Review

# Idiopathic inflammatory myopathies: one year in review 2021

C. Cardelli[1], G. Zanframundo[2], L. Cometi[3], E. Marcucci[4], A. Biglia[2], L. Cavagna[2], S. Barsotti[1,5]

[1]Rheumatology Unit, Department of Clinical and Experimental Medicine, University of Pisa;
[2]Division of Rheumatology, University and IRCCS Policlinico S. Matteo Foundation, Pavia;
[3]Department of Experimental and Clinical Medicine, Rheumatology Unit, University of Florence;
[4]Rheumatology Unit, Department of Medicine, University of Perugia;
[5]Department of Internal Medicine, Ospedale Civile di Livorno, Italy.

Chiara Cardelli, MD
Giovanni Zanframundo, MD
Laura Cometi, MD
Elisa Marcucci, MD
Alessandro Biglia, MD
Lorenzo Cavagna, MD
Simone Barsotti, MD

Please address correspondence to:
Lorenzo Cavagna,
Division of Rheumatology,
University and IRCCS Policlinico S. Matteo Foundation,
via Golgi 19,
27100 Pavia, Italy.
E-mail: lorenzo.cavagna@unipv.it

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**ABSTRACT**

*Idiopathic inflammatory myopathies (IIMs) are a heterogeneous group of rare and complex connective tissue diseases, mainly characterised by inflammatory involvement of skeletal muscles. Several other organs may be affected, particularly lungs, heart, skin, gastrointestinal tract and joints, often determining the morbidity and mortality associated with these autoimmune disorders. The course is generally chronic and the onset subacute. This latter aspect, together with the rarity of these conditions, can result in a clinical challenge for the physician with a considerable diagnostic delay. The scientific literature makes continuous advances in the understanding of these diseases, in particular with regards to the pathogenesis, serological findings, diagnostic strategies and therapeutic approaches. The aim of this review is to highlight the most relevant literature contributions published on this topic over the last year.*

## Introduction

Idiopathic inflammatory myopathies (IIMs) are a group of rare systemic autoimmune diseases primarily characterised by muscle weakness, often accompanied by extramuscular involvement. According to the most recent knowledge, this heterogeneous group of disorders recognises among its main subgroups polymyositis (PM), dermatomyositis (DM), sporadic inclusion body myositis (sIBM), immune-mediated necrotising myopathy (IMNM) and clinically amyopathic dermatomyositis (CADM). The presence of antisynthetase autoantibodies defines a specific syndrome, the antisynthetase syndrome (ASS).

The purpose of this paper is to provide an update on the most recent advances on IIMs, with the aim of identifying useful elements in the management and treatment of these conditions, following a well-established format as in the previous years (1, 2). For this review, we performed a Medline search of English language articles published in the PubMed database from 1st January 2020 to 31st December 2020. 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

Among the genetic risk factors for IIMs, the association with specific HLA haplotypes is probably the one with the higher impact and better studied so far. Furukawa *et al*. found that DRB1*08:03 and DPB1*05:01 are associated with IIMs (OR 2.11 and 1.96 respectively) and DM (OR 2.06 and 2.05) development, whereas DRB1*09:01 and DPB1*04:01 seemed to be protective toward PM occurrence (OR 0.35 and 0.05 respectively) in a Japanese cohort (3). On the other hand, DRB1*01:01, DRB1*04:10 and DRB1*15:02 were significantly more expressed in 83 Japanese IBM patients compared to controls (4). Susceptibility to antisynthetase syndrome (ASS), instead, was found increased in subjects expressing HLA-DRB1*03:01 and HLA-B*08:01 alleles, with the former significantly more frequent in anti-Jo1 *versus* non anti-Jo1 patients (5).

Other studies focused on the genetic predisposition of developing specific phenotypes of IIMs. Particularly, the risk of developing ASS was found to be related to some single-nucleotide polymorphisms (SNP) involving interleukin 1β (IL-1β) gene (6). Conversely, MUC5B polymorphism rs35705950, which is well known to be associated

with idiopathic pulmonary fibrosis (IPF) and rheumatoid arthritis-associated interstitial lung disease (RA-ILD), did not show any association with ASS, thus supporting the presence of genetic differences underlying these conditions (7).

In the last year, several research groups focused on the transcriptome analysis on specimens from patients with IIMs and found that the pathogenic pathways involved in DM and IBM may be related with both innate and adaptive immunity with differences according to the clinical phenotype or, as reported by Pinal-Fernandez *et al*., to the specificity for certain MSAs such as anti-Mi2 and anti-HMGCR (8-10) (Table I). Overall, in DM differentially expressed genes (DEGs) were mostly linked to type I interferon (IFN) pathways (11), in IBM to cell-mediated immunity, in IMNM to muscle cells' structural proteins and in ASS to both IFN pathway and muscle cells' structural proteins (Table 1). IFN-signature was present also in skin samples of patients with DM, unlike in patients with other kind of skin lesions, like eczema (12, 13).

Moreover, a study on a myositis mouse model showed an increased expression of inflammatory microRNAs (miRNAs) (including miR-146a) and dystrophin-targeting miRNAs possibly leading to an acquired dystrophin deficiency mediated by NFκB-regulated genes (14). Conversely, Jiang *et al*. found miR-146a to be reduced in macrophages from patients with PM and DM, thus favouring macrophage migration via the enhancement of REG3A expression (Regenerating Family Member 3 Alpha). REG3A was actually overexpressed in muscle samples from PM/DM patients and experimental autoimmune myositis mice model (15).

Furthermore, recent evidence suggested that the cellular mechanisms underlying IIMs pathogenesis may include mitochondrial pyroptosis as possible responsible for perifascicular atrophy in DM (16) and perimysial arterioles disease (wall thickening, thrombosis and endothelial lipid accumulation) for muscle ischaemia in anti-NXP2 DM (17). Although mitochondria from IIMs patients seemed to preserve their ability to respond to increased metabolic requests at a degree comparable with HCs, this respiratory effort would lead to increased rate of cell deaths in IIMs samples, thus suggesting that the decreased respiration observed in IIMs in normal conditions might be a compensatory response to improve cell survival rather than the cause of cell dysfunction (18).

As for the role of immune cells in IIMs pathogenesis, CD8+ T cells are confirmed to be responsible for muscle damage in PM and IBM also through apoptosis (19, 20). Monocytes, on the other hand, displayed a pro-inflammatory phenotype with enhanced expression of TLR2 and TLR4 in IIM sera, regardless of disease activity and prednisone treatment (21), whereas muscle monocytes decreased after 1 year of treatment and predicted the long term outcome (22). Dysregulated neutrophils (low-density granulocytes [LDGs]) and neutrophil extracellular traps (NETs) also play a role in IIMs pathogenesis, and anti-MDA5 autoantibodies were associated with higher values of circulating NETs and was found able to directly induce the formation of NET (23).

The role of protein misfolding in IBM pathogenesis was further investigated and was found to be associated with the overexpression of both T-complex protein 1 (TCP-1) and Na+/myo-inositol cotransporter 1 (SLC5A3). The first molecule seemed to induce a reduction of misfolded proteins' clearance, whereas the overexpression of the second one is thought to be a compensatory mechanism and a possible inductor of inflammation (24, 25). Another pillar of IBM pathogenesis is mitochondrial disfunction, as evidenced by the *in vitro* efficacy of the mitochondrial-homing drug mitochonic acid-5 (MA-5) in improving ATP production and myocyte survival in IBM samples (26). The chaperone-assisted selective autophagy (CASA) is a process that leads to the degradation of misfolded proteins mediated by the protein p62. The accumulation of p62 has been proposed as a marker for IBM, although Milisenda *et al*. found it also in other forms of myositis, thus questioning its specificity for IBM (27). Indeed, the CASA pathway seemed to be involved also in muscle necrosis of IMNM and might be linked to endoplasmic reticulum stress produced by anti-SRP and anti-HMGCR antibodies and to inflammation via overexpression of MHC I (28). Furthermore, infiltration of lymphocytes expressing Bcl-2 and beta-chemokine receptor 4 (CCR4) (both negatively affected by statins) seemed to be a marker of anti-HMGCR+ IMNM (29). The High Mobility Group Box Protein 1 (HMGB1, a DNA-binding acting as a damage signal and pro-inflammatory mediator) was also overexpressed in IIMs muscle samples and serum, especially in IMNM (30). Moreover, Day *et al*. (31) demonstrated that IMNM samples from different patients may display different degree of necrosis and that the amount of myofibre complement deposition was closely associated with clinical severity.

As for the environmental risk factors, sun exposure was related to an increased risk of DM development compared to other forms of IIM (32), while anti-MDA5+ disease displayed a seasonal pattern of occurrence (between October and March) and seemed to be more prevalent in areas closer to waterfronts (33).

**Take-home messages**

- Specific HLA haplotypes are associated with the development of IIMs in general and their subsets (3-5).
- A consistent number of DEGs was identified, with significant differences not only related to clinical phenotypes or specific MSAs, but also useful in distinguishing pathologies with similar clinical presentations (*i.e*. DM *vs*. eczema) (8-13).
- miRNAs are also involved in the pathogenesis of IIMs (14, 15).
- Cellular mechanisms involved in IIM pathogenesis seem to include mitochondrial pyroptosis and perimysial arterioles disease (16, 17).
- Immune cells involved in IIM pathogenesis include CD8+ T cells, monocytes and neutrophils (19-23).
- Misfolded proteins and mitochondrial disfunction have a key role in IBM pathogenesis (24-27).
- The infiltration of lymphocytes expressing Bcl-2 and CCR4 seems to be a marker of anti-HMGCR+ IMNM

**Table I.** Differently expressed genes (DEGs) in inclusion body myositis (IBM), dermatomyositis (DM), immune-mediated necrotising myopathy (IMNM) and antisynthetase syndrome (ASS). DEGs were selected from the original papers if displaying fold-change >10. Gene functions were retrieved at https://www.uniprot.org/.

| | Gene involved | Gene description-related protein | Function or pathway |
|---|---|---|---|
| IBM | PTPCR (9) | Interferon regulatory factor 8 | Cell surface glycoproteins of MHC-restricted $CD8^+$ T cells |
| | IRF8 (9) | Interferon regulatory factor 8 | Stabilise transcription of type I IFN promoters in monocytes |
| | TYROBP (9) | TYRO protein tyrosine kinase-binding protein | Regulates intestinal inflammation in mice models |
| | VCAM1 (9) | Vascular cell adhesion molecule I | Favours muscle invasion from leukocytes |
| | HLA-DRA (9) | Major histocompatibility complex, class II, DR alpha | HLA class II restricted antigen presentation pathway |
| | HLA-DRB1 (9) | Major histocompatibility complex, class II, DR beta 1 | HLA class II restricted antigen presentation pathway |
| | HLA-DOA (10) | Major histocompatibility complex, class II, DO alpha chain | HLA class II restricted antigen presentation pathway, B cells antigen recognition |
| | HLA-DQA1 | Major histocompatibility complex, class II, DQ alpha 1 chain | HLA class II restricted antigen presentation pathway, CD4 antigen recognition |
| | CD74 (9) | Major histocompatibility complex, class II invariant chain | Transmembrane glycoprotein upregulated by IFN-γ |
| | CCR5 (9) | C-C motif chemokine receptor 5 | Membrane chemokine receptor in monocytes |
| | CXCL9 (9) | C-X-C motif chemokine ligand 9 | Membrane chemokine receptor in IBM muscle fibres |
| | CCL13 (10) | Chemokine (C-C motif) ligand 13 | Chemotactic factor that attracts monocytes, lymphocytes, basophils and eosinophils |
| | C1QB (9) | Complement component 1, q subcomponent, B chain | Possibly involved in phagocytosis of degenerating neuromuscular synapses |
| | AQP4 (9) | Acquaporin-4 | Water channel that is expressed in the sarcolemma of muscle fibres |
| | CD8A (10) | T-cell surface glycoprotein CD8 alpha chain | Coreceptor for MHC class I molecule in T cells |
| | GBP1 (10) | Guanylate-binding protein 1 | IFN-induced antiviral activity against influenza virus |
| | GBP5 (10) | Guanylate-binding protein 5 | IFN-induced NLRP3 inflammasome assembly |
| DM | XAF1 (8) | X chromosome linked inhibitor of apoptosis protein related factor 1 | Inhibits apoptosis by binding to caspases and inhibiting the function of caspases |
| | NT5E (8) | Ecto-5´-nucleotidase | membrane nuclease, marker of lymphocyte maturation, modulate lymphocyte response |
| | UGCG (8) | UDP-glucose ceramide glucosyltransferase | Regulates apoptosis-related pathways |
| | CMPK2 (10) | mitochondrial UMP-CMP kinase 2 | Involved in cell respiration |
| | TLR3 (8) | Toll-like receptors 3 | Recognises ds-RNA and induce NF-ϰB and IFN-β |
| | DDX58 (RIG-1) (8) | Retinoic acid-inducible gene I | Recognises viral RNA and activates innate antiviral responses (IFN I and inflammatory cytokines) |
| | STAT1 (8) | Signal transducer and activator of transcription 1 | Involved in many cellular process, possibly type I interferon signal transduction |
| | GBP1 (8) | Guanylate binding protein 1 | Early-warning signal expressed in inflammatory skin diseases |
| | PLSCR1 (8) | Phospholipid scramblase 1 | Can promote the apoptosis through activation of caspase 3 |
| | SP100 (8) | Nuclear autoantigen Sp-100 | Involved in response to viral infections and in p53 and interferon signaling |
| | IGK (8) | Immunoglobulin k light chain | Housekeeping gene secreted by plasmacells, possibly activating NF-κB |
| | RSAD2 (8,10) | Radical S-adenosyl methionine domain-containing protein 2 | Type I IFN-induced endoplasmic reticulum gene, regulates differentiation in Th2 and B cells activation |
| | ISG15 (10) | Interferon-stimulated gene 15 | Type I IFN-induced antiviral protein, influencing the functions of several immune cells |
| | OAS1 (10) | Oligoadenylate Synthetase 1 | Type I IFN-induced antiviral protein, regulates innate response |
| | OAS3 (8,10) | Oligoadenylate synthetase 3 | Type I IFN-induced antiviral protein, regulates innate response |
| | IFI6 (10) | Interferon alpha-inducible protein 6 | Type I IFN-induced antiviral protein, regulates apoptosis |
| | MX1 (10) | Interferon-induced GTP-binding protein Mx1 | Type I IFN-induced antiviral protein, inhibits viral replication |
| | MX2 (10) | Interferon-induced GTP-binding protein Mx1 | Type I IFN-induced antiviral protein, inhibits viral replication |
| | IRF9 (10) | Interferon regulatory factor 9 | Type I IFN-induced antiviral protein, transcription factors for antiviral proteins |
| | IFITM (10) | Interferon-induced transmembrane protein 1 | IFN-induced antiviral protein, also antiproliferative action |
| | GBP2 (8) | Guanylate-binding protein 2 | IFN-induced proteins that mediates pro-inflammatory functions |
| IMNM (8) | SERPINA3 | Alpha-1-antichymotrypsin | Inhibits cathepsin G and chymases preventing tissue damage |
| | ACTC1 | Actin, alpha cardiac muscle 1 | Constituent of muscle contractile apparatus |
| | TNC | Tenascin | Implicated in axons development and tumour neoangiogenesis |
| | KRT80 | Keratin, type II cytoskeletal 80 | Structural protein of cytoskeleton |
| | TNNT2 | Troponin T, cardiac muscle | Structural protein of muscle tissue with Ca binding properties |
| | MYH3 | Myosin-3 | Structural protein of muscle tissue |
| | ANKRD1 | Ankyrin repeat domain-containing protein 1 | Cytokines induced nuclear proteins of endothelium and cardiac tissue |
| ASS (8) | ACTC1 | Actin, alpha cardiac muscle 1 | Constituent of muscle contractile apparatus |
| | MYH3 | Myosin-3 | Structural protein of muscle tissue |
| | GBP1 | Guanylate-binding protein 1 | IFN-induced antiviral activity against influenza virus |
| | PSMB8 | Proteasome subunit beta type-8 | IFN-induced component of the proteasome |
| | IFI30 | Gamma-interferon-inducible lysosomal thiol reductase | IFN-induced proteins involved in proteins unfolding and antigen processing |
| | NNMT | Nicotinamide N-methyltransferase | Involved in NAD metabolism |
| | SAA1 | Serum amyloid A-1 protein | Acute phase protein, possible role in T cells chemotaxis |

and the amount of myofibre complement deposition in muscle samples is related to clinical severity (29, 31).

## General and muscular involvement and muscular imaging

*Classification criteria*

Various classification criteria for IIMs have been published since 1970. Among them, the Bohan & Peter criteria and Tanimoto criteria for PM/DM are commonly used. In 2017 new criteria were approved by European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR). Jinnin *et al*. (34) validated these criteria in 420 IIMs and 402 non-IIM cases. The sensitivity and specificity of these criteria were respectively 89.3% and 91.0% in the total cohort. The sensitivity and specificity of the new criteria to diagnose PM/DM plus juvenile and amyopathic DM were greater than those of the Tanimoto criteria and were comparable with those of the Bohan & Peter criteria to diagnose these diseases except for amyopathic DM. Furthermore, Barsotti *et al*. (35) assessed the performance of the EULAR/ACR criteria in 439 IIMs patients and found that they had a higher sensitivity compared to the Bohan & Peter criteria. The EULAR/ACR criteria showed a very high specificity (>98%) for the major IIMs subgroups (PM, DM and IBM). The sensitivity was high in IBM and DM and lower in PM. Interestingly, when including interstitial lung disease (ILD) in the variables of the criteria, six more patients were classified as IIM cases.

*Disease activity criteria*

Accurate measurement of IIM disease activity is imperative for appropriate medical management and International Myositis Assessment and Clinical Studies Group (IMACS) "Disease Activity Core Set Measures" are the current gold standard. However recent studies focused on the validation of patients-reported outcomes, which evaluate domains as fatigue, pain, level of physical activity etc., not wholly measured by the IMACS Core Set Measures (36, 37). The current methods of measuring progression of IBM use the Inclusion Body Myositis Functional Rating Scale (IBM-FRS), that assesses self-reported functional difficulties of different regional modalities, together with grip strength and finger flexor strength, although it seemed not to correlate with disease duration and finger flexor strength (38). The performance of a novel portable device (MyoQuad) in assessing and monitoring maximal voluntary isometric knee extension torque (MVIT) was found to correlate excellently with the measurements of isokinetic dynamometer (39).

Over time, different tools to measure functional impairments have been developed to assess PM and DM patients. The Functional Index-2 (FI-2) involves testing repetitive tasks performed either bilaterally or unilaterally with a metronome, requiring a maximum of 33 minutes to complete. Ernste *et al*. (40) proposed a shorter version (FI-3), that takes a maximum of 15 minutes with bilateral assessment and a maximum of 9 minutes with unilateral assessment.

*Imaging*

Imaging is frequently used to aid in the diagnosis and monitoring of myositis, with magnetic resonance imaging (MRI) playing a key role in the identification of sites which can be targeted for muscle biopsy. Meyer *et al*. (41) found that histogram parameters could predict muscles with pathological spontaneous activity at electromyography (EMG), which may help to decide the site for muscle biopsy.

The whole-body MRI (WB-MRI) study of IMNM revealed that muscle damage was preferentially located at lumbar and pelvifemoral region,and correlate with disease duration (42), whereas in IBM the fatty infiltration of the thighs was prominent and displayed a proximal-to-distal gradient and a strong negative correlation with disease activity (43). Fatty infiltration at MRI was also found to correlate with histopathologic damage in IBM, while muscle oedema correlated with the amount of inflammation (44). Interestingly, in a study using computed tomography (CT), the patients with IBM exhibited a significantly greater muscular degeneration in the rectus femoris, vastus, sartorius, adductor, anterior calf and medial gastrocnemius muscles than those with PM or amyotrophic lateral sclerosis (45). IBM displayed also peculiar ultrasound (US) characteristics, showing higher echogenicity and lower muscle thickness than PM/DM patients (46).

As IIMs manifest with systemic muscle involvement, Xu *et al*. (47) enrolled 44 IIM patients that underwent 3T multiparametric cardiovascular magnetic resonance (CMR) at first diagnosis and 28 of these patients underwent follow-up scan after receiving standard treatment for more than 1 year. They found that at baseline IIMs patients showed significantly decreased haematocrit, higher left ventricular (LV) mass index, right ventricular (RV) volume index, myocardial and skeletal native T1, T2 mapping and extracellular volume (ECV) than HCs. Significant improvement in these parameters was observed during the follow-up assessment suggesting that quantitative T1, T2 and ECV techniques may have potential clinical value in these patients.

The new insights in imaging techniques are summarised in Table II.

### Take-home messages

- The new 2017 EULAR/ACR classification criteria seem to perform well in terms of both sensitivity and specificity (34, 35).
- In the last year various tools have been proposed to assess disease activity and functional impairment in IIM patients (36, 37, 39, 40).
- Muscle MRI and EMG seem to reflect disease activity in a similar way (41).
- Fatty infiltration at MRI is associated with muscle damage and disease duration, while is strongly negative correlated with disease activity (42-44).
- US could be useful for distinguishing IBM from PM/DM, in relation to higher echogenicity and lower muscle thickness in IBM (46).
- Several CMR parameters seem to correlate with disease activity in IIM patients (47).

## Extramuscular involvement

The extramuscular involvement is common and frequently affects prognosis of IIMs. In this context, lungs involve-

**Table II.** Summary of new insights in imaging techniques in IIMs from 2020 articles.

| Imaging technique | Main findings |
|---|---|
| **Magnetic resonance imaging (MRI)** | Strong associations were found between histogram analysis derived from morphological MRI sequences and EMG findings in myopathies (41). |
| | MRI findings found that most severely affected muscle groups in IMNM were located in the pelvifemoral and lumbar region (42). |
| | The whole muscle fat fraction found in MRI in the thighs and lower limb in IIMs has a strong negative correlation with the functional scores (43). |
| | Fatty infiltration on MRI correlates moderately with muscle histopathology; histopathological abnormalities can occur prior to the onset of fatty infiltration (44). |
| | Cardiac magnetic resonance (CMR) in IIM patients showed higher left ventricular (LV) mass index, right ventricular (RV) volume index, myocardial and skeletal native T1, T2 mapping and extracellular volume (ECV) than healthy controls and they correlated with disease activity (47). |
| **Computed tomography (CT)** | Patients with IBM who underwent lower limb CT exhibited a significantly greater muscular degeneration in the rectus femoris, vastus, sartorius, adductor, anterior calf and medial gastrocnemius muscles than those with PM (45). |
| **Ultrasounds (US)** | Parameters such as lower muscle thickness and higher echogenicity can distinguish between IBM patients and healthy controls (46). |
| **Nailfold videocapillaroscopy (NVC)** | The presence of bushy capillaries and/or NVC positivity in ILD patients with normal levels of creatine phosphokinase is associated with amyopathic IIM, regardless the presence of Raynaud's phenomenon (54). |

ment as ILD is one of the most severe.

In a retrospective study on 679 adult IIMs patients, the prognosis of patients with DM-ILD and CADM-ILD was worse than that of PM-ILD patients. Furthermore, the positivity for anti-ARS and anti-MDA5 antibodies correlated with ILD development (48), as well as anti-Ro52 (49).

In a cohort of 165 patients with PM/DM-ILD, Zuo *et al*. analysed the different radiological patterns of HRCT with their clinical correlations. The organising pneumonia (OP) pattern was the most frequent finding, especially in patients with anti-SAE and anti-MDA5 positivity, followed by the NSIP pattern. The ratios of OP and NSIP patterns were almost equal in patients with anti-ARS antibodies, whereas NSIP pattern was more frequent in patients with the others MSAs. The positivity for anti-PL7 with an OP pattern was found to be a risk factor for rapidly progressive ILD (RP-ILD) development, compared to the others anti-ARS antibodies. In OP pattern, lower lung zone consolidation was strongly associated with RP-ILD and correlated with levels of CEA and Ca19.9 in patients with anti-MDA5 antibodies and with Cyfra21.1 levels in ARS-positive patients. In this study RP-ILD patients had significantly higher amount of CD163+ macrophages at the alveolar spaces compared to the patients with chronic ILD, suggesting that activated macrophages may contribute to the development of RP-ILD (50). Another study found that a myofascial-dominant involvement on WB-MRI seems to be a risk factor for RP-ILD (51). In CADM, the elevation of Cyfra21.1 was correlated with ILD, while CEA and NSE with acute or subacute forms of ILD (52).The role of nailfold videocapillaroscopy (NVC) has been further investigated. Some peculiar alterations at NVC were found to be correlated with specific clinical phenotypes and prognosis, such as microhemorrhage and capillaries disorganisation with anti-MDA5; capillaries tortuosity with anti-ARS; neoangiogenesis with ILD and poor prognosis; avascular areas, giant capillaries and bushy capillaries with amyopathic DM (53, 54).

Among cardiac involvement, heart failure (HF) is rare but potentially fatal for patients with IIM. In a retrospective study on 32 Chinese patients, Liu *et al*. identified elevated cTnI values, rapid atrial arrhythmia, LV systolic disfunction and restrictive diastolic disfunction as the main features of IIM-HF (55).

As for oesophageal involvement, Taira *et al*. found that cricopharyngeal bar (CPB) on videofluoroscopic (VFS) examination seemed to be highly specific for IBM patients compared with the control group of elderly healthy individuals and patients with neuropsychiatric disorders (56). Moreover, the presence of CPB on VFS examination in IBM patients was a risk factor for aspiration pneumonia (57).

Regarding cancer-associated myositis (CAM), older age at onset, shawl sign, anti-TIF1γ and low albumin were described as risk factors, while ILD was identified as a protective factor (58) (59). Conversely, ILD along with female sex and onset age ≥50 years were found as independent risk factors for death among cancer-associated DM patients (60). Moreover, cancer seemed to develop 1 year before or after the diagnosis of myositis in most cases, especially for DM patients (61).

**Take-home messages**

- Anti-ARS, anti-MDA5 and anti-Ro52 antibodies positivity is associated with ILD development (48, 49).
- OP and NSIP are the most frequent HRCT patterns in PM/DM, with the former common especially in anti-SAE, anti-MDA5 and anti-ARS patients (50).
- Risk factors for RP-ILD include anti-PL7 positivity with an OP pattern, lower lung zone consolidation in OP HRCT pattern and a myofascial-

dominant involvement on WB-MRI (50, 51).
- Specific NVC alterations are associated with different clinical phenotypes (53, 54).
- Cricopharyngeal bar on VFS has a high specificity for IBM and seem to be a risk factor for aspiration pneumonia (56, 57).
- Older age at onset of IIM, shawl sign, anti-TIF1γ positivity and low serum albumin are identified as risk factors for CAM, while ILD seem to be a protective factor (although it is an independent risk factor for death among cancer-associated DM) (58-60).

**Laboratory investigations and autoantibodies**

The research of autoantibodies in IIMs is a topic in continuous update.

One of the most interesting updates since last year has been the identification of new possible MSAs: one, targeting eIF3 (a cytoplasmic complex with a role in translation initiation), would identify a PM subset not related to malignancy or ILD and with a favourable response to treatment (62), whereas the other one, targeting heat shock factor 1 (HSF1) protein, would mark cancer-associated myositis (63).

Many studies focused on the reliability of commercial kits for MSAs and MAAs detection. Interestingly, more than 80% of clinicians report that identification of a myositis autoantibody influences their diagnostic confidence and the treatment used (64). Among the methods for antibodies detection, the line blot immunoassay (LIA) displayed a high specificity for IIM in a proper clinical setting, although the rate of false positive increased if the pre-test probability was low and the autoantibodies resulted weakly positive, especially for anti-TIF1γ and anti-ARS (65-68).

Anti-nuclear antibody (ANA) positivity among IIMs was found in about 50-65% of patients with PM, DM and even IBM (69, 70). In a Chinese study at least one MSA was found in 63.2% of IIMs, with anti-MDA5 and anti-TIF1γ being the more common (71).

Autoantibodies and other serum markers can also provide information on disease activity and prognosis. In fact, MSAs positivity seemed to be associated with increased extramuscular disease activity but had no correlation with muscle disease activity, while MAAs did not relate to either muscular or extramuscular disease activity (72). The rate of sustained remission was significantly higher in MSA-negative patients than in MSA-positive patients, particularly in anti-ARS, anti-MDA5 and anti-TIF1γ positive patients (73). As for IIM-related ILD, several markers were indicated as markers of severity and poor prognosis: KL-6, serum sCD206 (a marker of macrophage activation), anti-MDA5, C-reactive protein (CRP), surfactant protein D (SPD), leucine-rich α2-glycoprotein (LRG) and clusterine (CLU) (74-78). Similarly, antiRo52 was found associated with RP-ILD and skin ulcers in anti-MDA5 patients (79).

Serum markers were found able also to identify IIM subsets, as soluble interleukin-2R (sIL-2R) in discriminating DM from IMNM, particularly in case of active disease with ulcerative skin lesions (80), or neopterin in discriminating anti-MDA5 DM with severe ILD from other forms of IIMs (81); also, circulating nucleosomes, markers of cell apoptosis, were elevated in sera from IIMs patients compared to HCs, particularly in patients with anti-ARS, anti-MDA5 and anti-TIF1γ DM associated with skin involvement (82). Serum IL-17 levels were higher in ASS patients than in matched HCs, although apparently unrelated with the disease activity (83). The presence of anti-Ro52, anti-Jo1, anti-PL7 and anti-EJ seemed to predict the development of ILD in IIM patients (84, 85), whereas aldolase predicted the positivity of one MSA/MAA in an ILD cohort tested for anti-Ro/SSA, ANA, aldolase and CK (86). Regarding ASS, an observational study reported that anti-ARS patients may satisfy criteria for many rheumatic diseases, although attention should always be paid to the possible development of ILD or myositis (87). ILD (mostly NSIP) was the presenting symptom in all 51 anti-EJ patients observed by Liu *et al*., while the myositis was most commonly amyopathic; response to steroids was good, but relapses were observed in 22% of cases (88).The first 2 Japanese anti-Zo patients displayed fever, myopathy, ILD and mechanic's hands, a clinical picture consistent with ASS (89), while anti-KS patients mostly displayed isolated ILD (90).

A cluster analysis conducted on anti-MDA5 patients revealed three possible disease phenotypes: 1) rapidly progressive ILD with poor prognosis; 2) dermato-rheumatologic symptoms (mainly arthralgias) with good prognosis; 3) severe cutaneous vasculopathy, myositis and intermediate prognosis (91).

The positivity for novel MSAs (anti-Ha, anti-Zoα and anti-cN1A) in ILD patients, instead, was found higher than in HCs and apparently marked specific clinical phenotypes of ILD, mostly CTD-ILD (92).

Moreover, anti-NXP2 was found to be prevalent in a subset of patients with bioptic findings of DM although not showing skin rashes (DM sine dermatitis). This clinical entity would account for approximately 8% of DM (93). The association of DM typical rash and muscle weakness with anti-Mi2 antibodies was described in two studies, although they reached different conclusions about the prognosis, described as favourable in the first study, while the second one reported high prevalence of necrotising myositis and malignancy (94, 95). The correlation between cancer and IIM was furtherly described especially for anti-TIF1γ DM/PM, with studies reporting a cancer diagnosis within 3 years since DM/PM diagnosis in approximately 88% of cases. Interestingly, anti-TIF1γ was detectable in serum up to five years before cancer occurrence (96, 97). Moreover, anti-TIF1γ serum titre correlated with myositis activity and, more importantly, with the presence of metastatic or recurrent malignancy (98, 99).

Of note, anti-HMGCR was retrieved in about 48% of patients previously diagnosed as MSA-negative IMNM and was associated with statin exposure, severe muscle weakness, high CK levels, paucity of extramuscular manifestations and good response to treatment (100). Conversely, anti-SRP IMNM may be refractory to steroid therapy in

about 32.5% of cases. Risk factors for disease refractoriness were identified in male sex, severe muscle weakness and concomitant ILD, rapid development of fatty infiltration at muscle MRI and muscular overexpression of B-cell activating factor receptor (BAFF-R) (101). Interestingly, the positivity for anti-cN1A antibodies was reported in about 50% of patients from a IBM cohort, although the disease phenotype did not differ from Ab-negative IBM patients (102).

**Take-home messages**

- Two new possible MSAs were identified, one targeting eIF3 and related to a PM subset with a favourable outcome, the other targeting HSF1 and related to CAM (62, 63).
- LIA for antibody detection seems to be highly specific for IIM in a proper clinical setting, with an increasing rate of false-positive in the case of low pre-test probability and weak positivity (65-68).
- MSAs positivity seems to correlate with extramuscular but not with muscular disease activity (72).
- Several serum biomarkers are associated with ILD severity and poor prognosis (74-79).
- Serum biomarkers could also be useful to identify IIM subsets (80-83).
- Different autoantibodies are associated with different IIM subsets and clinical phenotypes, with implications also on prognosis of these patients (88-99).
- Anti-HMGCR+ IMNM seems to be associated with a good response to treatment, unlike anti-SRP+ IMNM (100, 101).

**Treatment**

The management of IIMs makes use of systemic glucocorticoids (GCs), antimalarial agents and conventional immunosuppressive drugs, but is still challenging for clinicians.

Rituximab (RTX) showed a rate of efficacy of about 75% in refractory IIMs according to a retrospective analysis after 12 and 24 weeks of treatment (103). An alternative option for patients with limited responsiveness to conventional drugs is intravenous immunoglobulins (IVIg) use, allowing remission in half of the cases treated for a mean of 31±25 months. (104). IVIg monotherapy has also been used as first-line treatment for 9 weeks leading to clinically relevant improvement in 42% of patients, with a very fast response (among 3-6 weeks) (105). Short courses of IVIg at high doses (1 day IVIg 2 g/kg repeated 1 month apart for 3 months) may be a long-lasting effective treatment also for refractory dysphagia (106). The subcutaneous formulation (SCIg) showed similar positive results, not only on muscles, but also on skin involvement and dysphagia, allowing remission in about 89% of patients (107) with a greater convenience for the patients compared to IV formulation (108).

As ILD is a common feature of IIM with a significant impact on the prognosis and high short-term mortality rate, effective treatment of this condition remains a priority. A multicentre, single-arm clinical trial demonstrated that the initial combination of Tacrolimus (0.075 mg/kg/day) and GCs might improve the short-term mortality of IIM-ILD (52-weeks survival rate of 88%), with manageable safety profile (109). A combined immunosuppressive regimen with Tacrolimus, high doses of GCs and intravenous Cyclophosphamide demonstrated a significant improvement in forced vital capacity (FVC) and serum levels of KL-6 (110), as long as a significant improvement in 6-month survival in anti-MDA5-positive patients with ILD (111). Opportunistic infections should be carefully monitored during treatment, due to a frequent cytomegalovirus reactivation (110) (111). RTX constitutes a good therapeutic alternative to preserve lung function in patients with CTD-ILD (112). Plasma exchange (PE) showed promising results in RP-ILD in anti-MDA5-positive patients by increasing the 1-year survival rate of RP-ILD patients refractory to immunosuppressants, with the possibility to be used also in patients with active infectious disease (113).

Promising results also come from a prospective open-label clinical trial of tofacitinib in DM: all 10 patients met the primary outcome at 12 weeks (IMACS definition of improvement) and there was a statistically significant change in the CDASI activity score at 12 weeks (114). Bimagrumab, at present only available in clinical trials, is a fully human, receptor-neutralising monoclonal antibody that blocks myostatin from binding to the activin type II receptor. Although the primary endpoint of the study was not met, long-term treatment with bimagrumab in patients with IBM demonstrated a good safety profile and an increase in MRI-measured thigh muscle volume (115).

H.P. Acthar gel [repository corticotropin injection (RCI)] demonstrated its efficacy and safety in 10 active, refractory myositis patient: half of the subjects remained stable and maintained their clinical response after RCI suspension while the other half of subjects flared 4 months after completion of RCI trial (116).

A steroid-free regimen as induction therapy for statin related anti-HMGCR myositis was successful in 14 patients with CPK elevation and normal strength, whereas a regimen of IVIg/GCs/steroid-sparing immunosuppressants was effective in 73% of patients with proximal weakness and should be initiated as soon as possible in order to achieve GCs-free maintenance (117).

The expiratory muscle strength trainer (EMST), currently used in patients suffering of dysphagia from various neurological conditions, did not show significant beneficial effect in IBM patients (118). Moreover, a small study provided preliminary evidence for the use of botulinum toxin for refractory sialorrhoea in many neuromuscular conditions, such as IBM. The injection of botulinum toxin into bilateral parotid and submandibular gland determined a decrease in drooling thickness score after 4 and 6 weeks, with no reported adverse effects (119).

Finally, Kinder *et al*. performed an in vitro study on CRISPR/Cas9 genome-engineering human myoblasts to screen potential therapeutic molecules able to inhibit the type I interferon – HLA I pathway. Among the 12 compounds retrieved, ruloxitinib (a JAK-inhibitor) displayed a potent inhibition of the pathway, along with histone deacetylase inhibitors and hypoxia-inducible

factor 1 inhibitors (120). Notably, the injection of mesenchymal stem cells (MSCs) in mice with carrageenan-induced myositis, reduced the serum levels of TNF-α, IL-6 and CRP, thus supporting the potential use of MSCs in the treatment of myositis (121).

### Take-home messages

- RTX seems to be an effective treatment for refractory IIMs (103).
- IVIg, both as monotherapy or add-on to conventional drugs, have a beneficial effect on muscle involvement, dysphagia and skin involvement (104-106); SCIg have similar efficacy with greater patients' comfort (107, 108).
- Tacrolimus and RTX are good therapeutic options for IIM-ILD (109-112); PE should be considered for the treatment of RP-ILD (113).
- Tofacitinib seems to be effective on skin involvement at 12 weeks based on a clinical trial (114).
- Bimagrumab and RCI may have some effectiveness in the treatment of IBM and refractory myositis, with good safety profiles (115, 116).
- EMST does not seem to be able to improve dysphagia in IBM patients (118); botulinum toxin should be useful for refractory sialorrhoea (119).
- Ruloxitinib and MSCs could be potential treatment for myositis, inhibiting the type I IFN-HLA I pathway and reducing serum levels of pro-inflammatory molecules, respectively (120, 121).

### Conclusions

IIMs are a heterogeneous group of complex CTDs that can have a major impact on patients' lives in terms of quality of life and need for care. Given the rarity of these conditions, their diagnosis and treatment often require experienced clinicians. In this context, this review provides an overview of the most recent updates with the aim at improving the care of these patients also with personalised strategies. In the year that marked the outbreak of the COVID-19 pandemic, during which most of the scientific literature has focused on it, there was no shortage of new insights regarding IIMs. The main steps forward have been made in the field of biomarkers as indicators of disease activity and useful in prognostic stratification, as well as in therapy, promoting an ever more targeted approach to certain disease subsets and their pathogenetic pathways. It is desirable that research on IIMs will offer new contributions in the coming years, in order to obtain a precision medicine that helps in achieving the unmet needs in the management of these potentially life-threatening diseases.

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