Juvenile dermatomyositis: novel treatment approaches and outcomes

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Purpose of review
The aim of this article is to provide a summary of the recent therapeutic advances and the latest research on outcome measures for juvenile dermatomyositis (JDM).

Recent findings
Several new international studies have developed consensus-based guidelines on diagnosis, outcome measures and treatment of JDM to standardize and improve patient care. Myositis-specific antibodies together with muscle biopsy histopathology may help the clinician to predict disease outcome. A newly developed MRI-based scoring system has been developed to standardize the use of MRI in assessing disease activity in JDM. New data regarding the efficacy and safety of rituximab, especially for skin disease, and cyclophosphamide in JDM support the use of these medications for severe refractory cases.

Summary
International network studies, new biomarkers and outcome measures have led to significant progress in understanding and managing the rare inflammatory myositis conditions such as JDM.

Keywords
advanced treatment, juvenile dermatomyositis, outcome measures

INTRODUCTION

Juvenile dermatomyositis (JDM) is a rare systemic autoimmune disease characterized by a vasculopathy that primarily affects muscle and skin, but may involve the lung, bowel, heart and other organs [1,2]. JDM is the most common inflammatory myopathy of childhood, affecting 1.9 cases per million children in the United Kingdom [3] and 2.4–4.1 cases per million children in USA [4]. In this review, we will summarize the recent developments in the clinical assessment, treatments and outcomes in JDM.

CLINICAL OUTCOMES AND CORE SET CRITERIA

International collaborations have been undertaken to unify and standardize assessments and treatments of rare diseases such as idiopathic inflammatory myositis (IIM). The Paediatric Rheumatology International Trials Organization (PRINTO) and the International Myositis Assessment & Clinical Studies Group (IMACS) initial preliminary response criteria considerably improved clinical assessment and therapeutic response of JDM patients, but were lacking in sensitivity and still presented several differences in the individual core set measurement [5–7]. To overcome these issues, these two international organizations joined forces and developed a new set of consensus-driven response criteria for adult dermatomyositis/polymyositis and children with JDM. This new tool is based on a continuous model, with a total improvement score of 0–100, and with different thresholds for minimal (≥30), moderate (≥45) and major (≥70) clinical response based on weighted scores applied to an absolute percentage improvement [8▪▪]. The core set measures were identified by consensus among expert paediatric and adult rheumatologists, neurologists and dermatologists, using the Delphi method. The agreed measures were the following: Physician global activity; Parent or Patient global activity; Manual Muscle testing

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KEY POINTS

- European and American study groups proposed a consensus for optimal dataset and criteria of minimal, moderate and major response to treatment in JDM.
- New consensus-based guidelines are available for diagnosis and management of children with JDM, and particularly with predominant skin disease and persistent skin disease.
- New autoantibody association, especially combined with muscle biopsy histopathology, and a new MRI scoring system may help the clinician with treatment choice and disease prognosis.

(MMT) or Childhood Myositis Assessment Scale (CMAS); Childhood Health Assessment Questionnaire; Muscle enzymes (creatine kinase, aldolase, alanine aminotransferase, aspartate aminotransferase and lactate dehydrogenase) or Physical Summary Score of the Child Health Questionnaire-Parent Form 50 and Extramuscular activity or Disease Activity Score (DAS). These new response criteria provide a quantitative measurement of disease improvement and resolve the differences between PRINTO and IMACS criteria, enabling an easier comparison between different datasets and facilitating future trials.

Another important step towards effective communication between different study groups by using standardized clinical data has been created by International Group of Experts (McCann *et al.* [9▪]), who have defined an optimal dataset for JDM to capture disease subphenotype, activity, comorbidity and damage over time. Both an international panel of experts took part in a Delphi process, but also parents and patients with JDM participated in the survey, enabling the group to highlight what patients and families feel are essential items of the clinical assessment in JDM, with good agreement with the healthcare professionals.

A recent large analysis of the EuroMyositis registry, which includes both adult and paediatric onset cases of all types of IIM has highlighted the differences between JDM and adult dermatomyositis and polymyositis, the former being less associated with interstitial lung disease and malignancy and having different skin disease characteristics [10].

Little is known regarding long-term outcome in JDM, but two recent studies shed some light on this extremely important aspect of care. Silverberg *et al.* [11] evaluated over 14 million hospitalization of patients with JDM over a 10-year period and showed significantly higher odds for cardiovascular and cerebrovascular comorbidities in this US cohort of patients, especially for girls and ethnic minorities. Ethnicity and lower family income were found to be associated with worse outcome, increased morbidity and decreased function in another large American cohort study [12]. A further study showed worse cardiovascular outcome in JDM patients (tested with a 6-min walk test, timed 'up and go' test, CMAS, echocardiography, lung function test, thoracic high resolution computed tomography scan and MRI and health-related quality of life questionnaire) with a mean of 17 years of disease history when compared with sex-match and age-match controls, especially those with active disease [13].

One of the ongoing challenges of the management of JDM has been identifying a reliable, practical tool to measure the skin disease. A prospective study tested the PRINTO proposed criteria for clinically inactive disease, which stated that at least three of four conditions should be met: creatinine kinase 150 U/l or less, CMAS at least 48, MMT of eight groups at least 78 and physician global assessment of overall disease activity 0.2 or less [14]. This analysis by Almeida *et al.* [15] showed the importance of incorporating the physician global assessment of overall disease activity as an essential criterion of clinically inactive disease, as this helps prevent the misclassification of patients with active skin disease. Subsequent to this study, the same study group tested three different skin scoring tools in JDM, the Myositis Intention to Treat Activity Index, abbreviated Cutaneous Assessment Tool and DAS and correlated them with the physician's 10-cm skin visual analogue scale (VAS). All three tools were easy and quick to use, and this study showed that the DAS best correlated with the physician VAS. However, all three skin tools had limitations, suggesting that future studies should design a new tool with all the strengths of the existing ones [16].

ANTIBODIES

Juvenile myositis is a highly heterogeneous disease ranging from profound muscle weakness and visceral involvement to normal muscle strength. In recent years, autoantibodies have been identified in 60–70% children with myositis and have been able to identify clinically homogeneous groups [17–21]. This concept has been recently further validated in a large study including 379 juvenile myositis patients, which confirmed that the myositis-specific autoantibodies (MSA) are exclusively found in children with IIM, and not in healthy children or patients with other autoimmune diseases (including arthritis or lupus) or muscular dystrophy. Therefore, this study suggested that the presence of MSA should be considered highly suggestive of the

diagnosis of myositis [19]. In this study-specific MSA such as anti-transcription intermediary factor 1-gamma (TIF1-γ) was shown to be associated with the use of more powerful medication; in addition, anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) and antisignal recognition particle (SRP) antibodies were also found in patients with profound muscle weakness and slow/poor response to treatment.

These findings will help the clinician to predict disease features and outcome and to guide the treatment. Furthermore, Deakin *et al.* showed that the severity of the muscle biopsy (defined using a standardized score tool), in combination with MSA subtype can predict the risk of remaining on treatment in patients with JDM. Surprisingly, children with anti-Mi2 antibody were associated with a better prognosis, despite the severity of the muscle biopsy in these cases, whereas in patients with anti-nuclear matrix protein (NXP-2), anti-TIF-1g, or no detectable antibodies, the biopsy score was predictive of the probability of remaining on treatment over time [22▪▪].

IMAGING

The use of MRI has played an increasingly important role to help clinicians with diagnosis and follow-up of children with inflammatory myositis, especially as it does not involve ionizing radiation. It helps with selection of the muscle biopsy site, and it is not invasive, unlike electromyography or muscle biopsy [23,24]. A recent study showed that where a flare was questioned, if the MRI showed active myositis, the physician would change or escalate treatment. This biomarker can be useful especially as up to 75% of patients suspected of having a flare had no abnormal muscle enzymes [25].

To date the use of MRI is not standardized and might differ significantly in different centres, for example in terms of which part of the body is assessed, which planes to perform, the protocol used, and the usefulness of intravenous contrast. To overcome these limitations, Thyoka *et al.* recently improved the previously published MRI-based scoring system for JDM initially developed by Davis *et al.* [26]. Nine paediatric radiologists with an interest in musculoskeletal imaging and two paediatric rheumatologists reviewed and modified the previously developed criteria and tested it on a set of MRI scans from 20 patients with JDM. The resulting new scoring system showed good interobserver reliability with no significant difference when using either the coronal or the axial planes. The study showed that various combinations of techniques can be useful, T1-weighted to assess muscle atrophy and T2-weighted/fat suppression or short TI inversion recovery (STIR) to visualize inflammatory changes of the skin and soft tissue oedema. The panel considered MRI of gluteal and thigh muscle optimal to assess disease activity and severity and, also, was more easily available than whole body MRI, and gadolinium contrast was not needed [27▪].

CONSENSUS TREATMENT PLANS

In recent years, several international efforts have been undertaken to achieve evidence-based guidelines with the aim to standardize outcome measures and management of children with JDM. The Single Hub and Access point for paediatric Rheumatology group has been working on harmonizing the care of paediatric rheumatology patients in Europe since 2012 and have recently published consensus-based recommendations for the management of JDM developed by an evidence-informed consensus process involving systematic literature review, online survey and final consensus meeting among 21 experts in paediatric rheumatology and physical therapy [28▪▪].

In parallel, the Childhood Arthritis and Rheumatology Research Alliance (CARRA) has developed consensus treatment plans for several paediatric rheumatologic diseases including juvenile localized scleroderma, systemic juvenile idiopathic arthritis (JIA), polyarticular JIA, lupus nephritis and JDM [29]. With respect to JDM, the CARRA group has recently proposed a consensus-based treatment plan for JDM with predominant skin disease consisting of three different options for the clinician: option A included hydroxycloroquine alone, option B included hydroxycloroquine and methotrexate and option C consisted of hydroxycloroquine, methotrexate and corticosteroids [30]. The same study group also proposed a consensus treatment plan for JDM with persistent skin disease despite the resolution of the muscle disease with three different plans: Plan A to add intravenous immunoglobulin (IVIG), Plan B to add mycophenolate mofetil and Plan C to add cyclosporine [31]. Continuation of previous treatments including corticosteroids, methotrexate and IVIG was allowed in Plans B and C. The next step in both studies will be to collect prospective data to understand which treatment option is the most effective.

ADVANCES IN TREATMENT

To date, only two randomized controlled trials were performed including JDM patients. These were the PRINTO trial which showed that corticosteroids and methotrexate were the most effective and safest treatment option in new-onset JDM when compared with prednisolone alone and prednisolone

and cyclosporine [32▪▪], and the Rituximab in Myositis trial which, although it did not meet its primary endpoint, showed an overall good response rate and ability to taper corticosteroids in adult and JDM [33]. In the same cohort of patients, the efficacy of rituximab in treating the cutaneous disease was subsequently assessed. The disease activity was evaluated using the cutaneous assessment of the Myositis Disease Activity Assessment tool and the damage using the Myositis Damage Index. In JDM, Rituximab treatment significantly improved skin disease activity, especially cutaneous ulcerations, erythroderma, heliotrope rash and Gottron's sign/papules. No major changes were seen among damage items, including calcinosis [34].

Cyclophosphamide is currently used to treat malignancy, systemic lupus erythematosus and vasculitis. Clinicians may be reluctant to give cyclophosphamide in JDM because of the lack of evidence and its side effects. Recently, the efficacy on skin, muscle and global disease activity of cyclophosphamide has been reported in 56 severe and refractory cases of JDM. The long-term side effects are still unknown but its short-term safety profile in this study is encouraging [35].

A combination of cyclophosphamide, IVIG and Rituximab has proven to be effective in anti-SRP myositis, a very rare inflammatory myopathy characterized by profound muscle weakness, raised creatinine kinase and no skin rash with a much improve outcome compared with the very little literature available [36]. The CARRA group in North America conducted a survey regarding the use of biologic agents in treating JDM which showed that biologics were used only for refractory cases of JDM with the general belief that these were effective in reducing complications, particularly calcinosis, and therefore were an appropriate step when corticosteroids, methotrexate and IVIG fail to control the disease. The most common biologics used were Rituximab, Abatacept, antitumour necrosis factor and Tocilizumab suggesting that these agents could be considered for future studies [37]. An anecdotal report described a successful use of Ustekinumab (human mAb against IL-12/23) in treating a case of juvenile amyopathic dermatomyositis with psoriasis and active skin disease [38]. An analysis of a large number of JDM patients treated with tumour necrosis factor blockade, to date published in abstract form, suggests efficacy of blocking tumour necrosis factor for severe cases of JDM [39].

FUTURE TREATMENT OPTIONS

Promising options are coming from the world of adult dermatomyositis, including a randomized control trial of Infliximab in 12 refractory polymyositis and dermatomyositis which showed some benefit and good safety profile [40]. Another randomized control trial concluded that 50% of patients with adult dermatomyositis and polymyositis treated with Abatacept had lower disease activity [41]. In addition, Rituximab has been successful in improving respiratory symptoms and lung function tests, but also in reducing the daily corticosteroid dose in refractory progressive interstitial lung disease in anti-melanoma differentiation-associated protein 5 (MDA5)-positive amyopathic dermatomyositis, infection was the main side effect reported [42].

CONCLUSION

In conclusion, in the recent years several international efforts have achieved important goals with the ultimate aim to harmonize and standardize the management of children with juvenile inflammatory myopathies. Collaborative networks are essential to facilitate research in rare diseases and provide evidenced-based treatments for JDM.

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Conflicts of interest

There are no conflicts of interest.

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- ▪ of special interest
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