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Juvenile dermatomyositis: new developments in pathogenesis, assessment and treatment[☆]

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Juvenile dermatomyositis (JDM) is a rare, potentially life-threatening systemic autoimmune disease primarily affecting muscle and skin. Recent advances in the recognition, standardised assessment and treatment of JDM have been greatly facilitated by large collaborative research networks. Through these networks, a number of immunogenetic risk factors have now been defined, as well as a number of potential pathways identified in the aetio-pathogenesis of JDM. Myositis-associated and myositis-specific autoantibodies are helping to sub-phenotype JDM, defined by clinical features, outcomes and immunogenetic risk factors. Partially validated tools to assess disease activity and damage have assisted in standardising outcomes. Aggressive treatment approaches, including multiple initial therapies, as well as new drugs and biological therapies for refractory disease, offer promise of improved outcomes and less corticosteroid-related toxicity.

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Introduction

Juvenile dermatomyositis (JDM) is a rare, serious autoimmune condition of childhood involving a systemic small vessel vasculopathy, which typically affects skin and muscle, but can also involve the joints, gut, lung, heart and other internal organs. JDM is the most common of the idiopathic inflammatory myopathies (IIMs) of childhood and therefore is the focus of this review. Other paediatric IIMs, and also the parallel adult conditions, are referred to for comparison with their common features, where appropriate. Increasing evidence suggests that early aggressive management of JDM improves outcome, while conversely, a long duration of untreated disease is associated with longer time to reach remission and higher rates of complications such as ongoing skin disease or osteoporosis [1,2]. Therefore, the recognition, prompt referral to specialist care, and early treatment, of patients with JDM are of paramount importance.

JDM: incidence and diagnostic criteria

The incidence of JDM is between two and three children per million per year, with some differences between ethnic groups [3,4]. JDM is more common in girls than in boys, by a ratio of approximately 2.3:1 [4,5] although some reports suggest that this ratio may be lower in younger age groups [6]. The mean age of onset of JDM is just over 7 years; however, a recent report of 286 patients showed that 25% of cases present when less than 4 years of age [7], and some specialists suggest that young age of onset is associated with poor prognosis.

Clinical features are central to the diagnosis of JDM, the most frequent being the characteristic heliotrope rash and Gottron's papules over the extensor surfaces, and proximal muscle weakness. A wide range of other features may be present early in the course of disease [8], making the design of diagnostic criteria which are comprehensive, yet not too complex or unwieldy, difficult. In a study from a UK Registry including data on 151 children, 81% of cases had one or more 'systemic' symptoms at presentation, which included fever, malaise anorexia, weight loss, irritability or abdominal pain [5]. At present, the most widely used set of criteria remain those defined by Bohan and Peter in 1975 [9], which require the presence of one of the characteristic rashes, combined with three of the following features, for definite JDM: symmetric proximal muscle weakness, raised serum muscle enzymes (which may include creatine kinase (CK), transaminases, lactate dehydrogenase (LDH) and aldolase) and abnormal findings on muscle biopsy and electromyography (EMG). The presence of the rash with two of these features make a diagnosis of probable JDM. These criteria, now over 30 years old, no longer reflect modern diagnostic investigation of suspected cases of JDM. Although magnetic resonance imaging (MRI) findings are not part of the Bohan and Peter criteria, MRI is now widely used to detect typical inflammatory changes in proximal muscles, and quantitation of such changes has been shown to correlate with disease activity [10]. In an international survey of 118 clinicians from 92 centres caring for children with JDM, the routine use of EMG and muscle biopsy were found to be as low as 56% and 61%, respectively [11], primarily due to the consideration that these are invasive procedures. Until recently, there has been no standardised system for assessment of muscle biopsy tissue for JDM, resulting in the information obtained dependent on local expertise. A recent international consensus working group on JDM biopsy has proposed a score tool, which may improve routine assessment of JDM muscle biopsy tissue [12]. Muscle biopsy remains a critical investigation, especially in the absence of the characteristic rashes and where differential diagnoses such as genetic or metabolic myopathies are being considered.

A large international collaborative group, the International Myositis Assessment and Clinical Studies Group (IMACS) recently proposed that the Bohan and Peter criteria should be used for inclusion in therapeutic trials [13]. An international collaborative effort is now underway to revise criteria for the classification of IIM in both adults and children (<http://www.niehs.nih.gov/research/resources/collab/imacs/classificationcriteria.cfm>).

Aetiology and pathogenesis of JDM

While the aetiology of JDM remains unclear, the working hypothesis is that this involves environmental triggers, immune dysfunction and specific tissue responses (in particular those of muscle, skin and small vessel endothelium) in genetically susceptible individuals. Recently, there have been considerable advances

in our knowledge of genetic risk factors for a number of autoimmune conditions. These are complex polygenic disorders, in which variation at many genetic loci may contribute to susceptibility. It is known that several genes confer risk for an 'autoimmune' phenotype as a whole [14]. Until recently, the lack of large collections of genetic material linked to carefully phenotyped myositis patients hampered progress in this area. However, the past few years have seen enormous growth in multicentre collections and registries [4,5,15,16] as well as the establishment of an international genetics consortium in myositis, MYOGEN.

The human leucocyte region (HLA), which lies within the major histocompatibility complex (MHC), is one of the most highly polymorphic regions of the human genome, carrying alleles associated with increased risk for many autoimmune diseases, including JDM. Thus, HLA-B*08, DRB1*0301 and DQA1*0501 are part of an extended ancestral haplotype that confers risk of myositis in both adults and children in Caucasians [17–20]. Recent work has shown that HLA-DPB1*0101 also confers independent risk of myositis in both adults and children, in particular serological subgroups [21], and that the DQA1*0301 allele is an additional risk factor for JDM [19]. Caucasian patients with JDM also have several protective alleles, including DQA1*0201, DQA1*0101 and DQA1*0102 [19], which are less frequent in affected patients than in healthy controls and may mechanistically contribute to disease development through binding of self-reactive antigens and the elimination of self-reactive T lymphocytes from the thymus. Several other polymorphic loci have been shown to be risk factors for JDM, including the pro-inflammatory cytokine genes TNF α [16,22], IL-1 α and IL-1 β [16], the lymphocyte signalling gene PTPN22 [23] and phenotypes of the immunoglobulin heavy chain [24]. The TNF α variant known as TNF308A carries a higher risk of calcinosis and ulcerations [16,22], and in controls, this genotype is associated with higher levels of TNF production [25]. The TNF308A effect may be independent of the HLA-DRB1 locus, but may be in part due to linkage disequilibrium with the HLA-B locus [26]. An IL-1 polymorphism confers additional risk for the development of calcinosis [16].

Environmental factors associated with onset of JDM have been infrequently studied. A high frequency of symptoms consistent with infection within a few months prior to onset, have been reported in large cohorts and one case-controlled study [7,27]. Searches for infectious agents, including parvovirus and enteroviruses, have been negative in case-controlled studies [28,29]. Seasonality in birth distribution in certain subsets of disease, including Hispanic patients, those with a myositis autoantibody known as the p155/140 autoantibody, and those with the HLA-DRB1*0301 risk allele, suggest a role for perinatal environmental factors in the onset of illness later in childhood [30]. Anecdotal reports of JDM onset after exposure to drugs, biological therapies, vaccines and ultraviolet light also exist [31]. Additional case-controlled studies, including examination of non-infectious environmental factors, are needed to identify environmental risk factors for JDM.

Autoantibodies are common in JDM, and can be divided into two categories: myositis-specific antibodies (MSAs), typically directed at cytoplasmic or nuclear components involved in protein synthesis (such as the aminoacyl-tRNA synthetases) and nuclear transcription, which are relatively specific for myositis or subtypes of disease; and myositis-associated antibodies (MAAs), which are also found in other autoimmune conditions and overlap syndromes (Table 1). Approximately 70% of children with JDM have one or more detectable MSA or MAA if full serological testing is used [20,32], although the frequency of different antibodies differs in different ethnicities [24]. Clinical associations of such autoantibodies parallel those seen in adult disease in some cases, such as the association of anti-PM-Scl with sclerodermatous features, anti-Jo-1 with interstitial lung disease and other extra-muscular features, anti-SRP with severe polymyositis and anti-Mi-2 with classic DM rashes and milder disease [20,31,33]. From several studies in myositis, it has become clear that certain genetic risk alleles are associated with specific autoantibody phenotypes, and that these associations hold true across age groups in both adults and children. For example, the HLA-DRB1*03-DQA1*05-DQB1*02 haplotype is increased in patients with anti-PM-Scl autoantibody, the HLA-DRB1*04-DQA1*03-DQB1*03 haplotype with anti-U1-RNP autoantibody [20] and HLA-B*08-DRB1*0301-DQA1*0501-DPB1*0101 (as part of the ancestral haplotype) is associated with anti-Jo-1 autoantibody [21,34].

In addition to the well-characterised autoantibodies, several new specificities have recently been defined in JDM. An autoantibody to a 155-kDa protein, in most cases associated with a second weaker 140-kDa band, now known as anti-p155/140, has been shown to be present in sera of 23–29% of JDM cases and to associate with risk of more severe skin involvement and generalised lipodystrophy [35–37]. In adults, this anti-p155/140 autoantibody is associated with cancer-associated

Table 1

Myositis specific autoantibodies (MSAs) and Myositis associated autoantibodies (MAAs) in patients with JDM.

Autoantibody	Autoantigen target	Frequency in Caucasian patients ^a %	Clinical features and associations in JDM
MSAs			
Anti-ARS:	Aminoacyl-tRNA synthetases ^a :	1–5	Typically associated with those with moderate to severe weakness, may have arthritis, mechanics hands, Raynaud's, fevers, interstitial lung disease
Anti-Jo-1	Histidyl-tRNA synthetase	2–5	
Anti-PL-12	Alanyl-tRNA synthetase	1–3	
Anti-PL-7	Threonyl-tRNA synthetase	<1	
Anti-EJ	Glycyl-tRNA synthetase	<1	
Anti-OJ	Isoleucyl-tRNA synthetase	<1	
Anti-KS	Asparagynyl-tRNA synthetase	NA	
Anti-Ha	Tyrosyl-tRNA synthetase	NA	
Anti-Zo	Phenylalanyl-tRNA synthetase	NA	
Other MSAs			
Anti-Mi-2	DNA Helicase	~5	Classical cutaneous JDM
Anti-SRP	Signal recognition particle	1–3	Associated with severe, refractory polymyositis
Recently-Identified Myositis Autoantibodies:			
Anti-p155/140 or Anti-p155	Transcriptional intermediary factor (TIF)-1 gamma protein	23–29	More severe cutaneous involvement, generalized lipodystrophy
Anti-p140 (MJ)	Thought to be the MJ autoantigen, nuclear matrix protein NXP2	13–23	Associated with calcinosis, contractures
MAAs			
Anti-U1-RNP	U1 ribonucleoprotein (snRNP)	~6	Associated with sclerodermatous overlap features
Anti-U3-RNP	U3 ribonucleoprotein (fibrillarin)	~1	Associated with sclerodermatous overlap features
Anti-PM-Scl	Nucleolar multi-protein complex	5–7	Associated with sclerodermatous overlap features
Anti-Ro	52 or 60Kd ribonucleoproteins (hYRNA)	~2	
Anti-La	Ribonucleoprotein	~1	
Anti-Ku	p70/p80 heterodimer, DNA-associated proteins	~1	
Anti-Topo	DNA Topoisomerase 1	1	

Based on data from references[20,24,32,35,36,38,101].

NA- not available as data not yet reported in cohorts of JDM patients.

^a Frequencies quoted are from data in Caucasian patients; however frequencies vary considerably in different ethnicities. Notably certain autoantibodies which are higher in African American patients include anti-Jo1, anti-SRP, anti-Ro and anti-URNP [24].

dermatomyositis, but no such link has been seen in JDM. A second novel autoantibody known as anti-p140 has been demonstrated in the sera of 23% of JDM patients and is associated with a higher risk of calcinosis than patients who do not have anti-p140 autoantibody [38]. It is also of note that in a study of autoantibodies in 114 JDM cases, many ANA-positive cases had no identifiable known autoantibody, suggesting that further novel antibodies in JDM await identification [20].

Genetic variants and autoantibodies, or a combination of both, may prove useful to generate predictors of clinical phenotypes or disease course in juvenile myositis. In addition, some evidence has suggested potential roles for autoantibodies in the pathogenesis of myositis. Autoantigens to which MSA are directed may be up-regulated in inflammatory myopathy muscle biopsies, particularly in regenerating myoblasts [39]. Some of these same autoantigens are themselves chemoattractant to immune cells [40] and interestingly, a study in adult myositis recently showed that immune complexes of anti-Jo-1 or anti-Ro 52/anti-Ro60 autoantibodies can induce type I interferon production [41], a cytokine already linked with JDM pathogenesis [42,43].

In attempts to understand underlying mechanisms of muscle weakness and tissue damage in myositis, analysis of muscle biopsy tissue has been important. Typical features of JDM biopsies include inflammatory changes, classically lymphocytic infiltration in a perivascular pattern, and/or myeloid cell infiltration in a scattered distribution, muscle fibre MHC class I protein overexpression, endothelial and small vessel abnormalities (with complement C5-9, and/or immunoglobulin deposition), muscle fibre regeneration or necrosis and fibre atrophy. The consensus group on JDM biopsy proposed a system by which to score features and severity on JDM biopsy, using four domains: inflammatory, vascular/endothelial changes, muscle fibre abnormalities, including staining for MHC class I overexpression and connective tissue changes [12]. Prospective testing of the power of this tool to predict disease features is underway, while a retrospective study using a related scoring system suggested that arteriopathic changes and capillary loss are correlated with a more chronic disease course [44].

Typical changes on JDM biopsy of endothelial dysfunction and depletion of capillaries, combined with clinical features suggestive of small vessel angiopathy such as gut involvement and perforation, led to the proposal that JDM is a small-vessel vasculopathy [45]. Antibody deposition and complement activation likely contribute to endothelial dysfunction and damage in both muscle and involved skin. The endothelium within affected muscle itself produces immune mediators such as IL-1 and other cytokines [46] as well as enhances inflammation through up-regulated adhesion molecules ICAM-1 and VCAM [47]. Activated endothelium is also an important binding site for chemokines, which then attract inflammatory cells, and also influence blood vessel physiology and angiogenesis. JDM muscle shows an excess of angiostatic chemokines (so called ELR- chemokines) such as IP-10 (CXCL10) which may contribute to endothelial damage and vasculopathy [48], and a study using gene expression profiling indicated dysregulation of both angiogenesis and angiostasis in JDM [49]. Inflammatory cells (T and B lymphocytes, dendritic cells and macrophages) are important sources of cytokines (including TNF α and IL-1) and chemokines within the muscle. There is mounting evidence for an important role for type I interferons in both JDM and adult DM pathology [42,50], for which a major source is thought to be activated dendritic cells (DCs), in particular the plasmacytoid DCs, which are present within the muscle [51]. Plasmacytoid DCs also secrete chemokines, which may contribute to lymphocytic aggregates, typically perivascular, that have been suggested to associate with a more severe disease course [52]. In addition to inflammatory cells originating from the child, there is evidence that cells of maternal origin are also present in the peripheral blood and muscle inflammatory infiltrates of JDM patients (so-called microchimaerism). Microchimaeric cells are more common in children with JDM than their healthy siblings and may contribute to a 'graft-versus-host'-like process in several autoimmune conditions [53].

Many of the cytokines that are shown to play a role in JDM, in particular interferons and TNF α , would contribute to the upregulation of class I MHC proteins on muscle fibres, a change that frequently occurs early in the disease, when the muscle architecture is otherwise relatively unremarkable, and as such is a useful addition to pathological analysis [54]. It is not clear how alteration of MHC class I affects function although evidence suggests that it may induce ER stress in muscle fibres. However, in a transgenic model, where self-MHC is over-expressed selectively in skeletal muscle, mice become weak and develop autoantibodies that mimic human MSA [55]. In muscle fibres isolated from this model, the muscle is already weak as early as 2 weeks after MHC overexpression [56]. A recent adaptation of this model in very young mice, designed to mimic JDM, demonstrated that young skeletal muscle is particularly vulnerable to the insult afforded by class I MHC overexpression [57].

New approaches to the assessment of JDM

Through international collaboration among myositis experts (IMACS) and paediatric rheumatologists (the Paediatric Rheumatology International Trials Organization, PRINTO), two parallel processes have been used to develop core set measures for JDM. IMACS and PRINTO, despite some differences in their approaches, developed core set measures of disease activity for JDM that are remarkably similar and include measurement of global activity, muscle strength and physical function (Table 2). In the case of IMACS, extra-muscular activity and laboratory enzymes are also included in the core set, whereas in the PRINTO core set, a global activity assessment tool and health-related quality of life measure are included instead [58,59]. To derive the core set of activity measures, IMACS reviewed data on the performance and validity of various measures in studies and trials of treatment-refractory patients, followed by a consensus

approach that combined both nominal group technique (NGT) and a Delphi process. A consideration in the IMACS process was the availability and applicability of these measures to both juvenile and adult myositis. PRINTO, in contrast, undertook a consensus approach first on which measures to include in a provisional core set, followed by prospective validation in a multicentre study of recent-onset JDM patients, examining each measure's responsiveness and, in some cases, their construct validity, internal consistency and discriminant validity [60]. The main change to the final PRINTO core set was a deletion of serum muscle enzymes due a lower responsiveness, and a decrease in internal consistency with the inclusion of serum CK; nevertheless, reporting of serum muscle enzymes is still recommended.

IMACS subsequently developed a composite clinical endpoint for therapeutic trials that combines the core set measures, based on consensus ratings of improvement in paper patient profiles, the performance characteristics of various definitions of improvement and consensus formation using NGT based on their face validity [61]. The top candidate definition of improvement for JDM requires improvement of at least 20% in three of six core set measures, with no more than two measures allowed to worsen (which cannot be muscle strength). PRINTO has preliminarily confirmed this approach in a separate consensus process, with their top candidate definition of improvement requiring 20% improvement in at least three core set measures, allowing for no more than one to worsen, which cannot be the Childhood Myositis Assessment Scale (CMAS) [60,62,63]. The differences in these definitions of improvement may relate to differences in responsiveness between a recent-onset versus refractory JDM populations, from which these outcome measures were derived. These definitions of improvement are being prospectively tested and validated in a number of therapeutic trials in both juvenile and adult myositis, and further refinement of these is anticipated.

Several tools for assessment of skin disease in JDM have been developed and partially validated. The Cutaneous Assessment Tool (CAT) was developed for assessment of skin activity and damage in juvenile and adult myositis, by assessing activity in ten lesions, damage in four lesions and a combination of activity and damage in seven lesions, using an *a priori* weighting scale to determine severity in each lesion. This tool has been partially validated in a large JDM population and demonstrated good rater-reliability, content and construct validity and responsiveness [64,65]. An abbreviated method of scoring this tool performs similarly to the longer instrument [66]. An online photo essay of skin involvement in the IIM is now available, and is of educational value in improving recognition of the spectrum of cutaneous disease associated with JDM [67]. The Disease Activity Score (DAS) for JDM also includes assessment of skin involvement and distribution, has good reliability and is detailed in the assessment of vasculopathic features of skin disease, with a moderate correlation with periungual nailfold capillary changes [68,69]. Persistent skin rashes and nailfold capillary abnormalities are thought to indicate continuing active disease, and therefore their assessment is of great importance. Persistent nailfold capillary changes are associated with a chronic (non-unicyclic) disease course [2]; in a small pharmacokinetic study, poor oral absorption of prednisolone correlated with end row loss of nailfold capillaries, suggestive of gut vasculopathy [70]. Several tools to assess skin disease in adult DM have also been proposed; these include the Dermatomyositis Skin Severity Index (DSSI) modified from the Psoriasis Area and Assessment Index (PASI) [71] and the Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI) [72]. Calcinosis, also felt by some specialists to indicate continuing disease activity, is also an important cause of morbidity in JDM and therefore important to assess.

In terms of health-related quality of life, the Child Health Questionnaire (CHQ) has been examined in a large multicentre cohort by PRINTO, comparing physical and psychosocial components with healthy children [73]. Physical dysfunction scores on the CHQ most related to functional disability, parent's global assessment of well-being and ALT levels, while psychosocial well-being was most strongly associated with muscle strength and physical dysfunction.

The Myositis Damage Index is a modification of the Systemic Lupus International Collaborative Clinics (SLICC)/American College of Rheumatology (ACR) Damage Index with the intention of comprehensively assessing the extent of damage in different organ systems and the severity of damage using a series of visual analogue scales. Preliminary validation studies of the Myositis Damage Index in two large referral populations of juvenile myositis patients suggest that the majority of patients develop damage after several years of illness. Cutaneous scarring or atrophy was present in 30–40% of patients, joint contractures in 17–30%, calcinosis in 22–26%, persistent muscle dysfunction or weakness in 11–30% and persistent dysphagia and dysphonia in 5–20% of patients in these cohorts, with an

average of 2–6.8 years of follow-up from diagnosis [74,75]. In a recent report of 67 JDM patients, who were followed into adulthood (median time from diagnosis 16.8 years), a high number of individuals still had high disease activity and damage scores, with active disease present (defined as DAS >3) in 61% patients and Myositis Damage Index scores >1 in 90% [76]. However, this cohort would have received initial treatment on average 16 years ago when regimens were very different from current practice, and thus may not be reflective of the current JDM disease course.

Complications associated with JDM require specialised investigation. Many of these may be present at presentation or early in the course of the disease. Thus, severe features such as speech and swallowing changes require assessment by videofluoroscopy [77], and lung CT scanning is required where pulmonary involvement is suspected. While generalised and partial lipodystrophy are seen as a complication of JDM that is associated with insulin resistance and hyperlipidaemia [37], some JDM patients without lipodystrophy also have a number of risk factors for later development of cardiovascular disease, such as frequent insulin resistance, hypertriglyceridaemia and the metabolic syndrome, including elevated body mass index and systolic blood pressure [78]. Insulin resistance is correlated with thigh muscle atrophy, pro-inflammatory peripheral blood cytokines and a family history of diabetes but not with corticosteroid dose.

In the assessment of individual patients, serum levels of muscle enzymes may be helpful in determining ongoing active disease, but may also be normal or near normal, particularly with longer disease duration, and often do not reveal active disease in organ systems outside the muscles. MRI at selected therapeutic junctures can be helpful to visualise activity outside of the muscles in the skin, subcutaneous tissue or myofascia, which often does not correlate with muscle activity [79]. To better determine occult disease activity, a number of immunological biomarkers appear promising, including phenotypes of peripheral blood mononuclear cells assessed by flow cytometry, measures of endothelial cell activation and macrophage activation markers including neopterin and quinolinic acid [80]. Newer markers including IFN α , and downstream targets of IFN α , or IL-17- and IFN-regulated genes, are all under investigation, and may prove to be sensitive markers of disease activity [50,81].

Evolving treatment paradigms

The mainstay of treatment for JDM remains high-dose daily oral corticosteroid therapy, along with adjunctive steroid-sparing immunosuppressive therapies, which are used to treat disease activity, prevent mortality and attempt to reduce long-term disability and calcinosis. Several reviews on the medical treatment of JDM provide detailed information on the uncontrolled retrospective reports and open-label prospective case series that have led to the treatment paradigm currently most widely used (Table 3) [31,82]. Initial drug treatment can be safely combined with early physical therapy, and a study using MRI pre- and post- exercise showed no evidence of muscle damage in children with JDM who underwent an exercise programme [83].

Emerging data, albeit open-label and based on comparison to a historic reference group, suggests that introduction of agents beyond oral corticosteroids as part of the initial therapy, including methotrexate and pulses of intravenous methylprednisolone (ivMP), and with additional therapy for inadequate responders, may shorten the course of illness, reduce calcinosis, reduce the likelihood of flare later in the course of the illness and increase the chance of remission [84,85]. Early introduction of methotrexate (preferably given subcutaneously), alone or in conjunction with additional agents, may also be associated with reduced corticosteroid toxicity, including less weight gain, better growth velocity in the first year of treatment and reduced cataract formation, with an overall reduction in the duration and cumulative dose of corticosteroids [86]. IvMP (10–30 mg/kg/dose, maximum 1 g) is also often used as part of first-line therapy for JDM, with a goal of obtaining more rapid control of symptoms and reducing the toxicity associated with high-dose daily oral corticosteroids. The bioavailability of ivMP may be better than that of oral prednisone, particularly in patients with vasculopathy evidenced by reduced periungual nailfold capillary density [70]. A comparison of high-dose corticosteroid therapy (ivMP 30 mg/kg/day or oral prednisone 5–30 mg/kg/day at diagnosis) compared to standard dose therapy (1–2 mg/kg/day daily oral prednisone) in a matched propensity score analysis adjusted for differences in illness severity and factors that determined treatment revealed no difference in outcome at 36 months, except the group treated initially with high-dose intravenous therapy had higher levels

Table 2

Comparison of proposed sets of measures for disease activity in juvenile dermatomyositis, from two international collaborative efforts.

	IMACS	PRINTO
Domain	All IIM, including JDM	JDM
Physician assessment	Physician global assessment of disease activity by visual analogue scale (VAS) or Likert scale	Physician global assessment of disease activity by visual analogue scale (VAS) or Likert scale
Patient/parent assessment	Patient/parent global assessment of disease activity using by visual analogue scale (VAS) or Likert scale	Patient/parent global assessment of overall well being using by visual analogue scale (VAS) or Likert scale
Muscle strength	MMT	MMT, CMAS
Functional ability	CHAQ or CMAS	CHAQ
Laboratory measurement	At least two of CK, LDH, aldolase, ALT, AST	Not included in the final core set, but recommended to be reported: CK, LDH, aldolase, ALT, AST
Global disease activity tool	Not included	DAS or MDAAT
Extra-muscular disease activity	MDAAT	Not included
Health-related QOL	Not included; measured separately	CHQ Physical Summary score

PRINTO, Paediatric Rheumatology International Trials Organisation; IMACS, International Myositis Assessment and Clinical Studies Group; IIM idiopathic inflammatory myopathies; JDM, juvenile dermatomyositis; VAS, visual analogue scale; MMT, manual muscle testing; CMAS, Childhood Myositis Assessment Scale; CHAQ, Childhood Health Assessment Questionnaire; CK, creatine kinase; LDH, lactate dehydrogenase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DAS, Disease Activity Score; MDAAT, Myositis Disease Activity Assessment Tool, which combines the MYOACT (Myositis extra-skeletal muscle disease activity assessment by VAS) and the MITAX (Myositis intention to treat activity index) tools; QOL, quality of life; CHQ, Child Health Questionnaire. Modified from references [58–62].

of serum muscle enzymes [87]. Limitations of this analysis include that the most ill patients were treated with high-dose ivMP and excluded from analysis, and the propensity score analysis may not adjust for all of the factors that determined the initial selection of therapy, or for therapies used after the initial treatment period.

Table 3

Therapeutic Options for Juvenile Dermatomyositis.^a

First Line Therapies^a
Prednisone 1–2 mg/kg/day po
Intravenous Methylprednisolone 10–30 mg/kg/pulse
Methotrexate 0.4–1 mg/kg/week, or 15 mg/m ²
Adjunctive therapies:
Hydroxychloroquine 3–6 mg/kg/day po
Physical therapy
Photoprotective measures
Topical therapies for skin rashes
Calcium and vitamin D for bone protection
Second Line Therapies
Intravenous gammaglobulin 1–2 gm/kg/month
Cyclosporine 2.5–7.5 mg/kg/day po divided bid
Azathioprine 3–5 mg/kg/day
Combinations of the above
Third Line Therapies
Cyclophosphamide 500–1250 mg/m ² /month intravenous pulse
Mycophenolate Mofetil 30–40 mg/kg/day po divided bid
Tacrolimus 0.1–0.25 mg/kg/day po divided bid
Rituximab
Anti-tumor necrosis factor alpha agents
Combinations of the above

^a Agents as first-line therapies are among those most often used in the initial treatment of JDM, whereas second and third-line therapies are most often used in the treatment of refractory patients, patients considered to have severe features, or patients with unacceptable medication toxicities, that are supported by at least one publication in patients with JDM. The order in which therapies or combinations of therapies are used is not implied by the listing in this table.

Additional studies are in progress that may help guide clinicians on the choice of initial therapy. PRINTO is currently conducting a randomised controlled trial to compare prednisone alone versus prednisone in combination with methotrexate versus prednisone in combination with cyclosporine as initial treatments for JDM (<http://www.printo.it>). CARRA (Childhood Arthritis and Research Alliance based in North America) is developing consensus protocols for initial therapy of patients with moderate-to-severe JDM, that include combinations of prednisone, methotrexate, ivMP with or without intravenous gammaglobulin (IVIg). In a number of open label studies, both retrospective and prospective, IVIg appears beneficial for JDM patients with refractory disease, resulting in decreases in skin and muscle activity and reduction in corticosteroid dosage, and is thought to be particularly helpful in patients with rapidly progressing disease, including dysphagia [31].

For patients with severe, refractory or corticosteroid-dependent disease, combinations of second-line therapies or the addition of newer therapies are now frequently used. An open label study of IV monthly pulse cyclophosphamide administered to severe or treatment-refractory JDM patients demonstrated significant improvements in core set myositis activity measures (including muscle strength, function, extramuscular activity, enzymes and global activity) in 10 of 12 patients after 6 months [88]. Many of these patients notably had severe complications, including severe weakness, dysphagia, skin or gastrointestinal ulcerations or central nervous system disease that improved after the initiation of therapy. Complications of therapy included transient lymphopenia, herpes zoster and alopecia. Anecdotal open-label reports, primarily in adult patients, support the use of mycophenolate mofetil for patients with severe disease, with improvement in strength, skin disease, muscle enzymes and an ability to reduce corticosteroid dose in the majority of patients [89]. Side effects in adult patients have included B-cell lymphoma, elevated hepatic enzymes and urinary tract symptoms, which resolved upon discontinuation of the drug. Seven treatment-refractory JDM patients improved in their skin and muscle DAS after receiving mycophenolate mofetil in an open-label study. The major side effect was upper respiratory infections [90]. Use of oral tacrolimus receives some support from open-label studies in adult IIM patients with treatment-refractory disease, the majority of whom improved [91]. In three patients with refractory JDM treated with tacrolimus, all improved their skin disease, global disease activity, physical function and were able to reduce corticosteroid therapy, and the medication was well tolerated [92].

Biological therapies are beginning to emerge for the treatment of myositis, supported to date primarily by open-label studies. Anecdotal case series and small open-label trials suggest favourable responses to rituximab, a monoclonal antibody directed against B lymphocytes, in patients with severe, refractory disease, with a high frequency of response overall. In the first publication piloting rituximab in seven refractory adult DM patients, all patients had a response commencing 4–12 weeks after the infusions that paralleled depletion of peripheral blood B lymphocytes (4 weekly infusions of 100 mg/m² or 375 mg/m²), with a maximal response at 12–36 weeks, and duration of effect lasting 24 to more than 52 weeks, often, but not always, paralleling the return of circulating B cells [93]. In four patients with refractory JDM, three achieved marked clinical responses and one experienced disease worsening [94]. In one study of refractory adult DM, little improvement in skin disease was noted [95]. The results of a large randomised controlled trial of rituximab in JDM and adult DM/PM (the Rituximab in Myositis study, RIM), which uses a randomised placebo-phase design, are anticipated. While infusion-related adverse events are most frequent, rare serious adverse events reported following rituximab treatment include infections, cardiotoxicity, progressive multifocal leukoencephalopathy and intestinal perforation [96].

Responses to the anti-tumour necrosis factor alpha agents in the IIM have been mixed. In a series of five severe JDM cases treated with infliximab (3 mg/kg), all five improved after 8–30 months, measured by improvement in core set measures, and in some cases in calcinosis, with no serious side effects reported [97]. An open-label study of etanercept in 10 treatment-refractory JDM patients demonstrated minimal improvement in muscle and no improvement in skin disease activity [98]. Responses to infliximab and etanercept have varied in adult DM/PM, with disease progression in some patients [99].

Newly available biological therapies such as CAMPATH-1H or a monoclonal antibody directed against IFN α , that appear promising in the treatment of inclusion body myositis or other immune-mediated diseases, have not undergone formal testing in patients with juvenile myositis. Stem cell

transplantation has been successfully used in a few patients with severe, refractory JDM [100] and is suggested as a final option for severe unremitting disease.

Practice points

- The optimal recognition, detailed full assessment, and treatment, of children with JDM requires specialist multidisciplinary teams, working in centres with experience with this group of rare and serious conditions.
- Standardised approaches to assess JDM disease activity include a combination of measures to assess overall disease activity and damage, muscle weakness, functional disability, laboratory findings and extra-muscular activity, including the skin.
- Although controlled evidence is frequently lacking for treatment in JDM, a number of studies confirm the value of aggressive treatment, with the aim to induce stable remission early, and thereby reduce steroid use and prevent disability and complications.
- New and combined treatment regimens, including new disease modifying agents and biological therapies, are now in use for refractory JDM in many centres.
- New insights into pathogenesis, myositis-associated autoantibodies and genetic risk factors are generating novel ways to assess patients with JDM, and are likely to provide predictive biomarkers that may aid in the diagnosis or ongoing assessment of disease activity.

Research agenda

- New criteria based on clinical features and commonly used tests are needed to better diagnose and classify patients with JDM and other idiopathic inflammatory myopathies.
- Whole genome scanning approaches using large multi-centre collections of detailed clinical data and biological samples should enable the identification of a number of new genetic risk factors for JDM and possibly genetic severity factors.
- Several new autoantibodies have recently been identified as being common in JDM and may associate with risk of specific clinical features, outcomes and even pathogenesis.
- Recent data implicating new mechanisms of pathogenesis in JDM, such as type I interferons or upregulation of Class I MHC may provide novel therapeutic targets.
- Refinements in the combinations of core set measures to determine clinically significant improvement, as well as criteria for worsening or flare of disease, will aid in the assessment of novel therapies.

Conclusion

While the causes of JDM remain elusive, recent insights into genetics, autoantibodies, immune attack mechanisms and muscle response to injury all suggest mechanistic pathways which contribute to the pathology of JDM, both within muscle and also in other affected tissues. The standardised assessment of disease activity and damage in JDM has also led to the testing of new therapeutic agents. An initially aggressive approach with combination therapies as part of the early therapy of JDM may result in better long-term outcomes, including the possibility of less calcinosis, fewer corticosteroid side effects and a higher frequency of inactive disease, although these findings need to be confirmed in controlled studies and with long-term follow-up data. A number of disease-modifying drugs and new

biological therapies are emerging as therapeutic options for patients with refractory disease. The challenge now is to translate research findings on new aspects of pathogenesis into novel therapeutic strategies for those children who do not respond well to conventional management.

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