

One year in review 2017: idiopathic inflammatory myopathies

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Received and accepted on September 21, 2017.

Clin Exp Rheumatol 2017; 35: 875-884.

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EXPERIMENTAL RHEUMATOLOGY 2017.

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

ABSTRACT

Every year new concepts about pathogenesis, serology, diagnosis and treatment in inflammatory myopathies (IIMs) have been provided. The purpose of this manuscript is to summarise the most relevant literature contributions published over the last year about these complex and rare diseases.

Introduction

Idiopathic inflammatory myopathies (IIMs) are a group of rare systemic diseases involving skeletal muscles, lungs, heart, skin and gastrointestinal systems (1). The most common subtypes of disease were represented by adult dermatomyositis (DM), juvenile DM (JDM), clinically amyopathic DM (CADM), inclusion body myositis (IBM), polymyositis (PM), immune-mediated necrotising myopathy (IMNM) (2). In this manuscript, we will provide our annual update (3, 4) of the recent advances in pathogenesis, extramuscular manifestations, serological profile, imaging and treatment of IIMs. We performed a Medline search of English language articles published from the 1st January 2016 to 31st December 2016 using the following key words: “idiopathic inflammatory myopathies” and “myositis” (MeSH terms and semantic search) and pathogenesis, diagnosis, clinical manifestations, therapy. We reviewed all the articles and selected the most relevant studies.

Pathogenesis

Although the pathogenesis of IIMs is not yet well clarified, in recent years there has been great interest in the study of possible pathogenetic mechanisms in IIMs and several factors probably involved in the pathogenesis of IIMs have been identified.

Genetic association

Several data suggest that human leuko-

cyte antigens (HLA) gene family may be involved in the pathogenesis of IIMs.

A recent report on a Chinese population identified the association between DM and HLA-DPB1 polymorphisms identifying two novel susceptibility loci associated to the disease (5).

Moreover, also non-HLA genes may be involved in IIM pathogenesis. Maundrell *et al.* studied a single nucleotide polymorphism in the tyrosine phosphatase N22 (PTPN22) gene that encodes for lymphocytes phosphatase, strictly related to T-cell activation. The authors identified an association between the allele R620W in PTPN22 and IIM (6).

Another study conducted in a Chinese population with PM and DM identified an association between some genetic variations in the phospholipase C-like 1 gene that may be associated to the disease susceptibility in DM patients and in particular with interstitial lung disease (ILD) (7).

In inclusion body myositis (IBM) high levels of deletion in mitochondrial DNA have been identified; these mutations may play a crucial role in the processes of ageing that are strictly associated with the pathogenesis of the disease (8). Moreover, the expression of some genes required for mitochondrial oxidative phosphorylation may be related to IBM pathogenesis; these genes are shared between IBM and Alzheimer's disease and are particularly expressed during a cholesterol-enriched diet in an animal model (9). Furthermore, in IBM patients also mutations in genes coding for sequestosome 1 (SQSTM1) and valosin-containing protein (VCP) have been identified; these genes are involved in the pathogenesis of several genetic neurodegenerative diseases. These data may suggest some overlap aetiology between IBM and neurodegenerative diseases (10).

Competing interests: none declared.

Cytokines

Interleukins (IL) are a group of pleiotropic cytokines involved in several biological activities and in particular in the regulation of lymphocytes and other cells involved in the development and maintenance of the immune response (11).

IL-8 may be involved in the pathogenic mechanism of CADM and, in particular, in patients with CADM and ILD (12).

IL-15, is involved in the regulation of B and T cells, and in myoblast differentiation, muscular wasting and hypertrophy in several pathological conditions (13). In a recent study in an animal model of IIM, treatment with antibodies directed against IL-15 was able to reduce the levels of CD163 (14), a protein closely related to PM severity and with muscular inflammatory infiltration (15).

The levels of IL-17 are correlated to the levels of inflammatory macrophages infiltrates in muscles of PM/DM patients (16). The treatment with doxycycline inhibits the myogenic capacity of myoblasts induced by IL-17 and may reduce inflammation in an experimental model of IIM (17).

Recently, it has been suspected that IL-35 plays a critical role in the pathogenesis of several autoimmune diseases. In IIM patients, IL-35 was higher than both healthy control and patients with other autoimmune diseases, in particular in the early stage of the disease and the levels of IL-35 are associated with the presence of dysphagia and the levels of markers of inflammation such as erythrocyte sedimentation rate and ferritin (18).

A recent Chinese study confirmed a previous observation of a role of IL-1b and IL-18 in IIMs and identified a possible role of an inflammasome, NLRP3, in the pathogenesis of PM and DM. These observations suggest a possible role of NLRP3 pathway as a therapeutic target in IIM patients (19). Activated type I interferon (IFN) pathways have been suspected of being involved in the pathogenesis of IIM, in particular in DM and some autoantibodies as well as anti-Jo-1, and anti-SSb may induce IFN expression in IIM patients (20). These findings are also

confirmed by the expressions of the genes for type I IFN pathways in DM patients (21). A recent article identified higher levels of IFN in IIM patients, particularly DM and IBM, compared to healthy subjects. IFN signature was identified more frequently in patients with autoantibody positivity in particular in patients with anti-Jo-1, anti-Ro-60 and anti-U1RNP and in those with autoantibody multispecificity. Serum IFN α may be responsible for type I interferon pathway activation (22). In a proteomic study in DM patients, it was reported that interferon signature may be involved in the pathogenesis of skin manifestations and it is associated to reduced collagen in dermal fibroblasts (23). Type I IFN and IL-18 have been found to be associated to a dysfunction of endothelial progenitor cells in patients with PM and DM, in particular in their capacity to differentiate into mature endothelial cells (24). The activation of type I IFN may be also related to the expression of LL-37, a host defense peptide with several immunomodulatory activities. In IIMs, macrophages were the main cells related to LL-37 expression, and this expression may activate type I IFN which can initiate and perpetuate the inflammatory process (25).

Another study conducted by Toshihashi-Nakazato suggests that IFN gamma may reduce the inflammation in an experimental model of CD8⁺ mediated myositis (26).

MicroRNA

MicroRNA (MiRNA) are short non-coding regulatory RNA fragments that may regulate the expression of several genes and have a possible role in muscular pathogenesis (3, 27).

A recent study confirmed the possible role of MiRNA-21 and its correlation with CXCL-10, inflammatory chemokine, and oestrogen in humans and in an animal model of PM. The authors demonstrated that oestrogen levels are related to higher creatine kinase (CK) and CXCL-10 levels and lower MiRNA-21 expression; these effects are the opposite of the effects of corticosteroids and immunosuppressants. MiRNA-21 may decrease CXCL-10

expression and reduce macrophage migration, suggesting a possible role as a treatment of PM (28). Yin *et al.* showed that MiRNA-146a may regulate inflammatory infiltration in IIMs; MiRNA-146a levels in an animal model were related to a reduction of IL-17 and ICAM-1 levels and consequently a reduction in macrophage migration in the muscle (16).

Other MiRNAs that may play a role in IIMs, in particular, in PM (let-7b*, MiRNA-1234, MiRNA-3679-5p, MiRNA-4299, MiRNA-4310, MiRNA-498) and in DM (MiRNA-4299, let-7b*, MiRNA-3907) have a different expression compared to healthy subject. These MiRNA seems to be specific for PM and DM and are involved in the pathways of actin, myosin and innate immune response (29).

In patients with IIM and ILD, MiRNA-200c was related to the severity of lung involvement and the levels of this marker are negatively correlated to pulmonary function parameters (30).

In juvenile DM, several MiRNA alterations have been identified compared to healthy controls, in particular MiRNA-10 was the most downregulated and was associated to higher levels of pro-inflammatory cytokines as well as IL-6, IL-8, tumour necrosis factor alpha, vascular cell adhesion molecule (VCAM)-1 and macrophage chemoattractant protein (MCP)-1 (31).

Other pathogenetic pathways

Oxidative stress may play a crucial role in the pathogenesis of several autoimmune diseases. In IIM, reactive oxygen species (ROS) may be associated with damage to muscle fibres and/or muscle damage (32, 33). A recent article in a large group of patients with PM and DM evaluated the possible implication of serum antioxidants, bilirubin and uric acid; the study confirmed lower levels of bilirubin and uric acid in IIM patients compared to controls after eliminating the effect of gender and age. The reduced values of these scavenger molecules may be related to muscular damage in PM and DM patients (34).

Also the β -catenin was elevated in patients with IIM, and the activity of the

transcriptional factors of β -catenin was increased, in particular in patients with ILD. The activation of wnt/ β -catenin signalling is activated also in Duchenne muscular dystrophy and the authors conclude that this pathway may be involved in muscle regeneration (35).

Krebs von den Lungen-6 (KL-6) glycoprotein was found to be associated to connective tissue ILD and, in patients with PM and DM, the levels of this glycoprotein may represent a prognostic factor or may have a predictive value for developing of ILD (36).

In antisynthetase syndrome (ASSD) a novel promising pathway to explain some pathogenetic aspects has been identified: this pathway includes activation of the innate immune system and lead to the activation of natural killer (NK) cells with a probably direct impact on muscular and lung tissue damage in ASSD. A NK cell surface antigen, NKp30, is the main circulating antigen in ASSD and is related to ASS disease activity (37).

Extramuscular manifestations

Pulmonary involvement

ILD is a common extra-muscular manifestation of IIMs, with a prevalence ranging from 20 to 65% of cases (38, 39) and one of the main prognostic factors in terms of patients' survival (40). The most frequent patterns of lung involvement in IIMs are represented first by specific interstitial pneumonia (NSIP), followed by organising pneumonia (OP) and diffuse alveolar damage (DAD), whereas a usual interstitial pneumonia (UIP) pattern is quite rare (41, 42).

Recent researches showed that older age at diagnosis, arthritis/arthralgia, fever, increased levels of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), anti-Jo-1 and other antisynthetase antibodies, as well as anti-MDA5 antibodies, are factors associated with an increased risk of ILD in IIMs. Conversely, an underlying malignancy steadily reduces the risk of ILD in these patients (41).

Another retrospective cohort study showed that erythrocyte sedimentation rate (ESR) is significantly increased

in IIMs with ILD, in particular in the clinically amyopathic DM (CADM) subset. Interestingly, if ESR levels inversely correlated with forced vital capacity (FVC) and carbon monoxide diffusing capacity (DLCO), they did not correlate with muscle involvement parameters. Furthermore, mortality rate was significantly increased in DM patients with baseline ESR levels higher than 30 mm/hour (43).

If pulmonary hypertension (PH) is a well-established complication of IIMs with an extended ILD, the association of pulmonary arterial hypertension (PAH) and IIMs has rarely been reported. PAH seems to be associated with the DM subtype and with anti-Ro antibodies, suggesting that IIM-PAH might be the result of a specific microvascular disease (44).

Even if rare, spontaneous pneumothorax (PNM) is a refractory complication of IIMs. Ma *et al.* investigated the characteristics of 11 patients with DM-associated spontaneous PNM. The interval between DM onset and PNM occurrence ranged from 2 to 51 months (median 8 months). Compared with DM patients without PNM, patients with spontaneous PNM had a higher frequency of rapidly progressive ILD, anti-MDA5 antibodies, CADM diagnoses and cutaneous ulcers, but significantly lower CK levels (45).

Cutaneous involvement

Gottron papules and Gottron sign are the most typical cutaneous features of DM and CADM. These lesions may ulcerate but more commonly in CADM than in DM (46). In a Chinese retrospective study, DM or CADM patients with ulcerative Gottron papules/Gottron sign and who exhibit fever and/or arthralgia, anti MDA5 antibodies, baseline low white blood cell counts and CK levels and high ESR and ferritin levels, resulted to have an increased risk of ILD, especially acute interstitial pneumonia/subacute interstitial pneumonia (AIP/SIP) than patients without ulceration. This association may explain the reduced survival rate in this subset of patients (46).

An interesting association between serological profile and cutaneous le-

sion type has recently been reported, in particular, anti-Mi-2 antibody with facial dermatosis ($p=0.043$), the shawl sign ($p=0.020$) and flagellate erythema ($p=0.024$), anti-TIF-1c with facial dermatosis ($p=0.043$), and the shawl sign ($p=0.017$), anti-MDA-5 (strongly) with ulcerative vasculopathy ($p=0.002$), anti-Jo-1 with mechanic's hands ($p=0.035$).

Other cutaneous signs such as periorbital dermatosis, extensor rash, upper limb oedema, Raynaud phenomenon, nailfold changes, Gottron papules and photosensitive erythema were found instead in many patients regardless of MSA serotype (47, 48).

Calcinosis could develop in about 5–10% of cases, in particular in patients with DM, Gottron's papules, longer follow-up, positivity for anti NXP-2 and PM/Scl. Ab anti-NXP-2 depicts a distinct phenotype of calcinosis with early onset, quick widespread dissemination and low prevalence of muscle respiratory tract involvement (49).

Cardiac involvement

Cardiac involvement can occur in 9–72% of IIMs, depending on the diagnostic method used and selection of patients, and it is a relevant cause of death in these patients. ECG abnormalities, such as rhythm disturbances, signs of ventricular hypertrophy and conduction abnormalities, are not a rare finding. Left ventricular hypertrophy, left atrial enlargement, rhythm and conduction abnormalities were more frequent in PM than in DM, especially the left anterior fascicular block. Atrial fibrillation, supraventricular extrasystoles and first-degree atrio-ventricular block were observed only in patients with PM (50).

Diederichsen *et al.* recently confirmed these findings, and observed also the frequent occurrence of left ventricular diastolic dysfunction (LVDD) and longer QRS and QT intervals. In multivariate analysis, factors associated with LVDD were age, disease duration, presence of myositis-specific or -associated autoantibodies, and high cardiac ^{99m}Tc -PYP uptake (51).

Another study showed that the hazard ratio for myocardial infarction and

stroke in IIMs is increased in the first 5 years from disease onset and in particular in the first year, thus confirming the impact of cardiac involvement in these patients (52).

Malignancy

It has been established for several years now that IIMs, DM in particular, are significantly associated with a wide range of malignancies (53). The recent literature has confirmed that older age at onset, male sex, heliotrope rash, Gottron's sign, dysphagia, skin necrosis, periungual erythema, an "shawl" sign, anti-TIF-1gamma antibodies positivity, are independent risk factors for occult neoplasia occurrence in IIMs (54). In addition, it has been confirmed that the presence of ILD and of anti-synthetase antibodies seem to be protective for the development of cancer in these patients (55).

Antisynthetase syndrome

In the peculiar subset of ASSD, more recent news has confirmed the heterogeneous clinical spectrum time course of the disease (56).

Clinical manifestations and long-term outcome of 148 anti-Jo-1 positive patients with ASSD has been reported by a Spanish group. The majority of patients presented with isolated ILD (47 cases, 32.4%), isolated myositis (39, 26.9%) and isolated polyarthritis (26, 17.9%). The majority of patients developed further manifestations after disease onset and an isolated ILD was still reported in 21 patients (14.5%), an isolated myositis in 23 (15.9%), and isolated polyarthritis in 3 (2.1%) of cases. The median length of follow-up was 78.3 months and the estimated survival rates 87.7% at 5 years and 75.4% at 10 years. Mortality was four-fold higher with respect to the general population, mainly due to pulmonary complications and cancer (57).

As for PM and DM, also in ASSD lung involvement is mainly represented by an ILD with a NSIP or OP pattern (48, 58).

Finally, Andersson *et al.* found a good correlation between DLCO, FVC and the extent of ILD by high resolution computed tomography (HRCT) (59).

Recent insights into serological manifestations

The presence of autoantibodies is relatively common in IIMs. They are categorised into myositis-specific autoantibodies (MSAs) and myositis-associated autoantibodies (MAAs); the former are considered to be specific for IIM, while the latter group are usually associated with overlapping connective tissue diseases. The MSA group includes anti-synthetase antibodies (ARS), (anti-Jo1, anti-PL7, anti-PL12, anti-EJ, anti-OJ), anti-Mi2 and the most recent anti-TIF1γ, anti-NXP2, anti-SAE, anti-MDA5, anti-HMGCR, anti-cN1A and anti-SRP antibodies. Recent studies highlight the importance of MSAs not only as a diagnostic tool for IIM, but also as a prognostic factor predicting the disease evolution and the therapeutic response. Therefore, the detection of MSAs and MAAs facilitates disease diagnosis, clinical course prediction, and aids therapeutic decisions in the early stages of the disease.

Interstitial lung disease (ILD) represents a severe manifestation leading to high morbidity and mortality in IIM patients. Autoantibodies may help to identify patients at high risk of developing ILD. The autoantibodies that are more commonly associated to ILD are represented by anti-ARS antibodies (60) and anti-MDA5 antibodies (61). In particular, anti-MDA5 antibodies are specific indicators of patients with DM and CADM which is occasionally accompanied by fatal, treatment-resistant rapidly progressive (RP) ILD, histopathologically represented by diffuse alveolar damage (62). In a recent meta-analysis, Zhang *et al.* confirmed that the presence of anti-JO1 and anti-MDA5 antibodies are associated with an increased risk of developing ILD⁴¹; moreover, patients with ILD and anti-MDA5 positivity presented a poorer prognosis compared to ARS-positive patients, showing the highest frequency of acute/subacute ILD onset and a lower survivor rate (63), while ARS-positive patients presented chronic ILD (61). Moghadam-Kia *et al.* (64) confirmed the poor survival also in patients with CADM anti-MDA5 positive due to RP-ILD while patients without anti-

MDA-5 presented chronic progressive ILD. In addition, anti-MDA5 positive patients with RP-ILD exhibited higher levels of anti-MDA5 antibodies than those without RP-ILD (65). Anti-MDA5 antibody can be efficiently detected by the gold standard IP assay but also the newly developed anti-MDA5 antibody ELISA (65), which is efficient and useful also to detect anti-ARS antibodies (66). Data concerning the pathophysiology of anti-MDA5-positive DM are sparse; like in DM patients anti-MDA5 negative, expression of IFN-stimulated genes is up-regulated. However, only anti-MDA5-positive DM showed numerous nitric oxide synthase 2-positive muscle fibres with sarcoplasmic co-localisation of markers of regeneration and cell stress, perhaps with a protective effect on the skeletal muscle (67).

Among patients with anti-ARS antibodies, patients positive for anti-EJ often had acute onset of ILD with histopathological pattern consistent with non-specific interstitial pneumonia (NSIP)-like or unclassifiable interstitial pneumonia with acute inflammatory findings. These patients responded well to the initial treatment but may present frequent disease relapse (68).

Hosono *et al.* (69) observed that sera from 27 DM/CADM anti-MDA5ab positive patients presented an anti-110 kDa antibody. The corresponding autoantigen was identified as splicing factor proline/glutamine rich protein (SFPQ), which is known to play a role in innate immune responses. This antibody may be involved in the pathogenesis of DM/CADM and in the chronic disease course of DM/CADM. Therefore, anti-SFPQ antibody may be a new DM-specific autoantibody, particularly in anti-MDA5 positive patients (69).

According to the profiles of antibodies in patients with ILD and IIM, Yoshifuji *et al.* (61) propose the division into three groups: high risk group (patients with anti-MDA5 antibodies which required the most aggressive immunosuppressive treatment), moderate risk group (ARS, anti-U1-RNP, anti-PM/Scl anti-Ku antibodies, at risk of ILD recurrence) low-risk group (anti-Mi-2, anti-SRP and anti-TIF1gamma/delta

antibodies, less commonly affected by ILD). Anti-MI-2 antibodies showed a protective role against the development of ILD (60); anti-Ro52 could be detected also in anti-Jo1 antibody associated antisynthetase syndrome showing a more severe acute-onset ILD compared to anti-Ro52 negative (70); such patients responded worse to various immunosuppressant drugs but presented a good response to rituximab with no difference compared to anti-Ro52 negative patients (70).

The association between cancer and IIM, particularly DM, which is termed cancer-associated myositis (CAM), has been reported in the literature. Ceribelli *et al.* found a clear association with anti-TIF1 gamma/delta antibodies in dermatomyositis associated with malignancy (71); this observation was also confirmed in other studies (55, 72). Malignancy is also reported in patients with necrotising autoimmune myopathies IMNM, an IIM specifically associated with anti-SRP and anti-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMGCR) antibodies (73). In a group of 115 patients with IMNM, cancer occurred more frequently in HMGCR-positive or MSA-negative patients compared to anti-SRP positive patients (73). Further large-scale studies on cancer association with anti-HMGCR antibodies are necessary to demonstrate whether this antibody is another cancer-associated antibody. However, cancer screening should be obligatory in such patients. As yet there is no consensus as to the method or frequency with which patients with an IIM should be tested to rule out neoplasm.

Concerning the diagnosis of different subsets of IIM, in a large cohort of Indian patients, Srivastava *et al.* (60) confirmed that anti Mi2 antibodies were positively associated with DM, anti-SRP showed a poor response to multiple drugs and anti Ro52 antibody was most common in CTD myositis. IMNM could be associated to the presence of anti-HMGC and anti-SRP antibodies; the last one are associated with severe neurological symptoms more so than are anti-HMGC antibodies (74). Autoantibodies recognising cytosolic 5'-nucleotidase 1A (Anti-NT5C1A)

are found in 33–76% of patients with IBM and may be useful in making a correct diagnosis of IBM, a disease that is commonly mistaken for PM (75). Anti-NT5C1A were identifiable also in other autoimmune disorders such as systemic lupus erythematosus or Sjögren's syndrome but the authors demonstrated that in these diseases, Anti-NT5C1A were directed toward a distinct epitope region (76).

In patients with juvenile DM, the most common clinicopathologic form of juvenile IIM, anti-p155/140 are the myositis autoantibodies most often represented together with anti-MJ and anti-MDA5 (77); anti-p155/140 are associated with a chronic course of the disease (78) and the development of lipodystrophy and skin involvement (77), while anti-MJ are associated with severe calcinosis (70). In juvenile DM, anti-Mi2 Ab is associated with a good prognosis despite being linked to severe muscle disease, an opposite trend compared to patients presenting anti-MDA5 antibody which most often presented extra-muscular features (79). The screening of autoantibodies in patients with myositis cannot be based only on antinuclear Abs (ANA) detection by indirect immunofluorescence assays as they can be frequently negative, even though MSAs are present. In particular, in the setting of antisynthetase syndrome, a negative ANA is not uncommon because of the cytoplasmatic location of the target autoantigens. For that reason, Aggarwal *et al.* proposed anticytoplasmatic antibody assessed by indirect immunofluorescence (IIF) as a screening test for ASSD (80), which is particularly useful in anti-Jo1 negative because it allows a prompt diagnosis and treatment.

Imaging

IIMs may affect several different organs and the selection of the appropriate imaging technique may play a key role for the management of the patients in particular for muscular, articular, gastrointestinal and cardiopulmonary involvement.

Although muscle biopsy is often needed to make the correct diagnosis, a non-invasive procedure may be use-

ful to identify the pattern of muscular involvement and therefore identify the area of inflammation to biopsy. Moreover, non-invasive methods are preferable to assess response to therapy.

Magnetic resonance imaging (MRI) is recognised as an important technique in the evaluation of muscle abnormalities also in patients with negative biopsy (3). As Barsotti *et al.* observed in a recent paper, thigh MRI can distinguish muscle inflammation and oedema from atrophy, replacement of muscle tissue with fat and fibrosis or calcification too, providing additional data than clinical and biochemical examinations alone (81). The MRI examination may be performed with short tau inversion recovery, but recently also T2 muscle measurement and fat-corrected T2 seem to be useful in measuring the disease activity (82).

Muscular MRI allows the evaluation of large areas of muscle at one time, especially when performed as whole-body (WB) technique. According to this, Ellassawy *et al.* proposed the use of WB-MRI as diagnostic modality of choice for IIMs. They found out that it accurately detects the most severely affected muscles candidate for biopsy and it could provide a reliable baseline for follow-up of disease progression as well as the response to treatment (83). Finally, MRI could show a different pattern of muscle involvement in IIM such as DM, PM and IMNM which seems to be characterised by a more widespread muscle involvement according to Pinal-Fernandez *et al.*, particularly when positive to anti-SRP autoantibodies (84). Pipitone *et al.* observed that DM seems to affect the thighs anterior compartment more frequently than PM, while the posterior compartment seems to be equally involved in DM and PM (85).

Even if with non-definitive results, the use of US for the study of muscle and its pathological alterations in muscular diseases is still the objective of study. Last year a study from Nodera *et al.* reported that high echoic signals in the medial gastrocnemius compared with those of the soleus were suggestive of sporadic IBM over PM/DM (86). More recently, Yoshida *et al.* used power

Doppler US (PDUS) as a tool to detect fasciitis associated with DM; the authors concluded that the increased blood flow signal detected with PDUS could be involved in angiogenesis accompanying fasciitis in these patients, and could be a useful diagnostic tool specially in the early stage of the disease (87). As Gutierrez *et al.* concluded in their overview of how US is being used, implemented and applied in rheumatology, US increases the accuracy of the musculoskeletal clinical examination, influences the diagnosis, and the disease management (88).

MRI could also be a reliable diagnostic tool for the detection of oesophageal involvement, allowing early therapeutic intervention for these important causes of morbidity and mortality in IIM (3). Regarding dysphagia, a potential diagnostic role has been recently proposed, for real-time MRI (RT-MRI) which seems to be as safe and capable as videofluoroscopy to identify the cause of dysphagia in IBM with some advantages in the visualisation of soft tissue, timing analysis and x-ray exposure (89).

Casal-Dominguez *et al.* used high resolution manometry (HRM) to assess the pharynx and upper oesophageal sphincter (UES) involvement in IIM and they found, as expected, significant involvement of both regions and an association between oesophageal involvement and interstitial lung disease (ILD) (90).

Since ILD represent an important cause of morbidity and mortality in IIM patients, its assessment is still very important in these patients. Although plain radiographs may show reticulonodular opacities, particularly at the bases of the lung, high resolution tomography (HRCT) of the chest is the gold standard imaging technique in case of ILD (3) and is recommended in all patients due to its higher diagnostic accuracy. As Johnson *et al.* proved in their study, patients with lung involvement present a significantly higher mortality rate, especially in those with clinically evident ILD (40). Waseda *et al.* evaluated the CT findings in 64 patients with anti-aminoacyl-tRNA synthetase ILD and they concluded that they predominantly presented NSIP and in one-third of

cases OP with fibrosis (42). In any case, more than one finding may be present in the same patient. In a recent study, Kotani *et al.* found that the prognosis of patient with DM and acute/subacute interstitial pneumonia was poorer when the range of right middle lobe ground glass opacity was 25% or higher on limited three-level thin section CT (91). Since HRCT exposes the patients to radiations, during the last years, chest US with B-lines chest US with B-lines study has been proposed as a possible alternative technique to investigate lung involvement in patients with ILD and connective tissue diseases. More recently, Pinal-Fernandez has proposed the US evaluation of pleural irregularities (PI) as a new US sign for the detection of ILD in IIM patients (92).

Finally, the role of fluorodeoxyglucose positron emission tomography (FDG PET) is confirmed as a standard tool for detecting malignancies or systemic inflammatory involvement (3). According to these data, Uehara *et al.* examined the clinical utility of FDG PET/TC conducted under deep inspiratory breath-hold the evaluation of active ILD in patients with connective tissue diseases (CTD) as IIM. As they discovered, the procedure illustrated active ILD lesions in CTD and the extended signal distribution was associated with unfavourable clinical outcome (93).

Treatment

From the era when glucocorticoids were the only treatment available, in the last years several drugs have been used in IIMs, showing benefit in the management of both juvenile and adult DM/PM (94).

However, despite the progress, commonly shared guidelines for IIMs treatment are still lacking. High dose immunoglobulins, either intravenous or subcutaneous, have been reported as effective in various IIMs subsets and their use has a strong biological plausibility, but a recent review showed various limitations in the papers published so far, which were mainly open, uncontrolled or retrospective, with small samples, with short-term follow-up and with an unclear definition of outcome measures (95).

The switch from intravenous (IVIg) to subcutaneous (SCIg) has been assessed in a multi-centric French study. Twelve out of the 20 patients enrolled had PM or DM in clinical remission and had received long-term treatment with IVIg. Six months after the switch to SCIg, beneficial effect of IVIg were maintained, in terms of muscle strength measured with the Kendall score and quality of life levels assessed by the Short Form 36. Only an expected high percentage of local injection site reactions was recorded, with just one patient who discontinued due to lack of efficacy (96).

In a retrospective observational study involving 19 IIM patients, Cherin *et al.* confirmed the feasibility, safety and tolerability of SCIg, as well as the beneficial effects on muscle strength and serum muscle enzymes levels (97).

Combining various Swedish registers, Svensson *et al.* identified 95 patients with IIM receiving biotechnological therapies, including rituximab, abatacept, TNF-alpha inhibitors and anakinra, between 2000 and 2011, showing that these therapies are often tried and seldom successful. The paper showed that discontinuation reasons were mainly due to adverse events (ranging from 0 to 36%, with a higher prevalence in anakinra) or lack of efficacy (ranging from 25 to 44%, with a higher prevalence for TNF-inhibitors) (98).

Recently, Aggarwal *et al.* performed a post-hoc analysis of the rituximab in a myositis trial, taking into consideration only skin manifestations of adult and juvenile DM and evidencing a global improvement in skin manifestation activity (Gottron's papules and heliotrope rash), with a trend for better response in the early treated adult DM group ($p=0.052$) and a significant reduction of cutaneous ulcerations in the juvenile DM group ($p=0.02$) (99).

In a recent mono-centric study including 61 patients with anti-Jo1 antibody positive anti-synthetase syndrome, rituximab was more effective with respect to conventional immunosuppressants in terms of clinical and laboratory improvement, functional/diffusional and radiological signs of ILD and physician's/patient's evaluation of disease

Table I. Ongoing registered clinical trials in idiopathic inflammatory myopathies and main features.

Drug	Target	Route	Study identifier	Year of registration	Study type	Study design	Phase	Study population	Main primary and secondary endpoints
Belimumab	BLyss	IV	NCT02347891	2015	Interventional	Randomised, double blind, placebo controlled, cross over study	II-III	IIMs	Clinical improvement
Abatacept	CTLA4	SC	NCT02594735	2015	Interventional	Open label study	IV	jDM	Clinical improvement, AE
Abatacept	CTLA4	SC	NCT02971683	2016	Interventional	Randomised, double-blinded, placebo controlled	III	IIMs	Clinical improvement, AE
MEDI7734	plasmacytoid dendritic cell	SC	NCT02780674	2016	Interventional	Randomised, blinded, placebo controlled, single-dose, dose escalation study	I	DM (among Type I Interferon Mediated Autoimmune Diseases)	TEAE, ADAb, PK, PD
Interferon- α -kinoid	Interferon- α	IM	NCT02980198	2016	Interventional	Randomised, single blind, placebo controlled study	II	DM	Clinical improvement, AE, ADAb
Tofacitinib	Janus kinase 1-3	OS	NCT03002649	2016	Interventional	Single group, open label study	I	DM	Clinical improvement, AE
Octagam 10%	unknown	IV	NCT02728752	2016	Interventional	Prospective, double-blind, randomised, placebo-controlled study	III	DM	Clinical improvement, AE
Arimoclomol	Molecular chaperones and heat shock protein	OS	NCT02753530	2016	Interventional	Randomised, double-blind, placebo controlled study	II	IBM	Clinical improvement, AE

activity. Lung parameters had a statistically significant improvement in the 10 ILD patients treated with rituximab (mean improvement of 40%, 68% and 25% of FVC, DLCO and DLCO/VA at the last available follow-up, ranging from 6 to 42 months). Interestingly, concomitant anti-Ro52 antibody positivity and titre levels were associated with better response to rituximab than to standard immunosuppression (70). Also Lepri *et al.* confirmed the effectiveness of RTX on ILD in a cohort of CTD-ILD including 15 anti-synthetase syndrome, with a trend for improvement of PFTs during the follow-up (100).

Up to now only a few studies have focused on antifibrotic drug pirfenidone in IIM-related ILD. In a recent 12-month Chinese open-label study performed on 30 patients with clinically amyopathic DM complicated by ILD, and 27 patients used as a control group, showed that pirfenidone may improve the prognosis of patients presenting with subacute ILD related to CADM ($p=0.045$) (101).

The previously reported effectiveness of cyclosporine in IIMs related ILD (102-105), has been recently confirmed by Go *et al.* In particular, the authors showed that patients treated early with cyclosporine during the disease course showed a significantly increased sur-

vival rate ($p=0.009$) in a long-term follow-up (up to 96 months), as well as improvement of HRCT scores ($p=0.029$) (106).

The use of cyclosporine and methotrexate in juvenile DM has been evaluated in the PRINTO (Paediatric Rheumatology International Trials Organisation) trial. Three treatment arms were available: prednisone vs. prednisone plus cyclosporine and prednisone plus methotrexate. All patients received an induction treatment with intravenous methylprednisolone pulses and they continued with a slow tapering of the steroid maintenance dosage for about 24 months or less. Cyclosporine was administered at the dose of 4–5 mg/kg/day and MTX at the dose of 15–20 mg/m²/week.

In a long-term survival analysis, both combination groups were superior to prednisone alone in the improvement of the PRINTO core set criteria. Patients on MTX and CsA had a higher chance of achieving clinical remission (OR 2.45, CI 1.2–5.0) in a shorter time ($p=0.012$), and a shorter time to prednisone discontinuation ($p=0.002$) and a reduced rate of treatment failures ($p=0.009$). On the other hand, patients with DMARDs showed an increased rate of gastrointestinal and skin tissue adverse events, in particular in the CsA arm. Globally, this study supports the

efficacy of MTX and cyclosporine as steroid sparing immunosuppressants in treating juvenile DM patients, while the safety profile and steroid-sparing effect favoured the combination of prednisone plus methotrexate (107).

Nevertheless, it is important to remember that pharmacological treatment should always be associated with physical rehabilitation therapy and that physical exercise should be tailored according to patient's age, disease activity and levels of both pain and fatigue (108).

A further confirmation of this statement was published by Tiffreau *et al.*, who performed a randomised controlled trial comparing a hospital-based personalised rehabilitation programme including training for muscle strength, chest expansion, joint range of motion, improvement aerobic exercise capacity and gait, with an outpatient clinic. This trial involved a small number of PM patients (total 21). Comparing both arms, being treated for 4 weeks, the personalised rehabilitation groups showed a significant improvement in the Health Assessment Questionnaire score, in both the mental and physical domains of the Short Form 36 questionnaire and in pain evaluation after 4 weeks of treatment, which they maintained for a long period until the 12-month observation (109).

To date, a large number of clinical trials addressing IIMs are ongoing, including different therapeutic targets and different molecules (110-117) (see Table I).

Conclusions

Each year, a great number of articles are published on pathophysiology, clinical manifestations and treatment of idiopathic inflammatory myopathies. We have provided a critical review of the most relevant articles published in 2016. Although these articles may provide novel information about these rare diseases, greater knowledge pathogenetic mechanisms, prognostic factors and therapeutic strategies of IIMs is still needed to improve patient care.

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