Review

Idiopathic inflammatory myopathies: one year in review 2024

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ABSTRACT

Idiopathic inflammatory myopathies (IIMs) are a heterogeneous group of autoimmune diseases characterised by skeletal muscle inflammation and frequently by other organs involvement, in particular lung and skin, but also joints, heart and gastrointestinal tract. Although they are rare diseases, the literature on IIMs has been growing rapidly and many studies have been published in order to clarify the pathogenesis and to better define diagnosis, clinical manifestations (muscular and extra-muscular) and treatment. The purpose of this review is to summarise the most relevant contributions published over the last year on this topic.

Introduction

Idiopathic inflammatory myopathies (IIMs) are a heterogeneous group of rare and complex autoimmune disorders with varying clinical manifestations: muscle weakness is usually the classical clinical manifestation, but other organs can be affected, in particular lungs, skin, joints, heart and gastrointestinal tract.

Different myositis-specific auto-antibodies (MSA) have been identified and, on the basis of clinical, histopathological and serological features, IIMs can be classified into several subgroups: dermatomyositis (DM) (including clinically amyopathic dermatomyositis CADM), antisynthetase syndrome (ASSD), immune-mediated necrotising myopathy (IMNM), inclusion body myositis (IBM), polymyositis (PM) and overlap myositis (OM) (1).

In this manuscript, following the previous papers of this "one year in review" collection (2), we reviewed all original scientific articles published in the past year that addressed pathogenesis, muscular and extra-muscular manifestations, diagnosis (autoantibodies and imaging) and treatment of IIMs.

We performed a Medline search of English language articles published in the PubMed database from 1st July 2023 to 31st June 2024. The following key words were used: "idiopathic inflammatory myopathies", "myositis" (MeSH terms and semantic search), "pathogenesis", "diagnosis", "clinical manifestations", "therapy". All the articles obtained from such research were first screened by their abstract content. After the first round of selection, the full text of each article was assessed and the most relevant ones were included in this review.

Pathogenesis

Although the pathogenesis of IIMs remains not completely understood, it mainly consists in the activation of the immune system (both innate and adaptive) by environmental triggers in genetically predisposed subjects. Many of the proposed pathogenetic factors have also been proposed as possible biomarkers for IIMs (Table I).

New data on the relationship between the genetic background and the occurrence of IIMs has been obtained: Slater *et al*. observed an association between HLA-DRB1*03:01:01 and IBM. Interestingly, patients with the above-mentioned genotype developed symptoms on average five years earlier than patients without (3).

A wealth of evidence has pointed to the involvement of the adaptive branch of the immune response in the pathogenesis of IIMs. Reay and colleagues demonstrated a key requirement for T cells in driving histidyl-tRNA synthetase (HRS)-induced myositis in an animal model of experimental myositis (4). The role of T-cells has also been studied in muscular biopsies, suggesting that also identical expanded T-cell clones persisted at follow-up in the muscle tissue of two patients, which suggests

Table I. Novel biomarkers proposed in IIMs.

Interferon-λ3 (12)	Poor prognosis in anti-MDA5+DM-ILD.
p-STAT3/IL-17 (15)	Positive correlation with elevated levels of transaminases, myocardial enzymes, and higher scores of the health assessment questionnaire score in DM.
ESR1 (8)	Rituximab responders.
miRNAs (19)	Significantly different expression in muscle tissue of IBM patients.
YKL-40 (110)	PM/DM *vs*. HC.

a role in the disease chronicity (5). An abnormal T cell response, intended as an increased clonal expansion of the T Cell Receptor (TCR) B repertoire in muscle tissue correlated with a higher disease activity (6). Programmed-cell-death 1 (PD-1) expression is associated with T-cell activation and exhaustion. PD-1 cells infiltrated into PD-L1- expressing muscles and high levels of cytolytic molecules has been observed in active IIM patients (7).

Although the predominant cells type in the pathogenesis of IIMs are T cells, also activated B cells may play important roles in the disease pathogenesis. For example, it is well known that IIM patients respond differently to rituximab (B-cells depleting therapy). A recent hypothesis suggests as a novel estrogen-receptor-1 ESR1 (sphingomyelin phosphodiesterase acid-like 3B pathways) may mediate RTX response in IIM patients (8).

Interestingly, also the innate immunity represents a key player in pathogenesis of IIMs, especially for IMNM. For example, TNF-like weak inducer of apoptosis (TWEAK) and its sole receptor fibroblast growth factor-inducible 14 (Fn14) were overexpressed in IMNM muscle biopsies correlating with disease severity, myonecrosis, regeneration and inflammation infiltrates (9). TLR4 and the inflammatory cytokine IL-7 could represent immune biomarkers able to differentiate between IMNM patients' subgroups (SRP+ *vs*. HMGCR+ patients). Indeed, both seemed to be at significantly higher levels in SRP+ patients (10). PTX3 levels, a component of humoral innate immunity, were significantly higher in patients with IIM compared to controls and showed a direct correlation with creatine kinase (CK), Myositis Disease Activity Assessment Visual Analogue Scale (MYOACT) and the physician's global assessment of disease activity (11).

A Japanese study investigated the prognostic role of interferon-λ3 in anti-melanoma differentiation-associated gene 5-positive (MDA5) DM-associated interstitial lung disease (ILD), suggesting as higher IFNλ3 levels, as well as older age and lower PaO2, were significantly associated with poor prognosis and shorter life expectancy (12). Additionally, in anti-MDA5+ DM-ILD novel potential biomarker has been identified including IFN-β signalling and eukaryotic translation initiation factor 2 alpha kinase 2 (EIF2AK2) (13). In patients with anti-MDA5-DM the role of infections is crucial for the patient's survival, the expansion of exhausted $CD8^+$ T cells may play a role with an increased risk of fungal pneumonia in anti-MDA5-DM (14).

The p-STAT3/IL-17 signalling pathway seemed linked to muscle inflammation and necrosis in DM. The p-STAT3 levels were correlated with the number of Th17 cells as well as muscle and serum IL-17 levels.

Interestingly, the correlations of the p-STAT3 level with high values of transaminases, myocardial enzymes and the health assessment questionnaire score too, were significantly positive, while the correlation with manual muscle testing-8 was significantly negative (15).

Inclusion body myositis (IBM) represents a unique disease within IIMs with a dual myodegenerative-autoimmune physiopathology. Circulating miRNA provided new potential disease biomarkers. miRNAs in the serum of IBM patients were different compared to healthy controls, thus possibly reflecting pathological mechanisms typical of IBM and potentially representing disease biomarkers (16). Also, immunisation with cN1A peptide may present a potential role of such antibodies for diagnostic purposes (17). New evidence demonstrates that the presumed pre-degenerative condition IBM that can provide a link between inflammation and protein overload can be driven by senescent fibro-adipogenic progenitors indicated by expression of p21, increased β-galactosidase activity and associated with various pathways of inflammatory mediators and markers of senescence (18). Impairment of this cell type can result in reduced regeneration of skeletal muscle and initiation or sustainment of chronic inflammation and subsequent cell stress including protein overload.

A recent study suggests a possible role in IIM pathogenesis also for extracellular vesicles (EVs) for CAM (cancer associated myositis) and DM (19).

Abad *et al*. examined the role of interferon γ (IFNγ) using NOD female mice deficient in the inducible T cell costimulator, which have previously been shown to develop spontaneous IFNγ-driven myositis, mimicking the human disease. Using muscle proteomic and spatial transcriptomic analyses they revealed profound myofibre metabolic dysregulation in these mice and muscle mitochondrial abnormalities and oxidative stress markers in diseased mice. These results suggested that mitochondrial dysfunction and inflammation are interconnected in a self-maintenance loop, opening perspectives for mitochondria therapy in myositis (20).

Take-home messages

- T-cells have a crucial role for the pathogenesis of IIM (4), although also B cells mediated immunity is involved (8).
- The innate immunity may also be involved in IIM pathogenesis (9, 10).
- The prognosis of patients with anti-MDA5-ILD can be influenced by specific biomarkers such as IFNλ3 and EIF2AK2 (12-14).

Laboratory investigations and autoantibodies

There is a paucity of available biomarkers of disease activity in IIMs and some serum cytokines/chemokines

could hold potential as candidate biomarkers that may be also promising for diagnostic and monitoring purposes. Myositis patients with active disease had higher levels of lymphotoxin-α, CXCL-9, MIP-1α, MIP-1β and MMP-3 than patients in remission (21). CSCL16 may be useful for the monitoring of patients with rapidly progressive ILD (RP-ILD) (22)

Recently the serum uric acid concentration in IIM patients may be associated with differences in prognosis although with contrasting results. For example, higher uric acid levels seem to be associated with systemic arterial hypertension (22). On the contrary, hypouriacemia was associated with a higher mortality rate in anti-MDA5-positive ILD patients (24)

Myositis-specific and myositis-associated antibodies (MSA and MAA) are associated with different clinical phenotypes and prognoses, and an increasing number of associations has been described in recent years (2). Despite being part of the standard evaluation of IIM patients (23), the clinical relevance and applicability of these associations are not always clear or straightforward (24). Most studies are retrospective and include a small number of patients, and few are longitudinal. Even landmark studies have significant limitations (24). Therefore, it is often important to integrate the results of several studies to understand which associations are reproducible in different cohorts and represent clinically relevant differences.

In a Portuguese cohort of IIM patients, more than 90% of patients had at least one MSA or MAA, although less than two-thirds of patients had a positive indirect immunofluorescence assay (IIFA) on HEp-2 cells (25). Similarly, a study performed in Oman found that almost a third of IIM patients had negative antinuclear antibodies (ANA) (26). These results highlight that patients with negative ANA can be assessed for MSA and MAA. The most frequent MSA was anti-histidyl tRNA synthetase (anti-Jo1) in both these studies(25), (26), whereas a Chinese study identified more commonly anti-MDA5 autoantibodies (27). The most frequent MAA was anti-Ro in all three studies (25-27).

Notably, the prevalence of MSAs may vary with time. In a monocentric study, the most frequent MSA before the COVID-19 pandemic was anti-Mi2, but after the pandemic onset, anti-TIF1γ became the most commonly identified MSA (28). This higher anti-TIF1γ incidence was associated with a higher incidence of cancer-associated myositis, most likely due to the impact of the pandemics on the management of non-COVID-19 related diseases, including cancer screening (28).

The prevalence of autoantibodies may also vary with ancestry. In a North American study, anti-Jo1 and anti-MDA5 autoantibodies were associated with self-identified race and ethnicity (29). African American subjects had increased odds of being anti-Jo1-positive compared to non-Hispanic White subjects, although this difference was not significant after adjustment for age and gender. Non-Hispanic White patients were less likely to be anti-MDA5-positive (29).

In a Swedish study, anti-Four-and-a-half-LIM-domain 1 (anti-FHL1) autoantibodies were present in 27% of patients with IIM (30). Other autoimmune diseases had lower prevalence and levels of anti-FHL1(30). Importantly, anti-FHL1-positive IIM patients were seronegative for other autoantibodies in 25% of the cases, highlighting its potential as a diagnostic biomarker 24) (30). Of note, anti-FHL1 autoantibodies rarely appeared after initiating treatment (30).

The role of MSA is crucial for the Classification Criteria of Anti-Synthetase Syndrome (CLASS) project, a large international multicentre study that gathered serum samples from patients followed at several international centres for central antisynthetase antibodies (anti-ARS) reading with immunoprecipitation and at least one other concordant method (31). The results from local anti-ARS testing were compared with the central (gold-standard) reading to assess how local immunoassays perform in real-world settings (31). This study confirmed the reliability of real-world anti-Jo1 detection methods. However, the identification of anti-non-Jo1 anti-ARS, particularly anti-PL7 and rarer antibodies, such as anti-OJ and anti-KS, was not consistently reliable (31). Curiously, a Japanese study raised concerns about the comprehensibility of RNA immunoprecipitation, which is currently considered the gold standard for identifying anti-ARS but may miss a few patients' autoantibodies that can be identified using ELISA (32). Despite this, anti-ARS have some of the most reliable and reproducible clinical associations among the MSAs. Anti-ARS were independent predictors of ILD and arthritis in IIM patients (33). In particular, anti-PL7-positive ASSD patients had more extensive fibrosis and severe ILD than other groups (34).

Anti-MDA5-positive DM is often clinically amyopathic, frequently presenting with ILD. However, a German autopsy study showed that clinically amyopathic patients may present significant inflammatory changes in several skeletal muscles (35). This observation suggests that muscle may be sub-clinically affected in a widespread fashion in these patients (35). Similarly, anti-MDA5-positive DM patients have the greater severity of oesophageal involvement, even in asymptomatic patients (36). Male patients with anti-MDA-5 DM seem to have a more severe skin rash and a worse prognosis compared to females (37). In patients with anti-MDA-5 positivity, an increased severity of ILD has been identified in patients with higher BAFF concentrations (38) and higher serum interferon-λ3 levels (12).

Anti-small ubiquitin-like modifier activating enzyme (anti-SAE) autoantibodies are rare MSAs. A French multicentre study compared anti-SAE-positive and anti-SAE-negative DM patients (39) and an Italian monocentric study compared anti-SAE DM patients with anti-Mi2 DM patients (42). In both cohorts, most anti-SAE-positive patients had skin involvement (39, 40), and had a higher prevalence of skin itching and shawl sign than anti-Mi2 DM patients (40).

Take-home messages

- In the monitoring of IIM, a role can be played by the newly discovered biomarkers (21, 22) but also by the older ones like uric acid (23, 24).

- Studies on antisynthetase antibodies identified novel peculiar laboratory challenges (33, 34) and influence on particular subsets of the disease (35, 36)
- anti-MDA5 positivity has been associated with peculiar clinical features in IIM patients (37-40).

General and muscular involvement

A retrospective study demonstrated that the 2017 EULAR/ACR classification criteria for idiopathic inflammatory myopathies (IIM) are both sensitive and specific for accurately classifying IIM patients in the Mexican population (41), although they lack sensibility for patients with ASSD (42). This may be because several extra-muscular manifestations are not included, and over ten MSA are omitted in these criteria (43). The classification of the patients according to homogeneous clusters with different clinical involvement may be more useful for prognostic stratification (44). Ten years after the international ENMC criteria for IBM, an international ENMC workshop in 2023 produced a full revision (45). Regarding terminology, a consensus was achieved to omit the previous terms "hereditary" or "sporadic" and simply use IBM alone. Instead, for all genetically mediated conditions, the respective gene name should be used (*e.g.* GNE, VCP, etc.). Inflammation in a skeletal muscle biopsy continues to be an obligatory parameter. Supportive criteria include muscle pathology parameters on inflammation, mitochondrial changes or protein accumulation as well as cN1A autoantibodies, ultrasound of the deep finger flexors, or muscle MRI findings.

In addition to clinical, laboratory, and imaging data, muscle biopsy may assist in the diagnosis of myositis and its mimickers**.** In recent studies, the expression of CD163 and MHC class I in muscle tissue were significantly elevated in the IIM group compared to controls. Based on the CART analysis it was developed an algorithm that combines CD163 and MHC class I expression, achieving a diagnostic accuracy of 95.5% (46). The density of CD163+ macrophages in the perimysial connective tissue may also serve as a potential marker for predicting the prognosis of IMNM (47). In 62 muscular samples, correlations have been observed between the density of CD163+ macrophages in connective tissue and the symptom duration, cardiac involvement, dysphagia, CK levels, CRP and ESR.

In IBM, type 2 myofibres showed pronounced signs of muscle atrophy, accompanied by a higher number of associated quiescent satellite cells, centrally positioned myonuclei, macrophages, and capillaries compared to type 1 fibres. In contrast, type 1 fibres showed abnormal enlargement with larger myonuclear domains and fewer nuclei and capillaries per area compared to type 2 fibres (48).

A resident memory T cell signature within muscle tissue has been discovered in IIM and provides a transcriptomic map aimed at identifying novel therapeutic targets for IIM (5).

Imaging plays an important role in studying muscular involvement in IIM and in differentiating IIM from mimics. To aid in the diagnosis of IIM, Gramegna *et al*. (49) proposed a visual quantitative score for muscle oedema in lower limb MRI showing that a cut-off score ≥18 could accurately classify patients having an IIM. As well as, in sporadic IBM, significant differences were observed in all quantitative magnetic resonance imaging (qMRI) parameters averaged over all muscles when compared to healthy controls (50). MRI aids in identifying the presence and distribution of muscle inflammation, as well as specific disease characteristics that may influence therapeutic decisions. For example, comparing thigh MRI between anti-SRP myopathy and anti-aminoacyl-tRNA synthetase antibody-positive myositis (anti-ARS myositis), fascial oedema was identified only in the ARS group while gluteus maximus muscle lesions occurred more frequently in the SRP group (51). Finally, a positive correlation was demonstrated between histopathological findings (amount of fat, variation in myofibre sizes and inflammation) and quantitative magnetic resonance imaging (qMRI) fat fraction (FF) and water T2 mapping (52). A single-centre retrospective study (53) in IIM patients, identified as the baseline MMT-8 score showed a negative correlation with muscle oedema, fascial oedema, and muscle atrophy while levels of creatine kinase and aspartate transaminase positively correlated with muscle oedema. Another study (54) demonstrated that intravoxel incoherent motion diffusion-weighted imaging (IVIM-DWI) and fat quantification using 3.0 T MRI may be useful in predicting electromyography (EMG) findings in patients with polymyositis.

The administration of intravenous contrast media administration is not routinely recommended (55).

Quantitative muscle ultrasound can also be used to evaluate disease status in IIM patients. Muscle thickness of rectus femoris and echo intensity of biceps brachii and vastus medialis correlate with modified Rankin Scale, Physician Global Activity Assessment, Health Assessment Questionnaire and Manual Muscle Testing-8 (56). Similar results were also observed by Yoshida *et al*. (57). Furthermore, histopathologically, a correlation was observed between the number of infiltrating CD3+ inflammatory cells and muscle EI in the non-IBM group, but not in the IBM group. Differences in fascial thickness of vastus lateralis (FT-VL) and muscle bulk between males and females were identified, as well as a correlation between fascial thickness and disease progression (58).

In IBM, an increased echo intensity in the flexor digitorum profundus (FDP) has been reported, while the flexor carpi ulnaris (FCU) was relatively sparing (59).

Regarding nailfold capillaroscopy, a study suggests the lack of a significant correlation between the capillaroscopic abnormalities and the laboratory or clinical parameters of disease activity (60). On the contrary, in juvenile dermatomyositis, a nailfold capillary End Row Loop (ERL) loss is associated with a worsening of clinical symptoms (61).

Take-home messages

- The usefulness of the EULAR-ACR classification criteria is still under debate (43-45) and novel classification methods have been proposed (46).
- Novel biomarkers for muscular biopsies have been proposed (48-50).

- The study of the muscle by MRI (51-56) and US (57-61) is increasing our knowledge about the muscular inflammation patterns in IIM.

Extra-muscular manifestations

IIM can affect other organs besides muscles, with a consequent worsening of patients' prognosis. A summary of extra-muscular manifestations is provided in Table II.

Pulmonary involvement

One of the main extra-muscular involvements is pulmonary involvement, usually represented by an ILD. High-resolution chest tomography (HRCT) is the gold standard technique to detect ILD.

Quantitative ILD (QILD) score is gaining validity in IIM, showing that UIP pattern was significantly correlated with a radiological progression of ILD. In addition, high baseline QILD scores may have a negative prognostic value (62).

Risk factors for predicting ILD progression were investigated by quantitative lung densitometry, identifying higher attenuation areas and a mean lung attenuation in patients with ILD progression (63)

A prognostic score (CROSS score) was proposed to predict the risk of developing a rapidly progressive (RP)-ILD in anti-MDA5+ DM patients: in addition to clinical and laboratory parameters the CROSS score could provide a simple and accurate model to predict RP-ILD onset and its associated mortality risk (64). Ground glass opacity (GGO) score may be a reliable predictor for risk stratification in anti-MDA5-DM (65).

Some serum biomarkers could predict development of RP-ILD. Elevated serum B-cell activating factor (BAFF) (38) and secreted phosphoprotein 1 (SPP1) (66) levels were found to be associated with RP-ILD in anti-MDA5+DM patients.

Progressive fibrosing interstitial lung disease (PF-ILD) may occur in patients with IIM but its characteristics have not been studied as in other connective tissue diseases (CTDs). In a retrospective cohort study by Zanatta *et al*. PF-ILD was predicted by anti-MDA5, heliotropic rash, xerostomia and xerophthalmia (67).

Table II. Summary of extra-muscular involvements in IIM

Lung involvement	QILD score is significantly correlated with FVC and DLCO. Among HRCT pattern, UIP is significantly correlated with radiological progression of ILD (62).
	Elevated CEA levels, anti-EJ positivity, anti-Ro52 positivity, anti MDA5 positivity and HAA are prognostic factors for ILD progression (63).
	CROSS score (CRP, anti-Ro52 positivity, male sex, and short disease duration) can be an accurate model to predict RP-ILD onset and mortality risk in anti-MDA5-DM patients (64).
	GGO score can be a reliable predictor for risk stratification in anti-MDA5-DM patients (65).
	Higher serum levels of BAFF and SPP1 can be predictors of RP-ILD in anti-MDA5-DM patients (38, 66).
	Progressive ILD in IIM patients can be predicted by anti-MDA5, heliotropic rash, xerostomia and xerophthalmia (67)
	PH-DM patients have higher IL-6, IL-10 and lower IL-17, double positive (CD4+ CD8+) cell ratio and lower B lymphocyte ratio than in the non-PH-DM patients (68).
Heart involvement	Older age, high disease activity, high levels of interleukin-17A and of LDH, AMA and anti-MDA5 antibody are significantly correlated with development of MI (69).
	Pulmonary hypertension, arrhythmia, AMA-M2 positivity and high levels of NTproBNP are more prevalent in IIM patients with MI (70).
	Hs-cTnI levels are associated with MI in IIM patients and are significantly correlated with disease activity and with a poor prognosis (71).
	Tracking echocardiography has a prognostic value in IIM patients (72).
Oesophagus	HRiM is a safe, feasible and repeatable exam to detect oesophageal dysmotility. A worsening of dysphagia is associated with MDA5 antibodies and with a reduced DLCO (36).
Microcirculation	Capillaroscopic SSc pattern is observed mostly in DM and overlap myositis, and it is associated with skin involvement and anti-TIF-1γ autoantibodies (60).
Malignancy	NPC screening is highly recommended, especially in Asian IIM patients. NPC is more associated with skin involvement, dysphagia, and TIF1γ positivity (73).
	In European population a positive causal effect among IIM diagnosis and the risk of lung squamous cell carcinoma was observed (75).

Pulmonary hypertension (PH) may be a complication of IIMs, and in DM may be associated with higher IL-6, IL-10 and lower IL-17 levels, a double positive ($CD4^+$ $CD8^+$) cell ratio and a lower B lymphocyte ratio than non-PH-DM patients (68).

Heart

Clinically evident cardiac involvement is not common. High disease activity, high levels of interleukin-17A and of LDH, anti- mitochondrial-antibodies and anti-MDA5 antibodies were significantly correlated with the development of cardiac involvement (69). Distinct cardiac structural and functional changes, pulmonary hypertension, arrhythmia, positive serum anti-mitochondrial-M2 antibody and higher levels of NT-proBNP can be associated with death for cardiac disease (70).

Serum biomarkers are useful to detect cardiac involvement. For example, high-sensitivity cardiac troponin I (hs-cTnI) are associated with cardiac involvement and poorer prognosis in IIM patients (71).

Additionally, also reduced left ventricular (LV) global longitudinal strain (GLS) using speckle tracking echocardiography can represent a negative prognostic factor in IIM (72).

Oesophagus

Oesophageal involvement and a consequent dysphagia, are common in IIM. In addition to the widely used videofluoroscopy, high-resolution impedance manometry (HRiM) is a safe, fea-

sible and repeatable exam that can provide a rapid detection of oesophageal dysmotility in patients with IIM (36).

Malignancies

Adult-onset IIM are associated with an increased risk of cancer, particularly within the 3 years prior to and the 3 years after IIM onset. Nasopharyngeal carcinoma (NPC) is particularly frequent in Asian population and NPC-associated IIM are characterised by a more skin involvement, dysphagia, and a more frequent positivity for anti TIF1γ, whereas arthritis, Raynaud's phenomenon, and ILD were less common (73). Some genes linked to the negative regulation of viral gene replication pathway and in the type I interferon responses are associated to NPC-associated IIM (74).

In a European population, a diagnosis of IIM was a risk factor for the developmeant of LC (75).

This well-established routine has now received support and a detailed regimen on when to screen, how to screen and if or for how long a follow-up screening should be performed(76). The group provides a traffic-light system with three categories for cancer screening, based upon a high risk (red), intermediate risk (yellow) or low risk (green) and suggest a basic or enhanced screening and possible screening for nasopharyngeal carcinoma. Depending on the risk group, the screening should be performed with an enhanced protocol once per year for three years (high risk), or only at time of diagnosis (intermediate risk) or only a basic screening at time of diagnosis (low risk).

Take-home messages

- ILD is the main extra-muscular involvement in IIM, particularly in anti-MDA5 patients (66, 67).
- Novel biomarkers for cardiac involvement have been proposed (71-74).
- New data have been published about the role of nasopharyngeal carcinoma in Asian patients (75, 76).

Particular subsets of disease

Even though ASSD is typically characterised by the triad comprised of arthritis, myositis and ILD, many other organs or systems can be involved. Although not considered a typical localisation of disease, a non-neglectable ratio of ASSD patients may suffer from subclinical myocardial involvement identified by cardiac magnetic resonance (77).

When specifically focusing on ILD, which remains the most common and fearsome feature of ASSD, as well as a predictor of mechanic's hands (78), its extent and severity seems to be predicted by the positivity of anti-PL7, strongly associated to a more aggressive lung involvement (34, 79).

Regardless of specific disease features, ASSD remains a complex condition and patients, who are diagnosed with a mean diagnostic delay of one year, are burdened by several complications interfering with work and social activities (80). At the same time, also within the spectrum of all IIMs, ASSD seems to be associated to a higher hospitalisation ratio and worse outcome in case of COVID-19 infection (81).

Inclusion body myositis (IBM) represents one of the most severe form of myopathies, both for disease severity and poor response to treatment. Despite the lack of robust data on direct and indirect costs related to this condition, a recently published German study has estimated a mean total annual cost of US$ 102.682 pro capita, with an estimated total national cost ranging from US$ 42,7 million to 213,7 million (82). To such a relevant burden contribute palliative cares, too (83), the involvement of upper limbs and hands (84), which is closely related to the loss of functionality and to overall disability and, more relevantly, the evidence that also younger patients (median age at disease onset 36 years in a Swedish cohort) may suffer from IBM (85).

Among the clinical features, the involvement of axial muscles should not be overlooked, as dropped head syndrome and/or camptocormia have resulted to be highly specific for IBM in case of >70-year-old patients (86).

INMN are typically characterised by an abrupt onset and aggressive myositis with high levels of CK. Cutaneous involvement has been poorly described, but a Japanese study has reported that up to 42% of HMGCR positive IMNM may present a various range of skin lesions, whose histological findings present, just like in muscle biopsies, Bcl-2-positive lymphocytic infiltration (87). Still focusing on anti-HMGCR antibodies, they have an excellent positive predictive value and their positivity strongly addresses to a diagnosis of IMNM, with clinical features of proximal weakness, dysphagia and high levels of CK; notably, despite the fall of antibodies titre upon treatment, rarely become negative (88).

Immune checkpoint inhibitors (ICI), increasingly employed in oncology, may cause immune-related adverse events (irAEs); in particular, myositis are one of the most fearsome, often requiring the discontinuation of the treatment and, in some cases, intensive care unit admission. Nevertheless, the incidence seems low and in a Dutch study only 6 out of 5561 ICI-treated patients eventually developed an ICI-related myositis (89).

Take-home messages

- Lung involvement is the most frequent extra-muscular manifestation in patients with ASS (79-81), although cardiac diseases are also underestimated (78).
- IBM is one of the most severe forms of IIM and is associated to high disability (85-87) and high social costs (84).

Treatment

Although the cornerstone of idiopathic inflammatory myositis (IIM) therapy remains the steroid in combination with traditional immunosuppressive drugs (methotrexate, azathioprine, mycophenolate mofetil, calcineurin inhibitors, cyclophosphamide), more and more biologic therapies, in addition to the well-known rituximab, are used for their effectiveness and for their targeted action as steroid-sparing agents (90). In ASS patients, RTX remains the cornerstone of the treatment, to be effectively employed also in recalcitrant cases (91), while calcineurin inhibitors, given in association with oral steroids, seem to be a safe and effective alternative (92).

Interestingly, in the last year, the ther-

apeutic possibilities have increased thanks to the growing experience gained with the numerous biologic therapies available.

JAK inhibitors

Many studies have focused on evaluating the efficacy of JAK inhibitors (JAKis: tofacitinib, baricitinib, upadacitinib) for IIM treatment, since Janus kinases play a role in the signal transduction of interferon and genes regulated by IFN are up regulated in IIM (93). A summary of the studies is reported in Table III.

The largest source of data about JAKis in IIM is represented by a meta-analysis (93) which took into account the efficacy of baricitinib, tofacitinib and ruxolitinib in patients with dermatomyositis (DM) and polymyositis (PM) showing significant reductions in Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI) and significant improvement in Manual Muscle Testing (MMT) in the face of rare side effects. Tofacitinib has proven to be effective for treatment-refractory IIM (94), especially for cutaneous lesions. Patients treated with tofacitinib were able to reduce the dose of steroid for significant improvement of skin domain, refractory to previous therapy (95, 96). Tofacitinib has been also tested with encouraging results in the treatment of antri-MDA5 positive patients (96), especially in patients with shorted disease duration (97). A possible role of JAKis may be also identified in the treatment of severe ILD in anti-MDA5 patients (98). Some preliminary data (99) (100)also allow good feedback from the use of upadacitinib for IIMs, on the cutaneous domain.

Preliminary evidences support for the use of abatacept (ABA) for the treatment of ASSD-associated ILD (101) with low toxicity. Belimumab, an anti-B lymphocyte stimulator monoclonal antibody reduced muscle pain and led to a significant improvement in cutaneous manifestations (102).

Rituximab, an anti-CD20 monoclonal antibody, is known to be an effective therapy for severe and refractory IIM, allowing steroid tapering, and the main data derived from RIM (rituximab in myositis) trial (90) and a recent study confirmed with hypothesis, suggesting that patients treated with rituximab may show a sustained improvement in lung function test values with the possibility of reducing or discontinuing the steroid and oxygen therapy (91).

Table III. Therapeutic molecules studied in 2024 for the treatment of IIM. The domains or the clinical situations in which the different therapies have been shown to be effective are in the right column.

Molecular pathway	Therapy	Involvement
Jak inhibitor	Tofacitinib (94)	Cutaneous involvement, improvement of MMT8 in DM
Jak inhibitor	Baricitinib (98)	ILD in antiMDA5 (case series)
Jak inhibitor	Upadacitinib (99)	Cutaneous involvement in DM (case series)
Anti-CTLA4	Abatacept (101)	ILD in ASSD (case series)
Anti-Blys	Belimumab (102)	Cutaneous involvement in DM
Anti-CD20	Rituximab (91)	Recurrent progressive ILD in ASSD, severe and refractory IIM

Intravenous immunoglobulins (IVIg) are an effective therapy used for IIMs, both for muscular and extra-muscular manifestations (103). Aggarwal *et al.* (104) led the first international, randomised, placebo-controlled phase 3 trial demonstrating the safety of IVIg for DM patients. The most reported post-infusion side effects were headache, nausea and fever, but also thromboembolic events presented after treatment with high dose IVIg.

A variety of combination therapies are used in clinical practice for the most severe and refractory disease concerns, as in MDA5 myositis. The usage multiple and more aggressive therapies may improve the survival rate in MDA5 patients (105), although with a higher risk of complication such as opportunistic infections and leukopenia (106). Combination therapy may also be useful for the treatment of refractory IIM with ILD and myocarditis (107), particularly a combination of RTX and mycophenolate.

How to adequately treat immune-mediated necrotising myopathies (IMNM) is not yet known, but most studies have highlighted the good therapeutic effect of IVIG, possibly associated with immunosuppressant or corticosteroid (108). For IMNM prednisolone, tacrolimus, and intravenous immunoglobulin combination therapy has proven to be effective in a small study including 8 IMNM patients who were refractory to prednisolone or dual therapy with prednisolone and immunosuppressants (109).

Take-home messages

- Several studies reported a possible role of JAKi in the management of severe and/or refractory patients with IIM (95-102).
- In severe cases, in particular in anti-MDA5 rapidly progressive ILD, a combination therapy may be proposed (107-109).
- The first randomised placebo-controlled trial for the use of IvIg in IIM patients has been conducted (106).

Conclusions

Several studies added significant contributions to the IIM literature in 2024. 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 aiming at improving patients' care.

We critically analysed the progresses in the knowledge of disease pathogenesis and the advances in the disease treatment, passing by new insight into disease diagnosis and clinical manifestations. In particular, thanks to the great steps in understanding IIM pathogenetic mechanisms, their therapeutical horizons have been expanded. Much laboratory research has explored the role of serum cytokines/chemokines as potential biomarkers.

Numerous works have focused on the phenotyping of different patients: not all IIMs are the same. Clinicians should be aware that every IIM case requires a detailed assessment, including

the detection of MSA and possible extra-muscular manifestations. Additionally, the pathogenetic role of some of the MSA and on their correlation with some features of the disease has been studied, and how they can influence different clinical manifestations and potential response to the treatments.
Although further studies and research are needed to improve the knowledge on these rare and complex diseases, significant acquisitions were achieved in the assessment of IIMs.

Competing interests

J. Schmidt has received payments for advisory boards, speakers honoraria, travel expenses and research projects from Abcuro, Argenx, Biotest, CSL Behring, J&J, Kezar, LFB, Lupin, Momenta, Novartis, Octapharma, and UCB.
The other authors have declared no competing interests.

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