positivity: they found the lowest survival rates among anti-MDA5+ patients and the highest in the anti-SRP+ subgroup, with the development of RP-ILD and malignancy as the main independent risk factors for death in all IIM patients, including the MSA-negative subgroup (72).

Xu *et al*. performed a cluster analysis identifying three different phenotypes in a large cohort of patients with anti-MDA5+ DM, according to mild, moderate or high risk of RP-ILD: patients in the high risk of RP-ILD cluster showed more frequently than the other two groups anti-Ro52 positivity associated with high titres of anti-MDA5 antibodies (73). In addition, they developed a simple algorithm including age >50 years, disease course of <3 months, proximal muscle weakness, arthritis, C-reactive protein (CRP) and CK levels, anti-Ro 52 titre and anti-MDA5 titre, that allowed good accuracy in classifying anti-MDA5+ DM patients, with relevant prognostic value(73). In the same direction, Liu *et al*. identified advanced age, skin ulcer, lymphopenia, anti-Ro52 antibody and higher levels of lactate dehydrogenase (LDH), CRP and ground-glass opacity scores as increasing the risk of early death for anti-MDA5+ DM; notably, in contrast, they found that prophylactic use of the compound sulfamethoxazole was an independent protective factor (74). A Chinese group recently confirmed that anti-Ro52 antibodies are highly prevalent in anti-MDA5+ DM patients; the coexistence of these two autoantibodies correlates with a higher rate of RP-ILD and mortality, especially in patients with a short disease course and high inflammation (75).

Despite the potential severity of anti-MDA5+ DM, in the cohort of the Johns Hopkins Myositis Centre in Baltimore, almost one-fifth of patients achieved a long-term (>1 year) drug-free remission after a median disease duration of 4 years, with no specific clinical or biological factors associated with the remission state (76).

In partial contrast to what has been seen for anti-MDA5+ patients, in anti-NXP2+ DM age was the only independent predictive factor for ILD, as older patients are at higher risk (77). No association between ILD and death from all causes was found among these patients.

According to a Portuguese study by Bandeira *et al*., anti-SRP antibodies are confirmed to be predictive of cardiac involvement regardless of demographic factors, such as age, gender and ethnicity, and lung involvement (51).

Antibodies against cytosolic 5´-nucleotidase 1A (cN1A) are mainly found in IIM patients and particularly in IBM, where they are associated with the presence of dysphagia (78). In IIM subsets other than IBM, these autoantibodies appear to be associated with a non-severe disease phenotype (78).

Regarding the pathogenetic role of autoantibodies, Honda et al. recently demonstrated in vitro that IgG purified from sera of anti-Jo1+ IIM patients could bind to muscle endothelial cells and induce complement-dependent cellular cytotoxicity (79).

A study by Li *et al*. showed different patterns of serum IgG glycosylation between patients with DM, other systemic autoimmune diseases and healthy volunteers, with differences even among DM patients and N-acetylgalactosamine (GlcNAc) glycan level significantly lower in anti-TIF1γ+ DM (80).

Anti-cytoplasmic cysteinyl-tRNA-synthetase (CARS1) antibodies were identified as a new anti-synthetase antibody specificity, called anti-Ly (81). Besides, a recent Swedish study showed that almost all cytoplasmic aminoacyl tRNA synthetases (ARS) can act as autoantigens, leading to the discovery of autoantibodies against nine novel ARS (82). Notably, autoantibodies targeting new ARS were found in some previously seronegative IIM patients, with crucial diagnostic and prognostic implications (82).

Although their true clinical value has yet to be defined, as they are common to other autoimmune disorders, antibodies to valosin-containing protein (anti-VCP) were detected in 26.0% of patients with sporadic IBM with a significant specificity (87.2%) but low sensitivity (26.0%) (83).

Despite the fact that, in most cases, the coexistence of two or more MSAs represents a false positive, double positivity for MSAs is rare but may occur in IIMs, although the clinical phenotype is usually characteristic of only one of them and the double positivity does not seem to have an impact on the severity and prognosis of the disease (84).

Take-home messages

- Almost 20% of DM with anti-MDA5 antibodies achieve a long-term drug-free remission, with no specific clinical or biological factors associated with the remission state (77).
- Anti-Ly have been identified as new anti-synthetase antibody (81).
- Double positivity for MSAs does not seem to to have impact on the prognosis of the disease (84).

Treatment

Corticosteroids (CCs) are still considered the first-line therapy for patients with IIM (85), but immunosuppression is required to prevent the development of side effects (86). Mild to moderate disease may be successfully controlled with addition of steroid sparing agents including azathioprine (AZA), mycophenolate (MMF), methotrexate (MTX), calcineurin inhibitors but in refractory myositis second-line therapies such as high dose Intravenous immunoglobulin (IVIg) or rituximab (RTX) can be proposed (87).

In high-risk patients (*e.g.* dysphagia, severe weakness), IVIg, a purified liquid IgG concentrated from human plasma may be used as a first-line treatment (86). A randomised, placebo-controlled trial (88) involving patients with active DM showed that improvement in disease activity was clinically and statistically significantly greater in those who received IVIG than in those who received placebo. In this study, IVIG were associated with adverse events, including thromboembolism, although other studies identified a higher risk only in patients with prior events (89).

Additionally, RTX may improve the clinical features of IIM patients, as reported in a recent study in which RTX improved IMACS core set measures and had a robust efficacy as steroid sparing agent at 6 and 12 months in patients with refractory IIM in a registry-based study (90).

Furthermore, although the possible efficacy of tocilizumab in refractory IIMs has been evaluated in a multicentre, randomised, double-blind, placebo-controlled trial, it was not more effective than the placebo (91). Similar results were obtained in a trial with belimumab, where the primary end point was not met (92).

Interstitial lung disease (ILD) is a common extra muscular complication of IIM. Particularly patients with RP-ILD (usually associated with anti-MDA5 autoantibody) have a poor prognosis (93). Therefore, the treatment of this condition remains a priority.

A recent study showed that IVIG adjunct therapy is an effective treatment for patients with MDA5-RPILD. IVIG may increase the survival and remission rate by lowering ferritin concentration, anti-MDA5 titre and the ground glass opacification (GGO) score (94).

Although studies supporting the use of CYC in IIM associated ILD are scarce, a recent observational and multi-centre cohort study, suggested that patients with IIM-ILD receiving i.v. CYC showed a larger improvement of functional lung tests compared to other immunosuppressive regimes (95).

Among JAK inhibitors, the efficacy of tofacitinib (TOF) in the MDA5-RP-ILD has been described. Patients diagnosed with MDA5-ILD receiving TOF or tacrolimus (TAC) treatment were included. The 6-month and 1-year mortality rates in the TOF group were significantly lower than those in the TAC group (96). Shirai *et al*. (97) investigated the therapeutic efficacy and safety of an intensive treatment (which combined plasma exchange, rituximab and tofacitinib) in patients with MDA5-RPILD and multiple poor prognostic factors. Although several adverse events were observed, benefits outweigh the risks in younger patients with high serum ferritin levels.

If medical treatment fails, a possible alternative is represented by lung transplantation. Riviere and colleagues retrospectively reviewed data for 64 patients who underwent lung transplantation between 2009 and 2021 to assess survival and prognostic factors in lung transplant recipients with IIM-ILD. Post-transplantation survival in IIM-ILD was similar to that in international all-cause-transplantation registries. The main factor associated with worse survival was a history of muscle involvement (98).

Active skin disease in DM patients can be disfiguring and may remain refractory to standard of care, and thus a need exists for more effective and safer therapeutic options than the current ones.

A phase 2a, open-label, single-arm non-randomised controlled trial studied the efficacy and safety of apremilast as an add-on therapy in patients with refractory cutaneous dermatomyositis. Apremilast 30 mg orally twice daily was added to ongoing treatment regimens: apremilast was a safe and efficacious add-on treatment, with an overall response rate of 87.5% and associations with downregulation of multiple inflammatory pathways (99).

Inflammatory and fibrotic responses are modulated by the endocannabinoid system; lenabasum is a cannabinoid receptor type 2 agonist. A single-centre, double-blind, randomised, placebo-controlled phase 2 study (100) was conducted to evaluate the safety and efficacy of lenabasum in patients with recalcitrant cutaneous dermatomyositis despite treatment with steroids, steroid-

sparing agents, or both. Lenabasum treatment was well tolerated and was associated with greater improvement in Cutaneous Dermatomyositis Disease Area and Severity Index activity and multiple efficacy outcomes. However, the subsequent phase 3 study did not meet its primary end point (https://www.corbuspharma.com/press-releases/detail/361/corbus-pharmaceuticals-announces-topline-results-from).

Non-immunosuppressive treatments have also been explored in the treatment of IIM. For example, the efficacy and safety of branched chain amino acids (BCAAs) in addition to conventional treatment has been studied in a randomised, double-blind trial (101). The primary endpoint was the change of the muscle strength evaluated by MMT at 12 weeks. The response in both groups improved similarly. BCAAs were only partly effective for improving dynamic repetitive muscle functions.

Transcranial direct current stimulation (tDCS) is proved to improve the motor domain of patients with systemic autoimmune myopathies in a prospective, randomised, sham controlled, double-blind study (102). Even the physical aspects of Short Form Health Survey 36 (SF-36) improved significantly.

Non-pharmacological treatment includes physical therapy of the affected muscles to prevent disuse atrophy. A single site randomised, double-blind, placebo-controlled, crossover study assessed whether a combination of testosterone supplementation and exercise training would improve muscle strength, physical function and quality of life in men affected by IBM, more than exercise alone (103). Exercise and transdermal testosterone and placebo (exercise and placebo cream) were each delivered for 12 weeks, with a two-week wash-out between the two periods. The primary outcome measure was improvement in quadriceps isokinetic muscle strength. Transdermal testosterone was well tolerated but did not meet the primary or secondary efficacy outcomes.

Take-home messages

- Tocilizumab and Belimumab have not displayed superiority over placebo in two RCTs (91).
- CYC appears superior to other immunosuppressants in improving lung functionality (95).
- The combination of PE, TOF and RTX, although burdened by several adverse events, is associated with higher survival rates in patients with high ferritin serum levels (97).

Conclusions

Several studies have been carried out in the last twelve months, providing utmost novelties in the field of IIM. Intriguing steps forward have been made in the comprehension of pathogenetic mechanisms and, in particular, the role of IFN pathway has been widely indagated; similarly, some other studies have underlined the prominent role of T cells, as well that of complement and innate system, the latter often overlooked in the pathogenesis of IIM. Particularly, interesting insights have been reported in terms of organ involvement: most studies were addressed in the field of ILD and in particular for anti-MDA5 RP; in this regard, preliminary findings seem to display a potential role of novel imaging techniques in the early assessment and disease stratification of IIM-ILD. Similarly, certain serological, MRI and ECG findings have been proposed for an early identification of IIM patients with concomitant heart involvement. Among the other imaging procedures, NVC and MRI remain mainstays of the diagnosis and stratification of disease, while controversial data remain for US. At the same time, accumulating evidence remarks the role of MSA in the stratification of patients, as these antibodies are usually associated to a well-defined subset of disease. Additionally recent reports suggested as the presence of specific internal organ involvement, such as ILD, may be successfully treated with IVIg or TOF; on the other hand, for skin-limited disease, apremilast has provided a good efficacy profile.

In conclusion, the current number of ongoing and published studies summarised in this review is promising and will probably pave the way to further contributions, in order to provide clinicians a deeper knowledge of this complex, yet fascinating, diseases.

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