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Idiopathic Inflammatory Myopathies: an Update on Classification and Treatment with Special Focus on Juvenile Forms

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Abstract Juvenile inflammatory myopathies represent a heterogeneous group of rare and potentially fatal disorders of unknown aetiology, characterised by inflammation and proximal and symmetric muscle weakness. Beyond many similarities, specific clinical, laboratoristic and histopathologic features underlie different subsets with distinguishing demographic, prognostic and therapeutic peculiarities. Over time, several forms of inflammatory idiopathic myopathies have been described, including macrophagic myofascitis, immune-mediated necrozing myopathy and the spectrum of amyopathic dermatomyositis that include hypomyopathic dermatomyositis, inclusion body myositis and cancer-associated myositis occurring almost exclusively in adults. However, juvenile dermatomyositis is the most frequent in childhood, whereas polymyositis is relatively more frequent in adults. The aetiology is nowadays widely unclear; however, current theories contemplate a combination of environmental triggers, immune dysfunction and specific tissue responses involving muscle, skin and small vessels endothelium in genetically susceptible individuals. Myositis-specific autoantibodies, found almost exclusively in patients with myositis and myositis-associated autoantibodies, detectable both among patients with myositis and in subjects suffering from other autoimmune diseases, have an important clinical role because of their relation to specific clinical features, response to therapy and prognosis. The gold standard treatment for juvenile dermatomyositis is represented by corticosteroids, along with adjunctive steroid-sparing immunosuppressive therapies, which are used to counteract disease activity, prevent mortality, and reduce long-term disability. Further treatment approach such as biologic agents and autologous stem cell transplantation are emerging during the last years, in particular in patients difficult to treat and with poor prognosis. Therefore, a highly medical specialised approach is required for diagnosis and management of these conditions. This review comprehensively examines juvenile inflammatory myopathies focusing on clinical and laboratory classifications as well as on the current treatment approaches, referring in particular on biologic agents and latest therapeutic opportunities.

Keywords Autoantibodies · Autoimmune disorders · Polymyositis · Dermatomyositis · Myopathies

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Introduction

The juvenile idiopathic inflammatory myopathies (JIIM) are systemic autoimmune disorders characterised by chronic skeletal muscle inflammation, skin rashes and other systemic features [1, 2]. To date, diagnosis is based on the clinical and laboratory criteria proposed by Bohan and Peter [3, 4], with the limitation that many paediatric patients presenting typical rashes do not undergo electromyography or muscle biopsy [5]. These disorders can be classified based on clinical features

as well as on the presence of specific autoantibodies generally found in patients suffering from myositis, defined as myositis autoantibodies [6]. These subclassifications of JIIM assist physicians in identifying patients with common demographic and clinical features, laboratory findings, prognoses and responses to therapy.

In this paper, we provide an update on clinical classification, laboratory features and treatment of juvenile myositis.

Clinical Feature and Classification

Among the various clinical forms of JIIM, juvenile dermatomyositis (JDM) is the most frequent in childhood, whereas polymyositis (PM) is relatively more frequent in adults and inclusion body myositis (IBM) and cancer-associated myositis occur almost exclusively in adults. Over time, new forms of inflammatory idiopathic myopathies have been described, including macrophagic myofascitis, immune-mediated necrotizing myopathy and the spectrum of amyopathic dermatomyositis (DM) that include hypomyopathic DM [6].

In particular, JDM has an average age at disease onset of 7.5 years and is characterised by symmetrical proximal muscle weakness often associated to raised red patches overlying the interphalangeal joints or other joint extensor surfaces known as Gottron's sign (Fig. 1). The heliotrope rash, a red or purple discoloration over the eyelids, is another typical skin manifestation [3, 4]. In addition, malar rash, photosensitivity and linear extensor erythema are also frequent cutaneous manifestations. Muscle enzymes as creatinine kinase (CK) and aldolase are elevated. The prognosis of JDM is variable: approximately one third of patients have a monocyclic course achieving a complete disease resolution within a 2-year period, while 50–60 % of patients experience a chronic illness course and mortality involves 2–3 % of patients [6]. In particular, chronicity is associated to persistent periungueal capillary abnormalities, active skin disease, cutaneous or gastrointestinal ulcerations, and less frequently, to pneumomediastinum or pneumatosis intestinalis, as a consequence of vasculopathy [7, 8]. Calcinosis occurs in 20–40 % of patients, especially in those with diagnostic delay, cardiac involvement, and prolonged or severe illness course [6, 9].

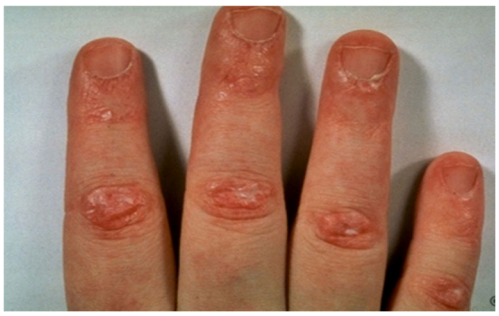

Fig. 1 Illustrates Gottron sign in juvenile dermatomyositis

Lipodystrophy, occurring in 10 % of cases, is another JDM complication characterised by progressive loss of subcutaneous fat in a widespread manner [10]. Figures 2 and 3 show Gottron sign, lipodystrophy and calcinosis in 52-year-old female patients with a 48-year history of DM.

Overlap myositis is the second most common clinical JIIM phenotype, occurring in 6–11 % of subjects [11]. Raynaud phenomenon, interstitial lung disease, arthritis and malar rash are the main clinical features. Notably, the presence of lung disease is associated with a higher mortality rate. The most common overlapping autoimmune conditions include systemic lupus erythematosus, juvenile idiopathic arthritis, systemic sclerosis and localised scleroderma [6].

Juvenile polymyositis (JPM), accounting for about 4–8 % of JIIM, is characterised by both proximal and distal muscle weakness, lacking the characteristic rashes of JDM. Histopathologic findings show endomysial infiltrate of affected muscle [12, 13]. Patients with JPM tend to be older than those with JDM and have higher CK levels. Muscle biopsy is mandatory for the diagnosis and highlights myopathic features and muscle atrophy. Of note, among JPM patients myositis associated autoantibodies (MAAs), particularly anti-aminoacyl-tRNA synthetase (anti-synthetase) and anti-signal recognition particle (SRP) autoantibodies, are frequently detected [6].

The other JIIM phenotypes are less common. Hypomyopathic DM is occasionally observed in patients showing laboratory evidence of muscle inflammation without detectable weakness. Among amyopathic DM patients, calcinosis is uncommon, while an association with interstitial lung disease has been rarely identified [6]. Notably, almost 26 % of these patients subsequently develop a classic JDM over several years [14]. For this reason, a close clinical monitoring aimed at identifying progression toward muscle involvement is mandatory beyond treatment of cutaneous manifestations.

Malignancies associated to JIIM are exceptional in childhood. However, it is mandatory to exclude malignancies when evaluating atypical JDM, in particular in the cases of prominent adenopathy, hepatosplenomegaly, palpable masses and

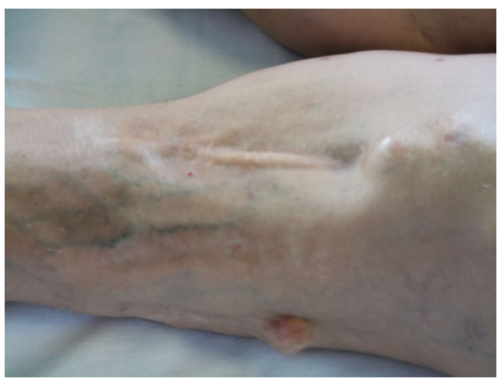

Fig. 2 Shows lipodystrophy at the popliteal fossa in a dermatomyositis female patient

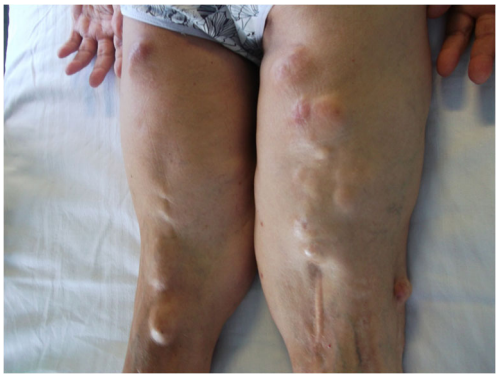

Fig. 3 Shows a patient with dermatomyositis characterised by typical calcinosis in the back of the thighs

atypical rashes. Cancers JIIM-related in children have included lymphoma, leukaemia and solid organ tumours [15, 16].

Classification Based on Serological Findings

A further classification of JIIM is based on the presence of myositis autoantibodies. In particular, myositis-specific autoantibodies (MSAs) are present almost exclusively in patients with myositis, while myositis-associated autoantibodies (MAAs) can be detectable both among patients with myositis and in subjects suffering from other autoimmune diseases [6]. These myositis autoantibodies are linked to specific clinical features, response to therapy and prognosis.

Anti-p155/140 and anti-MJ autoantibodies are the most frequent MSAs in JIIM and are primarily associated with JDM [17]. In particular, anti-p155/140 autoantibodies are linked to photosensitive skin rash, including malar rash, V-sign, shawl-sign rash and linear extensor erythema. Also, they are associated to periungueal capillaroscopic changes, cutaneous ulcerations and lipodystrophy [17, 18]. Patients with JIIM and anti p-155/140 autoantibodies frequently present with a chronic illness course in childhood [17] and are often related to cancer-associated myositis in adults [19]. Anti-MJ autoantibodies are common in JDM patients with muscle cramps, joint contractures, dysphonia and a monocyclic disease course [17, 20]. Subjects presenting with this autoantibody group have a more severe illness and a higher frequency of disease-related complications such as muscle atrophy [20], calcinosis [21] and gastrointestinal ulcerations [17].

Anti-synthetase autoantibodies are MSAs present in less than 5 % of JIIM, especially in JPM or juvenile overlap myositis. Among anti-synthetase autoantibodies, anti-Jo-1 autoantibodies are the most common and frequently associate with interstitial lung disease, arthritis, fever, Raynaud phenomenon and mechanic's hands [17]. Among patients with MSAs, this group shows the highest mortality rate, mostly caused by interstitial lung disease [22]. Anti-SRP autoantibodies are often identified in African-American girls with severe JPM, proximal and distal weakness, very high CK levels, wheelchair use, Raynaud phenomenon, frequent falling episodes, cardiac complications and chronic illness course. Disease course is often very severe and refractory to treatment [23].

Anti-Mi-2 and anti-CADM-10 are other traditional MSA. The former is associated with JDM and its typical cutaneous features. Conversely, the latter is linked to rapidly progressive interstitial lung disease and cutaneous ulcerations. Anti-small ubiquitin-like modifier activating enzyme autoantibodies have also been described in patients with JIIM in case reports [24, 25].

MAAs, such as anti-U1RNP, anti-Ro, anti-PM-Scl and anti-Ku autoantibodies, are found in up to 15 % of patients with JIIM, but are more frequently identified in patients suffering from overlap myositis [26, 27].

Ultimately, although MSAs and MAAs are important laboratory findings allowing a better clinical, prognostic and therapeutic stratification, approximately 28 % of patients have no identified MSAs or MAAs. This subgroup seems to suffer from a mild disease course [6]. Table 1 summarises the most frequent MSAs and MAAs, their frequencies and clinical associations [6, 17–29].

Aetiology and Pathogenesis

To date, the aetiology of JIIM remains unclear; however, current theories contemplate a combination of environmental triggers, immune dysfunction and specific tissue responses involving muscle, skin and small vessels endothelium in genetically susceptible individuals [30].

Regarding genetic factors, HLA-B*08, DRB1*0301 and DQA1*0501 are part of an extended haplotype that confers risk for myositis in both adults and children [27, 31]. In this regard, according to recent works, also HLA-DPB1*0101 confers independent risk for myositis in adults and children, while DQA1*0301 allele is an additional risk factor for JDM [31–34]. However, protective alleles have also been found, such as DQA1*0201, DQA1*0101 and DQA1*0102, which are less frequent in affected patients than in healthy controls and may be involved in the self-reactive antigen binding and in the elimination of self-reactive T cells from the thymus [30, 34].

Several other loci have been identified as possible risk factors for JIIM, including in genes coding for the pro-inflammatory cytokines tumour necrosis factor (TNF)-α, interleukin (IL- 1)α and IL-1β [31], as well as the lymphocyte signalling gene *PTPN22* [35], and the immunoglobulin heavy chains [36]. In particular, the TNF-α variant TNF308A is linked to a higher risk for calcinosis and ulcerations among patients [37] and to higher levels of TNF production in controls [30]. Similarly, the IL-1 polymorphism IL1α-889CC seems to confer additional risk for the development of

Table 1 More frequent myositis specific and myositis associated autoantibodies [6, 17–29]

Antibody	More common subgroups associated	Clinical features associated	Frequency
Anti-p155/140 (TIF1-γ)[a]	(J)DM	Severe skin disease, ulcerations, lipodystrophy. Strong association with malignancies in adults	25–30 %
Anti-MJ (NXP-2)[a]	(J)DM	Muscle cramps, dysphonia, joint contractures, gastrointestinal ulcerations, severe skin involvement, calcinosis. Worse functional status in children; possible association with malignancies in adults	20–25 %
Anti-Mi-2 (NuRD)[a]	(J)DM	Classical DM rash leading to a mild form; children show a more severe increase in serum CK than adults	20–30 %
Anti-CADM-140 (MDA 5)[a]	(J)DM	Classical DM or amyopathic DM; associated with rapidly progressive ILD, cutaneous ulceration, and cardiac involvement, with a high fatality rate and poor response to treatment	–
Anti-SAE[a]	DM	Cutaneous features precede muscle involvement. Lung disease occurrence is rare	0.2–8 %
Anti-aminoacyl tRNA synthetases (Anti-Jo-1)[a]	(J)PM; juvenile overlap myositis	Frequent ILD (presenting feature), arthritis, mechanic's hand, Raynaud's phenomenon, fever; high mortality rate	2–10 %
Anti-aminoacyl tRNA synthetases (other than anti-Jo-1)[a]	(J)PM	High frequency of ILD and arthritis. Myositis can be absent	Rare
Anti-SRP[a]	(J)PM	Severe muscle weakness, Raynaud's phenomenon, very high CK serum levels, chronic illness course, cardiac disease is also possible. Lack of treatment response is frequent	1 % (More frequent among African-American girls)
Anti Ro/SSA[b]	Overlap myositis	In adults, prednisone alone often shows a good clinical response. May be associated with anti-Jo1	2–19 %
Anti-U1RNP[b]	JPM and overlap myositis	Sclerodactyly	8–10 %
Anti-PM-Scl[b]	JPM and overlap myositis	Arthritis, Raynaud's phenomenon, ILD, and oesophageal dysmotility.	2–4 %
Anti-Ku[b]	Overlap myositis	Arthritis, Raynaud's phenomenon, and oesophageal dysmotility	0.2–1 %
Anti-HMG-coA[b]	Necrotising myositis	High CK serum levels; skin involvement is often absent	–

CADM clinically amyopathic dermatomyositis, *CK* creatine kinase, *HMG-coA* hydroxy-methylglutaryl-CoA, *ILD* interstitial lung disease, *(J)DM* (juvenile) dermatomyositis, *(J)PM* (juvenile) polymyositis, *MDA 5* melanoma differentiation-associated gene 5, *NuRD* nucleosome remodelling deacetylase, *NXP-2* nuclear matrix protein, *SAE* small ubiquitin-like modifier activating enzyme, *SRP* signal recognition particle, *TIF1-γ* transcriptional intermediary factor 1 γ, *tRNA* transfer ribonucleic acid

[a] Myositis-specific antibodies

[b] Myositis-associated antibodies

calcinosis [31]. Table 2 shows current most relevant evidences on genetic role in the pathogenesis of IIM.

Environmental factors associated with JIIM onset have also been studied. In this regard, infectious agents, including parvovirus and enterovirus, can play a role as triggers [38–40]. In addition, exposure to drugs, vaccines and ultraviolet light may also be risk factors [6].

Treatment Approaches

The gold standard treatment for JDM is represented by corticosteroids, along with adjunctive steroid-sparing immunosuppressive therapies, which are used to counteract disease activity, prevent mortality and reduce long-term disability and calcinosis.

An initial dose of prednisone at 2 mg/kg/day is recommended, and dosages tend to remain high for several months. The use of intravenous pulse methylprednisolone (IVMP) is common, particularly for moderate to severe cases, with a trend to initially deliver three to five daily doses of 30 mg/kg, followed by intermittent subsequent doses, particularly for severe disease [6].

Methotrexate represents the most used steroid-sparing agent, while hydroxychloroquine is used for mild disease and when cutaneous manifestations occur. Intravenous immunoglobulins (IVIG) are useful in severe or refractory cases, or for patients presenting with predominant skin disease [41, 42].

In a large Pediatric Rheumatology INternational Trials Organisation (PRINTO) study on 145 patients with recent-onset JDM and 130 patients experiencing a disease flare, North and South American patients were more frequently administered IVMP at disease onset than European patients. The use of methotrexate was similar in both regions, while cyclosporine and IVIG were favoured in Europe for flares [42].

Recently, the Childhood Arthritis and Rheumatology Research Alliance (CARRA) developed consensus protocols in order to optimise the baseline therapy for patients with moderate to severe JDM [43, 44]. In particular, three consensus treatment protocols have been suggested: steroids at dosage of 2 mg/kg/day and methotrexate at a dosage of 15 mg/m^2 or 1 mg/kg are common to all three treatment strategies. However, IVMP (30 mg/kg up to 1 g, for three consecutive days and then optionally once per week) or IVMP plus IVIG (2 g/kg every 2 weeks three times, then monthly) were also contemplated in an early disease phase in order to improve faster disease activity and reach better outcomes [45]. In any case, methotrexate and other corticosteroid-sparing medications may avoid steroid-related toxicity such as weight gain, growth delay and cataract [46].

With regard to corticosteroid tapering, according to a follow-up consensus report from CARRA, patients showing clinical improvement may undertake a steroid tapering every 2–4 weeks with a view to discontinue steroid treatment after 10–12 months from diagnosis [6]. In this regard, improvement or normalisation of muscle strength, muscle enzymes, skin rashes and other disease manifestations represent valid criteria for reducing steroids [44].

Noteworthy, a multicentre, randomised controlled trial conducted by PRINTO on 139 recently diagnosed JDM patients highlighted that prednisone plus methotrexate lead to a better response than prednisone plus cyclosporine or prednisone alone at 6 months follow-up [47]. Furthermore, time to inactive disease in the group administered prednisone plus methotrexate or cyclosporine was significantly shorter than treated

Table 2 Summarises the most notable genetic acquisitions on IIM

	Increased IIM risk [27, 31–34]	Reduced IIM risk [30, 34]
HLA	-B*0801	DQA1*0201
	-A*0101	DQA1*0101
	-DRB1*0301	DQA1*0102
	-DQA1*0501	DR4
	-DPB1*0101	DR7
	-DQA1*0301	
	-DQB1*02	
	-DRB1*15021 (Japanese patients)	
Other genes		Correlated features
	IL-1: polymorphism IL-1α-889CC [31]	Higher risk for calcinosis
	PTPN22 gene: variant R620W [35]	Associated with juvenile and adult idiopathic inflammatory myopathy
	TNF-α gene: variant TNF308A [37]	Higher risk for calcinosis and ulcerations

IIM inflammatory idiopathic myositis, *HLA* human leukocyte antigen, *PTPN22* protein tyrosine phosphatase N22, *TNF* tumour necrosis factor, *IL-1* interleukin-1

with prednisone alone. Similarly, time to major therapeutic changes in the group treated with prednisone alone was significantly shorter than in the combination groups. In the same study, the safety profile favoured the employment of methotrexate over cyclosporine [47].

Difficult to Treat Patients

Other treatment approaches are available in patients showing severe disease manifestations, such as interstitial lung disease and skin or gastrointestinal ulcerations, and in patients with poor prognosis, such as those with anti-synthetase or anti-SRP autoantibodies.

Intravenous immunoglobulins (IVIG) are recommended in JDM patients with moderately to severe disease manifestations, including severe weakness, dysphagia, ulcerative disease or calcinosis. Lam and colleagues [48] published a retrospective review on monthly IVIG infusions in 30 patients with JDM unresponsive to standard of therapy compared with 48 patients who did not receive IVIG treatment. The IVIG group included two subgroups of patients: steroid-resistant patients and steroid-dependent patients. The former were unresponsive to corticosteroids with or without methotrexate or suffered from dysphagia and severe weakness requiring initial IVIG. The latter were initially responsive to the standard treatment, but flared after corticosteroid tapering. Although patients on IVIG started with greater disease activity, they showed similar or lower disease activity than controls from 30 days to 4 years post-diagnosis. In particular, the improvement was most marked among steroid-resistant patients [48].

Mycophenolate mofetil (MMF) is one of the few disease-modifying antirheumatic drugs (DMARDs) studied in children with JDM. In a small retrospective case series, mycophenolate mofetil administered twice a day at a dosage ranging from 800 to 1350 mg/m^2/day, along with oral steroids, resulted in clinical improvement and a mean steroid tapering of 18 % after 3 months. At the last visit (3–26 months after starting treatment), seven patients were still administered MMF and showed muscle strength improvement as well as steroid tapering. In addition, although a transient neutropenia occurred during a viral infection and on a concomitant methotrexate administration, a good safety profile was seen [49].

Oral tacrolimus has been reported to be beneficial for resistant or severe interstitial lung disease and myositis in adult patients with anti-synthetase autoantibodies [50]. Similarly, tacrolimus has been reported to induce beneficial effects in children with refractory JDM, especially in those with severe skin involvement [51]. Intravenous cyclophosphamide pulse therapy was used in 12 JDM patients, with a significant improvement in muscle function, muscle strength, extramuscular disease activity score and cutaneous disease in 10/12 patients at 6-month follow-up. Although the ulcerative disease had been successfully treated in all patients, skin disease was the main persisting extramuscular feature after 6 months. In addition, there was a trend toward creatine kinase, alanine aminotransferase, prednisolone dose and erythrocyte sedimentation rate reduction, despite not reaching statistical significance. Since completing the cyclophosphamide course, clinical improvement was maintained until the last follow-up visit. The authors specified that two of the 12 patients given cyclophosphamide died before the drug could be effective. Finally, no major short-term side effects resulted from cyclophosphamide treatment [52].

Adrenocorticotropic hormone (ACTH) gel can be used in peculiar cases such as inadequate oral corticosteroids absorption and non-compliant patients. In this regard, subcutaneous ACTH gel injections of 80 U once or twice weekly over the course of 12 weeks lead to improved muscle strength, decreased pain, and resolution of skin involvement in five DM or PM adult patients with no side effects [53].

Biological therapies

Biological agents are emerging as treatment choices for myositis. In particular, the importance of humoral immunity and autoantibodies has led to increasing interest in B cell-targeted therapy in such disorders. In this regard, in 2011 Chiu et al. identified 12 previously reported children with JDM who received the chimeric anti-CD20 monoclonal antibody rituximab. Most of them had failed standard of therapy and received rituximab at a dosage of 375 mg/m^2 weekly for 4 weeks. Nine out of 12 patients showed improvement of their cutaneous or muscle disease. However, two out of these nine patients had relapses that necessitated further rituximab courses, one required maintenance rituximab every 4 months, and one relapsed requiring autologous stem cell transplantation. Overall, five of the 12 patients reached disease remission with one rituximab course, and only minor side effects were reported [54]. Conversely, an open-label trial of rituximab therapy conducted in eight adult patients with DM found modest effects on muscle disease and limited effects on skin disease after two infusions of rituximab (1 g each) 2 weeks apart. In particular, only three out of eight patients showed at least 50 % reduction in muscle deficit, and no significant changes in skin disease were observed through 24 weeks of follow-up [55].

More recently, a large multicentre trial enrolled both paediatric and adult subjects (76 PM/76 DM/48 JDM patients) refractory to standard treatments. Subjects were randomised to either ‘rituximab early’ or ‘rituximab late’, and glucocorticoid and immunosuppressive therapy were allowed at entry. The former group received rituximab at the dosage of 575–750 mg/m^2 (according to the body surface area) at weeks 0 and 1, and placebo infusions at weeks 8 and 9. Conversely, the latter received placebo infusions at weeks 0 and 1 and rituximab at weeks 8 and 9. The primary endpoint was the time to the International Myositis Assessment and Clinical Studies

Group definition of improvement (DOI) which was compared between the 'rituximab early' and 'rituximab late' groups. The secondary endpoints were time to achieve at least 20 % of improvement in muscle strength and the proportion of early and late rituximab patients achieving DOI at week 8. At the end of the study, neither the primary nor the secondary endpoints significantly differed between the two treatment groups. However, 83 % of enrolled subjects had met the DOI by the end of the trial, and rituximab had provided a significant steroid-sparing effect. For these reasons, the authors suggested that the agent had an effect, but certain aspects of the study design had made identification of such an effect difficult [56]. A recent retrospective analysis on 19 adult PM or DM patients highlighted that 73 % of these patients responded to rituximab within 5.6 months from their first treatment course. In particular, response had been defined as a reduction of at least 50 % of both the baseline CPK level and the daily prednisolone dose after week 12 at the earliest. If the CPK was ≤10 μmol/l/s or the prednisolone dose was <20 mg/day at baseline and had not increased later, ≥50 % improvement in the other parameter was considered sufficient for a response. Also, total lung capacity improved in six out of the eight PM patients with lung involvement and remained stable in the other two. Notably, all five DM patients responded, and none required a rituximab re-treatment. Conversely, eight of ten PM patients with anti-synthetase antibodies needed a second rituximab cycle, seven out of ten received a third cycle, and two required a fourth cycle. However, an 81-year-old male patient with rapid progressive anti-SRP myositis died from aspiration pneumonia 3 weeks after the first rituximab infusion and other six more severe infections occurred under treatment in four patients. In addition, one patient developed symptomatic secondary antibody deficiency [57].

Although many recent studies and case reports insist on the high rates of clinical response to rituximab [58–60], larger clinical trials aiming to address the benefit of rituximab as therapy in inflammatory myopathies are awaited. In particular, the relationship between response to rituximab and clinical and serological subsects of patients should be explored. In this regard, myositis overlap, a lower disease damage, JDM subset (versus adult myositis) and patients with anti-synthetase antibodies seem to respond better than other patient subsets [60, 61]. In addition, severe adverse events rarely reported in patients undergoing rituximab treatment should be taken into account [62].

With regard to anti-TNFα agents, available data are conflicting: some studies and case reports seem to indicate them as having an effective role in such patient [63–68], while other studies seem to state just the opposite [69–73]. In particular, according to many case reports, infliximab can lead to clinical benefit in myositis patients [63–65]. In line with these findings, a retrospective study of eight PM or DM patients refractory to standard of therapy and administered with anti-TNF agents showed that this treatment approach may be useful in such patients. More precisely, in this study six patients were treated with etanercept alone, one with infliximab and one sequentially with both agents. Six out of eight patients showed a favourable response. Of the two non-responding patients, one was treated with infliximab and the other with etanercept [66]. Similarly, another retrospective study assessing infliximab therapy in 14 amyopathic DM and 4 DM patients with acute interstitial pneumonia found that ten patients presenting an early disease achieved satisfactory relief, while four patients with a late stage did not respond to treatment and died [67]. On the contrary, a randomised controlled clinical trial of infliximab in DM and PM adult patients showed that infliximab had only limited efficacy as only 3/12 patients improved by manual muscle testing and 7/12 patients improved by International Myositis Assessment and Clinical Studies Group (IMACS) criteria [69]. In addition, open-label trials even reported disease progression or worsening with infliximab treatment in refractory DM and PM adult patients [70, 71]. In this regard, the pilot study by Dastmalchi et al. on 13 PM, DM, or IBM refractory patients treated with infliximab concluded that this treatment was not effective in such cases. In particular, infliximab at a dose of 5 mg/kg four times (weeks 0, 2, 6, and 14) led to clinical improvement in two out of five patients with PM/DM who completed the study. On the contrary, one subject remained unchanged and two even worsened according to the IMACS definition. Functional index improved >20 % in one responder, and no patient improved in muscle strength by manual muscle test [71].

Regarding etanercept, a randomised, double-blind, placebo-controlled trial in DM patients disclosed a good safety profile and a steroid-sparing effect. Indeed, in all patients, placebo failed, whereas 5/11 patients treated with etanercept (at the dosage of 50 mg weekly for 52 weeks) were successfully weaned off prednisone. In addition, there were no significant differences in adverse event rates between the 11 patients randomised to etanercept and the five subjects randomised to placebo [68]. However, a recent pilot study of etanercept in nine refractory JDM patients concluded that etanercept did not provide improvement and some patients showed worsening of disease. More specifically, seven patients showed a mild decrease in the disease activity score (DAS) and one patient even a worsening of the DAS at 12-week follow-up. At 24-week follow-up, one patient showed to be stable, two patients had a worsened DAS, and three patients had improvement of the DAS. Only six out of nine patients completed the study. Furthermore, there was no significant change in serum muscle enzymes or Childhood Myositis Assessment Scale throughout the study [72]. Similarly, a case series reporting five DM patients showed etanercept ineffectiveness as all patients experienced an exacerbation of disease [73]. Noteworthy, cases with either induction or exacerbation of DM after etanercept or adalimumab administration have

also been reported, thus inducing caution in their employment [74–76].

Other biologic agents as possible treatment alternatives for inflammatory myositis have been reported. Regarding anakinra, a 12-months follow-up mechanistic study involving six PM and four DM adult patients with refractory myositis found that five patients (2 DM, 2 PM, 1 IBM) fulfilled the improvement criteria according to IMACS definition at month 3, one at month 6 (PM), and one at month 12 (DM). Conversely, five patients showed unchanged disease activity, and three patients worsened. Furthermore, the subgroup of patients with more extramuscular symptoms responded better to anakinra, while CD163 macrophages and IL-1α muscle expression as well as blood CD4 activated/memory T cells seemed negative predictors for anakinra response [77]. On the contrary, according to another pilot open-label trial, anakinra leads to no improvement in muscle strength or stabilisation over a 5–12-month period in four adult patients with IBM. In addition, one patient experienced disease worsening during therapy [78].

The humanised anti-IL-6 receptor antibody tocilizumab has been reported to be effective both in a murine model of PM and in two adult patients with refractory PM [79, 80]. To date, the fully human fusion protein of the cytotoxic T lymphocyte antigen 4 abatacept has been identified as showing a good clinical response in three case reports [81–83]. In particular, abatacept at a dose of 10 mg/kg administered at 0, 2, and 4 weeks, followed by monthly dosing, proved to be an effective steroid-sparing agent for the treatment of a refractory 14-year-old Caucasian girl with severe JDM [83]. Also, the anti-CD52 monoclonal antibody alemtuzumab has proven to be a possible therapeutic approach: a proof-of-principle study on 13 IBM patients found that one series of alemtuzumab infusions (0.3 mg/kg/day for 4 days) could slow down disease progression up to 6 months, reduced endomysial T cells and stressor molecules, and improved strength [84]. In line with these findings, a refractory 48-year-old woman with PM therapy had been previously described to be responding to a single course of alemtuzumab at a dosage of 120 mg over 4 days [85]. However, ineffective alemtuzumab administration and unusual side effects such as Epstein-Barr virus-driven lymphoproliferative disorder following alemtuzumab therapy in PM patients have also been described [86, 87].

Recently, the investigational anti-IFNα monoclonal antibody sifalimumab has been investigated: a phase 1b randomised, double-blind, placebo controlled, dose-escalation, multicentre study found that the type I interferon gene signature was suppressed by 53–66 % across three time points (days 28, 56, and 98) in blood and by 47 % at day 98 in muscle specimens after sifalimumab administration. Notably, a positive trend between target neutralisation and clinical improvement was identified: patients with at least 15 % improvement from baseline manual muscle testing showed greater neutralisation of the type I interferon gene signature than patients with lower amelioration. In addition, this neutralisation highly correlated with suppression of leucocyte infiltration in muscle [88]. Sifalimumab has also proven to suppress serum T cell-related proteins that may lead to a reduction of T cell infiltration in the muscle on PD or DM patients [89].

Figure 4 summarises various treatment lines, from the baseline therapeutic approach to the more complicated cases unresponsive to standards of therapy.

Other treatment approaches

Autologous stem cell transplantation has been anecdotally reported to induce dramatic improvement and sustained remission in severe progressive JDM, SRP- or Jo-1-associated PM and adult DM patients unresponsive to conventional treatment [87, 90–92]. Nevertheless, less remarkable results have also been reported [93, 94].

With regard to localised involvement, treatment of cutaneous manifestations of amyopathic JDM is based on photoprotection and topical therapies: a daily application of sunscreens protecting against both UV-A and UV-B light is recommended. In recalcitrant skin-limited manifestations, oral antimalarials represent a useful treatment choice, while systemic corticosteroids, methotrexate, intravenous immunoglobulin, and rituximab are controversial in such patients. Conversely, topical corticosteroids or topical immunomodulators such as tacrolimus can be helpful for limited rashes, while the presence of itching can be dealt with antihistamines and moisturisers [95].

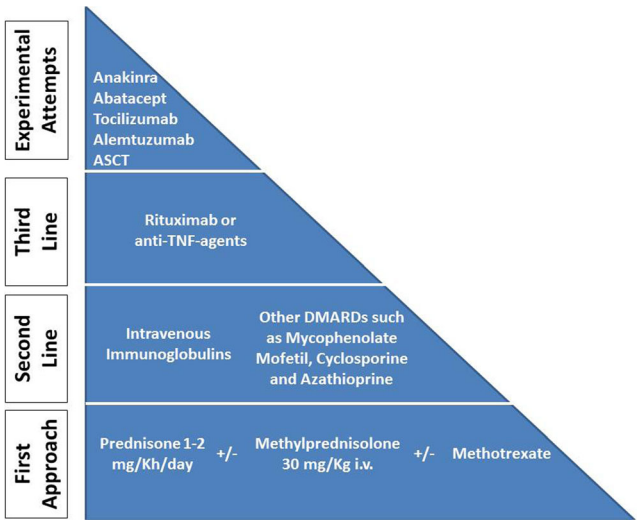

Fig. 4 Exemplifies the different treatment lines from the initial JIIM therapeutic approach to the latest experimental attempts for patients unresponsive to standard therapies. *ASCT* autologous stem cell transplantation, *DMARDs* disease-modifying anti-rheumatic drugs, *TNF* tumour necrosis factor

Treatment of calcinosis often requires an aggressive approach in order to counteract the underlying disease activity. In this regard, treatment with IVIG, IVMP, mycophenolate mofetil, cyclophosphamide, infliximab, abatacept and other immunosuppressive agents have all been reported [6]. Medications affecting metabolism of calcium or phosphate such as calcium channel blockers, aluminium hydroxide and probenecid have shown conflicting results [96]. Among drugs used to counteract calcinosis, bisphosphonates and topical sodium thiosulfate have also been tried [83, 96, 97].

Conclusions/Summary

JIIM represent a heterogeneous group of diseases characterised by different features and autoantibody profiles corresponding to similar demographic, clinical, laboratory and prognostic subsets. Treatment approach is tailored according to clinical severity, ranging from topical medications and skin protection for cutaneous manifestations of amyopathic JDM to newly identified therapeutic alternatives for life-threatening conditions unresponsive to standards of therapy. Identifying definite subgroups of patients may allow a more optimised therapeutic course in order to obtain a good outcome avoiding overtreatment. Nevertheless, large randomised trials and high-quality clinical studies are needed to better identify more correct medical approaches and the role of latest therapeutic alternatives.

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