Review

Idiopathic inflammatory myopathies: one year in review 2022

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ABSTRACT

Idiopathic inflammatory myopathies (IIM) are a heterogeneous group of disorders in which chronic inflammation of the skeletal muscle, leading to muscle weakness, is a common feature. Different phenotypes have been identified within the IIM spectrum based on extra-muscular manifestations, immunology, muscle histology, responsiveness to therapy, and prognosis. The pathogenesis, classification, treatment, and prognosis of the different IIM subtypes are subject to active discussion and research. This review highlights the most relevant literature published on this topic over the last year.

Introduction

Idiopathic inflammatory myopathies (IIM) are a heterogeneous group of disorders in which chronic inflammation of the skeletal muscle, leading to muscle weakness, is a common feature. Dermatomyositis (DM) generally includes the classic skin and muscle involvements of IIM. Antisynthetase syndrome (ASS) is characterised by myositis, interstitial lung disease (ILD), arthritis, or mechanic's hands in the presence of an antisynthetase antibody. Immune-mediated necrotising myopathy (IMNM) is characterised by severe muscle involvement, with necrotic muscle fibres and scarce or no inflammatory cell infiltrates. Finally, inclusion-body myositis (IBM) is suggested by finger flexor or quadriceps weakness and the presence of rimmed vacuoles in the muscle biopsy. Myositis-specific (MSA) and myositis-associated (MSA) antibodies are associated with distinct clinical features, adding further complexity to the IIM subtypes. This paper aims to update the latest knowledge on IIM, following a well-established format as in previous years. For this review, we performed a Medline search of English-language articles published in the PubMed database from 1st January 2021 to 30th June 2022. The keywords used were "idiopathic inflammatory myopathies", "myositis" (MeSH terms and semantic search), "pathogenesis", "diagnosis", "clinical manifestations", and "therapy". All the articles were critically reviewed to select the most relevant publications.

Pathogenesis

Despite the progress achieved in the last years (1, 2), the exact cascade of mechanisms leading to the occurrence of different subsets of IIM is largely unknown. However, it probably involves a dysregulation of the immune system determined by a genetic susceptibility on which different epigenetic triggers act.

Regarding general genetics advances, a family-based study based on a Sweden nationwide healthcare register (3) highlighted a risk of aggregation among first-degree relatives and a heritability of about 20%, thus confirming that clinicians should consider the possible occurrence of family clusters carefully. Many studies focused on identifying genes involved in the pathogenesis of IIM, mainly linked to the IFN pathway. Xiao *et al*. (3) identified ten hub genes in muscle tissue as potential biomarkers in DM through bioinformatic analysis. Interestingly, all these genes are involved in the immune response to virus infections and the type I interferon (IFN) signalling pathway. Chen *et al*. confirmed the role of IFI16 as a putative hub gene in DM and polymyositis (PM) and identified four other putative hubs (TRIM22, IFITM1, IFI35, and IRF9) (4). Similar results were found in studies looking for IBM marker genes (5). Conversely, Cordel *et al*. highlighted the possible role of TRIM33 (the TIF1γ gene) somatic mutations in triggering anti-

TIF1γ DM by coding for neoantigens that induce an autoimmune response (5). Remuzgo-Martinez *et al*. identified some human leukocyte antigens (HLA) that confer susceptibility for the ASS, particularly a higher frequency of HLA-DRB1*03:01 and HLA-B*08:01 alleles compared to healthy individuals (6). Mucin 1 (Krebs von den Lungen, KL-6) is a transmembrane mucin found on lung cells, and it is a biomarker of interstitial lung disease (ILD). KL-6 levels are high in ASS and idiopathic pulmonary fibrosis (IPF) and are not significantly different in the two diseases. However, MUC1 rs4072037 TC and CC genotypes and C allele frequencies were significantly different between ASS-ILD+ and IPF patients (7). Of note, high serum KL-6 is also associated with rapidly-progressive ILD (RP-ILD) in anti-melanoma differentiation-associated protein 5 (anti-MDA5)-positive DM patients (8).

On the other hand, the immune system's dysregulation is responsible for numerous pathological implications in IIM. In Chinese patients, CD19+ B cells and naïve B cells are expanded, but a small number of memory B cells is found (9). Furthermore, the different levels of the B cell subtypes were different in different clinical subgroups: patients with a rash had lower non-switched memory B cells. The higher frequency of CD19+ B cells was associated with anti-MDA5 positivity. Also, follicular T helper (TFH) cells are increased in anti-MDA5 syndrome (10). TFH cells stimulate B cell differentiation and autoantibody production, so they may play a key role in the pathogenesis of the autoimmune process. Some immune-cell-activating antigens are more expressed on IIM muscle cells. CD26 is a membrane glycoprotein which acts as a T lymphocyte activation antigen. CD26 is selectively expressed in IIM, particularly in tissue presenting greater necrosis and vascular inflammation (11). Some cytokines are associated with particular clinical expressions of disease. IL-15 plays a role in activating NK and other immune cells responsible for tissue damage. Serum and bronchoalveolar lavage fluid IL-15 is increased in patients with RP-ILD (12). The IFN pathway is also central in IIM. In particular, immune complexes formed by MDA5 and anti-MDA5 have been recognised as inducers of IFN-α in an RNA-dependent manner *in vitro* (13). In IMNM, the cytokines IP-10 and MIP-1α were proposed as possible biomarkers (14). Its levels were prominently increased before treatment, decreased after immunosuppressive therapy, and correlated with serum creatine kinase levels.

Endothelial damage and microvascular inflammation are also involved in the pathogenesis of IIM, particularly DM. PON1 is a protein that protects the vascular endothelium from oxidative injury and damage. The levels of PON1 were significantly lower in IIM patients, especially in cases with severe ILD and anti-MDA5 or antisynthetase antibodies positivity (15). Therefore, some genetic PON 1 polymorphisms may be associated with worse outcomes in IIM.

Several potential disease activity markers and treatment response predictors in IIM have been proposed. The levels of HSP-90, a chaperone protein, were increased in IIM patients with pulmonary, cardiac, oesophageal and skeletal muscle involvement and patients with higher disease activity(16). Additionally, HSP-90 levels decreased after treatment (16). The plasma or skeletal muscle levels of clusterin were also raised in IIM patients and directly correlated with the disease activity (17). Serum levels of galectin-3, a protein linked with inflammation and tissue fibrosis, are high in IIM patients and correlate with disease activity, particularly with ILD, making it a possible biomarker for disease activity (18). Although traditionally related to IBM, subsarcolemmal accumulation of autophagosome cargo protein p62 aggregates is common in all IIM, and it may represent a general response to muscle injury rather than a marker of IBM (19). SIGLEC-1 expression was shown to be upregulated on monocytes in patients with DM and JDM and the magnitude of expression correlated with the disease severity, suggesting that SIGLEC-1 can be a biomarker of type I IFN activity (20, 21).

Take-home messages

- IIM has a significant risk of aggregation among first-degree relatives and a heritability of about 20% (3).
- CD26 is selectively expressed in IIM patients' muscle cells, particularly in tissues presenting greater neccrosis and vascular inflammation (11).
- Serum HSP-90, clusterin and galectin-3 levels correlate with IIM disease activity (16-18).
- SIGLEC-1 correlates with disease activity in JDM and DM and may serve as biomarker for type I IFN activity (20, 21).

Laboratory investigations and autoantibodies

MSAs and MAAs have a central role in the assessment of IIM, but not all IIM patients are positive for these antibodies. A recent study highlighted that seronegative DM frequently have strong indirect positivity of antinuclear antibodies (ANA) on HEp-2 indirect immunofluorescence (IIF), mainly in a fine speckled pattern (22). On the other hand, a low titre of MSAs is not always a marker of IIM or connective tissue disease, but its significance is increased by IIF ANA positivity (23). A positive concordance between the ANA pattern on IIF and MSAs may improve test accuracy (24). Furthermore, MSA positivity is linked to increased extramuscular disease activity (25). We should also consider the possibility that ANA could be negative in some subsets, even if we consider the ANA cytoplasmic positivity, as recently observed in a large cohort of IIM patients positive for anti-MDA5 antibodies (26). MSA and MAA negativity appeared to be associated with less severe forms of ILD (27, 28), but it should be noted that ILD patients present MSA positivity in most cases. Moreover, among patients with circulating MSAs, ILD was a dominant feature, more frequent than muscle or skin manifestations at the time of the initial detection of the MSAs (29). Recent evidence has confirmed and extended previous data on myositis associated auto-antibodies anti-Four-and-a-half-LIM-domain 1 (antiFHL1)(30), which recognise a muscle-specific antigen, have been observed in some seron-

egative IIM and systemic sclerosis patients (31). Anti-RuvBL1/2 antibodies were also found in patients with IIM/systemic sclerosis overlap syndrome without other known autoantibodies, in association with nuclear fine or coarse speckled HEp-2 IIF pattern (32).

Recently, Ogawa-Momohara *et al*. confirmed that digital ulcerations and alopecia are more frequent in anti-MDA5 positive patients, while flagellate erythema and V-neck/shawl sign were observed more commonly in anti-TIF1γ positive patients (33). The correlation between anti-TIF1y and tumours is well known. In particular, a recent study identified, in a group of anti-TIF1y positive DM patients, a higher risk of cancer in male patients with severe rash, while ILD was less represented (34). In DM patients with anti-TIF1y antibodies, co-presence of anti-CCAR1 antibodies has been demonstrated to be associated with a lower probability of cancer (35). Higher levels of anti-TIF1y, determined by enzyme-linked immunosorbent assay (ELISA), are associated with more severe disease activity, particularly with higher biopsy total scores, muscle fibres scores and inflammatory infiltration scores in myositis without cancer and lower survival rate in cancer-associated myositis (36). A Japanese study confirmed the association between anti-Zo positivity and the occurrence of classic ASS features, such as myopathy, ILD, and mechanic's hands (37), but not arthritis (38). Anti-Ro52 is a possible marker of RP-ILD with higher mortality rates in IIM, particularly in anti-MDA5 positive patients (26, 39). Anti-mitochondrial autoantibodies (AMA) may be found in a small percentage of adults with DM, PM and IBM. AMA positivity is associated with Raynaud's phenomenon, dysphagia, cardiomyopathy, and more severe disease (40). In a single-centre study, serum samples from an IIM cohort were screened for autoantibodies against 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMGCR) autoantibodies by ELISA and confirmed by immunoprecipitation (IP). More than 4% of patients were positive for anti-HMGCR autoantibodies (41). Of these, only 15% had a history of statin use (41). In the anti-HMGCR-positive group, 38% of patients had a clinical phenotype compatible with dermatomyositis, although muscle biopsies of patients with anti-HMGCR autoantibodies showed findings consistent with IMNM in all cases except for one (41). At the last visit, most anti-HMGCR-positive patients had chronic active disease (41). Since only a minority of patients had previous statin exposure, the addition of anti-HMGCR autoantibodies to routine diagnostic procedures in patients with IIM should be considered. Anti-CN1A antibodies are found in IBM. In an Italian study, a clinical correlation between antiCN1A positivity and more severe dysphagia was found (42). Another Italian multicentre study evaluated the differences between anti-NXP2 positivity detected with commercial line blot (LB) and IP. Only 62% of LB-positive patients were confirmed NXP2-positive in IP. Furthermore, dysphagia and myositis were found more frequently in NXP2 LB+/IP+ patients, while patients only positive by LB did not display clinical features typical of NXP2 positivity (43).

Many authors focused on searching for clinical biomarkers of ILD with prognostic value. Serum KL-6 was confirmed as a predictor of RP-ILD in anti-MDA5+ DM (8), and elevated serum levels of carcinoembryonic antigen (CEA) and some other tumour markers were predictors of RP-ILD in general (44, 45). Notably, elevated serum ferritin values predicted short-term mortality in MDA5+ DM patients with RP-ILD (44). HLA-DR expression on myofibers from muscle biopsy samples was also associated with ILD (46).

Take-home messages

- ANA can be negative in some subsets of IIM patients, even if we consider the ANA cytoplasmic positivity (26).
- Anti-FHL1 is a MAA that can be positive in seronegative IIM and systemic sclerosis patients (31).
- Higher levels of anti-TIF1y are associated with more severe disease activity in myositis without cancer and a lower survival rate in cancer-associated myositis (36, 47).
- Co-presence of anti-CCAR1 antibodies in DM patients with anti-TIF-1y is associated with a lower risk of cancer (35).
- Not all anti-HMGCR-positive patients have a history of statin exposure, and some present clinical features compatible with DM (41).
- Elevated serum ferritin levels predict short-term mortality in anti-MDA5+ DM patients with RP-ILD (44).

General and muscular involvement

Despite the recent improvement in the management and treatment of IIM patients, the disease still has significant mortality and morbidity. In an IIM inception cohort at a tertiary care centre in northern India, lower respiratory infections were the most common cause of death, followed by malignancy and RP-ILD (48). More than 15% of the IIM patients died in the first ten months after diagnosis, and the one-year survivals for anti-MDA5 and ASS syndromes were 30% and 75%, respectively. Older age and anti-MDA5 positivity were independent predictors of early mortality (48). A study from the same Indian centre showed that more than a third of IIM patients experienced infections, frequently major or recurrent (49). The most common infection was community-acquired pneumonia, followed by tuberculosis (49). The mortality at one year for IIM patients with and without a major infection was 60% and 89%, respectively (49).

Classification criteria

The 2017 European Alliance of Associations for Rheumatology (EULAR)/American College of Rheumatology (ACR) IIM classification criteria performed better than Bohan and Peter's and Tanimoto's criteria in a Japanese juvenile myositis cohort (50) and better than Bohan and Peter's criteria in an adult anti-MDA5-positive IIM cohort (51). However, the sensitivity of the EULAR/ACR criteria in this cohort could be further improved if anti-MDA5 positivity was considered a criterion (51). The EULAR/ACR criteria performance was also tested in a large cohort of MSA-positive myosi-

tis patients (52). Although more than 90% of the patients were successfully classified, those with autoantibodies against HMGCR, signal recognition particle (SRP), and anti-threonyl-tRNA synthetase (PL-7) were frequently misclassified (52).

Disease activity

Ten times arm lift (AL) test and two-minute walk distance (2MWD) are two task-based patient-centred outcome measures (PCOMs). In a study including 22 IIM patients, the AL test and 2MWD showed excellent test-retest reliability (53). In addition, AL exhibited a moderate to strong correlation with manual muscle testing 8 (MMT-8), physician- (PhGDA) and patient-global disease activity (PtGDA), and health assessment questionnaire (HAQ-DI) (53). Additionally, AL time discriminated between active and inactive myositis in the original and a validation cohort with negative predictive values (NPV) of over 90% (53). In contrast, 2MWD was highly variable, did not correlate with standard myositis core set measures, and did not discriminate between active and inactive disease (53). However, a different study, including 42 IIM patients, showed that 2MWD had a moderate to strong correlation with Δ MMT-8 among those with active IIM and correlated with Δ functional index 2 (FI-2) in active and inactive disease (54). Patient-reported outcome measure information system physical function-20 (PROMIS PF-20) was also recently tested in IIM patients. PROMIS PF-20 showed strong test-retest reliability and moderate to strong correlations with MMT-8, PhGDA, PtGDA, HAQ-DI, SF-36 physical function-10 (PF10), and functional tests, indicating good convergent validity (55). In addition, Δ PROMIS PF-20 strongly correlated with total improvement score, demonstrating good responsiveness to change (55).

Nailfold video capillaroscopy (NVC) is a non-invasive tool routinely used to diagnose and monitor systemic sclerosis patients. Nailfold capillary density was independently associated with disease activity measured by the Myositis Intention to Treat Index (MITAX) in adult DM patients, reflecting disease activity improvement with treatment (56). Nailfold capillary density is a potential dynamic marker of global disease activity in adult DM that can be used to monitor disease activity.

Histology

A comprehensive serologic-pathological correlation study performed in DM muscle biopsies found several myopathologic features characteristic of specific MSA. For example, biopsies from anti-TIF1y positive patients more frequently had vacuolated/punched-out fibres and perifascicular enhancement in the HLA-ABC stain (57). Muscle samples from anti-MDA5-positive patients typically had a diffuse staining pattern of perifascicular myxovirus resistant protein A (MxA) with less muscle pathology and inflammatory features (57). Anti-NXP-2 was associated with microinfarction, and anti-small ubiquitin-like modifier-activating enzyme (SAE) and seronegative dermatomyositis were associated with HLA-DR expression (57). On the other hand, biopsies from anti-complex nucleosome remodelling histone deacetylase (Mi2)-positive patients more frequently had major muscle fibre damage, inflammatory cell infiltration, perifascicular atrophy, perifascicular necrosis, increased perimysial alkaline phosphatase activity, central necrotic peripheral regenerating fibres, and sarcolemmal membrane attack complex deposition (57). These results parallel those from a histopathological study on muscle biopsies performed for diagnostic purposes in DM patients that showed that anti-Mi2-positive DM patients had more necrotic/ degenerative fibres and macrophage infiltration than anti-Mi2-negative DM patients and were not statistically different from immune-mediated necrotising myositis (IMNM) patients (58). In a systematic literature review to evaluate the different definitions and characteristics, the combination of perifascicular necrosis, atrophic fibres, and perimysial fragmentation at muscle biopsy seems more common in ASS than in other IIM (59).

An artificial intelligence algorithm based on deep convolutional neural networks was trained to differentiate IIM from hereditary muscle diseases (HMD) in microscopic images of haematoxylin-and-eosin-stained pathology slides. The trained algorithm managed to differentiate IIM from HMD with better sensitivity and specificity than nine physicians and successfully and accurately classified four subtypes of IIM (60). These results support the reliability of the algorithm and suggest that it has the potential to be used in a clinical setting.

Muscular imaging

A study using muscle biopsy to determine the impact of muscle magnetic resonance imaging (MRI) on suspected myopathy showed that muscle oedema, atrophy, fatty replacement, and contrast medium enhancement were observed in both inflammatory and non-inflammatory myopathies (61). Notably, less than a third of myositis patients showed medium contrast uptake (61). A Japanese group developed a machine learning model to predict disease subgroups in patients with IIM using muscle MRI radiomics features. The machine learning-based MRI radiomics models showed the potential to distinguish between polymyositis, DM and amyopathic DM (62). In contrast, the accuracies of radiomics models distinguishing between non-IIM and IIM disease groups were low (62). The results from these two studies do not support qualitative MRI as a valuable tool in distinguishing inflammatory from non-inflammatory myopathies. Inflow-based vascular-space-occupancy (iVASO) MRI is a non-invasive perfusion method that does not involve administering exogenous contrast agents. A study including DM patients and healthy volunteers used iVASO MRI to measure the arteriolar muscle blood volume (MBV). Compared with normal muscles in healthy subjects, morphologically normal-appearing muscles, oedematous muscles, and atrophic or fat-infiltrated muscles in DM patients showed significantly lower maximum and mean arteriolar MBV (63). Additionally, both parameters were significantly lower in atrophic or fat-infiltrated muscles than in morphologically normal-appearing and oedematous muscles (63). In con-

clusion, the iVASO MRI could reproducibly quantify arteriolar MBV and discriminate patients with DM from healthy volunteers (63). The effectiveness of MRI-based measurements distinguishing IIM patients from healthy controls was also recently assessed. Fat fraction and T2 values were higher in IIM patients, whereas muscle volume was lower than in healthy controls, with no significant differences in diffusion (64). Notably, in a subgroup of patients scored as unaffected by radiologists, T2 values were still significantly higher in IIM patients (64).

A prospective study designed to compare ultrasound (US) and whole-body MRI to detect muscle abnormalities compatible with IIM evaluated newly diagnosed IIM patients at diagnosis and after nine weeks of monotherapy with intravenous immunoglobulin (IVIg). At diagnosis, MRI was more sensitive than the US to detect muscle abnormalities compatible with IIM. However, semi-quantitative and qualitative US detected abnormalities in most patients (65). Besides, semi-quantitative and qualitative US but not quantitative US or MRI showed change over time after nine weeks of treatment(65). The Siena Myositis Ultrasound Grading Scale (SMUGS) is a promising new score trying to standardise the US application to IIM diagnosis and monitoring. The evaluation includes a US examination of both thighs in axial and longitudinal scans and scoring of three domains (grey-scale oedema, grey-scale atrophy and Power Doppler) (66). Muscle oedema and the Power Doppler scores were positively correlated with PhGDA and negatively correlated with disease duration. On the other hand, the muscle atrophy score positively correlated with Myositis Damage Index, disease duration and patients' age (66).

A systematic review combined with a large meta-analysis of 944 assessments demonstrated that ultrasound of the deep finger flexors (flexor digitorum profundus, FDP) is a sensitive measure to determine muscle damage in IBM (67). This is relevant for routine evaluation of IBM diagnosis and confirms earlier findings on ultrasound of the FDP in IBM (68).

A systematic literature review and meta-analysis to evaluate the diagnostic accuracy of fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT) for active IIM calculated a pooled sensitivity of 0.94 and a pooled specificity of 0.90 (69). In conclusion, 18F-FDG PET/CT was sensitive and specific at detecting active IIM.

Take-home messages

- Infections, malignancy and RP-ILD are common causes of death in IIM (49).
- Nailfold capillary density is a potential dynamic marker of global disease activity in adult DM that can be used to monitor disease activity (56).
- Semi-quantitative and qualitative muscle US but not quantitative US or MRI showed change over time after nine weeks of treatment with IVIg (66).
- Ultrasound of the deep finger flexors can help to discriminate patients with IBM from other myositis subsets (67).

Particular subsets of IIM

Inclusion body myositis

A population-based Swedish study determined an IBM prevalence of 32 per million inhabitants, 19 per million women and 45 per million men. The mean incidence was 2.5 per million inhabitants/year. The mean age at symptom onset was 64.4 years, quadriceps weakness being the most common presenting symptom, followed by finger flexor weakness. Dysphagia was a common presenting symptom and occurred in 74% of men and 84% of women during the disease course. The mean survival was of 14 years from symptom onset (70). Survival rates from diagnosis and symptom onset were decreased compared to the matched population (70). Another epidemiological study compared IBM patients to other IIM and population controls. The frequency of neurodegenerative disorders and solid cancer was not different between groups (71). Dysphagia was most common in IBM (64%) patients, but peripheral neuropathy (36%), haematologic malignancies (10%) and Sjögren's syndrome (6%) were also frequent (71). IBM patients were 2.7 times more likely to have peripheral neuropathy, 6.2 times more likely to have Sjögren's syndrome, and 3.9 times more likely to have a haematologic malignancy than population controls. IBM patients had increased mortality, with a 10-year survival of 36% from the index date, compared with 67% in IIM and 59% in population controls. Respiratory failure or pneumonia were the most common causes of death (71). Respiratory failure in IBM patients is frequently related to diaphragmatic involvement. A recent study using diaphragm US has compared IBM patients and matched controls. The diaphragm thickening fraction (a surrogate measurement of diaphragm contractility) was significantly lower in IBM patients and correlated with the time since symptom onset (72). Patients had significantly lower forced vital capacity (FVC) and higher dyspnoea scores than controls. Furthermore, IBM patients with lower diaphragm activity had lower 6-minute walking distances, higher resting and exertional dyspnoea and a larger positional decrease in vital capacity than patients with higher activity (72). In conclusion, diaphragm involvement in IBM increases with disease duration and has detrimental effects on lung function.

A prospective observational study was designed to delineate the natural history of IBM and document patients' muscle strength and physical function decline. Multilevel modelling of change in percentage MMT-8, quantitative muscle testing (QMT), and IBM Functional Rating Scale (IBMFRS) over time yielded an average decline of 3.7%, 3.8%, and 6.3% per year, respectively. The decline was steeper in the initial years of the disease. The median time to use a mobility aid was 5.4 years, significantly affected by greater age at disease onset (73). In conclusion, MMT-8, QMT and IBMFRS accurately detected disease progression in a reliable and useful way to be used in trial design.

Despite concerns due to IBM pathophysiology, a cross-sectional study using neuropsychological tests covering multiple cognitive domains found

that memory and executive function in patients with IBM did not differ from published normative data adjusted for age, sex, and education (74).

Immune-mediated necrotising myopathy (IMNM)

IMNM is a rare subtype of IIM, but its incidence and prevalence are not well defined. A recent study identified all adult patients with IMNM, as defined by the 2016 European Neuromuscular Centre diagnostic criteria, among residents of Olmsted County, Minnesota, over 20 years. The incidence of IMNM during the 2010-2019 decade was 8.3 per million person-years (75). The prevalence of IMNM in 2010 was 1.85 per 100 000 people at least 50 years of age. The most common autoantibody was anti-HMGCR. The incidence of malignancy in IMNM was not higher than that of the general population. In conclusion, IMNM is a rare disease with a prevalence of one-tenth of that of IBM in Olmsted County, Minnesota (75).

A work that reviewed the medical records of IMNM patients positive for anti-SRP antibodies showed that 45% of patients were diagnosed with ILD based on lung imaging, mostly nonspecific interstitial pneumonia (NSIP) but also organising pneumonia in a third of patients (76). A third of patients with available PFTs had mild ILD, defined as a percentage of predicted FVC (%pFVC) over 75% and a percentage of predicted diffusing capacity of the lung for carbon monoxide (DLCO%) over 55%, and more than half had moderate ILD (%pFVC 50 to 75% or %pDLCO 35 to 55%)(76). The average age at the time of ILD onset was significantly higher than that of patients without ILD(76). Notably, the frequency of dysphagia in the ILD group was higher than in the group without ILD (76).

Since MSA became clinically available and different IIM subsets were better characterised, it is often easier to distinguish IMNM from other IIM subtypes than from IIM mimickers, such as limb-girdle muscular dystrophy (LGMD) 2B and lipid storage myopathy (LSM). Muscle biopsy is usually vital to make this distinction. In a large muscle biopsy cohort, IMNM patients had a higher age of onset and more frequent dysphagia than LGMD 2B and LSM patients (77). In addition, muscle biopsy from IMNM patients more frequently had muscle fibre necrosis, overexpression of major histocompatibility complex-I on the sarcolemma, and CD4+ T cell endomysial infiltration than those from LGMD 2B and LSM patients (77).

Antisynthetase syndrome

A new subset of ASS patients with recurrent fever and systemic inflammation episodes was recently described. Patients with two or more non-infectious fever attacks and within the upper three quartiles of attack frequency were defined as the high-inflammation ASS subgroup (78). These patients had an average of 1.12 attacks/patient-year and were most commonly anti-Jo1 or anti-PL7-positive (78). Compared to the low-inflammation ASS group, defined by at most a single attack and a frequency lower than 0.5 attacks/patient-year, the high-inflammation ASS group had a higher occurrence of fever and RP-ILD as the disease presentation (78). Of note, positivity for anti-PL-7 was associated with the high inflammatory phenotype (78). In addition, cumulative disease-modifying anti-rheumatic drug (DMARD) exposure was much higher in the high-inflammation subgroup (78). Therefore, ASS with recurrent systemic inflammatory episodes seems to represent a disease subtype of more aggressive and refractory disease.

To test the ability of the Systematic COronary Risk Evaluation (SCORE) and its EULAR modified version (mSCORE) to identify ASS patients at high cardiovascular (CV) risk, SCORE/mSCORE and the gold standard marker of aortic stiffness/carotid-femoral pulse wave velocity (cfPWV) were examined in ASS patients and healthy controls. Additionally, carotid arteries US were performed. According to mSCORE, 10% of the patients had a high CV risk (79). However, cfPWV and the carotid US revealed an increased CV risk in 21% and subclinical carotid atherosclerosis in 86% of the patients, respectively(79). cfPWV was higher in ASS patients than in controls and correlated significantly with age, body mass index and diabetes (79). In conclusion, even after adjusting for confounders, ASS patients had higher aortic stiffness and subclinical carotid atherosclerosis than controls. SCORE/mSCORE performed poorly in identifying high-risk patients compared with cfPWV and the carotid US. Thus, cfPWV and carotid sonography may improve CV and cerebrovascular screening in ASS.

To evaluate eventual ASS-specific MRI muscle-lesion patterns, qualitative and semi-quantitative thigh MRI evaluations were conducted in patients with ASS, DM and IMNM. Thigh MRI revealed myofascial oedema (90%), fatty infiltration of muscles (67%), muscle oedema (63%), and subcutaneous tissue oedema (61%) in ASS patients (80). Compared with IMNM, ASS and DM more frequently spared adductor muscles and more commonly had subcutaneous tissue oedema (80). In addition, muscle lesions in the ASS group were less frequently symmetrical and more frequently showed myofascial oedema of the tensor fasciae latae than those from DM and IMNM patients (80). In conclusion, ASS oedema patterns resembled those of DM more than those of IMNM (80). Asymmetry, adductor-muscle relative sparing and remarkable myofascial oedema of tensor fasciae latae were the most characteristic ASS imaging findings (80).

Take-home messages

- Survival rates of IBM patients are decreased compared to matched populations of healthy volunteers and other IIM patients. Respiratory failure and pneumonia are common causes of death (70).
- The frequency of neurodegenerative disorders and the memory and executive functions of IBM patients do not differ from matched controls (74).
- ILD is not rare in IMNM patients positive for anti-SRP antibodies, although typically mild to moderate in severity (76).
- ASS with recurrent systemic inflammatory episodes seems to represent a disease subtype of more aggressive and refractory disease. Anti-PL7 positivity was associated with this phenotype (78).

Extramuscular aspects

Extramuscular involvement represents a major cause of morbidity and mortality in IIM patients. ILD is common, and many contributions to this topic have been published in the past year. PET/CT scan appeared to be a reliable tool for quantifying the degree of lung inflammation (81) and has been proposed within a model that includes elevated bilateral lung mean standard uptake value, abnormal mediastinal lymph nodes and decreased DLCO% as predictors of RP-ILD (82). However, the gold standard for ILD assessment remains chest CT. In this regard, an Italian group found inverse correlations between semi-quantitative and quantitative radiologic scores for ILD and the values of DLCO% and total lung capacity (TLC)% on pulmonary function tests (27). Xu *et al*. proposed a novel CT scoring method based on ground glass opacities and consolidations as an applicable tool for predicting six-months mortality in anti-MDA5+ DM patients (83). A FVC <50% on PFTs has also been shown to predict a significantly higher six-months mortality in a multicentre cohort of anti-MDA5+ patients (84). Furthermore, a prediction model based on fever, serum lactate dehydrogenase levels, age and white blood cell count (the FLAW model) seemed to satisfactorily predict the development of RP-ILD in this kind of patient (85). In contrast, although inflammatory cells in the bronchoalveolar lavage fluid (BALF) of DM-ILD patients differ in acute/subacute and chronic ILD, this, as well as the finding of pathogens in the BALF, did not seem to influence the prognosis (86).

Myocardial involvement is rare but potentially severe, sometimes leading to congestive heart failure (HF) and severe arrhythmias. According to data from a multicentre cross-sectional study based on the Chinese Rheumatism Data Center-Myositis Registry, myocardial involvement was found in 5.5% of IIM patients; the anti-mitochondrial antibody-subtype 2 (AMA-M2) positivity, the presence of pulmonary hypertension and elevated CPK and C-reactive protein (CRP) values were significant risk factors for this condition (87). Distinct phenotypes of myocardial involvement in different IIM subtypes can be identified by cardiac magnetic resonance (CMR). Various studies have shown that IIM patients with cardiac involvement had elevated global native T1 and extracellular volume (ECV) values; in addition, PM and DM patients displayed a different distribution of late gadolinium enhancement (LGE), with the former having a greater proportion of positive LGE segments and consequently a more severe cardiac involvement (88, 89). An observational study conducted in the US showed a higher prevalence of supraventricular arrhythmias among patients with PM and DM than in matched controls, also exhibiting increased in-hospital mortality odds in patients diagnosed with arrhythmias (90). A Scandinavian cross-sectional study found a longer mean corrected QT (QTc) duration in IIM patients compared to healthy controls, with prolonged QTc in nearly one-fifth of patients; anti-Mi2 and anti-PL7 positivity and high CRP values correlated with prolonged QTc and may serve as biomarkers of cardiac impairment in IIM(91). Concerning ECG changes, furthermore, a low T wave was associated with disease activity in anti-MDA5+ patients and proved to be reversible after immunosuppressive treatment (92). Lin *et al*. found a higher risk of new-onset HF in PM/DM patients compared to the general population and a significantly increased risk of HF-related hospitalisation; the HF risk seemed to be the highest during the first year following the diagnosis of IIM but persisted for up to 10 years (93). Similar data were also highlighted by a study on the Danish population (94).

IIM patients may develop a non-inflammatory proliferative vasculopathy which can burden the disease's morbidity. Yeo *et al*. described the angiographic features of the vasculopathy of patients with myositis or systemic sclerosis (SSc), comparing it with the inflammatory vasculopathy typical of vasculitis. Diffuse narrowing, tapered occlusion and delayed distal flow on conventional angiograms seem to be more frequent in IIM/SSc vasculopathy if compared to polyarteritis nodosa (PAN), as opposed to multifocal stenosis and aneurysms formation (95). Moreover, IIM/SSc vasculopathy tended to have poorer outcomes than PAN, with a higher rate of auto- and surgical amputations, highlighting the need to investigate this possible extramuscular involvement.

As for microcirculation, NVC has proved to be a useful tool to support the diagnosis of DM in cases of difficult differential diagnosis (for example, with respect to cutaneous lupus erythematosus (CLE), although the diagnosis of certainty may remain challenging: according to Monfort *et al*., the sensitivity and specificity of scleroderma pattern for the diagnosis of DM were respectively 80% and 70%; in their study, the prevalence of scleroderma pattern and NFC abnormalities was significantly higher in DM patients than in those with CLE, especially in the absence of digital lesions (96). Furthermore, in anti-MDA5+ DM, NVC abnormalities appeared to be correlated with disease activity and showed improvement after immunosuppressive treatment, according to a prospective observational study by Sugimoto *et al*. (97).

Xu *et al*. suggested pseudoangioedema as a rare but clinically significant manifestation, potentially associated with severe disease and poor prognosis, in DM patients (98), although the underlying pathogenetic mechanism has not yet been clarified.

In a study on 198 Japanese DM patients, the pattern of distribution of skin lesions helped predict positivity for MSAs and MAAs: positive patients for anti-MDA5 antibodies often had skin lesions on both the face/scalp and the extremities, anti-TIF1γ+ patients presented widespread skin lesions, while anti-aminoacyl-transfer-RNA synthetase (anti-ARS) positivity was associated with an extremities-dominant rash; conversely, more than half of the patients with face/scalp-limited lesions had neither MSAs nor MAAs (33).

According to Zychowska *et al*., videodermoscopy may help distinguish Gottron's papules from other dermatoses involving the dorsal surface of the hands, such as psoriasis, chronic dermatitis and lichen planus (99). In particular, their study showed that Gottron's papules

were characterised by pleomorphic vessels arranged in an unspecified pattern, often accompanied by white or pink structureless areas.

By using imaging mass cytometry, partially in contrast to what is known that the inflammatory infiltrates of DM skin lesions consists mainly of CD4+ lymphocytes, Patel *et al*. have seen that the most represented cells are macrophages and myeloid dendritic cells (100), with possible future implications for the development of new therapeutic targets. Additionally, in this study, CD14+ macrophages correlated positively with the Cutaneous DM Disease Area and Severity Index (CDASI) scores. A similar immunophenotype, with some differences at the cellular level, has been found in DM-like skin lesions in antisynthetase syndrome (101).

Dysphagia is a common symptom in patients with IBM; these patients should also be investigated for the presence of gastroesophageal reflux since, according to what was reported by self-administered questionnaires in a UK third-level centre, they often also have symptoms secondary to this condition (102). Investigated by videofluoroscopy (VFS), most common features of IBM patients with dysphagia were impairment of tongue base retraction, residual pharyngeal pooling, pharyngeal constrictor impairment and cricopharyngeal hypertrophy (102). The presence of a cricopharyngeal bar on VFS is associated with a higher risk of aspiration and subsequent pneumonia (103); moreover, the cricopharyngeal bar appears to be related to an underlying endomysial fibrosis in this muscle (104).

A retrospective chart review from a large Voice Clinic showed that IIM patients had significantly higher odds of presenting with muscular voice disorders and dysphagia than controls (105). Interestingly, most of these IIM patients had laryngeal pathology among the presenting symptoms of myositis (105). Furthermore, in a study retrospectively reviewing the flexible endoscopic evaluation of swallowing videos of IIM patients, pharyngeal residue with risk of post-deglutition aspiration was the most common dysphagia pattern, and the attenuation of the endoscopic white-out was related to residue severity (106). Importantly, dysphagia severity was an independent predictor for pneumonia, which occurred in almost a quarter of the patients(106).

As for cancer-associated myositis (CAM), alongside known risk factors such as older age and male sex, low serum CPK values were associated with malignancy in both DM and PM, according to a retrospective study on a large cohort of patients in Taiwan (107). After an adequate cancer-risk stratification of IIM patients, performing a PET/CT scan at myositis onset seems to be an efficient approach to rule out CAM, with a high negative predictive value according to the experience of a Spanish tertiary centre (108).

Machine learning algorithms can help identify anti-TIF1γ+ patients at higher cancer risk, with disease duration, neutrophil-to-lymphocyte ratio and CRP values as significant clinical parameters for recognising these patients (109). Furthermore, higher anti-TIF1γ levels and certain inflammatory cytokines, such as TNF and TNF receptor superfamilies, and recently identified accompanying antibodies such as CCAR1 (see above) may strengthen cancer prediction in DM patients (110).

COVID-19 and vaccinations

IIM patients are more likely to experience fatigue, chest pain, and breathlessness than healthy controls (HC) when they have COVID-19 (111). However, the severity of COVID-19 infection seems comparable to the HC. IIM patients are also more likely to experience dyspnoea, rashes, and muscle weakness 30 days post-COVID than HC (111).

Vaccination against COVID-19 is the primary therapeutic widely available. A prospective phase 4 controlled trial of Sinovac-CoronaVac, an inactivated virus vaccine against SARS-CoV-2, found that IIM patients had a moderate but significantly lower seroconversion than HC (112). IIM patients also had a significantly lower anti-S1/S2 IgG geometric mean titre and frequency of neutralising antibodies. However, median neutralising activity was comparable to HC. Immunosuppressives were less frequently used among patients positive for neutralising antibodies(112). IIM subtype, disease status, non-immunosuppressive drugs and comorbidities did not influence immunogenicity. In conclusion, Sinovac-CoronaVac seems safe and has a moderate short-term immunogenicity in IIM, although reduced compared with HC (112).

Regarding safety, a large study found that DM patients did not have a difference in risk for immediate anaphylaxis at one-day post-immunisation compared to HC (113). Additionally, at 30 days post-vaccination, vaccinated DM patients did not experience a difference in risk for adverse events of special interest (AESI), breakthrough infection (BI), or all-cause hospitalisation (ACH) compared to HC. However, at 60 days post-vaccination, the DM group had a greater risk for AESI, despite having a small absolute risk of 0.6%. No differences in risk for BI and ACH were observed 60 days post-vaccination. DMARD and glucocorticoid use did not impact AESI, BI, or ACH at any time. Nevertheless, the benefits of vaccinating DM patients greatly outweigh the risks, especially given the minimal absolute risk (113).

Take-home messages

- An FVC<50% predicts a significantly higher six-months mortality in anti-MDA5+ patients (84).
- PM/DM patients have a higher prevalence of supraventricular arrhythmias and new-onset HF than matched controls. The HF risk seemed to be the highest during the first year following the IIM diagnosis but persisted for up to 10 years (90).
- Pseudoangioedema is a newly described rare but clinically significant DM manifestation, potentially associated with severe disease and poor prognosis (98).
- After an adequate cancer-risk stratification, performing a PET/CT scan at myositis onset seems to be an efficient approach to rule out CAM, with a high negative predictive value (108).
- Dysphagia is an important symptom in myositis and can be associated with aspiration and pneumonia in

IBM. The swallowing abnormality in IBM can be evidenced by videofluoroscopy (VFS) to demonstrate a cricopharyngeal bar (103), which has been suggested to be related to fibrosis of the upper oesophageal sphincter (104).

Treatment

To date, no specific therapeutic guidelines are widely approved for the treatment of IIM. The treatment still classically relies on the combination of glucocorticoids (GCs) and conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs), rituximab (RTX), IVIg or subcutaneous immunoglobulins (SCIg).

In this regard, the recently published guidelines by the British Society of Rheumatology recommend a cautious stratification according to age, severity and organs involved. GCs and csDMARDs should be employed as first-line treatment, while RTX, cyclophosphamide (CYC) and IVIg should be considered for severe and/or refractory IIM. Remarkably, such guidelines are the first ones to mention abatacept in the case of refractory myositis in adult patients (114).

GCs remain the milestone for the treatment of IIM. Nevertheless, according to a survey administered to 122 British patients, the duration and mean daily dosage of GCs remain high, and patients commonly suffer from adverse events, receiving inadequate information about their treatment in more than half of the cases (115). Additionally, a daily prednisone dose greater than 6.25 mg/day predisposed to major infections (49).

According to real-life data from the Indian MyoCite cohort (116), methotrexate (MTX) is the most employed drug, particularly in children, in whom it is prescribed as first-line treatment in 90% of cases. Azathioprine (AZA) and mycophenolate mofetil (MMF), as well as CYC and RTX, are preferred in the case of ILD and ASS (117). Anti-CD20 agents have the highest retention rate relapse-free survival (116). In ASS, MTX is generally restricted to managing arthritis, and AZA is preferred in the case of myositis (117).

Among synthetic immunosuppressants, MMF is an inactive drug hydrolysed to mycophenolic acid (MPA). A retrospective study has evidenced no correlation between the MPA area under the curve and disease activity (118), thus suggesting poor usefulness of monitoring it in IIM. On the other hand, a large, retrospective, South Asian study evidenced an overall good efficacy of MMF, irrespective of the presence of ILD (119). MMF was similar to MTX, but non-ILD patients treated with the latter tended to relapse more frequently (119).

Calcineurin inhibitors, ciclosporin A (CsA) and tacrolimus (TAC) may be effectively employed in severe ILD (120); a randomised, open-label trial evidenced a slight, non-statistically significant superiority of TAC in achieving progression-free survival (121).

Antimalarials have provided poor efficacy in the management of IIM. In this regard, a retrospective study in 20 patients evidenced a modest efficacy of quinacrine, which was beneficial only in 50% of them (122). Similarly, in a Chinese single-centre retrospective study performed on a cohort of 64 CADM, hydroxychloroquine, although prescribed as first-line treatment in 72,6% of patients, was ineffective in 68,8% of them (123).

IVIg has a well-established role in the treatment of recalcitrant IIM(124), particularly in dysphagia. In this regard, a retrospective analysis has evidenced a good long-term efficacy of 3 monthly doses of IVIg 2g/kg in dysphagic patients who are not responsive to GCs and MTX or AZA (125). IVIg, as well as cyclosporin, may also be employed as a rescue treatment in case of ILD relapse (126) and, in combination with early pulse methylprednisolone, may lead to rapid and prolonged remission (127) and GCs discontinuation (128), when employed as first-line treatment (129). A real-life, retrospective Italian study on 123 patients has evidenced an overall good efficacy (78%) of IVIg, particularly in oesophageal and muscle domains. A shorter disease duration and aggressive muscle involvement (high levels of CK at baseline) correlated with a good response to treatment, while skin involvement was associated with treatment failure (130). IVIg has also been studied in the first prospective, double-blind, randomised, placebo-controlled, phase III trial ("ProDERM study"), which has evidenced a good long-term efficacy and safety of 2g/kg IVIg every four weeks, with an assessed response at week 16 (131).

Moreover, a systematic literature review and meta-analysis including 29 studies and 576 patients treated with IVIg reported the achievement of partial response in 88.5% of patients, particularly in cutaneous disease activity and dysphagia (132). Both skin disease and dysphagia, as well as high MITAX, seem to predict a good response to IVIg or SCIg (133).

Aside from DM and PM, in which long-term efficacy and safety were assessed (134, 135), SCIg was recently employed in IMNM. In particular, SCIg displayed good efficacy as a maintenance treatment in 3 anti-HMGCR positive patients previously treated with IVIg (136). The latter, prescribed in association with GCs and csDMARDs, remain an effective option in patients affected by anti-HMGCR IMNM, prescribed alone or in association with AZA or MTX (137). Conversely, in the case of anti-SRP IMNM, early RTX administration should be preferred (138).

RTX has also displayed a good safety profile in all domains and a robust efficacy as a steroid-sparing agent in two retrospective cohorts (139, 140) and may be an effective option even in anti-MDA5 DM with severe lung involvement (141).

Few data are available for other biologic DMARDs: tocilizumab (TCZ) was effective in 5 anti-MDA5+ Chinese patients affected by severe, refractory ILD (142). Moreover, TCZ was also prescribed in an open-label pilot study in patients suffering from refractory IMNM (143). Notably, the seven patients who responded to the treatment displayed high serum levels of IL-6.

Among JAK inhibitors, whose efficacy had been previously demonstrated in retrospective cohorts of difficult-to-treat DM (144), tofacitinib (TOF) has to date, provided the most robust evidence (144). In an open-label pilot

study of 10 patients (145), which is the first prospective trial of a JAK inhibitor in IIM and has been followed by a long-term extension (146), TOF has met primary outcome in all subjects, which displayed minimal to moderate improvement in disease activity. JAK inhibitors in general, and TOF in particular, may therefore play a role in anti-MDA5 DM with prominent lung involvement(147) and in severe, refractory skin disease (148).

Among small molecules, apremilast, too, has been evaluated for refractory cutaneous DM in a phase 1b clinical trial, displaying a good efficacy in the face of adverse events, which led 2 out of 5 patients to withdraw from the study (149).

Novel treatments targeting different molecules are now being explored in the treatment of IIM: 12 weeks of treatment with Lenabasum, a cannabinoid type 2 receptor (CB2R) reverse agonist, were proved to reduce CD4+ T cells, CB2R, IL-31, IFN-γ, and IFN-β at peripheral blood mononuclear cells and immunohistochemistry staining of skin biopsies from patients affected by DM (150). Immunofluorescence also evidenced an upregulation of CB2R in skin biopsies from DM patients compared to healthy controls, as well as on dendritic cells, B cells, T cells, and macrophages (150).

The recent approval of antifibrotic drugs may change the prognosis in patients affected by ILD. The outcome of IIM-associated ILD is poor (120), even in the case of a lung transplant. A retrospective, single-centre study on patients who underwent transplants evidenced that the ones suffering from IIM had a higher rate of primary graft dysfunction, a longer time in the intensive care unit and a lower survival rate (151). In case of rapidly progressive forms, non-responsive to immunosuppressants, venovenous ECMO may be employed as the bridge to recovery (152).

Fewer data are available for the non-immunosuppressive or nonpharmacological treatment of specific aspects of IIM, such as dysphagia. Nevertheless, interesting data emerged for botulinum, which has been effectively employed in a small cohort of IBM patients (153). Similarly, cricopharyngeal myotomy may be an effective and durable technique in IBM in case of recalcitrant dysphagia (103, 154).

Prophylaxis against *Pneumocystis jiroveci* (PJ), too, should not be overlooked. In a retrospective study of 21587 rheumatic patients, no opportunistic pneumonia was reported in those who underwent prophylaxis. Conversely, the incidence of PJ was highest among untreated IIM patients (155), particularly anti-MDA5 positive ones (156). Indeed, infectious adverse events represent a common and fearsome complication of IIM-ILD, with a mortality rate of 41.2% (126).

Nonpharmacological treatments, too, have a paramount role in IIM: low-load blood-flow restricted resistance training may reduce the rate of muscle loss in IBM (157), as well as constant training and physical activity in all patients affected by IIM, in whom aerobic and resistance exercises, as well as yoga (158), may be helpful in the overall management of the disease (159-161).

Take home messages

- Recently published guidelines suggest GCs and csDMARDs should be employed as first-line treatment, while CYC, IVIg, RTX, and abatacept should be considered for severe and/or refractory IIM (114).
- MMF seems to have an overall good efficacy in treating IIM, irrespective of the presence of ILD. Despite being widely used, antimalarials have poor efficacy in managing IIM (119).
- IVIg 2g/kg every four weeks has good safety and long-term efficacy in the treatment of DM. IVIg is a valid option for treating IIM as first-line therapy and patients with refractory dysphagia, muscle, skin and lung involvements (129).
- Early RTX administration should be considered in anti-SRP IMNM (138).

Conclusions

Several studies added significant contributions to the IIM literature in 2022. As previously believed, MSA positivity is associated with extra muscular disease activity and different mortality rates. Higher levels of anti-TIF1y were associated with lower survival rates in CAM, anti-MDA5 positivity was an independent predictor of early mortality, and anti-Ro52 positivity and elevated serum ferritin were associated with RP-ILD with an even higher mortality rate in anti-MDA5 positive patients. Nailfold capillary density is a valuable marker of global disease activity in adult DM that can be used to monitor disease activity. Artificial intelligence and machine learning algorithms are increasingly used in IIM research and may be helpful for muscle pathology analysis, distinguishing between different IIM subtypes, or even identifying anti-TIF1γ-positive patients with higher cancer risk. Regarding treatment, the mean daily dosage and duration of treatment with GCs remain high, and patients commonly suffer from adverse events. On the other hand, accumulating evidence supports the use of IVIg in the treatment of IIM, including as first-line treatment and in relapsing or recalcitrant cases, particularly in patients with dysphagia. Finally, considering the persisting inconsistencies in IIM subgroup classification, the incomplete characterisation of phenotypes identified by the available biomarkers, and the lack of homogeneous clustering of IIM patients, the complete characterisation of each patient is the only way to ensure that all the information regarding treatment responsiveness and prognosis is available to the assisting physician.

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