One year in review 2018: idiopathic inflammatory myopathies

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Received on July 8, 2018; accepted in revised form on August 27, 2018.

Clin Exp Rheumatol 2018; 36: 937-947.

Key words: review, polymyositis, dermatomyositis, treatment, pathogenesis

Competing interests: none declared.

ABSTRACT

Idiopathic inflammatory myopathies (IIMs) are a group of chronic autoimmune systemic diseases affecting the skeletal muscle and other organs. IIMs are also a complex group of diseases, in some cases, difficult to manage. Literature on IIMs has been growing fairly rapidly and keeping up-to-date on such a topic is of utmost importance for any rheumatologist who looks after IIM patients. Thus, the aim of this review is to summarise the most relevant literature contributions published over the last year on the pathogenesis, serology, diagnosis and treatment of IIMs.

Introduction

Idiopathic inflammatory myopathies (IIMs) are a group of autoimmune diseases targeting primarily the skeletal muscles, but also other organs such as the skin, the lungs, the heart, and the gastrointestinal system (1). The most common subtypes of IIMs are dermatomyositis (DM), polymyositis (PM), inclusion body myositis (IBM) and immune-mediated necrotising myopathy (IMNM) (2), whereas antisynthetase syndrome represents a peculiarity within the spectrum of IIMs (3). Furthermore, we decided not to include juvenile DM (JDM) as it differs in several aspects from adult DM and it is usually managed by paediatric rheumatologists.

IIMs are rare and potentially lethal, due to multi-visceral involvement in general and to lung involvement and occult neoplasia occurrence in particular (4). On the other hand, it is not rare that IIMs overlaps with other conditions, in particular, systemic sclerosis (5); therefore, a thorough evaluation of the literature with the most updated evidence on how to diagnose, manage and treat the different aspects of IIMs is a crucial factor in order to provide the best healthcare for these patients.

Following the previously published annual reviews (6, 7), we will here provide an overview of the recent literature on the pathogenesis, clinical features and novel treatments of IIMs. We reviewed all original scientific articles published in the past year that addressed pathogenesis, extramuscular manifestations, serological profile, imaging and treatment of IIMs. We performed a systematic med-line search of English language articles published from 1st January 2017 to 31st December 2017 using the following key words: "idiopathic inflammatory myopathies" and "myositis" (MeSH terms and semantic search) and "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

Despite the progress made in recent years, the pathogenesis of IIMs is not completely understood. However, the pathogenic steps leading to the currence of IIM are the focus of an intense area of research, with relevant information added to our knowledge of this field year by year. Genetic predisposition, cytokines and autoantibody profile have been the main areas of research and those with the most relevant advances in the last year.

New information on the relationship between the genetic background and the occurrence of IIMs has been obtained, in terms of both increased and reduced risk of occurrence. Chen *et al.* reported that HLA-DRB1*04:01 and *12:02 conferred susceptibility to anti-melanoma differentiation-associated

protein 5 (anti-MDA5) production in DM and PM, independently of the alleles associated with the shared epitope (8). Lin *et al*. confirmed the association between HLA-DRB1*09:01 and an increased risk of developing DM, while HLA-DRB1*12:01 was associated to anti-MDA5 positive DM (9).

Interestingly, also non-HLA loci have been found of interest: the A variant of the rs7731626 single nucleotide polymorphism (SNP) in the gene ANKRD55 was protective for the development of DM/PM-interstitial lung disease (ILD) in a Chinese population (10). On the other hand, the PTPN22 R620W minor allele, one of the most important non-HLA loci to confer susceptibility to autoimmune diseases (11), was also associated with the development of IIMs (12). The rs35705950 SNP in the MUC5B gene – known to be associated with the development of idiopathic pulmonary fibrosis – was not found to contribute to the risk of developing ILD in patients with IIMs (13). This result is not a secondary issue, because ILD is the most important prognostic factor in IIMs and sometimes even the only clinical evident finding. On this basis, a better identification of borders between idiopathic and IIMs associated forms of ILD is crucial, not only for classification purposes but also for treatment planning.

Cytokines regulate many aspects of both the innate and adaptive immune system and several studies have investigated the cytokine profile in IIM patients in order to identify crucial mediators in the pathogenesis of these diseases.

Both Th1 and Th2 cytokines have been involved in DM pathogenesis: levels of interleukin (IL)-4 and interferon (IFN) -γ were significantly elevated, whereas IL-17 levels were comparable with controls (14). IL-21, a crucial mediator in orchestrating humoral immune responses, was upregulated in patients with DM and PM in both muscles and serum, and the IL-21 receptor was also expressed in the muscles of patients with DM and PM (15). In both PM patients and in a mouse model, toll-like receptor (TLR) 4 was found to be hyperactivated; by blocking this receptor, the levels of proinflammatory cytokines, IFN-γ and IL-17A, decreased (16).

The production of proinflammatory cytokine by *in vitro* stimulated peripheral blood mononuclear cells (PBMCs) of PM patients was associated with lower expression of Ro52/TRIM21 (17). Finally, transcripts of Th1, Th2, and Th17 in the blood of patients with DM correlated with disease activity. Interestingly, Th17 associated transcripts decreased with treatment (18). All in all, the activation of different T helper pathways has been demonstrated in both the muscle and blood of DM/PM patients, indicating heterogeneity in different forms of disease that requires further investigation.

The type I IFN system has been proposed to play an important role in the pathogenesis of myositis. Although the quantity of type I IFNs (*i.e*. IFNα) cannot be directly assessed, the signature of genes induced by these cytokines, known as type I IFN signature, may be used to assess the presence of interferons in tissues. The blood type I IFN signature is highly correlated with cutaneous activity scores and muscle disease in DM (19, 20). Rodero *et al*. showed that serum concentrations of IFNα in patients with different autoimmune diseases were increased compared to controls. However, in IIM patients, lymphocytes, monocytes and dendritic cells did not produce more IFNα than controls, indicating that other cellular types may be responsible for the IFN signature or that other cytokines play a role in activating these pathways (21). The sources and the mechanisms that drive the production of IFN in IIMs are still poorly understood. Levels of DNase1l3 were lower in the DM/PM patients, possibly leading to impaired clearance of immune complexes containing DNA that activate the production of interferons (22). De Luna *et al*. identified hypoxia as a regulator of the protein RIG-I, which in turn enhances the expression of IFNs in human muscle cells (23). Aside from their immunological effects, interferons may directly affect the muscle biology: IFN-β induced mitochondrial dysfunctions and production of reactive oxygen species (ROS), contributing to poor exercise capacity (24).

A wealth of evidence has pointed to the involvement of the adaptive branch of the immune response in the pathogenesis of IIMs. Signalling molecules controlling T cell activation (*e.g*. ZAP70, STAT, SOCS3) in patients with DM/PM were found to show different degrees of hyper- or hypo-responsiveness of T cells in DM and PM (25). Autophagy, an important process in regulating T cell homeostasis, appeared to be reduced in T cells of patients with DM/PM, and treatment with rapamycin restored this alteration (26).

Muscle fibres and vessels are active players in the pathogenesis of IIMs. Distinctive autoantigens of DM were elevated in both skin and muscle tissues in DM patients, together with stress molecules, suggesting that cellular stress may be one of the first steps of the pathogenesis of muscle inflammation (27). The activity of Cathepsin G (CTSG) was significantly increased in the muscle tissue of DM patients, controlling, in particular, the permeability of vascular endothelial cells and the chemotaxis of inflammatory cells (28). In DM patients with early disease, inflammatory infiltrates and neoangiogenesis were detected mainly in the fascia rather than in the muscle, highlighting the importance of other structures besides muscle fibres in the pathogenesis of DM (29).

New genetic loci (both HLA and non-HLA SNPs) associated with the development of IBM were identified (30, 31). By considering IBM, besides genetic, also other pathways may be implicated in its pathogenesis. Murata-Shinozaki *et al*. showed that rimmed vacuoles of muscles of IBM patients are enriched in proteins associated with the Wnt signalling pathway, similar to the granulovacuolar degeneration of neurons in Alzheimer disease, thus strengthening the link between the two diseases (32). Impairment of the autophagic processes may lead to rimmed vacuoles formation in IBM (33). Autophagy may be also impaired in IBM (34). Noda *et al* showed an upregulation of the transforming growth factor (TGF)-β signalling in the muscle of IBM patients (35).

A perturbation in intracellular calcium regulation and in the activation of a Ca2+-activated protease, calpain-1, was found in IBM patients (36).

Autoantibodies

Autoantibodies in IIMs can be divided into two different groups: myositis-specific autoantibodies (MSA) and myositis-associated autoantibodies (MAA), prevailing in overlap syndromes. In particular, MSA are associated with distinct clinical phenotypes and are helpful in the diagnostic process as well as subclassification of patients and prognostic factors, and they represent more than a purely diagnostic biomarker, but a new instrument for disease characterisation (37).

When an IIM is clinically suspected, patients are commonly tested for the presence of antinuclear autoantibodies (ANA) by immunofluorescence (IF) on Hep2 cell substrates but this test may produce false negative results in up to 18% of patients (38) mainly because some antigens, such as Jo-1 and Ro52, sometimes observed and frequently co-occurring in ASSD (3), and are scarcely expressed on Hep-2 cells. Furthermore, it is always important to remember that cytoplasmic positivity of ANA test is a suspect finding for IIMs in general and for antisynthetase syndrome (ASSD) in particular (39). However, after ruling out other non-autoimmune causes of myopathy, when an IIM is suspected, a specific test for myositis-related autoantibodies should always be performed (40).

The recent literature has highlighted the clinical significance of anti-MDA5, that defines a specific subset of DM associated with the occurrence of an acute ILD, frequently leading to Intensive Care Unit admission due to respiratory failure, with milder or no muscle involvement (41, 42). Patients frequently present arthritis, profound weight loss over 1–2 months and concomitantly with the onset of ILD, a cutaneous phenotype characterised by tender palmar papules and skin ulcerations (41). High levels of ferritin is common and may represent one of the most significant prognostic factors in anti-MDA5 associated ILD (43, 44). Similar results were observed in patients with ASSD (45). It has also been suggested that circulating levels of anti-MDA5 antibodies could be used as a biomarker for the occurrence of respiratory failure due to ILD in patients with IIM, and its variation in level may predict the response to therapy and the probability of ILD relapse (46, 47).

ILD is also frequently observed in patients positive for anti-aminoacyl-transfer RNA synthetase antibodies (anti-ARS Ab), such as anti-Jo-1, anti-PL-7, anti PL-12, anti-EJ, anti-OJ, anti-Zo, anti-Ha and anti-KS antibodies. Despite lung involvement, patients with anti-ARS ILD showed a better prognosis in the first 3 months of the disease compared to anti-MDA5 positive patients (48).

Although patients with anti-ARS Ab share many common clinical features, several investigators have reported on the heterogeneity of ASSD, especially in presence of MAA. Shi *et al*. found that RP-ILD is more frequent in patients with anti-PL7 ASS and in those with double positivity for anti-Ro52 (45). In addition to anti-PL7, also anti-PL12 is associated to severe ILD, while anti-Jo1 is associated to a more severe muscle involvement (49), isolated arthritis (often erosive) as a presenting feature (50), and a lower degree of pulmonary fibrosis (51), at least at disease onset (27). Of note, even if the term RP-ILD is regularly used in the rheumatology setting, there is no shared definition for RP-ILD in the pneumology setting, thus indicating a not secondary bias in papers published so far.

IMNM usually presents with prominent muscle cell necrosis and only minimal lymphocytic infiltration on muscle biopsy and is associated to positivity for antibodies against signal recognition particle (SRP) or HMG-CoA reductase (HMGCR). Those with anti-SRP may have a more severe muscle involvement than anti-HMGCR positive patients (52), presenting a more elevated creatine kinase (CK) level and more weakness (53); younger patients with anti-HMGCR were more likely to have refractory disease and a worse prognosis than older patients (54).

Recently Lilleker *et al*. (55) explored the usefulness of anti-cN-1A antibody testing to perform an IBM subgroup classification and found that the presence of such antibody presents a more severe phenotype with a higher mortality risk, independent of age, gender, comorbidities and the presence of dysphagia.

Nowadays, in DM patients, it is possible to define specific phenotypes according to the antibody expressed. Anti-NXP-2 antibody-positive patients had a higher prevalence of myalgias and dysphagia and there is an association with the development of calcinosis (56, 57) and peripheral oedema (56); dysphagia occurs more frequently in patients with anti-SAE (58). DM is frequently a paraneoplastic disease, particularly if positive for anti-TIF1-γ, described as a marker of paraneoplastic DM and not reported in patients with solid cancer without IIMs or in non-IIMs paraneoplastic rheumatic syndromes (59). It is important to remember that also anti-NXP2 antibodies (in adult males) and anti-SAE antibodies have been linked to an increased risk of paraneoplastic IIM (58).

Clinical and diagnostic aspects

The main clinical manifestations of PM/DM are proximal muscle weakness and myalgia, associated with impaired muscle function. Alexanderson *et al*. showed that patients might be more limited in dynamic repetitive muscle function (DRMF) than in isometric muscle strength, pointing out the importance of assessing DRMF in addition to the recommended manual muscle test 8 (MMT8), also because DRMF correlates well with patient-reported physical function (60).

In the ASSD, the muscular involvement is similar to PM/DM and relatively homogeneous, even though a Japanese study pointed out that, among the various autoantibodies, anti-OJ antibodies are associated with a more severe muscle weakness (61).

In contrast, in IBM we have both proximal and distal muscle involvement, mainly quadriceps muscles and the digital extensor. Jørgensen *et al*. published data revealing a positive relationship

between objective measures of functional capacity and self-reported physical function in IBM patients: timed up & go test (TUG) test performance appeared the strongest predictor of self-perceived physical function (r2=0.56, $p<0.05$) while between-limb asymmetry in lower limb muscle strength can be considered the strongest predictor of gait function (62). The presence of anti-M2 antibody may be associated to a characteristic distribution of affected muscles, in particular a lesser degree of limb muscle involvement and atrophy, but a frequent paravertebral muscle atrophy, as demonstrated by biopsies (63).

In 2017 the new EULAR/ACR classification criteria for IIMs were published: they consist of 16 items divided into 6 groups, each corresponding to a weighted score, in order to provide a probability of IIMs: a score ≥90% defines a definite IIM, ≥55% and <90% a probable IIM, while a score <55% identifies a possible IIM. They subsequently define adult/juvenile IIMs (based on the age of the onset of symptoms) and, among adult IIMs, they distinguish PM, IBM, DM and amyopathic DM (ADM) based on clinical findings and muscle biopsy (64).

These criteria have a sensitivity of 87% and specificity of 82% (65), greater than the Bohan and Peter criteria, and similar to other published myositis classification criteria (64), in contrast to the observations by the Slovenian group who found a lower sensitivity, attributed to the absence of the necrotising myopathy in the muscle biopsy item and the presence of only anti-Jo1 in the antibody item (66). Moreover, the skin variables of these criteria (Gottron's sign/papules, and heliotrope rash) may be inadequate to correctly classify patients with ADM: in the study by Patel *et al*., 26.3% of ADM patients did not meet the minimum probability cut-off (67). It is interesting to observe that neither dysphagia, nor ILD have been included in these classification criteria, which should be again validated and which, as reported by authors, need 6 months of disease duration before the full application, with relevant limits for patient management.

In 2017 the response criteria for adult DM and PM were updated. They identify thresholds for minimal, moderate, and major improvement and were defined as ≥20, ≥40, and ≥60 points in the total improvement score, which is the sum of the absolute percent changes in each of the 6 core set measures – physician, patient, and extra-muscular global activity by a visual analogue scale (VAS), MMT8, health quality assessment (HAQ), and muscle enzyme levels. The sensitivity and specificity in DM/PM patient cohorts were 85–92%, 90–96%, and 92–98% for minimal, moderate, and major improvement, respectively (68).

Novel data about the muscular involvement in DM have been identified. In DM patients the pathogenic process seems to start from the fascia: biopsy studies demonstrated a higher angiogenesis and inflammation in the fascia of DM patients compared to those with PM and even higher in the fascia compared to muscle, in the early phase of disease (29). In addition, myalgia appears to be associated with the presence of fasciitis rather than that of myositis (69).

An important histopathological element is perifascicular atrophy; in these areas there is a demonstrated reduction of capillary density (2-fold) and of transverse vessel density (3-fold) (70), and an elevated expression of retinoic acid inducible-gene I (RIG-I) that typically increases in hypoxic conditions, inducing an augmented release of IFN (71). In particular, RIG-I positive fibres were found in 50% of DM samples (*vs*. 11% in non-DM samples), suggesting that perifascicular RIG-I expression is a good biomarker for the diagnosis of DM (23). Moreover, patients with DM showed significantly elevated muscle tissue IL-4 and IFN-γ levels, confirming the involvement of Th1-type and Th2-type immunity in DM pathogenesis (14).

Perifascicular damage is also present in ASSD but, unlike DM that has numerous atrophic, non-necrotic perifascicular fibres with evidence of diffuse reduction of COX staining (consistent with mitochondrial dysfunction), in ASS necrosis is often limited to isolated foci of fibres with scattered COX-deficient fibres, and associated with myocyte regeneration and inflammatory T-CD4 and CD8 infiltrate (72). A transcriptomic analysis of early untreated DM muscles revealed a down-regulation of mitochondria-related genes. Mitochondrial dysfunctions, mediated by ROS, contribute to poor exercise capacity and, in turn, increased ROS production that drives IFN-I inducible gene expression and muscle inflammation, and may thus self-sustain the disease (24).

In IBM, conversely, muscle fibres exhibited greater TGF-β, TβRI, and TβRII immunoreactivity in the cytoplasm, reflecting the central role of TGF-β signalling dysregulation in the pathogenesis of IBM (35).

Muscle MRI is a commonly used diagnostic tool in myositis; recently a Chinese group proposed whole-body MRI as a sensitive, non-invasive and efficient imaging method useful for muscular involvement in 66 newly diagnosed IIM patients. They compared the sensitivity of the technique for peculiar lesions on STIR sequences (muscular oedema or fatty infiltration) with muscular biopsy, serum CK and EMG and they found that whole body MRI exhibited a similar positive diagnostic rate compared to muscular biopsy and a higher positive rate than serum CK and EMG (73). The detection of ischiofemoral impingement, defined as the presence of oedema pattern and crowding of fibres of the quadratus femoris muscle, was found in 11% of IIM patients, and was independently associated with fatty atrophy of hip stabilising muscles (74).

In IMNM, the MRI shows a more widespread muscle involvement compared to PM or DM ($p<0.01$) and, as previously reported, anti-SRP positive patients have a more severe muscle involvement than anti-HMGCR-positive patients (52). On the other hand, IBM presents with a typical pattern of muscle involvement on MRI: fat infiltration more extensive in the distal muscles, in the lower extremities, usually asymmetrically (typically medial gastrocnemius, flexor digitorum profundus, and quadriceps muscles) (75). According to what was found on biopsies, in ASSD MRI revealed a higher frequency of oedema in muscles and fascia (in the anterior

compartment) and fatty replacement (in the posterior compartment) in these patients than in the matched healthy controls ($p<0.001$) (76).

In this regard, Andersson *et al*. investigated the validity of MRI by describing the differences between ASSD patients and healthy matched controls. A composite semi-quantitative score including both disease activity (oedema extent, oedema intensity and fascial oedema) and damage (fatty replacement and presence of muscle volume reduction) was used for analysis. The results showed that ASSD patients had a significantly higher MRI score than controls ($p<0.001$) and worse muscular function ($p<0.001$), with a higher frequency of oedema in muscles and fascia in the anterior compartment) and fatty replacement in the posterior compartment (76).

Among the other imaging techniques, ultrasonography (US) is a useful tool to complement patient evaluation, since it is able to detect oedema, inflammation, fat, fibrosis and calcification, with a good correlation with disease activity (77).

Finally, Technetium-^{99m}-pyrophosphate (^{99m}Tc-PYP) scintigraphy has been proposed as an effective imaging technique in IIM. In the study of Thøgersen *et al*., muscular ^{99m}Tc-PYP uptake appears higher in patients with PM/DM than in healthy controls and in the proximal than in the distal part of the thigh muscle, with a gradient down along the thigh muscle in acute patients. The muscular ^{99m}Tc-PYP activity of patients correlates with clinical parameters of disease activity (MMT8, HAQ, VAS) (78).

ILD is a common feature of IIM with a severe impact on patients' survival (79). Recent studies have focused the attention on potential predictive factors for ILD severity and mortality, particularly in ASSD. The presence of anti-PL7 antibody and lower % FVC at initial diagnosis has emerged as predictive factors of increased risk of long-term respiratory deterioration (80). Anti PL-12 antibodies and black race have also been found to be related to a more severe lung involvement if compared with anti-Jo1 positive patients (49). In addition to the levels of anti-MDA5 autoantibodies (46, 47), also the initial serum ferritin levels ≥450 ng/ml ($p=0.006$), ground glass opacities score of right middle lobe >2 ($p=0.002$) and P[A-a]O2 ≥30 mmHg ($p=0.02$) have been found to predict mortality in anti-MDA5 patients in a retrospective study on 18 patients observed for 24 weeks. Other parameters such as serum markers and global ground glass opacities score, did not show significant association with mortality (43).

Anti-MDA5 positive patients are more prone to show ILD related respiratory failure, worse short-term prognosis and scarce response to therapy compared to ASSD patients. Conversely, according to Isoda *et al*. after 2 years from initiation of treatment, no significant differences were detectable in terms of mortality between ARS and anti-MDA5 positive patients, with ARS positive patients showing a higher rate of ILD relapse (81, 82). Yura *et al*. investigated the clinical characteristics of three distinct populations: 1. patients with idiopathic interstitial pneumonia (IIP) and positivity for ARS, who did not fulfil the criteria for any connective tissue disease (n=18); 2. patients with PM/DM ARS+ ILD (n=20); and 3. patients with ARS negative-IIP (n=284). NSIP was the most common ILD pattern in group 1 and 2, while usual interstitial pneumonia (UIP) was the most frequent finding in group 3. Interestingly, group 1 was affected by a higher prevalence of honeycombing compared to group 2. Mechanic's hands were present in group 2 and, to a lesser extent, in group 1. Group 1 and 2 showed also higher lymphocyte count and lower C4/CD8 ratio in bronchoalveolar lavage fluid compared to group 3. The presence of Raynaud's phenomenon, the need for long-term oxygen therapy and survival rates did not significantly differ between the three groups (83). On the contrary, differences in prognosis have emerged between myositis-associated UIP and idiopathic pulmonary fibrosis UIP, the former showing better event-free survival and cumulative survival than the latter (84).

Cutaneous involvement, with Gottron papules and sign and heliotrope rash, is a typical feature of DM (85). A multicentre prospective study reported associations between peculiar cutaneous manifestations and MSA. Anti-MDA5 patients showed a higher frequency of palmar violaceous macules/papules, mechanic's hands and cutaneous necrosis; anti-NXP2 showed associations with calcinosis, and a lower risk of Gottron's sign/papules; anti-ARS antibodies with lower incidence of eyelid involvement. Cancer was associated only with cutaneous necrosis (86). A small cohort study found that calcinosis may be predicted by a longer follow-up period, diagnosis of DM, positivity for PM/Scl and NXP-2 antibodies; the latter were also associated with an early onset and a diffuse form of calcinosis (87). Cox *et al*. focused on "Hiker's feet", which is the hyperkeratosis of the toes and plantar surface of the feet, and its association with DM and ASSD (88).

Two retrospective studies conducted by the American and European NEtwork of Antisynthetase Syndrome Collaborative Group (AENEAS) on their cohort of anti-Jo1 patients, focused on the clinical evolution of the syndrome. They found that, in patients with incomplete ASSD (*e.g*. without the entire triad of the disease, represented by arthritis, ILD and myositis) at the beginning of disease, the appearance of accompanying findings such as fever, Raynaud's phenomenon and mechanic's hands, predicted the development of a lack of triad findings over the follow-up (89).

Furthermore, the same group showed that 58 out of 243 ASSD patients referring to the AENEAS cohort at the time of the evaluation had a disease onset characterised by the occurrence of an isolated arthritis, frequently polyarticular and symmetrical. A consistent proportion of these patients showed rheumatoid factor (39%) and/or anti-citrullinated protein autoantibody positivity (28%) and/or erosions on plain radiography (about 35%). Manifestations such as Raynaud's phenomenon and Mechanic's hands were present only in a third of the cases and 71% of the patients satisfied the 1987 American College of Rheumatology criteria

for rheumatoid arthritis. The most important point was the subsequent occurrence in almost all cases of the remaining manifestations of typical clinical triad (ILD and myositis) during the follow-up, suggesting that we should think about ASSD even when other diagnoses seem to be more likely (50).

The well-known association between cancer and IIMs has been confirmed by a recent meta-analysis (90). Yang *et al*. investigated the association between cancer and specific MSA in a population of 627 patients with IIM, followed for a median time of 33 months. Among them, 72 developed malignancy and 60 of them had cancer-associated myositis (CAM, cancer or paraneoplastic syndrome occurring within 3 years of the disease onset). An overall increased risk of malignancy, compared to the general Chinese population and measured by standardised incidence ratio (SIR), was found in patients with anti-TIF1-γ (SIR=17.28), NXP-2 (SIR=8.14) and anti-SAE1 antibodies (SIR=12.95) and in MSA-negative patients (SIR=3.99), as reported in a previous paragraph. Despite this data, a close temporal relationship between IIM and cancer onset was found also in other MSA groups (anti-Jo1, anti-HMGCR, anti-PL12), even if to a lesser extent than anti-TIF1-γ, NXP-2 and anti-SAE1 antibodies. Similarly, all of these patients showed a distinct clinical course of myositis and cancer. Although no associations between MSA and any particular type of cancer were found, the authors observed that the anti-TIF1-γ group never developed haematological cancer while the MSA-negative group had a high prevalence of this kind of malignancy. Interestingly, the prognosis did not differ between different MSA groups, but it was significantly poorer for patients with CAM compared with myositis unrelated to cancer (HR) of 10.8 (95% CI 1.38–84.5, p=0.02) (91).

A systematic review of the literature highlighted the importance of screening for colorectal cancer in DM patients, although this association remains rare, because DM may completely regress after resection of the malignancy (92).

Heart failure, myocarditis, rhythm abnormalities, pericarditis, PAH and coronary disease are well known to be potential manifestations of cardiac involvement in IIM (93). According to Albayda *et al*., the presence of anti-mitochondrial antibodies (AMA) in the context of a DM/PM might identify a peculiar subset of disease with a more severe cardiac involvement (94). A recent meta-analysis focused the attention also on the incidence of venous thromboembolism in IIM and found an increased risk of venous thromboembolism, pulmonary embolysm and deep vein thrombosis for both PM and DM patients (95). Furthermore, an increased prevalence of coeliac disease, detected by duodenal biopsy, was described in a Swedish retrospective study (96).

A speckle-tracking echocardiography (STE) study by Guerra *et al*. aimed to investigate subclinical cardiac dysfunction in IIM patients. Two-dimensional STE measurements were performed in 28 IIM patients and 28 controls. Standard indices of systolic and diastolic function of LV and RV showed no differences between the 2 groups. Global longitudinal strain (GLS), on the other hand, was significantly lower in the IIM cohort for both left ventricule (LV) and right ventricule (RV) (p=0.006 and p=0.033, respectively). No correlation with muscle or other organ involvement, nor with disease duration, was found (97). Zhong *et al*. obtained similar results in a 3D STE study on 60 IIM patients, but a correlation emerged between GLS of both ventricles and the Myositis Damage index (LV R^2=0.44, p=0.002; RV R^2=0.56, p<0.001) and between LVGLS and disease duration (R^2=0.24, p=0.002) as well as between RVGLS and ILD (R^2=0.30, p<0.001) (98).

Treatment

Only a few large clinical trials are available to guide clinicians in the treatment of IIM. Outcome measures to assess treatment response have been available for only a few years and the response criteria continue to evolve (99).

Although glucocorticoids remain the anchor drug of initial IIM treatment, several immunosuppressive and immunomodulatory agents have been proposed for the management of IIMs, and the development of biologic agents against potential pathogenic pathways offers hope for targeting the treatment of IIMs (100). Additionally, the use of adrenocorticotropic hormone (ACTH) gel has shown promising results in a recent open-label clinical trial by Aggarwal *et al*. This treatment seems to be safe and effective in patients with refractory IIM, allowing a concomitant steroid sparing effect (101).

A case-based review by Lopes Koyama *et al*. points to mycophenolate mofetil (MMF) as a promising drug combined with low doses of steroids for the treatment of ILD in patients with CADM (102). Shimojima *et al*. studied the use of a combination therapy with calcineurin inhibitors for the treatment of severe ILD in patients with IIMs (103).

As we previously reported (7), even if some experts recommend the use of high dose intravenous immunoglobulins (IvIg) as a first line therapy, their role in IIM treatment remains quite uncertain since the data on this treatment derive mostly from open studies and uncontrolled retrospective trials with small samples, short-term follow-up and *ad hoc* outcome measures (104). A recent Australian study conducted by Foreman *et al*. *c*onfirmed the overall efficacy of IvIg in PM, DM and also in IBM. The treatment with IvIg was confirmed to be safe and the response rate was higher in patients that were treated early (105). The use of IvIg was also proposed for the treatment of skin lesions in patients with classical or amyopathic DM, with or without rapid progressive ILD, refractory or intolerant to conventional treatments (100), since these treatments can be ineffective (106) or may be a cause of toxicity (as for hydroxychloroquine) (107). A Japanese study described how IvIg can help to control anti-MDA5 antibody-associated DM with palmar macules/papules skin lesions (108). Recently, also the self-administered home-based subcutaneous administration of Ig (ScIg) in IIMs has been proposed as an effective and safe alternative to IvIg, confirming a short-term clinical equivalence between IvIg and ScIg (109).

A pivotal double-blind, randomised, placebo-controlled, phase III study is ongoing to confirm the efficacy and safety of this kind of treatment in patients with refractory DM (110). At the moment, given that Ig is a costly and limited resource, the data from the literature recommend frequent monitoring with the aim of preventing unnecessary use.

For the treatment of refractory skin rash in DM patients, leflunomide (111) and rituximab (RTX) (112) may be effective in addition to the standard therapy. Tofacitinib treatment was similarly associated with improvement in multidrug-resistant cutaneous disease in DM, firstly in three patients in 2016 and a subsequent report in 2017 showed improvement also in joint and muscle involvement (113, 114).

A pilot study by Tjärnlund *et al*. has recently evaluated the treatment with abatacept in IIM patients, identifying that half of the treated patients obtained a lower disease activity and, in the repeated muscle biopsy, an increased frequency of Foxp3+ Tregs cells was identified, suggesting positive effects of the treatment in muscle tissue (115). These encouraging results have led to an ongoing phase III clinical trial on abatacept in IIMs (110), and to a randomised pilot trial for the treatment of ILD in ARS-positive patients (116).

Since tocilizumab has been reported to be effective in patients with refractory PM and DM (100), another interesting spontaneous, multicentre, randomised, double-blind, controlled trial using the newly revised Definition Of Improvement (DOI) is ongoing (117) to evaluate the efficacy of tocilizumab IIM (118).

After the Rituximab in Myositis (RIM) study in 2013, no other randomised controlled trials are currently available for rituximab treatment in IIM. However several studies are still reporting the efficacy of this drug in refractory skin (126), and lung involvement related to IIMs (119, 120).

Even if recently, a paper re-proposed the possible use of anti-TNF-α agents as a potential therapy for refractory IIMs (121), their use should be carefully evaluated because of the findings of another paper that described the occurrence of myositis after anti-TNF-α treatment (122). It has been suggested that anti-TNF-α therapies may induce myositis occurrence, but if we look at ASSD (50, 89, 123), it seems easier to suggest that myositis occurrence in ASSD patients treated with anti-TNF-α drugs is related to the natural history of the disease and to the frequent ineffectiveness of these drugs in this setting.

As biologic therapies used to treat IIMs are frequently prescribed off-label, the development of a structured nationwide register such as the Swedish Rheumatology Quality of care Register (SRQ), may be useful to better understand which patients can benefit from which therapies and the reason for discontinuation of the treatment. According to a recent report from SRQ, the main reasons for discontinuation of biotechnological drugs were mostly adverse events or lack of efficacy (124).

As in other rheumatic diseases, also in IIMs an evaluation of the potential effect of oral Janus Kinase (JAK) inhibitors is ongoing in a clinical trial of patients with DM and refractory cutaneous features (125); also the effect of blocking TLRs in the same kind of patients is being assessed in a multicentre international study (126).

Although IBM are usually considered refractory to treatments, there is encouraging data from studies that have evaluated the possibility of alleviating dysphagia using botulinum toxin (127) and the potential role of follistatin gene therapy for this kind of IIM in general (128).

Current evidence supports the safety and efficacy of exercise to reduce impairments and activity limitations and to improve quality of life in patients with IIMs. Intensive exercise could be considered an anti-inflammatory treatment in adult patients with PM and DM (129). Munters *et al*. have just demonstrated that gene expression and proteomic analysis of skeletal muscle from patients with IIMs identified important changes and molecular adaptations in exercised skeletal muscle after endurance exercise over 12 weeks. In particular, they demonstrated the activation of the aerobic phenotype including mitochondrial oxidative phosphorylation, mitochondrial biogenesis, and capillary growth and found evidence that endurance training activated the muscle growth programme that could overwrite the muscle atrophy process, and that it suppressed the inflammatory response in muscles (130). As also explained last year, recent studies have demonstrated the decisive role of a standardised and individually adapted rehabilitative therapy to disease activity, glucocorticoid dose and the level of pain and fatigue. Exercise should be introduced at low loads and intensity under the supervision of a trained physical therapist, and the effects should be monitored by validated objective and patient-reported outcome measures. Therefore, even if the optimal physical activity level in patients with myositis is another area that needs to be assessed, physical exercise is no longer contraindicated even during the induction of remission of the IIMs (7, 131).

Conclusions

IIMs are complex conditions with multi-visceral involvement that deeply affect the patient's prognosis. A continuous update on these conditions is crucial for every rheumatologist in order to better deal with this wide spectrum of conditions. In fact, the heterogeneity of manifestations, the large number of myositis-related antibodies, from ARS to anti-MDA5, together with the increased risk of neoplasms or overlap with other connective tissue diseases clearly explain the large number of problems that every clinician interested in IIMs deals with on a daily basis. Furthermore, the complexity of IIMs is evident from pathogenic mechanisms to final therapeutic decisions. However, one of the problems in the management of IIMs is the wide range of involved specialists that increases the risk of different points of view on the same patient. This update would surely represent an advantage for clinicians, by putting the attention on more recent news and by identifying new potential targets of discussion, in order to facilitate the continuous improvement of our knowledge on this fascinating group of diseases.

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