# Review

# One year in review 2015: idiopathic inflammatory myopathies

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## ABSTRACT

*Idiopathic inflammatory myopathies (IIM) are a group of rare acquired muscle diseases that mainly affect skeletal muscles. Recently, novel insights into the pathogenesis, diagnosis and treatment of these complex diseases have been provided. Herewith we provided an overview of the most significant literature contributions published over the year.*

## Introduction

Idiopathic inflammatory myopathies (IIM) are a group of rare acquired muscle diseases. Based on a specific combination of clinical, immunopathological and histological features, four subtypes can be distinguished: dermatomyositis (DM), polymyositis (PM), necrotising autoimmune myopathy (NAM) and inclusion body myopathies (IBM). Recently, novel insights into the pathogenesis, diagnosis and treatment of these complex diseases have been provided. The aim of this review was to provide an overview of the most significant literature contributions published over the year. We performed a med-line search of English language articles published from the 1st January 2013 to 31st December 2014 using the following key words: idiopathic inflammatory myopathies, pathogenesis, diagnosis, clinical manifestations, therapy. We reviewed all the articles and selected the most relevant works.

## Pathogenesis of IIM

Basic research in IIM has been focused on the genetic as well as on immuno-pathologic aspects and on the role of innate and adaptive autoimmunity in their pathogenesis.

Regarding the genetic background of IIM, some differences have recently been pointed out comparing Caucasian and Asiatic populations. More specifically, HLA-DRB1*0301 and HLA-DQA1*0501 alleles have been reported as risk factors for IIM in Western populations, whereas it has been shown that DRB1*0803 increases PM susceptibility among the Japanese population (1). Among Caucasians, the allele DRB1*0301 has been linked to the production of anti-Jo1, whereas in the Japanese population the DRB1*0803 has been associated with susceptibility to IIM and to the production of anti-amminoacyl-tRNA synthetases (ARS) (2). Moreover, in the Chinese population, it was found that DRB1*07-DQA1*01-DQB1*02 and the DRB1*07 and DQA1*0104 alleles were associated with an increased risk of dermatomyositis (DM), while DRB1*03 seems to have a protective role (1). Noteworthy, a recently published genome-wide association study (GWAS) including European patients has shown the role of non-HLA novel risk loci, including phospholipase C-like 1, B lymphoid tyrosine kinase, and chemokine (C-C motif) ligand 21 (CCL21) (3).

In DM, the inflammatory infiltrate involves primarily CD4+ T cells, macrophages and a small number of B cells and plasma cells. It localises mainly in the perivascular and perimysial level but a pivotal role is played by complement membranolytic attack complex that damages endothelial cells with vascular injury and subsequent muscle fibre damage. On the other hand, PM and IBM, are characterised by an endomysial mononuclear inflammatory infiltrate complex including CD8+ T cells, macrophages and myeloid dendritic cells. CD8+T cells surround and invade non-necrotic muscle fibres that aberrantly express MHC class I, causing a perforin-mediated cytotoxic injury. MHC class I expression is probably induced by cytokines secreted by activated T cells (4); in addition, it has been observed that the up-regulation of RIG-I (DDX58) promotes a persis-

tent local immune response through interferon (IFN)-β secretion and consequently MHC-I up-regulation in DM patients (5).

The typical feature of IBM is represented by rimmed vacuoles that accumulate thanks to block of autophagosome-lysosome fusion and lysosomal activity through autophagy marker over-expression (6). Degenerative changes and mitochondrial abnormalities have been traditionally implicated in IBM pathogenesis. IBM muscle fibre degeneration shares several pathomolecular aspects with Alzheimer's disease, including accumulations of Aβ and phosphorylated tau proteins, increasing γ-secretase activity and impaired autophagy (7). Moreover, in IBM, intracellular accumulations of human beta-defensin-3 (HBD-3) co-localised near β-amyloid and LCR (markers of degeneration and autophagy) together with a stronger endosomal overexpression of toll-like-receptor-3 (TLK-3) (4). Another potential autoantigen for IBM cytoplasmic 5'nucleotidase 1A (cN1A) was found abnormally expressed in IBM vacuoles and myonuclear degeneration. Using immunodeficient mice, Fréret *et al.* have found that MCH-I expression is directly toxic for myofibres, through the induction of endoplasmic stress and the unfolded protein response (URP) (8). MCH-I overexpression alone was sufficient to induce the URP and a symptomatic myopathy. URP is triggered in IBM as a function of the level of intracellular MCH-I accumulation (8). A recent study has discovered the expression of chemokines, stress protein (heat shock proteins-HSP), and inducible iNO synthase (iNOS) around the invaded non-necrotic muscle fibres in PM and IBM (9). Upregulation of iNOS, in the actively invading macrophages, and subsequent production of NO with other pro-inflammatory factors has shown myocytoxicity in PM and IBM.

While the pathogenic mechanisms that lead to inflammation in PM and DM have been extensively studied, a limited number of studies have explored the pathogenesis of muscle dysfunction. Muscle biopsy does not always show inflammatory cell infiltrates and,

moreover, when infiltrates are reduced after treatment, muscle weakness could persist. Zong *et al.* had already demonstrated that a TLR4 ligand high mobility group box protein 1 (HMGB1) is involved in the acceleration of the development of muscle fatigue and induction of MHC-class I expression in muscle fibres from mice (10). Exposing mouse muscle fibres to HMGB1 results in the induction of MHC class I expression as well as impaired sarcoplasmic reticulum Ca homeostasis. The HMGB1 release (from the nuclei of muscle fibres and endothelial cells) acts on muscle fibres via TLR4 initiating a cascade of event that ultimately results in the decrease of the Ca release from the sarcoplasmic reticulum resulting in weaker muscle contractions. All these data suggest that HMGB1-TLR4 signalling (through MHC class I overexpression) can become a target of the immune system and cell damage (10).

*Cronic inflammation and cytokines*
The role of B cells in the pathogenesis of PM and DM is supported not only by the presence of autoantibodies but also the presence of B cell and plasma cells in muscle tissue and in the peripheral blood of patients with PM and DM. In the biopsies of muscle tissue, somatic mutation and isotype switching was found, as well as the presence of clonal expansion of cell B. A recent molecular analysis, conducted by McIntyre *et al.*, has demonstrated that B cell infiltration of DM and PM is actively proliferating in response to antigen in situ in the affected tissue with somatic hypermutation and affinity selection of their antibody receptors (11). Patients with IIM have a high serum level of B cell activating factor (BAFF), an important survival factor of autoreactive B cells, but it is impossible to determinate the membrane-bound BAFF. To overcome this problem, López de Padilla *et al.* have proposed a measurement of messenger RNA (mRNA) levels of BAFF that might be a more sensitive measurement of peripheral activity (12). All these findings, with the favourable clinical response to the B cell blocking agent (including rituximab), support the important role in the pathogenesis

of DM and PM by B lymphocytes. B cell production and activation requires help from T cells; all the subtypes of CD4+ helper T cells (including Th1, Th2 and Th17) are involved in myositis to a different degree and proportion (13); Th17 cells particularly correlate with disease severity activity and CPK levels (13). Recently, in IBM patients' blood and muscles, activation with Th1 polarisation was found involving the IFN-gamma pathway and CD8+CD28-T cells (apoptosis-resistant CD8+lacking the CD28 ligand which are thought to be like cytotoxic effector cells, involved in PM) associated with peripheral T regulatory cell (Tregs) deficiency (14). Georgantas *et al.* has demonstrated that increased levels of TNF lead to reduced levels of microRNAs (miRNAs) in the muscle of patients with myositis. In particular, miRNAs are critical regulators of both inflammatory cytokine signalling and adult skeletal muscle differentiation and maintenance. Moreover, an increased expression of cytokine pro-inflammatory levels and, in particular TNF, was found in the muscles of the patients (15). An interesting role within cytokines is played by IL-6 that supports both the innate and adaptative inflammatory immune response. IL6 is a potent pro-inflammatory cytokine and with IL-1β it is essential in the differentiation of Th17 in DM patients. IL-6 serum levels were found to be higher in DM patients in comparison with healthy controls (although lower in contrast to RA patients) and positively correlated with C-reactive protein and serum ferritin (16). Another cytokine that is probably involved in the pathogenesis of IIM is IL-22, produced by activated T cells that can stimulate an inflammatory immune response. A recent report has found a significantly IL22 up-regulation (at the protein level) in PM and DM patients and its positive correlation with disease activity. In this study, it was demonstrated for the first time the imbalance between IL-22 and its inhibitor (IL-22BP) in addition to overexpression of IL-22 receptor (occurred in myeloid cells infiltrating the inflamed muscle) and p-STAT3 in the myositis muscle (17).

## Clinical features of IIM

From clinical perspective, lately, a great effort has been made in the attempt of elaborating novel classification criteria for IIM. To date, twelve classification criteria for IIM have been published, however, no single criteria set has received universal acceptance (18). The scientific community is at work to overcome these limitations and novel criteria are expected for the next future (19). In parallel, novel entities have been proposed including necrotising autoimmune myopathies (NAM) and inflammatory myopathy with abundant macrophages (IMAM).

NAM is a heterogeneous group of disease supported by autoimmune inflammatory mechanisms, paraneoplastic conditions, exposure to toxins or drugs and often a combination of these mechanisms (8) and, therefore, may be classified in different categories including cases associated to malignancy, connective tissue disease, viral infection and statin treatment.

The autoimmune nature of this type of acquired necrotising myopathies was suggested by the frequent association with specific autoantibodies such as anti-signal recognition particle (anti-SRP) autoantibody or anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase (anti-HMGCR) antibody in statin associated disease (20). Autoimmune necrotising myopathies (NAM) characterised by significant necrosis of muscle fibres with regenerating fibres and minimal or no inflammatory infiltrate. An association between anti 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGCR) and NAM patients has been reported, particularly in statin-exposed patients. In the first European study on NAM, Allenbach *et al.* confirmed an association with anti-HMGCR (21) and, according to a recently published paper on a USA cohort (22), confirmed the correlation between anti-HMGCR titers and CPK levels, suggesting an important role of anti-HMGCR in the pathogenesis of NAM. Anti-SRP associated NAM is typically sudden with severe, painful motor impairment and high serum CK levels (23). Moreover, anti-SRP positive patients are less responsive to conventional drug treatment.

IMAM clinically resembles DM but differ from the latter because of the fascia inflammatory cell infiltrate represented mainly by CD68+ macrophages (24). An interesting finding suggests that IMAM patients have MEFV polymorphisms and TNFRS1A mutation, although none of these patients were diagnosed with familial Mediterranean fever (FMF) and tumour necrosis receptor-associated periodic syndrome (24). Anti-SRP was the first autoantibody specifically associated with necrotising myopathy that mainly affects adults of around 45 years old, with a seasonal (autumnal) and female predominance.

In addition to the relatively common self-limiting episodes of statin-induced myalgia, a statin-induced necrotising myositis is increasingly being recognised, associated with the presence of autoantibodies anti HMGCR and non-responder to discontinuation of statins. Statin-induced autoimmune myositis is a clinical entity distinct from the other statin myopathies (25), which tends to have an aggressive phenotype with significant myonecrosis, an irritable pattern on electromyographic testing and higher serum CK levels than one would normally associate with idiopathic inflammatory myositis (IIM).

Regarding IIM clinical features in recently published papers, those contributions focusing on cardiac involvement in IIM are worthy of note. Cardiac involvement has recently been identified as one of the most important causes of morbidity and mortality in patients with DM. The increase in mortality has been linked primarily to congestive heart failure (21% of total cardiac mortality) (26, 27) that has been related to old age, metabolic syndrome and hypertension. Metabolic syndrome, particularly, is highly prevalent in DM, and prior hypertension seems to be a major determinant of its development, while disease- and therapy-related factors do not appear to play a relevant role (28).

In addition to cardiac involvement, during the last two years more attention has also been given to acute kidney injury and chronic kidney disease in IIM patients. Renal involvement was probably not a direct manifestation of IIM, but rather the result of drug- and myoglobin-induced renal damage. Nevertheless, the authors identified a peculiar pattern of acute vascular damage (consisting of oedematous thickening of the intima of arterioles), most probably directly related to IIM and part of the spectrum of renal diseases associated disorders (29).

## Diagnostic assessment

Basic tools for diagnosis in the IIM are clinical examination and a precise medical history. Muscle involvement, in particular the muscle weakness, is a common feature of all forms of myositis but the distribution and the trend of this aspect may reveal a specific pattern for an accurate diagnosis. The laboratory test (serum muscle enzyme levels and autoantibody), biopsy and instrumental investigations (electromyography and MRI) are key tools to confirm the suspected diagnosis. A recent works underlined this aspect in particular for IBM demonstrating that the clinical features are more sensitive than the histopathological findings in establishing diagnosis (30).

Indeed, CK, aldolase and LDH are important tools for diagnosis and follow up, however, the treatment of IIM should be guided primarily by patient's strength evaluation and not by serum abnormalities (31).

Autoantibodies are powerful diagnostic tools in idiopathic inflammatory myopathies, especially for confirming the diagnosis and for the definition of disease subsets (24). They are present in over 80% of patients with immuno-mediated myositis. Despite the presence of more than twelve diagnostic criteria for IIM, only a small part of them consider MSA (myositis specific autoantibodies) or MAA (myositis associated antibodies) to be a useful diagnostic tool (32). Recent studies suggest that the prevalence of reactivity to any MSA or MAA in large case series of patients with IIM was more than 50% (24). MSA appear to be more clinically relevant and include antibodies directed against aminoacyl-tRNA synthetases (Jo-1, PL-7, PL-12, EJ, OJ, JS, and KS), signal recognition particle (SRP), nuclear helicase Mi-2, and p155. The presence of MSA and MAA

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is useful to categorise patients with IIM but it will not rule out the importance of histopathologic findings at muscular biopsy. Regarding this topic, Fernandez et al. (33) retrospectively reviewed a cohort of adult patients with a diagnosis of IIM according to the Bohan and Peter classification and muscle biopsy abnormalities suggestive of myositis as defined by the ENMC international workshop (34). Then, the patients were re-assigned using the Troyanov et al. criteria for IIM, which is essentially a clinic-serologic classification (35). Whereas PM was the most common IIM according to the classification of Bohan and Peter (45% of the cohort, vs. 28% for DM and 24% for overlap myositis), using their new classification system, the frequency of overlap myositis rose to 67%, the frequency of DM remained stable, and the frequency of PM fell to 10%. The overall frequency of MSA was 42% and Anti-Jo-1 were the most common overlap autoantibodies. Muscle biopsy by itself was not able to distinguish the different serologic subgroups as clinic-serologic classification cannot fully predict the hysto-patological findings. In this context, the correlation between the pathologic classification and the clinical and serologic classification shows that the two criteria for IIM diagnosis are complementary. In recent years, new MSA and MAA have provided evidence of their putative clinical prognostic value and specific organ involvement. Many study groups have recently demonstrated that anti-melanoma differentiation-associated gene 5 (anti-MDA5) is associated with rapidly progressive interstitial lung disease (RP-ILD) and poor prognosis (36–39). In a cohort of Asian patients, anti-MDA5 antibody titer also seems to be related to disease activity in patients with IIM associated with RP-ILD (38). On the other hand, the presence of anti-MDA5 antibody appears to be associated to amyopathic DM in a group of European patients (6). Recently it has been demonstrated that the presence of NXP-2/MJ antibodies is associated with calcinosis during DM. On the contrary, the presence of anti-TIF1-γ seems to be inversely associated to calcinosis (40). Interestingly,

Fiorentino et al. evaluated the presence of anti-TIF1-γ and NXP-2/MJ antibodies in a cohort of 111 patients with DM and evaluated their relationship with cancer. Both antibodies were associated with cancer but the anti-TIF1-γ and anti–NXP-2 antibody groups are almost entirely non-overlapping, with only 2 patients having antibodies to both proteins (41). Moreover, new antibodies have been found to be related to DM, such as anti-SAE (42) or anti-CTTN (43). Some MSA are related to specific clinical syndrome, like "anti-synthetase syndrome"; these groups of MSA are direct against aminoacyl-tRNA synthetases (anti-ARS abs). Based on a unique combination of clinical features commonly observed in patients with anti ARS Abs, a disease entity has been recognised characterised by: myositis, ILD, fever Raynaud's phenomenon, arthritis and mechanic's hand. Although anty-synthetase syndrome has common clinical manifestations, further observations have distinguished some differences in clinical features associated with individual anti-ARS Abs. Patients with non-Jo-1 anti-ARS Abs have a worse survival rate than anti-Jo1 positive patients. Nevertheless, the presence of anti-PL7 in a large case series of patients seems to be a good prognostic factor (44). Antibodies such as anti-EJ or anti-PL-12 seem to be related to clinically amyopathic DM (45). Finally, in recent years, some important antibodies related to IBM have been found. The identification of autoantibodies directed against cN1A shed new light on the pathogenesis of IBM. cN1A is a cytosolic 50-nucleotidase that is most abundant in the skeletal muscle where it catalyses nucleotide hydrolysis to nucleosides. The apparent perinuclear and vacuole rim accumulations of cN1A reactivity have important potential implications for an understanding of the relationship between IBM autoimmunity and myofibre degeneration (46). Anti-cN1A autoantibodies have been found greatly expressed in patients with IBM (47) In some case series of patients, anti-cN1A were present in up to 60% of IBM patients (48). The presence of anti-cN1A has the potential to improve the care

and management of patients with suspected IBM.

Muscle biopsy remains critical for the diagnosis and is perhaps the most important tool to make the correct diagnosis for its specificity in distinguishing between the different subtypes of IIM. Immunopathologic features are complementary to clinical and sierological findings and can help to predict outcome (33).

MRI is the imaging tool of choice for the assessment of muscle involvement and to guide the selection of the best muscle on which to perform biopsy. The affected muscle usually presented inflammatory oedema at the fat suppression T2 weighted STIR sequences (49).

Some authors have pointed to FDG-PET as a helpful tool in revealing extramuscular manifestations in myositis, including interstitial lung disease and hidden tumours (50).

## Treatment of IIM
The treatment strategies in IIM are targeted to muscular and internal organ involvement and in the last two years important steps have been made toward new therapies.

### Traditional DMARDs
The non-biologic DMARDs have been extensively studied in IIM but in the last two years the authors have focused their attention on the treatment of interstitial lung disease (ILD) related to IIM, in particular, the pulmonary involvement in patients with antisynthetase-associated ILD.

Cyclosporine A (CYA) is a calcineurin inhibitor found to be effective in PM/DM-related ILD and also in limited series/case reports of antisynthetase syndrome patients with ILD. In a recent article, Cavagna et al. (51) reported the results of a retrospective analysis of a monocentric cohort of patients with antisynthetase syndrome, assessed with pulmonary function tests (PFT) and high resolution computed tomography (HRCT). Patients were treated with CYA 3 mg/kg daily and corticosteroids. The authors reported a statistical significant improvement of spirometry, diffusion lung capacity of CO and HRCT

(evaluated with Kazerooni score) even after only one year of treatment and the results were maintained during the follow-up; major side effects reported were hypertension and increase of creatine kinase that made it necessary to reduce the CYA dose and drug withdrawal. The authors concluded that CYA use can be effective and substantially safe in patients with antisynthetase-associated ILD. Similar data were reported by Labirua-Iturburu and collegues (52) in a retrospective Spanish study about 15 patients with antisynthetase-associated-ILD treated with calcineurin inhibitor (CYA or tacrolimus); the authors reported improvement (≥10% increase in FCV) or stabilisation of FVC in the 87% of the patients.

Cyclophosphamide (CYC) is an alkylating agent that interferes with DNA replication. For several years, the use of CYC pulse in IIM patients has been considered to be an effective therapy (53). Recent studies have confirmed these data, particularly in a recent retrospective analysis, Nagappa *et al.* (54) reported encouraging results in a group of 9 patients with PM and DM with improvement in all the treated patients.

CYC and CYA were proposed in association in a recent case series (55) in which three patients with severe acute ILD associated with DM. The patients with severe ILD and acute worsening dyspnea were treated by steroid pulse therapy, biweekly intravenous pulse CYC and CYA. The authors reported a very rapid improvement of the patients' conditions after this treatment even if all the three patients experienced cytomegalovirus (CMV) viremia and needed to be treated with antiviral drugs.

*Biological DMARDs*
• *Rituximab*
Rituximab (RTX) is a chimeric monoclonal antibody against the CD20 protein, which is primarily found on the surface of immune system B cells. Rituximab acts as a B cell depleting agent. The effectiveness of rituximab in PM and DM has been suggested by case reports and case series in adult and paediatric patients with refractory disease. In 2013 Oddis *et al.* conducted a multicentre randomised placebo-phase trial to assess the efficacy and safety of RTX in adult with PM and DM and in juvenile DM (56). In this trial, patients were randomised to "rituximab early" (RTX infusion at week 0 and 1, placebo infusion at week 8 and 9) or "rituximab late" (RTX infusion at week 8 and 9, placebo infusion at week 0 and 1); both groups were allowed to receive glucocorticoid and immunosuppressive therapy at entry. The authors concluded that the trial itself showed no statistical difference between the treatment groups. However, the overall response rate in a refractory group of patients, the ability to taper glucocorticoid therapy and the re-treatment responses suggest that the agent had an effect but that certain aspects of the study design made identification of such an effect difficult.

In an editorial, De Visser (57) identified several issues in the design of the trial. The major criticism of this study was that the authors had assumed an effect of rituximab at week 8 in more than half of the patients but an improvement was observed only at week 20. This could lead to an underestimation of the anticipated placebo rate. Another limitation of the study identified was that the authors classified patients according to the Bohan and Peter criteria (58) and not with the most recent classification criteria; moreover, not all muscle biopsy samples were available for review and it is possible that cases were misdiagnosed as "true PM" when it was possible that they were other inflammatory or non-inflammatory myopathies. Finally, muscle imaging, in particular MRI, was not used to select patients with active disease.

However, even if the Rituximab in Myositis trial did not reached the endpoints, in the last two years several studies have reported cohorts of real life population describing the good efficacy, safety and the long-term remission of IIM patients treated with RTX (59–63).

The major limitations of all these case series are the heterogeneous clinical and serological characteristics of patients enrolled. However, myositis overlap (60) and anti-synthetase syndromes (60, 64) seem to respond better than other patient subsets, even though a recent study reported that, in contrast to the subgroup with DM, where one cycle of RTX appeared sufficient, patients with anti-synthetase syndromes commonly experienced flares necessitating re-treatment with RTX (63). Moreover, also the juvenile onset and lower disease damage strongly predicted clinical improvement in refractory myositis patients (64).

• *TNF inhibitors*
A TNF inhibitor is a pharmaceutical drug that suppresses response to tumour necrosis factor (TNF), which is part of the inflammatory response. The observations on the genetic and immunologic role of TNF-α in the pathogenesis of DM provide a theoretical basis for the use of TNF inhibitors in the treatment of patients with IIM (65).

Chen *et al.* (66) in a recent retrospective study reported their experience on the use of infliximab in a cohort of 14 female patients with DM with acute interstitial pneumonia. The authors reported that out of the 14 patients, 10 (71.4 %) had a favourable response with muscular and pulmonary improvement. A favourable prognostic factor was the start of treatment at an early stage of the disease, while the four patients treated at a late stage failed to respond to the treatment and died.

Rouster-Stevens *et al.* (67) conducted a small pilot study on etanercept in a group of patients with juvenile DM refractory to standard treatment. The authors concluded that etanercept did not demonstrate appreciable improvement of clinical parameters and some patients worsened during the treatment. The worse response to treatment was identified in patients with the TNF308A allele.

A case report on the use of TNF-inhibitors reported efficacy of adalimumab (68) in a patients with refractory PM.

In conclusion, considering the data available as regards anti-TNF-α therapy use in IIM, anti-TNF-α agents should not be recommended as an alternative treatment in patients with resistant myositis (69). Furthermore, safety concerns have been raised in anti-TNF-α treated IIM patients, particularly for infective disease (69).

**• Anakinra and other biotechnological agents**

Anakinra is a recombinant IL-1 receptor antagonist, which inhibits IL-1 activitiy. Interleukin (IL)-1α and IL-1β are hyperexpressed in muscular tissue particularly in PM, DM and IBM (70, 71). IL-1 receptors are expressed on endothelial cells and recently it was demonstrated that they are expressed on sarcolemma, and co-localised with its reciprocal ligands in PM and DM patients, further supporting a role of IL-1 in the pathogenesis of myositis (70). IL-1 is mainly produced by activated macrophages and endothelial cells, and increases expression of adhesion molecules that are upregulated in muscle tissue in patients with myositis (72).

In a recent study of 15 patients with IIM treated with anakinra, Zong *et al.* (73) reported an improvement in 7 patients according to the IMACS criteria. Responders had higher baseline extramuscular score compared with non-responders. In muscle biopsies, baseline macrophages and IL-1α expression were inversely correlated with muscle performance after 6 months treatment; all responders had IL-1 receptor antagonist expression in the post-treatment biopsies but only 3/8 non-responders. Kosmidis *et al.* investigated the efficacy of anakinra in a group of patients with biopsy proven IBM (74). In this small pilot study, patients received anakinra for a mean period of 7.7 months. In this study, neither improvement in muscle strength nor clinical stabilisation was observed in the treated group of patients. The authors concluded that the failure of the treatment may be due to an insufficiency of anakinra to suppress the intramuscular IL1 the short study period or the irrelevance of IL1 in the disease process.

In recent articles, some authors proposed the use of adalimumab (75) and tocilizumab (76) in the treatment of refractory IIM; however, few data are available and other studies are needed to test the effectiveness of these drugs in the treatment of IIM patients.

*Endovenous immunoglobulins*

An alternative approach to improving the treatment of dermatomyositis and polymyositis is the use of immunomodulatory therapy. This includes intravenous immunoglobulin (IVIg). IVIg can influence several immunopatogenetical aspects of IIM, including inhibition of autoantibodies production, interference with activation of complement, modulation of the expression and function of Fc receptors on macrophages, regulation of the activation, differentiation, and effector functions of T and B cells, and suppression of the activity of neurodegenerative molecules, cytokines, chemokines or adhesion molecules (77).

Dalakas proposed the use of IvIg as second line treatment if steroids are inadequate to increase strength (78). However, the evidence from a systematic review of medical literature and meta-analysis is contrasting (79) and IvIg should be considered as a therapeutic option only in patients with severe, refractory or rapidly progressive diseases (80).

A recent retrospective study reported (81) the successful use of IVIg in a group of 13 patients with cutaneous DM. All patients experienced an improvement of the cutaneous involvement with IvIg with rapid response after the first treatment cycle. IVIg demonstrated a steroid-sparing effect and allowed for discontinuation of all previous immunosuppressive medications, except in 3/13 patients. IVIg was reported to be well tolerated, with adverse effects consisting of headaches in 2 patients.

In the last few years, great interest regarding the use of subcutaneous immunoglobulins (SCIg) has arisen (82). A recent report describes the positive effect of SCIg in a patients affected by IBM (83) and also data has been published on a small population of patients with IIM (84). The authors reported a their experience in two groups of patients treated with sequential IvIg-SCIg or directly with SCIg. A total of thirteen patients were enrolled and a good response was observed in both groups.

*Non-pharmacological therapy*

Muscular weakness, pain and fatigue are common symptoms in patients with IIM, all of which contribute to a decreased quality of life. In healthy persons, the best intervention to improve strength and cardiorespiratory function is physical training. Strength training or aerobic exercise programmes in people with IIM might maximise muscle and cardiorespiratory function and prevent additional disuse atrophy. However, the benefit from strength training or aerobic exercise training in muscle diseases is still not clear (85). Recently, a systematic review for exercise training in muscular disease (86) reported that only one RCT was conducted in people with DM and PM (87) but, even though the authors reported aerobic training as safe and efficacious in patients with IIM, the study had several uncertainties regarding the generation of the randomisation list, allocation concealment and blinding of the assessor, therefore the overall results of this study were judged as being unclear.

A recent study was made on 10 patients who had recovered from juvenile dermatomyositis (JDM) and trained for 12-week aerobic programme (88). Their CK levels did not change with training, reflecting no muscle damage, and their heart rate was lowered significantly after the 12-week training period, indicating an improvement in cardiovascular fitness. The authors concluded that aerobic training is an effective and safe method to increase oxidative capacity and fitness in persons who have recovered from JDM, and recommended that frequent supervised aerobic training should be incorporated into the treatment of JDM patients in remission.

Although exercise is fundamental to improve muscle performance and health in IIM, in a review of the medical literature, Alemo Munters *et al.* underlines that there is a need for RCTs to study the effects of exercise in active disease and IBM (89).

*Treatment of skin calcinosis*

Calcinosis cutis is a term used to describe a group of disorders in which calcium deposits form in the skin and is a recognised feature of many connective tissue diseases. Although commonly observed in JDM, it is less frequent in the adult form, affecting only 10% of these patients (90). Calcinosis burden can result in pain, skin ulcera-

tions expressing calcified material, secondary infection and joint contractures with severe functional disability in performing everyday life activities. Different treatments have been used in an attempt to clear calcinosis lesions and prevent the recurrence but none has been clearly effective.

In juvenile myositis patients, recent articles have reported the efficacy of topical sodium thiusulphate applied to the calcifications in a 3-year-old male patient (91), and endovenous pamidronate in a 7-year-old girl (92). Both patients improved rapidly with the treatment.

In a severe case of adult dermatomyositis patients with calcinosis universalis treated with pamidronate, the treatment allowed a total recovery of the range of movement and improvement in the quality of life (93).

## Conclusions

To sum up, great efforts have been made during the last two years to clinically and histologically characterise the different phenotypes of IIM. These progresses have been paralleled by novel insights into treatment strategies. However, there are still several unmet needs in IIM, which hopefully will be covered in the near future, particularly an international consensus on classification criteria, guidelines on treatment and the development of new drugs for the treatment of IIM.

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