Review

One year in review 2016: idiopathic inflammatory myopathies

M. Orlandi[1], S. Barsotti[2,3], E. Cioffi[2], S. Tenti[4], C. Toscano[4], C. Baldini[2], R. Neri[2]

[1]Rheumatology Unit, Department of Experimental and Clinical Medicine, University of Florence, Italy;
[2]Rheumatology Unit, University of Pisa, Italy;
[3]Department of Medical Biotechnologies, University of Siena, Italy;
[4]Rheumatology Unit, Department of Medical Sciences, Surgery and Neurosciences, University of Siena, Italy.

Martina Orlandi, MD
Simone Barsotti, MD
Elisa Cioffi, MD
Sara Tenti, MD
Carmela Toscano, MD
Chiara Baldini, MD
Rossella Neri, MD

Please address correspondence to:
Rossella Neri, MD,
Reumatologia,
Università di Pisa,
Via Roma 67,
56126 Pisa, Italy
E-mail: r.neri@int.med.unipi.it

Received on October 15, 2016; accepted in revised form on October 19, 2016.

Clin Exp Rheumatol 2016; 34: 966-974.

Key words: 2016, review, polymyositis, dermatomyositis, treatment, pathogenesis

Competing interests: none declared.

ABSTRACT

Idiopathic inflammatory myopathies (IIM) are a group of rare, acquired, clinically heterogeneous autoimmune inflammatory muscle disorders characterised by muscle weakness and multisystem involvement. Recently, new concepts about pathogenesis, diagnosis and treatment of these complex diseases have been provided. The purpose of this manuscript is to summarise the most relevant literature contributions published over the last year.

Introduction

Idiopathic inflammatory myopathies (IIM) are a group of systemic diseases primarily involving skeletal muscle; however several internal organs can be affected, in particular lungs, heart, skin and gastrointestinal systems (1). The most recent classification allow to distinguish different subtypes of disease: 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, following the previous papers of this "one year in review" collection (3-11) we will provide our annual update of the recent advances in pathogenesis, diagnosis and treatment of IIM. We performed a medline search of English language articles published from the 1st January 2015 to 31st December 2015 using the following key words: "idiopathic inflammatory myopathies" (MeSH terms and semantic search) and pathogenesis, diagnosis, clinical manifestations, therapy. We reviewed all the articles and selected the most relevant studies.

Recent insights into the pathogenesis of IIM

The pathogenesis of IIM is still largely unknown and huge efforts have been recently made aimed at clarifying IIM underlying molecular pathways. IIM clinical phenotypes are extremely heterogeneous thus reflecting the involvement of different pathogenic mechanisms; on the other hand, the presence of symmetrical proximal muscle weakness and poor muscle endurance, presented by the vast majority of the patients suggest that some pathogenic mechanisms are probably shared by all the IIM subsets (12).

Several genome wide-association (GWA) studies have lately confirmed the importance of HLA and non-HLA genes in IIM pathogenesis (13). In genetically predisposed patients, different environmental factors can contribute to the pathogenesis of these diseases too, ultimately, leading to the production of both autoimmune and non-immune mediators that contribute to IIM muscle damage and extra-muscular clinical manifestations (14).

Environmental factors

Last year, two studies have been conducted in Canada and in Sweden, to investigate the association between air pollution (15), occupational exposure (16) and IIM. However, among the different environmental factors, the major suspected agents associated with the onset of IIM remain viral infections.

Several acute and self-limited forms of IIM may be caused by Coxsackie, Echo and Influenza viruses, but their role in chronic forms is still uncertain. Recently, Uruha *et al*. (17) conducted a case-control study that provided the statistical evidence of an association between IBM and HCV infection, suggesting a possible link between these two conditions.

Interestingly, also vitamin D deficiency seems to represent a potential risk factor for development of IIM. According to Bodoki *et al*., it could be linked to

some vitamin D receptor gene polymorphisms and haplotypes (18).

Genetic factors

IIM disease susceptibility is closely associated with human leucocyte antigen (HLA) genes, particularly with HLA class II alleles, such as HLA-DRB1*0301 and DQA1*0501 in Caucasians and DRB1*0801 in Japanese population. Moreover these alleles have been reported to be associated with the production of anti-aminoacyl-tRNA synthetases (ARS). Two recent large studies conducted by Rothwell *et al*. (19) and Miller *et al*. (20), confirmed that alleles of the 8.1 ancestral haplotype (8.1AH) are the primary genetic risk factors associated with IIM and its main phenotypes.

Regarding non-HLA genes, a strong correlation has been recently confirmed between PTPN22 gene single nucleotide polymorphism (SNP) and IIM, especially in PM (19,20). In Chinese Han population CCL21 SNP rs951005 seems to confer genetic predisposition to PM and to IIM-related interstitial lung disease (ILD) (21), while other SNPs (rs2736340, rs7812879, rs13277113, rs2618479 and rs2254546), have been associated to an increased risk for DM (22). STAT4 and FAM167A-BLK SNPs seem to be associated to DM in the Japanese population (19).

Shinjo *et al*. (23) considered also the potential role of the angiotensin-converting enzyme (ACE) insertion/deletion (I/D) gene polymorphism, in particular ACE D/D, in determining the susceptibility to DM.

Regarding IBM, great attention has been given to the possible role of mitochondrial DNA and its rearrangements (24) since, in genetically predisposed individuals, oxidative stress-related activation of nuclear factor kappa-B (NF-kB) may be involved in both degenerative and inflammatory mechanisms observed in IBM. In line with these observations, a great attention has been given to SNP (rs5754467) YDJC gene which seems able to amplify NF-kB activation (25).

Immunological abnormalities

Both innate and adaptive immunity are supposed to play a crucial role in IIM pathogenesis. However, although some experimental murine models have developed in order to foster the understanding of the immunopathologic processes of IIM (26-27) it remains unclear why and how muscle may become a specific target of the immune response/attack.

It is widely recognised that humoural factors (antibodies and complement system) directed against endomysial capillary endothelial cells are mostly involved in DM pathogenesis while cytotoxic T cell-mediated muscle fibre injury plays a crucial role in PM and IBM. Despite their widespread localisation, the precise role of T cells in the pathogenesis of IIM remains not completely clarified (1).

Espinosa-Ortega *et al*. (28) described an expansion of peripheral proinflammatory T cells, such as follicular helper T cells (Tfh) and T helper type 17 (TH17), as well as pro-apoptotic CD28 null cells and a deficiency of suppressor populations of regulatory T cells (Tregs) $CD4^+$ and $CD8^+$ in IIM patients. An increased level of some inflammatory cytokines, such as IL-15 and IL-17, in serum and skeletal muscle of patients with IIMs has been described. Particularly, IL-15 seems to promote in the skeletal muscles the effector function of memory-like $CD8^+$ T cells, which facilitates the formation of a pro-inflammatory skeletal muscle microenvironment during myositis progression; on the contrary IL-15 seems not to be required for muscle growth and regeneration and it could be a good therapeutic target (29). Furthermore, Rucket *et al*. (30) proposed a pathological model, where muscle cells start to express NKG2D ligand (an activating receptors on T cells implicated in autoimmune diseases). The authors noticed that interaction with $CD8^+$ T cells leads to the generation of highly pathogenic $CD8^+$NKG2D high T cells maintaining the local inflammatory milieu and ultimately leading to muscle cells death. From this perspective, IL-15 and NKG2D might be important in stabilising the immunological correlation between $CD8^+$ T cells and MHC class I expressing muscle cells in IIM (31).

Another pathway that leads to the activation of NFkB is represented by the Toll-like receptors (TLRs) signalling, which represents an important link between innate and adaptive immune systems. The cytokine milieu created by the TLR activation directs T cell differentiation towards the desired subset. Several studies have demonstrated an increased expression of TLRs in muscle biopsies from IIM patients and, in a recent study, Ling *et al*. demonstrated that the endogenous overproduction of type I interferon (IFN) in DM may be generated by plasmocytoid dendritic cells, mainly through the TLR-9 pathway. Furthermore, also TLR-7 mediated type I IFN production may be present and TLR-3, which is expressed preferentially in peri-fascicular fibres, could be implicated in the atrophy detected in DM muscular biopsy (32).

Also the DNA-binding High-mobility group box protein 1 (HMGB1), a pro-inflammatory molecule also called "alarmin", has been recently described as overexpressed in muscle fibres of patients with IIM. It up-regulates MHC class I expression in muscle fibres through TLR-4 pathway and it impairs calcium release from sarcoplasmic reticulum, contributing to muscle fatigue (13). According to this observation, Muth *et al*. examined the expression of HMGB1 and its receptor RAGE, which seem to be crucial for β-amyloid associated neurodegeneration, particularly in IBMs, and they found that alarmin contributed to the interplay between inflammation and degeneration in IBMs. The authors concluded that the HMGB1-RAGE axis could be an interesting target for future therapeutic strategies against diseases characterised by chronic inflammatory cell stress and accumulation of β-amyloid (33).

Furthermore, some studies have evaluated the potential role of HMGB (34) and of DM autoantigen transcriptional intermediary factor 1γ (TIF1 γ) (35), in IIM muscle tissue regeneration. Apparently, higher levels of autoantigens in damaged and regenerating muscle fibres could contribute to myositis immunopathology by providing an ongoing source of autoantigens able to drive and maintain the autoimmune response (35).

Recently, it was also suggested that an aberrant expression of circulating micro-RNA patterns (c-miRNAs) could play a role in IIM. Georgantas *et al*. proposed that the inhibition of myogenic mi-RNAs 1, 133 and 206 by inflammatory cytokines could link inflammation and muscle degeneration in adult IIM (36). Furthermore, Misunova *et al*. analysed circulating serum mi-RNA gene expression profile in 28 patients suffering from IIM and they found that the mi-RNA expression profile in serum of such patients was disease specific and created a disease specific signature. It is expectable that this dysregulation of mi-RNA molecules expression could take part in the pathogenesis of IIM (37).

Recent insights into serological manifestations of IIM

Autoantibodies and other laboratory tests

Lately, laboratory tests have gained increasing interest in the assessment of IIM patients. In particular myositis-specific autoantibodies (MSA) have been increasingly recognised as pivotal elements in supporting IIM diagnosis and in correctly identifying IIM clinical subsets. Furthermore, MSA may have a prognostic value thus predicting patients' response to the therapy and long-term outcomes.

As confirmed by Mammen *et al*., MSA are very specific for IIM (38): anti-Jo-1-positive patients usually present a characteristic "necrotising perifascicular myositis" (39), TIF1-γ or anti-NXP2 have a more prominent perifascicular atrophy and perivascular inflammation, Mi-2 antibodies are associated with a higher prevalence of muscular infiltrates, and anti-PM-Scl to an even higher prevalence of muscular infiltrates (40).

Several studies have demonstrated that MSA vary according to different ethnicities or geographic areas. Compared to Japanese patients, in Chinese DM and clinically amyopathic DM (CADM), an higher prevalence of anti-melanoma differentiation-associated gene 5 antibodies (anti-MDA-5) and a lower frequency of anti-signal recognition particle (anti-SRP) has been reported (41).

Furthermore, MSA have been correlated with peculiar clinical phenotypes: in Asian population, anti-MDA-5 positivity strictly correlates with the development of rapidly progressive (RP) ILD. These data were recently confirmed by Ikeda *et al*. that correlated anti-MDA-5 positivity with biomarkers of lung injury such as lower Krebs von den Lungen-6 (KL-6) and surfactant protein D (SP-D) serum levels and $CD4^+/CD8^+$ ratio in the bronchoalveolar lavage (BAL) fluid. Furthermore, high-resolution computed tomography (HRCT) frequently showed ground-glass opacity (GGO) or irregular linear opacity in the anti-MDA-5 positive group (42).

Last year, the association of anti-MDA-5 with ILD, RP-ILD and survival was specifically investigated in two groups of CADM and classic DM. The frequency of anti-MDA-5 was similar in the two groups and the authors strongly correlated anti-MDA-5 with presence and severity of ILD and RP-ILD in both groups (43). Anti-MDA-5 autoantibodies have been also associated to chemokine (C-X3-C motif) ligand 1 (CX3CL1), suggesting a role of CX3CL1 in the pathogenesis of pulmonary fibrosis in CADM (44).

Finally, Anti-MDA-5 are also associated to cutaneous digital ulcers localised in DM patients (45).

ARS autoantibodies have been associated to ILD as well. The most common ILD pattern at HRCT in ARS group seems to be non-specific interstitial pneumonia (NSIP) associated to a more favourable treatment response and greater survival (46). Rojas-Serrano *et al*. confirmed that anti-Jo1 positive patients have a better survival compared to anti-Jo-negative patients (47). The clinical severity of ILD was not significantly different in patients with ARS, in particular in anti-PL7 and anti-Jo1 positive groups, except for a higher bronchoalveolar lymphocyte ratio anti-Jo1 positive patients (48).

Very recently, new MSA directed against a four-and-a-half LIM domains protein 1 (FHL1) were identified in a subset of IIM patients with severe skeletal muscle involvement and a poorer prognosis (49).

Finally, in the sporadic inclusion body myositis (sIBM) Goyal *et al*. explored the value of the NT5c1A antibodies. The authors reported a greater motor and functional disability and a more frequent bulbar, facial and respiratory involvement in patients with anti-NT-5c1A positivity (55).

In addition to MSA, a number of novel diagnostic ad prognostic biomarkers has been extensively investigated last year. Chen *et al*. prospectively reported that serum KL-6, SP-A and SP-D were significantly elevated in PM/DM patients with ILD compared with those without ILD. Furthermore, KL-6 showed the highest predictive value for ILD among these markers and was particularly useful to monitor ILD progression (51). Other prognostic factors, including skin ulcerations, serum ferritin level and lymphocyte counts may also help to predict RP-ILD in patients with CADM (52). The age of onset and serum ferritin levels were apparently poor predictors for ILD outcome (53).

Recently, a Chinese study reported that higher serum levels of the heat shock 70 kDa protein 5 (HSPA5), a protein involved in the folding and assembly of proteins in the endoplasmic reticulum (ER), were associated to a higher disease activity in IIM (54). Also osteopontin (OPN), a pro-inflammatory cytokine, resulted higher in IIM patients with respect to healthy controls, particularly in DM subgroup. Osteopontin positively correlated with CK and CRP and after steroid treatment a significant decrease of OPN levels was observed (55).

Adipokines resulted involved in the regulation of immune and inflammatory processes in autoimmune diseases. Among them visfatin and resistin gene expression seemed to correlate with disease activity (56).

Finally, among the putative potential biomarkers for ILD in patients with IIM a mention should be made to progranulin (PGRN) (57) and serum LIGHT, a member of the TNF superfamily (58).

In conclusion, traditional and novel biomarkers have been extensively investigated in IIM; however, further research is warranted in order to validate their role in clinical practice.

Imaging in IIM

Last year, the most relevant contribution published regarding imaging ap-

plications in IIM have essentially analysed the value of different techniques in both the assessment of muscle inflammation/damage and in the assessment of heart and lung involvement.

The assessment of disease activity and muscle inflammation in IIM patients is still challenging, since some of the most frequently used parameters to evaluate disease activity (*e.g.* serum CK levels or muscle strength) can be influenced by muscular atrophy and/or fatty tissue infiltrates. Recently, the use of magnetic resonance imaging (MRI) has been increasingly proposed as an useful tool for the assessment of muscle involvement in IIM patients. Van De Vlekkert *et al*. confirmed the diagnostic accuracy of MRI also in patients with a negative muscle biopsy (59). MRI can also be useful for IBM patients, indeed Tasca *et al*. proposed a typical MRI pattern recognition that may significantly improve the accuracy of the diagnosis of IBM (60). On the contrary, the quantification of muscle diseases by MRI is still a challenge, even if recently T2 muscle measurement and fat-corrected T2 were presented as a measure of IIM activity (61). Moreover, the use of whole-body MRI (WB-MRI), evaluating a large portion of skeletal muscles, may identify clinically "silent" myositis, especially in the early stages. Very recently, a restricted WB-MRI protocol, omitting the imaging of the trunk, was assessed and it showed similar diagnostic accuracy to WB-MRI (62).

Regarding heart involvement, Cardiac magnetic resonance (CMR) has appeared as a reliable diagnostic tool for the detection of subclinical heart involvement, thus allowing an early therapeutic intervention for this important cause of morbidity and mortality in IIM patients (63).

New insights on Computed tomography (CT) applications have been published as well last year.

CT seems useful to identify low density muscle areas that correspond to lipid-rich skeletal muscle. Recently, it was demonstrated that the poor muscle quality, measured by CT-low density muscle areas, was a good predictor of muscle function in patients with IIM (64).

Chest CT remains a cornerstone for the identification and the monitoring of ILD in IIM patients. Little is known about CT features of ILD in antisynthetase syndrome (ASS) and CADM patients. Last year, Debray *et al*. found that, at presentation, many ASS patients reported CT features of NSIP or OP, isolated or often in combination with consolidations, while Zou *et al*. demonstrated that HRCT score, together with high serum ferritin levels, were associated with poor prognosis in CADM patients with acute ILD (65-67).

Finally, although the results of the studies are not definitive, muscle ultrasonography (US) has been proposed as another important diagnostic tool to investigate the muscular structure and the pathological alterations in muscular diseases. US may identify fascial thickening, which can indicate a concomitant fasciitis that may be associated with muscular activity of the disease (68). Furthermore, a peculiar US feature was described in IBM patients, consisting in a dissociation of echo intensities (EI) in the triceps surae (preferential involvement of gastrocnemius over the soleus), that could allow to differentiate IBM from PM/DM (69). Chest US with B-lines study has emerged over the last years as an alternative to HRCT to investigate ILD in patients with connective tissue diseases and the detection of pleural irregularity (PI) resulted a new US sign for the diagnosis of ILD in IIM (70).

[18F] Fluorodeoxyglucose positron emission tomography (FDG PET) is a standard tool for detecting malignancies or systemic inflammatory disorders, such as rheumatoid arthritis, vasculitis and polymyalgia rheumatic. In recent years, its usefulness in the clinical practice of PM/DM patients emerged, indeed it is able to evaluate muscle lesions using visual evaluation and standardised uptake value measurement (71). Finally, also the role of bone scan in IIM was tested by quantitatively assessing the global uptake of Tc-99 m phosphate by proximal muscle groups as a marker of disease activity (72).

Extra-muscular manifestation

Although the main phenotypical characteristics of IIM is muscular involvement, in the last years medical literature focused the attention also on the extra-muscular manifestation of IIM, that represent the most common causes of morbidity and mortality in these patients.

Recently, several authors reported a substantially increased occurrence of coronary artery calcification (CAC) in patients with IIM, with and increased subsequent risk of acute coronary syndrome and myocardial infarction (73-74). These findings were not associated with disease specific factors, but with an increased prevalence of traditional cardiovascular (CV) risk factors in patients with PM and DM (75).

Interesting, is the occurrence of myocarditis, rare in IIM, but potentially severe and so far poorly described. Recently, a study by Dieval *et al*., aimed at describing myocarditis in the context of ASS, showed that the prevalence of myocarditis in ASS is 3.4% and was not linked to any autoantibody specificity. In 42% of the cases is the first manifestation of ASS and was always associated with extra-cardiac symptoms in accordance with ASS activity, including active myositis in all cases. Furthermore, although rare and difficult to diagnose, myocarditis must be carefully sought out in ASS patients, to preventing the development of chronic dilated cardiomyopathy (76).

It is well-known that IIM may be a paraneoplastic manifestation of malignancy, and this association has been confirmed in different populations. However, the variable strength of such association has been observed across different reports from different countries. Mustafa *et al*. did not confirm the previously described strong association between IIM and malignancy in Jordan population. Indeed, the authors showed a low prevalence of malignancy in IIM Jordan patients, in contrast with the majority of previous reports from other populations. Such variability could be due to genetic factors, age differences among the different reports, selection bias or geographical factors (77).

Another study by Galimberti *et al*. explored the clinical features and malignancy-associated (MA) risk factors in patients with CADM. As result, they observed that no CADM patient with

malignancy showed skin ulcers, periungueal erythema or ragged cuticles (78).

Among clinical study published this year, another that should be mentioned is the one by De Souza F.H.C. *et al*. aimed at assessing ovarian involvement reserves in adult patients with DM. The authors performed a cross-sectional study including 16 DM patients and 23 healthy controls, each of whom was evaluated during the early follicular phase, with the evaluation of IgG anticorpus luteum (anti-CoL), follicle stimulating hormone (FSH), estradiol, inhibin B, anti-Mullerian hormone (AMH) serum levels and determined a sonographic antral follicle count (AFC). They obtained that both AMH and AFC were reduced and the most reliable screening test for ovarian reserve could include both of them. Therefore, in DM patients there is a premature reduction of ovarian reserve but the related factors are unclear and further studies are necessary (79).

Previous studies have demonstrated an increased susceptibility of infections in patients with IIM, in particular Herpes Zoster (HZ) infection was reported to be associated with DM or PM and these patients should be screened for HZ immunity and vaccinated prior to start with immunosuppressive therapies. A recent study by Shin-Yi Tsai *et al*. supports the association of IIM with a greater risk of subsequent HZ in Taiwan IIM patients. In the study population, a higher incidence of HZ was observed in patients with IIM who were predominantly female, aged older than 50 years, and had one or more comorbidities or those who underwent medical treatment with immunosuppressants or corticosteroids (80).

Regarding the infective risk in the IIM patients, another evaluation was made about the risk of active tuberculosis (TB) by Ping-Hsun Wu, who conducted the first study to investigate this matter in a large-scale cohort and demonstrated an increased risk of active TB with respect to healthy subjects. Therefore, the authors underlined the importance to perform a TBC screening test in IIM patients with respiratory symptoms (81).

Interestingly, some novel studies have focused joint involvement in anti Jo-1 positive aSS and particularly the data obtained in an international retrospective multicentr estudy by Cavagna *et al*. The authors confirmed that joint involvement could be the first aSS manifestation thus highlighting the importance that anti Jo-1 should be tested not only in patients with myositis and ILD but also in subjects with peripheral arthritis, even though a diagnosis of RA is more likely (82).

Treatment

There are not standardised therapeutic guidelines in literature for IIM because at present only few randomised, double-blind, controlled clinical trials have been completed Currently, corticosteroids (CCs) represents the standard first line treatment for DM and PM but the treatment commonly used in the therapy of IIM also include other traditional immunosuppressive or immunomodulatory agents, such as methotrexate (MTX), azathioprine (AZA), mycophenolate mofetil (MMF), cyclophosphamide (CYC), cyclosporine (CYA), tacrolimus (TAC), intravenous immunoglobulins (IVIg) or, recently, biologic agents such as rituximab (RTX) (83-84). The indications for the introduction of these others immunosuppressive agents include severe refractory disease with extramuscular features, flares on glucocorticoid tapering or the necessity to taper CCs as soon as possible to avoid the development of CCs-associated side effects (85). Thus the choice of a secondary immunosuppressive agent is often empirical (86-88).

Some studies have been published in the last year in order to provide novel treatment strategies for IIM patients especially focusing on the early use of immunosuppressive agents as CCs sparing drugs (89). This represents a hot topic and remains quite debated with studies supporting and other not supporting the use of CCs in monotherapy. A recent retrospective study reviewed 42 PM/DM patients that were divided in 2 groups: the first one was treated with conventional monotherapy (prednisone) while in the second group the patients have taken prednisone and TAC. TAC demonstrated a corticosteroid sparing effect, improved creatine kinase levels, reduced the length of hospitalisation and extended survival reducing the occurrence of serious infections and disease relapses. Notably, the time required for CK normalisation and the proportion of patients who required additional immunosuppressive medications for remission induction was comparable in two groups, and all patients achieved remission (90).

Johnson *et al*. retrospectively evaluated the disease course of 100 DM patients over time in the context of treatment with CCs and immunosuppressant agents: MTX, AZA, MMF and IVIg. By the 6-12 month follow-up period all groups demonstrated an improvement in muscle function. None of the immunosuppressive agents was shown to provide a superior benefit over CCs in terms of improving average composite or proximal manual muscular testing (MMT) scores or prednisone requirement at 6-12 months or 12-18 months after the initiation of the secondary agent (91).

Different results come from the Second Line Agents in Myositis (SELAM) trial. This was a RCT evaluating the effect of MTX and CYA, in 58 patients with active IIM receiving corticosteroids. In comparison with placebo, neither CYA or MTX monotherapy, and neither CYA-MTX combination therapy showed evidence of significant benefits. Moreover, the authors reported that the immunosuppressive treatment did not permit to reduce glucocorticoid dose. SELAM had several limitations: patients with severe IMM were not enrolled, only a minority of screened patients were enrolled, only few patients completed 12 months of treatment and the outcome measures might have been too insensitive (92).

Rituximab (RTX) has been widely used as a therapeutic agent in refractory IIM. The use of RTX in myositis has been evaluated for several years, manly in small case series, and appeared effective in patient with refractory inflammatory myopathies (93). The Rituximab in Myositis (RIM) trial suggests the possible use of rituximab in refractory PM and DM (94). Reed *et al*. re-analysing the data collected in

the RIM study, tried to identify a biomarkers signature able to predict disease improvement after rituximab therapy. They observed that patients with ARS or anti-Mi2, expressing interferon chemokines (IFNCK) presented a better clinical improvement (95).

A recent multicentre, open-label, phase II study evaluated the efficacy of RTX treatment in patients with refractory ASS. In this pilot study 7/10 patients had an increase of at least 4 points on MMT 10, but only 2 patients presented an improvement of at least 4 points on at least two muscle groups (primary end-point). RTX allowed a reduction of CCs doses and of immunosuppressive drugs, and reduced CK levels. Moreover 5/10 patients presented an improvement and 4 patients a stabilisation of the ILD (96). In a retrospective study RTX permitted to reach a significant improvement in both PFT (FVC, FEV1 and DLCO) and ILD extent in HRCT images, especially in patients with a disease duration <12 months (97).

Lung disease is a major cause of morbidity and mortality in myositis patients. PM and DM complicated with ILD are more aggressive and refractory to conventional treatment (98). More of 50% of patients with ILD are resistant to CCs monotherapy (99-100). From this perspective, the possible efficacy of calcineurin inhibitors, cyclosporine A (CYA) and tacrolimus (TAC) in lung involvement in IIM patients has been evaluated. In a retrospective cohort study, Dong *et al*. demonstrated that DM and ACAM–ILD patients that received early CYA treatment (within two weeks after the ILD diagnosis) had a better survival benefit than those in whom the treatment were delayed. The early CYA treatment showed a significantly improvement in pulmonary disease, demonstrating a favorable radiologic response (HRTC score over the 1-year follow-up) compared to the delayed CYA treatment. Delayed CYA treatment was associated with a higher mortality due to the ILD progression and complications. Therefore, early CYA treatment should be considered as first line treatment at DM-ILD diagnosis, especially in patients with a higher risk of developing RP ILD (101).

Recently, two studies investigated the effect of TAC therapy in PM/DM related ILD. In a retrospective study, Kurita *et al*. divided 49 patients with PM/DM related ILD in two groups: one treated with TAC plus the conventional treatment (CCs) and one treated with conventional therapy alone. They did not demonstrate statistically significant differences between the two groups, probably because patients who received TAC had more severe disease. Patients treated with TAC, had significantly longer event-free survival compared with the conventional therapy alone group and they had significantly longer disease-free survival. However, the association between CYC was more frequent in the TAC group and the better prognosis in this group might be due in part to the concomitant effect of CYC (102).

Morisset *et al*. have proposed a treatment algorithm based on the ILD severity and presentation. Patients with severe ILD, rapidly progressive disease, or respiratory failure should be treated more aggressively (high dose of CCs, CYC and/or calcineurin inhibitor). Otherwise, in patients presenting with milder disease or with a chronic stable ILD, agents with an overall safer side effect profile should be considered (CCs and MMF; AZA) (99).

Kawasumi *et al*. took into account the clinical manifestation of pulmonary disease and the presence of some negative prognostic factors including hyperferritinemia, the anti-MDA-5 and the ARS. Combination therapy with CCs, intravenous CYC pulse, and calcineurin inhibitors should be administered as soon as possible in RP- ILD, especially if there are hyperferritinemia and MDA-5 positivity. In contrast, patients with ARS show better responses to corticosteroids alone but become refractory to corticosteroid monotherapy. An association of CCs and immunosuppressant agents could be consider in chronic, mild ILD (100).

Recently, some authors have suggested that also cathepsin B (CB) could have a role in the development of lung fibrosis and that CA-074Me may be the potential therapeutic target for ILD-PM (103).

Finally, in PM/DM patients with lung involvement and oesophageal involvement another potential option taken into consideration last year was represented by IVIg therapy. Although data about the use of IVIg in IIM are conflicting (6), IVIg can reduce the CCs dose required for maintenance, and seems to be effective in the treatment of adult patients with PM/DM and appears to be relatively well tolerated and safe (104).

Recently, an alternative route of administration, subcutaneous immunoglobulins (SCIg), was made available. SCIg administered weekly by a programmable pump are equally efficacious suppressing inflammatory and immune-mediated processes without an excessive immunosuppressive effect. SCIg are also suitable and reduce the costs due to hospitalisations and surveillance (105-106).

Conclusions

In this review we provided a critical analysis of the progresses in the pathogenesis, classification and therapeutic approach of IIM of 2015. The studies cited, underline the complexity and the heterogeneity of the disease, in particular on the histopathology, positivity for myositis specific autoantibodies and prognosis. The advances in this field will hopefully allow to better classify the disease allowing to predict the response to novel therapeutic target and the prognosis of the disease.

References

1. DALAKAS MC: Inflammatory muscle diseases. *N Engl J Med* 2015; 372: 1734-47.
2. LUNDBERG IE, MILLER FW, TJÄRNLUND A, BOTTAI M: Diagnosis and classification of idiopathic inflammatory myopathies. *J Intern Med* 2016; 280: 39-51.
3. ADINOLFI A, VALENTINI E, CALABRESI E *et al*.: One year in review 2016: systemic lupus erythematosus. *Clin Exp Rheumatol* 2016; 34: 569-74.
4. CALABRÒ A, CATERINO AL, ELEFANTE E *et al*.: One year in review 2016: novelties in the treatment of rheumatoid arthritis. *Clin Exp Rheumatol* 2016 May-Jun; 34: 357-72.
5. FERRO F, VAGELLI R, BRUNI C *et al*.: One year in review 2016: Sjögren's syndrome. *Clin Exp Rheumatol* 2016; 34: 161-71.
6. BARSOTTI S, TERENZI R, LA PAGLIA GM, BELLUCCI E, BALDINI C, NERI R: One year in review 2015: idiopathic inflammatory myopathies. *Clin Exp Rheumatol* 2015; 33: 593-601.
7. GIOVANNINI L, ORLANDI M, LODATO C *et al*.: One year in review 2015: spondyloar-

thritis. *Clin Exp Rheumatol* 2015; 33: 769-78.
8. PICERNO V, FERRO F, ADINOLFI A, VALENTINI E, TANI C, ALUNNO A: One year in review: the pathogenesis of rheumatoid arthritis. *Clin Exp Rheumatol* 2015; 33: 551-8.
9. MIRABELLI G, CANNARILE F, BRUNI C, VAGELLI R, DE LUCA R, CARLI L: One year in review 2015: systemic lupus erythematosus. *Clin Exp Rheumatol* 2015; 33: 414-25.
10. LUCIANO N, VALENTINI V, CALABRÒ A *et al*.: One year in review 2015: Sjögren's syndrome. *Clin Exp Rheumatol* 2015; 33: 259-71.
11. GUIDELLI GM, BARSKOVA T, BRIZI MG *et al*.: One year in review: novelties in the treatment of rheumatoid arthritis. *Clin Exp Rheumatol* 2015 Jan-Feb; 33: 102-8.
12. HAQ SA, TOURNADRE A: Idiopathic inflammatory myopathies: from immunopathogenesis to new therapeutic targets. *Int J Rheum Dis* 2015; 18: 818-25.
13. BARSOTTI S, TERENZI R, LA PAGLIA GMC, BELLUCCI E, BALDINI C, NERI R: One year in review 2015: idiopathic inflammatory myopathies. *Clin Exp Rheumatol* 2015; 33: 593-601.
14. LAHOUTI AH, CHRISTOPHER-STINE L: Polymyositis and dermatomyositis: novel insights into the pathogenesis and potential therapeutic targets. *Discov Med* 2015; 19: 463-70.
15. BERNATSKY S, SMARGIASSI A, BARNABE C *et al*.: Fine particulate air pollution and systemic autoimmune rheumatic disease in two Canadian provinces. *Environ Res* 2016; 146: 85-91.
16. BLANC PD, JÄRVHOLM B, TORÉN K: Prospective risk of rheumatologic disease associated with occupational exposure in a cohort of male construction workers. *Am J Med* 2015; 128: 1094-101.
17. URUHA A, NOGUCHI S, HAYASHI YK *et al*.: Hepatitis C virus infection in inclusion body myositis: A case-control study. *Neurology* 2016; 86: 211-7.
18. BODOKI L, CHEN J-Q, ZEHER M *et al*.: Vitamin D receptor gene polymorphisms and haplotypes in Hungarian patients with idiopathic inflammatory myopathy. *BioMed Res Int* 2015; 2015: 809895.
19. ROTHWELL S, COOPER RG, LUNDBERG IE *et al*.: Dense genotyping of immune-related loci in idiopathic inflammatory myopathies confirms HLA alleles as the strongest genetic risk factor and suggests different genetic background for major clinical subgroups. *Ann Rheum Dis* 2016; 75: 1558-66.
20. MILLER FW, CHEN W, O'HANLON TP *et al*.: Genome-wide association study identifies HLA 8.1 ancestral haplotype alleles as major genetic risk factors for myositis phenotypes. *Genes Immun* 2015; 16: 470-80.
21. CHEN S, WANG Q, WU CY *et al*.: A single-nucleotide polymorphism of CCL21 rs951005 T>C is associated with susceptibility of polymyositis and such patients with interstitial lung disease in a Chinese Han population. *Clin Exp Rheumatol* 2015; 33: 639-46.
22. CHEN S, WU W, LI J *et al*.: Single nucleotide polymorphisms in the FAM167A-BLK gene are associated with polymyositis/dermatomyositis in the Han Chinese population. *Immunol Res* 2015; 62: 153-62.
23. SHINJO SK, UNO M, OBA-SHINJO SM, MARIE SKN: Angiotensin-converting enzyme insertion/deletion gene polymorphism is associated with dermatomyositis. *J Renin-Angiotensin-Aldosterone Syst JRAAS* 2015; 16: 666-71.
24. LINDGREN U, ROOS S, HEDBERG OLDFORS C, MOSLEMI A-R, LINDBERG C, OLDFORS A: Mitochondrial pathology in inclusion body myositis. *Neuromuscul Disord NMD* 2015; 25: 281-8.
25. LEWIS MJ, VYSE S, SHIELDS AM *et al*.: UBE2L3 polymorphism amplifies NF-κB activation and promotes plasma cell development, linking linear ubiquitination to multiple autoimmune diseases. *Am J Hum Genet* 2015; 96: 221-34.
26. SCIORATI C, MONNO A, ASCHERMAN DP, SELETTI E, MANFREDI AA, ROVERE-QUERINI P: Required role of apoptotic myogenic precursors and toll-like receptor stimulation for the establishment of autoimmune myositis in experimental murine models. *Arthritis Rheumatol* (Hoboken NJ) 2015; 67: 809-22.
27. OKIYAMA N, HASEGAWA H, OIDA T *et al*.: Experimental myositis inducible with transfer of dendritic cells presenting a skeletal muscle C protein-derived CD8 epitope peptide. *Int Immunol* 2015; 27: 327-32.
28. ESPINOSA-ORTEGA F, GÓMEZ-MARTIN D, SANTANA-DE ANDA K, ROMO-TENA J, VILLASEÑOR-OVIES P, ALCOCER-VARELA J: Quantitative T cell subsets profile in peripheral blood from patients with idiopathic inflammatory myopathies: tilting the balance towards proinflammatory and pro-apoptotic subsets. *Clin Exp Immunol* 2015; 179: 520-8.
29. HUANG P-L, HOU M-S, WANG S-W, CHANG C-L, LIOU Y-H, LIAO N-S: Skeletal muscle interleukin 15 promotes $CD8^{(+)}$ T-cell function and autoimmune myositis. *Skelet Muscle* 2015; 5: 33.
30. RUCK T, BITTNER S, AFZALI AM *et al*.: The NKG2D-IL-15 signaling pathway contributes to T-cell mediated pathology in inflammatory myopathies. *Oncotarget* 2015; 6: 43230-43.
31. NOTARNICOLA A, LAPADULA G, NATUZZI D, LUNDBERG IE, IANNONE F: Correlation between serum levels of IL-15 and IL-17 in patients with idiopathic inflammatory myopathies. *Scand J Rheumatol* 2015; 44: 224-8.
32. LI L, DAI T, LV J *et al*.: Role of Toll-like receptors and retinoic acid inducible gene I in endogenous production of type I interferon in dermatomyositis. *J Neuroimmunol* 2015; 285: 161-8.
33. MUTH IE, ZSCHÜNTZSCH J, KLEINSCHNITZ K *et al*.: HMGB1 and RAGE in skeletal muscle inflammation: Implications for protein accumulation in inclusion body myositis. *Exp Neurol* 2015; 271: 189-97.
34. CSERI K, VINCZE J, CSERI J *et al*.: HMGB1 expression and muscle regeneration in idiopathic inflammatory myopathies and degenerative joint diseases. *J Muscle Res Cell Motil* 2015; 36: 255-62.
35. MOHASSEL P, ROSEN P, CASCIOLA-ROSEN L, PAK K, MAMMEN AL: Expression of the dermatomyositis autoantigen transcription intermediary factor 1γ in regenerating muscle. *Arthritis Rheumatol* (Hoboken NJ) 2015; 67: 266-72.
36. GEORGANTAS RW, STREICHER K, GREENBERG SA *et al*.: Inhibition of myogenic microRNAs 1, 133, and 206 by inflammatory cytokines links inflammation and muscle degeneration in adult inflammatory myopathies. *Arthritis Rheumatol* (Hoboken NJ) 2014; 66: 1022-33.
37. MISUNOVA M, SALINAS-RIESTER G, LUTHIN S *et al*.: Microarray analysis of circulating micro RNAs in the serum of patients with polymyositis and dermatomyositis reveals a distinct disease expression profile and is associated with disease activity. *Clin Exp Rheumatol* 2016; 34: 17-24.
38. MAMMEN AL, CASCIOLA-ROSEN L, CHRISTOPHER-STINE L, LLOYD TE, WAGNER KR: Myositis-specific autoantibodies are specific for myositis compared to genetic muscle disease. *Neurol Neuroimmunol Neuroinflammation* 2015; 2: e172.
39. MESCAM-MANCINI L, ALLENBACH Y, HERVIER B *et al*.: Anti-Jo-1 antibody-positive patients show a characteristic necrotizing perifascicular myositis. *Brain J Neurol* 2015; 138: 2485-92.
40. PINAL-FERNANDEZ I, CASCIOLA-ROSEN LA, CHRISTOPHER-STINE L, CORSE AM, MAMMEN AL: The prevalence of individual histopathologic features varies according to autoantibody status in muscle biopsies from patients with dermatomyositis. *J Rheumatol* 2015; 42: 1448-54.
41. CHEN Z, HU W, WANG Y, GUO Z, SUN L, KUWANA M: Distinct profiles of myositis-specific autoantibodies in Chinese and Japanese patients with polymyositis/dermatomyositis. *Clin Rheumatol* 2015; 34: 1627-31.
42. IKEDA S, ARITA M, MORITA M *et al*.: Interstitial lung disease in clinically amyopathic dermatomyositis with and without anti-MDA-5 antibody: to lump or split? *BMC Pulm Med* 2015; 15: 159.
43. MOGHADAM-KIA S, AGGARWAL R, ODDIS CV: Treatment of inflammatory myopathy: emerging therapies and therapeutic targets. *Expert Rev Clin Immunol* 2015; 11: 1265-75.
44. TAKADA T, AOKI A, ASAKAWA K *et al*.: Serum cytokine profiles of patients with interstitial lung disease associated with anti-CADM-140/MDA5 antibody positive amyopathic dermatomyositis. *Respir Med* 2015; 109: 1174-80.
45. NARANG NS, CASCIOLA-ROSEN L, LI S, CHUNG L, FIORENTINO DF: Cutaneous ulceration in dermatomyositis: association with anti-melanoma differentiation-associated gene 5 antibodies and interstitial lung disease. *Arthritis Care Res* 2015; 67: 667-72.
46. HOZUMI H, ENOMOTO N, KONO M *et al*.: Prognostic significance of anti-aminoacyl-tRNA synthetase antibodies in polymyositis/dermatomyositis-associated interstitial lung disease: a retrospective case control study. *PloS One* 2015; 10: e0120313.
47. ROJAS-SERRANO J, HERRERA-BRINGAS D, MEJÍA M, RIVERO H, MATEOS-TOLEDO H, FIGUEROA JE: Prognostic factors in a cohort of antisynthetase syndrome (ASS): serologic profile is associated with mortal-

ity in patients with interstitial lung disease (ILD). *Clin Rheumatol* 2015; 34: 1563-9.
48. TOMONAGA M, SAKAMOTO N, ISHIMATSU Y *et al*.: Comparison of pulmonary involvement between patients expressing anti-PL-7 and anti-Jo-1 antibodies. *Lung* 2015; 193: 79-83.
49. ALBRECHT I, WICK C, HALLGREN Å *et al*.: Development of autoantibodies against muscle-specific FHL1 in severe inflammatory myopathies. *J Clin Invest* 2015; 125: 4612-24.
50. GOYAL NA, CASH TM, ALAM U *et al*.: Seropositivity for NT5c1A antibody in sporadic inclusion body myositis predicts more severe motor, bulbar and respiratory involvement. *J Neurol Neurosurg Psychiatry* 2016; 87: 373-8.
51. CHEN F, LU X, SHU X, PENG Q, TIAN X, WANG G: Predictive value of serum markers for the development of interstitial lung disease in patients with polymyositis and dermatomyositis: a comparative and prospective study. *Intern Med J* 2015; 45: 641-7.
52. XU Y, YANG CS, LI YJ *et al*.: Predictive factors of rapidly progressive-interstitial lung disease in patients with clinically amyopathic dermatomyositis. *Clin Rheumatol* 2016; 35: 113-6.
53. ISHIZUKA M, WATANABE R, ISHII T *et al*.: Long-term follow-up of 124 patients with polymyositis and dermatomyositis: Statistical analysis of prognostic factors. *Mod Rheumatol* 2016; 26: 115-20.
54. XIAO F, TAN J-Z, XU X-Y, WANG X-F: Increased levels of HSPA5 in the serum of patients with inflammatory myopathies--preliminary findings. *Clin Rheumatol* 2015; 34: 715-20.
55. XIAO F, TAN J, XU X, ZHU B, FANG S, WANG X: Increased osteopontin in muscle and serum from patients with idiopathic inflammatory myopathies. *Clin Exp Rheumatol* 2015; 33: 399-404.
56. OLAZAGASTI JM, HEIN M, CROWSON CS *et al*.: Adipokine gene expression in peripheral blood of adult and juvenile dermatomyositis patients and their relation to clinical parameters and disease activity measures. *J Inflamm* (Lond) 2015; 12: 29.
57. TANAKA A, TSUKAMOTO H, MITOMA H *et al*.: Serum progranulin levels are elevated in dermatomyositis patients with acute interstitial lung disease, predicting prognosis. *Arthritis Res Ther* 2015; 17: 27.
58. KOTANI T, TAKEUCHI T, ISHIDA T *et al*.: Increased serum LIGHT levels correlate with disease progression and severity of interstitial pneumonia in patients with dermatomyositis: a case control study. *PloS One* 2015; 10: e0140117.
59. VAN DE VLEKKERT J, MAAS M, HOOGENDIJK JE, DE VISSER M, VAN SCHAIK IN: Combining MRI and muscle biopsy improves diagnostic accuracy in subacute-onset idiopathic inflammatory myopathy. *Muscle Nerve* 2015; 51: 253-8.
60. TASCA G, MONFORTE M, DE FINO C, KLEY RA, RICCI E, MIRABELLA M: Magnetic resonance imaging pattern recognition in sporadic inclusion-body myositis. *Muscle Nerve* 2015; 52: 956-62.
61. YAO L, YIP AL, SHRADER JA *et al*.: Magnetic resonance measurement of muscle T2, fat-corrected T2 and fat fraction in the assessment of idiopathic inflammatory myopathies. *Rheumatology* (Oxford) 2016; 55: 441-9.
62. FILLI L, MAURER B, MANOLIU A, ANDREISEK G, GUGGENBERGER R: Whole-body MRI in adult inflammatory myopathies: Do we need imaging of the trunk? *Eur Radiol* 2015; 25: 3499-507.
63. ROSENBOHM A, BUCKERT D, GERISCHER N *et al*.: Early diagnosis of cardiac involvement in idiopathic inflammatory myopathy by cardiac magnetic resonance tomography. *J Neurol* 2015; 262: 949-56.
64. CLEARY LC, CROFFORD LJ, LONG D *et al*.: Does computed tomography-based muscle density predict muscle function and health-related quality of life in patients with idiopathic inflammatory myopathies? *Arthritis Care Res* 2015; 67: 1031-40.
65. KOTANI T, TAKEUCHI T, YOSHIMATSU Y *et al*.: Initial limited three-level thin-section computed tomography scorings predict the prognosis of acute/subacute interstitial pneumonia in patients with dermatomyositis. *Mod Rheumatol* 2016; 1-5.
66. DEBRAY M-P, BORIE R, REVEL M-P *et al*.: Interstitial lung disease in anti-synthetase syndrome: initial and follow-up CT findings. *Eur J Radiol* 2015; 84: 516-23.
67. ZOU J, GUO Q, CHI J, WU H, BAO C: HRCT score and serum ferritin level are factors associated to the 1-year mortality of acute interstitial lung disease in clinically amyopathic dermatomyositis patients. *Clin Rheumatol* 2015; 34: 707-14.
68. BHANSING KJ, VAN ROSMALEN MH, VAN ENGELEN BG, VONK MC, VAN RIEL PL, PILLEN S: Increased fascial thickness of the deltoid muscle in dermatomyositis and polymyositis: An ultrasound study. *Muscle Nerve* 2015; 52: 534-9.
69. NODERA H, TAKAMATSU N, MATSUI N *et al*.: Intramuscular dissociation of echogenicity in the triceps surae characterizes sporadic inclusion body myositis. *Eur J Neurol* 2016; 23: 588-96.
70. PINAL-FERNANDEZ I, PALLISA-NUÑEZ E, SELVA-O'CALLAGHAN A *et al*.: Pleural irregularity, a new ultrasound sign for the study of interstitial lung disease in systemic sclerosis and antisynthetase syndrome. *Clin Exp Rheumatol* 2015; 33: S136-141.
71. TATEYAMA M, FUJIHARA K, MISU T, ARAI A, KANETA T, AOKI M: Clinical values of FDG PET in polymyositis and dermatomyositis syndromes: imaging of skeletal muscle inflammation. *BMJ Open* 2015; 5: e006763.
72. AN Y-S, SUH C-H, JUNG J-Y, KIM H-A: Role of bone scan in the assessment of polymyositis/dermatomyositis. *Clin Rheumatol* 2015; 34: 699-706.
73. LIN Y-N, LIN C-L, CHANG K-C, KAO C-H: Increased subsequent risk of acute coronary syndrome for patients with dermatomyositis/polymyositis: a nationwide population-based retrospective cohort study. *Scand J Rheumatol* 2015; 44: 42-7.
74. RAI SK, CHOI HK, SAYRE EC, AVIÑA-ZUBIETA JA: Risk of myocardial infarction and ischaemic stroke in adults with polymyositis and dermatomyositis: a general population-based study. *Rheumatology* (Oxford) 2016; 55: 461-9.
75. DIEDERICHSEN LP, DIEDERICHSEN ACP, SIMONSEN JA *et al*.: Traditional cardiovascular risk factors and coronary artery calcification in adults with polymyositis and dermatomyositis: a Danish multicenter study. *Arthritis Care Res* 2015; 67: 848-54.
76. DIEVAL C, DELIGNY C, MEYER A *et al*.: Myocarditis in Patients With Antisynthetase Syndrome: Prevalence, Presentation, and Outcomes. *Medicine* (Baltimore) 2015; 94: e798.
77. MUSTAFA KN, AL-HERESH AM, KHATAYBEH OY, ALAWNEH KM, KHADER YS: Low prevalence of malignancy in patients with idiopathic inflammatory myopathies in Jordan. *Clin Exp Rheumatol* 2015; 33: 731-3.
78. GALIMBERTI F, LI Y, FERNANDEZ AP: Clinically amyopathic dermatomyositis: clinical features, response to medications and malignancy-associated risk factors in a specific tertiary-care-centre cohort. *Br J Dermatol* 2016; 174: 158-64.
79. DE SOUZA FHC, SHINJO SK, YAMAKAMI LYS *et al*.: Reduction of ovarian reserve in adult patients with dermatomyositis. *Clin Exp Rheumatol* 2015; 33: 44-9.
80. TSAI S-Y, LIN C-L, WONG Y-C *et al*.: Increased risk of herpes zoster following dermatomyositis and polymyositis: a nationwide population-based cohort study. *Medicine* (Baltimore) 2015; 94: e1138.
81. WU P-H, LIN Y-T, YANG Y-H, LIN Y-C, LIN Y-C: The increased risk of active tuberculosis disease in patients with dermatomyositis - a nationwide retrospective cohort study. *Sci Rep* 2015; 5: 16303.
82. CAVAGNA L, NUÑO L, SCIRÈ CA *et al*.: Clinical spectrum time course in anti Jo-1 positive antisynthetase syndrome: results from an international retrospective multicenter study. *Medicine* (Baltimore) 2015; 94: e1144.
83. AGGARWAL R, ODDIS CV: Therapeutic advances in myositis. *Curr Opin Rheumatol* 2012; 24: 635-41.
84. VERMAAK E, TANSLEY SL, MCHUGH NJ: The evidence for immunotherapy in dermatomyositis and polymyositis: a systematic review. *Clin Rheumatol* 2015; 34: 2089-95.
85. MATHUR T, MANADAN AM, THIAGARAJAN S, HOTA B, BLOCK JA: Corticosteroid monotherapy is usually insufficient treatment for idiopathic inflammatory myopathy. *Am J Ther* 2015; 22: 350-4.
86. GORDON PA, WINER JB, HOOGENDIJK JE, CHOY EHS: Immunosuppressant and immunomodulatory treatment for dermatomyositis and polymyositis. *Cochrane Database Syst Rev* 2012; CD003643.
87. ODDIS CV: Update on the pharmacological treatment of adult myositis. *J Intern Med* 2016; 280: 63-74.
88. SHINJO SK, NASCIMENTO JJ, MARIE SKN: The effect of prior corticosteroid use in muscle biopsies from patients with dermatomyositis. *Clin Exp Rheumatol* 2015; 33: 336-40

89. GE Y, ZHOU H, SHI J *et al*.: The efficacy of tacrolimus in patients with refractory dermatomyositis/polymyositis: a systematic review. *Clin Rheumatol* 2015; 34: 2097-103.
90. YOKOYAMA Y, FURUTA S, IKEDA K, HIROSE K, NAKAJIMA H: Corticosteroid-sparing effect of tacrolimus in the initial treatment of dermatomyositis and polymyositis. *Mod Rheumatol* 2015; 25: 888-92.
91. JOHNSON NE, ARNOLD WD, HEBERT D *et al*.: Disease course and therapeutic approach in dermatomyositis: A four-center retrospective study of 100 patients. *Neuromuscul Disord NMD* 2015; 25: 625-31.
92. IBRAHIM F, CHOY E, GORDON P *et al*.: Second-line agents in myositis: 1-year factorial trial of additional immunosuppression in patients who have partially responded to steroids. *Rheumatology* (Oxford) 2015; 54: 1050-5.
93. FASANO S, GORDON P, HAJJI R, LOYO E, ISENBERG DA: Rituximab in the treatment of inflammatory myopathies: a review. *Rheumatology* (Oxford) 2016 Apr 27 [Epub ahead of print].
94. ODDIS CV, REED AM, AGGARWAL R *et al*.: Rituximab in the treatment of refractory adult and juvenile dermatomyositis and adult polymyositis: a randomized, placebo-phase trial. *Arthritis Rheum* 2013; 65: 314-24.
95. REED AM, CROWSON CS, HEIN M *et al*.: Biologic predictors of clinical improvement in rituximab-treated refractory myositis. *BMC Musculoskelet Disord* 2015; 16: 257.
96. ALLENBACH Y, GUIGUET M, RIGOLET A *et al*.: Efficacy of rituximab in refractory inflammatory myopathies associated with anti-synthetase auto-antibodies: an open-label, phase II trial. *PloS One* 2015; 10: e0133702.
97. ANDERSSON H, SEM M, LUND MB *et al*.: Long-term experience with rituximab in anti-synthetase syndrome-related interstitial lung disease. *Rheumatology* (Oxford) 2015; 54: 1420-8.
98. MIMORI T, NAKASHIMA R, HOSONO Y: Interstitial lung disease in myositis: clinical subsets, biomarkers, and treatment. *Curr Rheumatol Rep* 2012; 14: 264-74.
99. MORISSET J, JOHNSON C, RICH E, COLLARD HR, LEE JS: Management of myositis related interstitial lung disease. *Chest* 2016 Apr 18 [Epub ahead of print].
100. KAWASUMI H, GONO T, KAWAGUCHI Y, YAMANAKA H: Recent treatment of interstitial lung disease with idiopathic inflammatory myopathies. *Clin Med Insights Circ Respir Pulm Med* 2015; 9: 9-17.
101. GO DJ, PARK JK, KANG EH *et al*.: Survival benefit associated with early cyclosporine treatment for dermatomyositis-associated interstitial lung disease. *Rheumatol Int* 2016; 36: 125-31.
102. KURITA T, YASUDA S, OBA K *et al*.: The efficacy of tacrolimus in patients with interstitial lung diseases complicated with polymyositis or dermatomyositis. *Rheumatology* (Oxford) 2015; 54: 1536.
103. ZHANG L, FU X-H, YU Y *et al*.: Treatment with CA-074Me, a Cathepsin B inhibitor, reduces lung interstitial inflammation and fibrosis in a rat model of polymyositis. *Lab Investig J Tech Methods Pathol* 2015; 95: 65-77.
104. WANG DX, SHU XM, TIAN XL *et al*.: Intravenous immunoglobulin therapy in adult patients with polymyositis/dermatomyositis: a systematic literature review. *Clin Rheumatol* 2012; 31: 801-6.
105. HACHULLA E, BENVENISTE O, HAMIDOU M *et al*.: High dose subcutaneous immunoglobulin for idiopathic inflammatory myopathies and dysimmune peripheral chronic neuropathies treatment: observational study of quality of life and tolerance. *Int J Neurosci* 2016; 1-8.
106. DANIELI MG, MORETTI R, GAMBINI S, PAOLINI L, GABRIELLI A: Open-label study on treatment with 20 % subcutaneous IgG administration in polymyositis and dermatomyositis. *Clin Rheumatol* 2014; 33: 531-6.