

**Title page**

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**Treatment of Juvenile Dermatomyositis: An Update**

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**Abstract:**

The Idiopathic Inflammatory Myopathies of childhood consist a heterogeneous group of autoimmune diseases characterised by proximal muscle weakness and pathognomonic skin rashes. The overall prognosis of juvenile myositis has improved significantly over recent years, but the long-term outcome differs substantially from patient to patient suggestive of distinct clinical phenotypes with variable responses to treatment. High doses of corticosteroids remain the cornerstone of therapy along with other immunosuppressant therapies depending on disease severity and response. The advent of biological drugs has revolutionised the management of various paediatric rheumatologic diseases, including inflammatory myopathies. There are few data from randomised controlled trials to guide management decisions, thus several algorithms for the treatment of juvenile myositis have been developed using international expert opinion. The general treatment goals now include elimination of active disease and normalization of physical function, so as to preserve normal growth and development, and to prevent long-term damage and deformities. This review summarizes the newer and possible future therapies of juvenile inflammatory myopathies, including evidence supporting their efficacy and safety.

**Key points:**

- Treatment of juvenile inflammatory myopathies mainly constitutes corticosteroids and methotrexate as a steroid-sparing agent, but must be tailored according to disease severity
- Much of our knowledge on the use of DMARDs and biologic agents in JDM is based on anecdotal experience because of the lack of randomised control trials.
- A multi-disciplinary approach to care by a team including a paediatric rheumatologist, a physiotherapist, an occupational therapist and a podiatrist is essential in order to achieve the best therapeutic outcome.

## **1.1 Introduction**

Idiopathic Inflammatory Myopathies (IIM) consist of an heterogeneous group of autoimmune diseases characterized by a chronic inflammatory process affecting muscles, skin and other organs [1]. Juvenile Dermatomyositis (JDM) is the most common IIM accounting for approximately 85% of cases [2, 3] while juvenile polymyositis (JPM) is seen in less than 5% of cases in most cohorts [2, 4]. Some patients with inflammatory myopathy may also demonstrate features of other autoimmune diseases including systemic lupus erythematosus (SLE), systemic sclerosis (SSc) and juvenile idiopathic arthritis (JIA). These patients are described as having overlap syndromes, and treatment should be personalised depending on the predominant features.

Adult and juvenile myositis share characteristic clinical features such as the pathognomonic skin rashes and muscle inflammation but are both also highly heterogeneous, with distinct additional clinical features and distinct outcomes. Important clinical manifestations such as calcinosis, interstitial lung disease and malignancy differ substantially in prevalence between adult and juvenile myositis [5]. Children are more likely to develop calcinosis, vasculopathy and ulceration, despite which they still have a significantly better prognosis compared to adult cases which are more commonly complicated with malignancy and lung disease [6].

Previously, the prognosis of JDM was poor with a reported mortality of 30% but also a significant percentage of disability [7]. With the advantage of recent therapeutic strategies and the development of new treatments, survival and outcomes have improved significantly with a reported mortality of <2% [8, 9]. As JDM is rare, much of our knowledge on treatment is based on anecdotal experience or small case series. In this review, we will discuss current therapeutic management, recent advances in the therapeutic strategies of JDM and avenues for further research.

## **1.2 Pathogenesis and the role of myositis specific antibodies**

The exact pathogenesis of JDM is not yet known. It is thought to be related to both humoral and cell-mediated mechanisms affecting small vessels and leading to vascular and muscle damage. Vasculopathy seems to play a central role in the pathogenesis of myositis and cutaneous involvement [10, 11], but is also central to other severe systemic features of the disease that contribute significantly to the burden of disease in children. The exact nature of

vasculopathy remains unclear but there is evidence of a true inflammatory small vessel vasculitis driven by interferons and other cytokines [11, 12] and a non-inflammatory occlusive vasculopathy with capillary drop out [13, 14]. Muscle biopsy shows not only immune cells infiltrates but also C5b-9 deposits. Since JDM is strongly associated with the presence of autoantibodies, it is presumed though yet not clearly demonstrated, that autoantibodies may activate complement triggering the release of pro-inflammatory cytokines, upregulation of adhesion molecules on endothelial cells, and migration of B and CD4<sup>+</sup> T lymphocytes and plasmacytoid dendritic cells, into muscle tissue [15-17]. Type 1 interferons produced by dendritic cells, in turn, stimulate the production of pro-inflammatory cytokines and enhance the expression of HLA class I and class II molecules [17].

The overall prognosis of JDM has improved significantly over recent years, but the long term outcome differs substantially from patient to patient [4, 18] suggestive of distinct clinical phenotypes. Predicting these different disease trajectories has been challenging. In recent years, IIM can be defined into more homogeneous subsets as there is now increasing evidence to support a critical association between genotype, serotype and clinical phenotype in adult and juvenile inflammatory myopathies [19-21]. Myositis specific antibodies (MSA) and myositis associated antibodies (MAA) in IIMs are present in 60% of cases [6]. They have different prevalence and associations across the myositis spectrum depending on the age of disease onset. In some cases the antibody levels may reflect disease activity. Certain myositis-specific antibodies and their associated clinical phenotype remain unchanged across different age groups; for example, anti-PM-Scl with scleroderma overlap features, anti-Mi-2 with classic skin rash of dermatomyositis, and antihistidyl RNA synthetase (Jo-1) with interstitial lung disease [6], though the latter is rare in childhood. Other associations differ: anti-TIF1-gamma (p155/140) is found in 23–29% of patients with JDM and is associated with an increased risk of cutaneous disease and a prolonged course [22] while in adult DM is found in 13-21% and is strongly associated with the development of malignancy [5]. Anti-NXP2 (p140) is present in 11-23% and is associated with the development of calcinosis in children with JDM [23], in an age dependent fashion, in contrast with adults where it is found in only 1.6% of cases [5]. It is not known whether particular antibodies predate the specific features with which they are associated: they could be useful as prognostic biomarkers. In support of this, a recent study demonstrated that the MSA status in combination with the muscle biopsy score can be a significant prognostic tool [24].

### **1.3 Clinical manifestations**

The inflammatory myopathies are characterized by symmetric, proximal muscle weakness which is present in 95% patients at the time of diagnosis [25]. This may present with functional limitations, such as difficulty getting up from the floor, getting in and out of motor vehicles, climbing stairs, or lifting the head up when lying flat on a bed. In JDM patients pathognomonic skin rashes are typically present consisting mainly of Gottron's papules and heliotrope rash. These cutaneous abnormalities are apparent in approximately three-quarters of patients presenting with JDM [26]. Cutaneous manifestations may precede or follow the onset of muscle involvement by months or even several years, and may be the most active or difficult feature of the IIM to manage [27]. Nailfold capillary changes are present in most of the patients at the time of diagnosis [28]. Arthritis is another common manifestation of JDM with a reported prevalence of 23-64% of cases. It may occur early in the disease course and is usually non-erosive [29]. Small vessel vasculitis is a characteristic feature of that group of diseases and thought to be related with the severe extramuscular manifestations of the disease such as intestinal ischaemia and perforation, interstitial lung disease, skin ulceration and development of calcinosis. Pulmonary manifestations are much less common in children with JDM than adults, but interstitial lung disease may occur. Subclinical systolic and diastolic dysfunction has been demonstrated in patients with JDM [30, 31], while pericarditis has also been reported [32]. Lipodystrophy has been reported in a number of JDM patients and usually occurs years after disease onset and is often associated with other metabolic abnormalities [33].

#### **1.4 Diagnosis of Juvenile Dermatomyositis**

Diagnosis of JDM is based on Peter and Bohan Criteria published in 1975 [10]. Diagnostic criteria include characteristic cutaneous changes, proximal muscle weakness, elevated muscle enzymes, electromyography (EMG) demonstrating denervation and muscle biopsy displaying necrosis and inflammation. The diagnosis of JDM is probable if rash is present plus two of the other four criteria are present and definite in the presence of rash and three out of the other four criteria. In an international survey of paediatric rheumatologists published in 2006, clinical manifestations (proximal muscle weakness and characteristic skin rash) and laboratory findings (muscle enzymes) were routinely used in the diagnosis of JDM, while magnetic resonance (MRI) was also deemed important and used by 60% of responders to detect inflammatory muscular changes [34]. Muscle biopsy and EMG were used only by 61.3% and 55.5% [34], respectively, suggesting for the first time that a number of children would fail to meet the current diagnostic criteria necessary for the inclusion in research and

other collaborative studies. That necessitates the revision of current criteria. An international effort is currently ongoing to agree and validate new classification criteria.

### **International consensus discussions for treatment pathways**

In rare diseases, such as JDM, international collaboration is necessary to facilitate research, better understand the pathogenesis and develop new therapeutic strategies. To accommodate international collaboration, a number of core sets of variables have been developed to be used in the clinical trials for quantification of response and clinical improvement [35, 36]. Despite being used in clinical trials, these core sets have not been completely adopted into clinical practice, as they require significant clinical time to be performed. Recently, a big effort has been underway for the development of an internationally accepted minimal core dataset which is very important for monitoring of disease status in each patient, development of standards of care, assessment of quality care, and as potential end points in clinical trials [37].

As there are few data from randomised controlled trials to guide management decisions in the children with IIM, recently several algorithms for the treatment of moderately severe JDM were developed using international expert opinion [38-40]. The Childhood Arthritis and Rheumatology Research Alliance (CARRA) has described several treatment strategies for initial therapy for JDM based upon a North American survey of practice [39], while recently consensus-based recommendations for the management of JDM were published by a European initiative called Single Hub and Access point for paediatric Rheumatology in Europe (SHARE) [40] to optimise and disseminate diagnostic and management regimens in Europe for children and young adults with rheumatic diseases.

### **1.5 Current Therapeutic options**

The aim of drug therapy in patients with JDM is to induce and maintain a complete remission of all symptoms, and thus to allow a child to achieve normal growth, development, and allow full participation in school, career, sport and all other aspects of normal life. While most children do very well overall with this condition, quality of life can be significantly affected, often as a consequence of associated complications, which can result in pain and disruption of daily tasks and activities. Early pharmacological and non-pharmacological treatment of the disease is imperative for the prevention of irreversible soft tissue and organ damage. The intensity of initial therapy differs according to the increasing severity of the symptoms [41], which range from mild disease to serious, life-threatening weakness with internal organ

damage, ulcerative skin lesions and development of extensive calcinosis. Pharmacological interventions for JDM include glucocorticoids (GCs), disease-modifying drugs (DMARDs) and biologics. Non-pharmacological interventions, such as physiotherapy interventions (e.g. therapeutic exercises, massage), podiatrist and occupational therapist input when required, may help patients maintain their functional status while also contributing to maintenance of an increase in bone mineral density, and ultimately to the prevention of osteopenia. This combined multi-disciplinary approach to care is essential for overall better management of symptoms and leads to better ultimate outcomes.

### **1.5.1 Corticosteroids**

The prognosis of JDM has significantly improved over the last decades with the use of steroids as first line treatment. Early aggressive treatment is reported to improve the long-term outcome [42]. Corticosteroids act quickly to stop the disease process. Different corticosteroid regimes have been proposed for the initial treatment of JDM with the most reported used being oral prednisolone in a dose of 2 mg/kg/day and pulses with intravenous methylprednisolone (IV MP) 30mg/kg/day followed by oral prednisolone. A comparative study [43] failed to demonstrate superiority of one regime over the other in the 3-year outcome scores although more severe cases were always treated with IV MP, while other reports [44-46], suggested that residual weakness, relapsing disease and calcinosis are lower in patients receiving pulse intravenous rather than oral therapy. Moreover, a study published in 2000 [47] suggested that IV MP although more costly, is cost effective when compared to oral corticosteroids. In the presence of dysphagia, gastrointestinal symptoms or more severe disease, IV MP is generally used as there is reported reduced absorption of oral prednisolone, especially when gastrointestinal vasculopathy is suspected [48]. Many specialist centres now prefer the use of IV MP pulses for 3-5 days followed by a 2mg/kg/day dose of prednisolone (or IV MP equivalent) and the subsequent oral steroid dose to be given as a single morning dose, as this regimen has less effects on the hypothalamic-pituitary-adrenal function and growth, even in young children [49]. According to the response, the daily dose of steroid treatment is then tapered. Low dose of steroids may be needed long term especially in some types of IMM (for example, anti-SRP Ab positive- myositis [50], as complete discontinuation may precipitate a disease flare.

The significant anti-inflammatory effects of corticosteroids cannot however be separated from their metabolic effects. Children are more vulnerable to steroid side effects than adults, particularly the effects on growth, immunity and adrenal suppression. Corticosteroid

treatment is connected to significant side effects, including growth retardation, Cushingoid appearance, hypertension, secondary glucose intolerance/ diabetes cataract osteoporosis, and vertebral fractures. Moreover, apart from the physical side effects, steroid therapy has been associated with adverse psychological side effects, ranging from psychotic symptoms to mild changes in mood and cognition [51]. Early introduction of steroid sparing agents may allow faster weaning of steroid treatment.

## **1.5.2 Disease-modifying antirheumatic drugs (DMARDs)**

### **1.5.2.1 Methotrexate (MTX)**

Methotrexate (MTX) has been the first-line conventional DMARD with marked efficacy in JDM for over 30 years. Despite the recent advances in pharmacotherapy, MTX remains an important cornerstone of therapy for JDM and is used extensively both as mono- and combination therapy worldwide. Until recently, most of the knowledge about MTX use in JDM was mainly based on case reports and small cohorts [52-56]. The only randomised controlled trial (RCT) comparing prednisone alone vs combination of prednisone with either MTX or Ciclosporin recently demonstrated that the combination of steroids and MTX had the best outcome regarding efficacy and safety [57]. A large retrospective study on treatment practise in Europe and South America involving 490 children with IIM demonstrated a 50% use of MTX in these regions [58]. In general, for children with JDM, MTX therapy is started at a dose of 15-20 mg/m<sup>2</sup>/week, and given by the subcutaneous route [40]. Around 70% of patients with JDM benefit significantly from MTX therapy, with the maximum therapeutic effect usually becoming apparent 3 months after the beginning of treatment [57]. Treatment with MTX is usually continued for one year after remission is achieved.

MTX administration has been related with gastrointestinal side effects, including oral ulceration, nausea, vomiting, abdominal pain and diarrhoea with a reported prevalence ranging between 10 to 50% in different cohorts of Juvenile Idiopathic Arthritis patients [59-61], [62,63] Anticipatory and associative gastrointestinal adverse effects experienced before MTX administration are also common [62, 63]. Fewer data are available on how common these gastrointestinal side effects are for children with JDM taking MTX. Serious side effects such as bone marrow suppression and hepatotoxicity (as demonstrated by elevated liver enzymes) are less frequently reported and usually transient once MTX dose is omitted [64]. It is important to highlight that in children with active JDM it may be difficult to distinguish MTX related hepatopathy against elevation of muscle isoenzymes of transaminases. The

concomitant use of folic or folinic acid has been suggested to try to prevent the development of these side effects [65]. Blood tests for monitoring of full blood count, liver and renal function are recommended while on MTX treatment with the optimal frequency of testing yet to be established [64].

### **1.5.2.2 Ciclosporin**

Ciclosporin has also been used in many centres as a steroid-sparing agent. The use of ciclosporin was mainly based on findings of efficiency in series of cases [66-68]. The RCT discussed above comparing isolated glucocorticosteroids and its association with methotrexate or ciclosporin suggested that combination treatment with prednisone plus either ciclosporin or methotrexate was superior to prednisone monotherapy in patients with JDM, at 6 months and after at least 24 months of treatment [57]. Of note ciclosporin is more commonly used in Europe than in North America centres.

Ciclosporin is usually given in divided doses 3-5mg/kg/day. It necessitates monitoring during the first few months to ensure its trough serum level is optimal (90-150mg/mL). Furthermore, ciclosporin is toxic to many organs, i.e.: the kidneys, liver and bone marrow [69].

Consequently, renal tests should be closely monitored; when creatinine levels increase more than 30%, cyclosporine should be discontinued. Cases of posterior reversible encephalopathy syndrome (PRES) have been reported in patients treated with ciclosporin with increasing risk when combined with steroid treatment [70, 71]. In current practice, because ciclosporin use is difficult, this drug may be reserved for patients who have failed to respond adequately to steroids, other immunosuppressive agents and intravenous immunoglobulins.

### **1.5.2.3 Mycophenolate Mofetil (MMF)**

Mycophenolate mofetil (MMF) is emerging as a promising drug, especially when used in refractory IIM [69] and in patients with interstitial lung disease (ILD) refractory to steroids [72]. Two retrospective studies where 12 [73] and 50 [74] JDM patients were treated with MMF demonstrated a good response and safety profile. It is usually given at starting dose of 600mg/m<sup>2</sup>/day, then can be increased to 1200mg/m<sup>2</sup>/day divided in two doses if well tolerated. Side effects include gastrointestinal intolerance (diarrhoea), leukopenia, kidney and liver toxicity [75]. Response to MMF is expected within 2–3 months.

### **1.5.2.4 Azathioprine**

Azathioprine has been used as an alternative to MTX in children with refractory JDM [54]. Most of the knowledge on azathioprine comes from the experience in adult patients [76]. It is usually given at an initial dose of 1mg/kg/day for two weeks and then increased to 2mg/kg/day according to thiopurine-methyl-transferase enzyme activity. Bone marrow suppression and elevated liver enzymes are the commonest side effects [75] and routine blood monitoring is also recommended. In our practise, azathioprine may be used if methotrexate is not tolerated and in some cases with persistent mild skin disease in conjunction with MTX with good results (unpublished data).

#### **1.5.2.5 Cyclophosphamide (CyC)**

Cyclophosphamide has been used as a third line therapeutic agent [77]. It is reserved for IMM patients refractory to most other therapies and/or for cases complicated with severe pulmonary involvement, ulcerative skin disease or gastrointestinal vasculopathy. Several case studies demonstrate the efficacy of treatment with CyC in both paediatric and adult patients with IIMs [72, 77]. It is usually given at a dose of 500-1000 mg/m<sup>2</sup> (usually to a maximum dose of 1.2gr) monthly for 6 doses [77]. Main side effects include alopecia, haemorrhagic cystitis, sterility, teratogenicity and increased risk of infection and malignancy [72]. Close monitoring of blood tests is suggested to decide about further dosing. In boys of reproductive age, sperm banking should be advised while in girls of reproductive age the use of a gonadotropin-releasing hormone agonist for ovarian protection should be thought [78]. It is important though to highlight that there may be limitations in the use of the above mentioned fertility preservation options including severe or life threatening cases, when CyC needs to be given urgently and cost barriers, particular to each country and local regulations. A recent analysis of a large cohort of JDM patients treated with CyC indicated efficacy and low rates of adverse events [79].

#### **1.5.2.6 Hydroxychloroquine (HCQ)**

Hydroxychloroquine is an antimalarial agent commonly used in the treatment of rheumatologic diseases. Data on the use of HCQ in JDM is limited, primarily based on anecdotal experience and two small, retrospective reviews [80, 81]. HCQ is mainly used in milder cases for skin rashes. The usual dose of hydroxychloroquine in children is 3-5 mg/kg kg/day divided 1-2 times per day with a maximum of 400mg per day. Hydroxychloroquine is generally considered to be a very safe medication. The most concerning side effect is ocular toxicity for which yearly ophthalmological examinations are recommended [82].

### **1.5.2.7 Tacrolimus**

Tacrolimus binds the immunophilin FKBP12, inhibits calcineurin, and suppresses T lymphocytes secreting cytokines, such as interleukin-2. Small case series have reported the use of tacrolimus in children with refractory JDM, skin disease, global disease activity and physical function were reported to improve. Patients were able to reduce corticosteroid therapy, and the medication was well tolerated [83, 84].

### **1.5.2.8 Intravenous immunoglobulins (IVIG)**

Intravenous immunoglobulins (IVIG) is recommended in IIM patients refractory to steroids and methotrexate. IVIG has been used in the treatment of JDM since the 1980s as reported in case reports and small case series. The majority of reported patients experienced improvement in skin disease and muscle strength, and the use of IVIG also reduced the cumulative glucocorticoid dose in most patients [85-88]. In 2011 a large retrospective study including 78 JDM patients confirmed the efficacy of IVIG in controlling JDM disease activity, particularly for steroid resistant patients [89]. Both the Childhood Arthritis and Rheumatology Research Alliance (CARRA) and SHARE proposed the use of IVIG in refractory JDM once conventional treatment with steroids and methotrexate has failed [38, 40]. IVIG is usually given as a dose of 2 g/kg (maximum dose 70 g), administered as a single dose or divided over two days. Two different regimes have been proposed [89-91]. IVIG is either given every two weeks, initially for three doses, and is then generally administered monthly for up to two years or it is given in monthly infusions starting from the first dose. At present there is no robust evidence for superiority of one or other of these regimes. The decision to begin IVIG typically occurs when patients experience persistent or increasing symptoms as glucocorticoids are weaned, indicating steroid resistance or steroid dependence. However, IVIG is often used earlier in very severe cases of JDM.

Most of the adverse effects associated with IVIG administration are mild and transient. The immediate AEs include headache, flushing, malaise, chest tightness, fever, chills, myalgia, fatigue, dyspnoea, back pain, nausea, vomiting, diarrhoea, blood pressure changes, tachycardia, and anaphylactic reactions, especially in IgA-deficient patients. Severe anaphylactoid or anaphylactic reactions are more likely to occur in patients with severe IgA deficiency (< 1.2 mg/dl) and those with anti-IgA antibodies of the IgE type [92, 93]. Complete absence of IgA has been recently shown to be a significant risk factor for the development of anaphylactic reactions [94]. The IgA content of the different IVIG

preparations varies and also plays a significant role in the development of severe anaphylactic reactions in the high risk patients [95]. However, using a IVIG preparation with low IgA concentration does not preclude that the infusion will be reaction free and up to date there have been no studies to support the evidence that increasing levels of IgA in the different IVIG preparations relate with increasing numbers of side effects. Late AEs are rare and include acute renal failure, thromboembolic events, aseptic meningitis, neutropenia, and autoimmune haemolytic anaemia, skin reactions, and rare events of arthritis. Immediate AEs can be treated by the slowing or temporary discontinuation of the infusion and symptomatic therapy with analgesics, non-steroidal anti-inflammatory drugs, antihistamines, and glucocorticoids in more severe reactions [96].

## **1.6 Biologic agents**

Biologic agents are genetically engineered drugs designed to target specific areas of the immune system and selectively block inflammatory pathways implicated in disease processes [97]. They include monoclonal antibodies, soluble cytokine receptors and recombinant receptor antagonists [98]. There are several reports of the safety and efficacy of biologics in a range of other inflammatory conditions [97, 99]. Outcomes such as elimination of any pain and inflammation, normalization of short-term and long-term function and achievement of normal growth, physical and psychosocial development are now realistic priorities for clinicians and patients. On the other hand, biologic therapies while demonstrating significant efficacy, have also been linked to rare but severe adverse events such as lymphoma, serious infections, demyelination and hepatotoxicity [100, 101]. All biological agents are available either as a subcutaneous injection or should be administered intravenously, complicating their use in the paediatric population [97]. In addition, the evidence for many of the treatments used in paediatric rheumatology is incomplete and currently all biologic therapies are off-label in the indication of JDM. We herein discuss current evidence for the biologic agents used in juvenile IIM (**Table 1**).

### **1.6.1 Targeting B cells**

#### **1.6.1.1 Rituximab (RTX)**

Rituximab is a chimeric monoclonal antibody directed against the human CD20 receptor, which is present only on B cells. Until recently, the effectiveness of rituximab was suggested by case reports and case series in adult and pediatric patients with refractory disease [102, 103]. A randomized trial (that included 152 adults with myositis as well as 48 children with

JDM), demonstrated that most patients eventually had some benefit, although the time that it took to show improvement was long and there was no statistically significant difference between subjects who received rituximab early or after a delay of nine weeks [104].

Interestingly, in a follow-up sub-analysis of the Rituximab in Myositis trial, JDM cases a quicker initial improvement and a better outcome when compared to adult [105]. There is an increasing interest about the place of rituximab in the treatment of anti-SRP myositis with a recent report suggesting an improvement in muscle strength and/or decline in CK levels as early as two months after rituximab treatment in adult cases [106].

Current UK practice regarding dosing of rituximab consists of two doses 750 mg/m<sup>2</sup> two weeks apart [107]. Pre-dosing with 100mg IV methylprednisolone, chlorphenamine and paracetamol an hour before the infusion is recommended to prevent the mild side effects that occur during or up to 24 hours after receiving rituximab and include mild throat tightening, flu-like symptoms, rash, itchiness, dizziness and back pain. Severe allergic reactions have been reported [103]. Infections have been reported in some patients with prolonged hypogammaglobulinemia while late-onset neutropenia might also occur after RTX and may result in serious infections [108]. Thus, monitoring of white cell count should be performed in the event of fever or infection after treatment with Rituximab [108].

### **1.6.1.2 Anti-Tumour Necrosis Factor (TNF) agents**

The two modalities used for TNF inhibition involve soluble receptors (Etanercept) and antibodies (Infliximab, Adalimumab, Golimumab, and Certolizumab). There is currently only limited formal evidence for the use of Adalimumab and Infliximab in paediatric cases of IIMs.

#### **1.6.1.2.1 Infliximab and Adalimumab**

Infliximab is a chimeric human-murine IgG1 monoclonal antibody produced in murine hybridoma cells by recombinant DNA technology. It was marketed first for treatment of rheumatoid arthritis in the late 90s. The rationale for using anti-TNF treatment in myositis is the up-regulation of TNF $\alpha$  and its receptor in muscle tissue of these patients and also the expression of this cytokine in the endothelium of subjects with DM [109]. In 2008, a case series reported effect of Infliximab in children with refractory JDM and development of calcinosis [110]. Evaluation of 66 patients with JDM, recruited from the UK JDM Cohort and Biomarker Study and actively treated with anti-TNF agents, both Infliximab and Adalimumab showed significant improvements in muscle and skin involvement, as well as in

overall disease activity. There were also significant improvements in skin involvement assessed using the modified skin Disease Activity Score [111]. Paradoxically, there have been cases of adults with inflammatory myopathies where Infliximab induced an increase in type I IFN serum activity resulting not only in no clinical improvement but even in disease exacerbation [112]. Moreover, a recent review reported 20 patients who developed dermatomyositis and polymyositis after receiving anti-TNF treatment for other autoimmune diseases [113]. This could be the result of the cross-regulation between TNF $\alpha$  and type I IFN, which is known to play a significant role into the pathogenesis of the inflammatory myopathies [114].

Infliximab is given as an infusion at a dose of 6mg/kg every 2 weeks for the first three doses followed by monthly doses. Severe adverse reactions include anaphylactic reactions, while mild to moderate adverse reactions include infection [115, 116]. Adalimumab is a sc injection given at a dose of 24mg/m<sup>2</sup> fortnightly, up to a maximum dose of 40mg. The most common side effect of Adalimumab is localized reaction at the injection site while increased risk of infection and specifically tuberculosis is a well recorded adverse effect [117].

### **1.6.1.3 Other biologic agents**

There are few reports coming from adults reporting the use of other biologic agents in adults with DM/PM. A recently published review of current pharmacological treatment of idiopathic inflammatory myopathies [69] described three cases of refractory myositis treated with tocilizumab with promising results [118-120] and three case reports showing beneficial effects of co-stimulation blockade using Abatacept in myositis [121-123]. A randomized clinical trial is underway to test this hypothesis (ClinicalTrials.gov Identifier: NCT02594735).

## **1.7 Adjunctive therapies**

Adjunctive therapy includes a number of pharmacological and non-pharmacological therapies which contribute significantly to a better long-term outcome and prevent complications related to the disease process but also to the medications used. JDM rash is known to be a photosensitive rash and sun exposure is known to exacerbate disease flares. It is thus recommended the daily use of high factor sun sunscreen [40]. Concomitant use of calcium and vitamin D supplements is recommended to prevent osteoporosis, as long term high doses

of corticosteroids are usually required for the treatment of IIMs [124, 125]. Moreover, a large systematic review and meta-analysis demonstrated that corticosteroid use is associated with increased risk of gastrointestinal bleeding and perforation [126]. Thus, it is suggested the use of gastroprotective drugs for as long as the patient is on corticosteroid treatment.

Physical and occupational therapy are important adjunctive measures to pharmacologic therapy. Children with IIMs are usually hypoactive leading to deconditioning and reduction in functional ability. Even when disease is well controlled, they still experience significant fatigue [127] and anaerobic- and aerobic exercise intolerance [128]. Moreover, decreased physical activity is known to be related with complications associated with a sedentary lifestyle including cardiovascular disease and obesity. Several studies have demonstrated the benefit of a specialized physiotherapy program in increasing muscle strength and improving muscle endurance [129, 130].

## **1.8 Future treatment options**

### **1.8.1 JAK inhibitors**

A number of agents have been used in one to a few patients with refractory disease who have failed other immunosuppressive therapies. It is now increasingly recognised that JDM falls into the category of diseases driven by interferons collectively referred to as “interferonopathies” [131, 132]. Excessive interferon expression may drive endothelial injury ultimately leading to poor outcomes in JDM. Patients with evidence of ongoing endothelial injury may therefore benefit from janus kinase (JAK) inhibition, which acts directly downstream of interferon activation [133]. JAK inhibitors have been successfully used in other interferonopathies, notably the proteasome associated auto-inflammatory syndromes that clinically and immunologically share similar features with JDM [133]. A compassionate use program for JAK inhibition has already begun in North America for severe refractory JDM and we have now recruited the first refractory case of JDM in our institute. We predict that JDM patients with persistent endothelial injury could be ideal candidates to stratify for this new treatment.

## **1.9 Conclusions**

Despite recent therapeutic advances, the treatment of juvenile myositides remains challenging. Current practise is mainly based on anecdotal experience and only recently consensus treatment protocols have been developed for the standardisation of treatment as a result of international efforts. Disease rarity and heterogeneity is the main obstacle in

conducting clinical trials. Corticosteroids remain the first line treatment followed by steroid sparing agents. In refractory cases, IVIG can be added, while in regards to biologic agents knowledge comes mainly from case series with the exception of rituximab.

Cyclophosphamide is emerging as a third line agent in more severe or refractory cases but toxicity should not be dismissed. Although, the overall prognosis of JDM has significantly improved over the recent years, a number of children with JDM still suffer significant complications and have a poor outcome highlighting the heterogeneity of the disease and the need of better understanding its pathophysiology. Vasculopathy is central to the severe extra-muscular manifestations of the disease, thus understanding the nature of vasculopathy and monitoring overtime may give insight to new therapeutic modalities such as JAK inhibitors and anti-complement agents. In conclusion, the use of targeted personalised treatment has been elucidated as the way forward.

#### **‘Compliance with Ethical Standards’**

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**Table 1. Biologic agents currently used in Juvenile Myositis**

<b>Medication</b>	<b>Mode of action</b>	<b>Administration</b>	<b>Doses</b>
Abatacept	Humanised selective T-cell co-stimulatory modulator	IV infusion over 30 min.	10mg/kg at 0,2,4 weeks, then every 4 weeks, max dose 1gr
Adalimumab	Humanized soluble anti-TNF monoclonal antibody	SC	24mg/m <sup>2</sup> up to 40 every 2 weeks
Infliximab	Chimeric human-murine anti-TNF IgG1 monoclonal antibody	IV infusion	6 mg/kg at 0, 2, 6 weeks, then every 4-8 weeks according to response
Rituximab	Chimeric anti-CD20 monoclonal antibody	IV infusion	750mg/m <sup>2</sup> on day 0-14 (given with 100mg methylprednisolone and often cyclophosphamide)
Tocilizumab	Humanised recombinant anti-IL-6 receptor monoclonal antibody	IV infusion	<ul style="list-style-type: none"> <li>• ≥30 kg: 8 mg/kg once every 2 weeks,</li> <li>• BW &lt;30 kg: 12 mg/kg once every</li> </ul>

			2 weeks,
BW, body weight; IV, intravenous; IL, interleukin; SC, subcutaneous; TNF, Tumour Necrosis Factor.			



