

# Juvenile Dermatomyositis

## Advances in Pathogenesis, Evaluation, and Treatment

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### Abstract

Juvenile dermatomyositis (JDM) is a rare, presumably autoimmune illness that causes proximal muscle weakness and a variety of typical cutaneous features. The study of this illness has been hampered by its rarity but, in recent years, important developments have increased our understanding of JDM. Genetic factors are likely important in the pathogenesis of JDM. These include several Human Leukocyte Antigen alleles, in particular those associated with the 8.1 ancestral haplotype and the tumor necrosis factor- $\alpha$  gene 308 polymorphism. Microchimerism, activation of plasmacytoid dendritic cells, and upregulation of type-I interferon inducible genes also appear to play an important role in the pathogenesis of JDM.

The study of JDM has also been limited by a lack of validated assessment tools. Recent work has validated the Childhood Myositis Assessment Scale and the Childhood Health Assessment Questionnaire as measures of muscle strength and function, and the Cutaneous Assessment Tool as a measure of skin disease activity and damage. Development of core sets of tools that should be used in all JDM studies has also been an important step. The use of magnetic resonance imaging and novel laboratory assessments (such as type-I interferon inducible gene products, peripheral blood B cell and natural killer cell numbers, and myositis-associated and myositis-specific autoantibodies) are also playing an increasing role in the diagnosis and assessment of JDM.

Current treatment is with corticosteroids, frequently in combination with other medications such as methotrexate or intravenous gammaglobulin. Newer therapies, such as anti-tumor necrosis factor agents and rituximab are currently being evaluated; it is not clear what role these medications will have in the future.

Juvenile dermatomyositis (JDM) is the most common of the juvenile idiopathic inflammatory myopathies (IIM). However, it is still a rare illness with an incidence of ~2–4 per million.<sup>[1]</sup> The cause of JDM is unknown, but is assumed to be auto-immune given the clinical similarities with systemic lupus erythematosus, association with autoantibodies, and a variety of immunologic observations (some of which are discussed in this review).

JDM is typically manifest by muscle involvement, including proximal weakness, poor endurance, physical dysfunction, and pathologic changes on muscle biopsy and electromyography, and by skin involvement, which may include a variety of pathognomonic and non-specific rashes. Involvement of other organs, such as the heart, lungs or gastrointestinal tract, is not infrequent and can be an important feature of the illness. Since the advent of corticosteroids to treat JDM, mortality is uncommon (likely <2%), but the frequent chronicity of the illness and the need for prolonged courses of corticosteroids and other immunosuppressant medication results in considerable morbidity.<sup>[2,3]</sup>

In the last few years, considerable gains have been made in the understanding of this serious illness. This review considers these advances in the areas of pathogenesis, evaluation, and treatment. It focuses on publications from the last 5 years, although some older references have been included in order to provide a context for the more recent work.

## 1. Pathogenesis

As noted in the introduction, the underlying etiology of JDM remains elusive. However, in recent years there have been a variety of interesting observations reported that provide important insights into the pathogenesis of JDM. These should one day lead to a much clearer understanding of the mechanisms leading to the development of this disease.

### 1.1 Human Leukocyte Antigen Associations

It is likely that genetic factors are important in JDM. Human leukocyte antigen (HLA) associations have been a focus of attention for some time, and there have been several relevant recent publications. Wedderburn et al.<sup>[4]</sup> studied 114 children (87 with classical JDM, 27 with JDM with sclerodermatous features) and 537 control subjects, performing *HLA-DRB1* and

*HLA-DQB1* typing and deriving *HLA-DRA1* results from standard haplotype tables. They found an increased incidence of *HLA-DRB1\*03* and *HLA-DQA1\*05* in JDM patients (strongest in the sclerodermatous group). This work is significant in that it helps to confirm previous reports of associations of JDM with these alleles. Additionally, these alleles are part of a well recognized haplotype (the 8.1 ancestral haplotype), which has been associated with a variety of autoimmune diseases.<sup>[5]</sup> Mamyrova et al.<sup>[6]</sup> showed similar results, reporting *HLA-DRB1\*0301* and *HLA-DQA1\*0501* as well as *HLA-DQA1\*0301* as risk factors for JDM, and noting that *HLA-DRB1\*0301* had a greater relative importance in conferring risk. Both of these papers also noted protective alleles (*HLA-DRB1\*01* and *HLA-DQB1\*05* in the Wedderburn et al.<sup>[4]</sup> study; *HLA-DQA1\*0101*, *HLA-DQA1\*0201* and *HLA-DQA1\*0102* in the Mamyrova et al.<sup>[6]</sup> study), but as these were not replicated, their significance is unclear.

O'Hanlon et al.<sup>[7]</sup> studied 262 African American patients with IIM (55 juvenile onset, 32 with JDM). They showed that *HLA-DRB1\*0301* (as noted by Wedderburn et al.<sup>[4]</sup> and Mamyrova et al.<sup>[6]</sup>) and *HLA-DQA1\*0601* (novel to the African American cohort) were risk factors for dermatomyositis in this population (no difference between adult and juvenile onset). In a much smaller study of 12 children with JDM, Tomono et al.<sup>[8]</sup> identified what may be a novel HLA allele conferring risk for JDM in the Japanese population (*HLA-DRB1\*15021*). This finding requires confirmation in larger numbers of patients. These studies are particularly important in that they show that although some risk-conferring HLA loci are common to different ethnic populations (in particular the 8.1 ancestral haplotype), some appear to be specific to certain ethnic groups. It is not clear if these differences are related to other genes that are in linkage disequilibrium in these ethnic populations, or if there are similarities in the HLA molecules that have been identified as risk factors.

### 1.2 Tumor Necrosis Factor (TNF)- $\alpha$ Polymorphisms

It has been suggested that polymorphisms in the *TNF* gene, encoding tumor necrosis factor (TNF)- $\alpha$ , may be one possible explanation for the HLA associations that have been observed in JDM. This gene, found near both the *HLA-B* and *HLA-DR3* loci, is in linkage disequilibrium with both loci.

Pachman et al.<sup>[9]</sup> reported that the TNF $\alpha$ -308 polymorphism, located in a transcription-regulating region of the gene, is increased in Caucasian children with JDM compared with age-matched controls. They found that this polymorphism was associated with an increased risk of disease chronicity, as well as with increased production of TNF $\alpha$  by both peripheral blood mononuclear cells<sup>[9]</sup> and muscle cells.<sup>[10]</sup> It is also associated with capillary occlusion in muscle biopsies, a factor that is considered integral to the pathophysiology of JDM.<sup>[11]</sup> A possible explanation for this observation is that the TNF $\alpha$ -308 polymorphism is associated with increased levels of thrombospondin-1, an antiangiogenic factor that is known to be associated with smooth muscle proliferation, and vascular luminal narrowing.<sup>[12]</sup> More recently, association with the TNF $\alpha$ -308 polymorphism has also been documented in adults with polymyositis and DM.<sup>[13,14]</sup> As a whole, this body of work shows that TNF polymorphisms are risk factors for the development of inflammatory myopathies (including JDM) in both adults and children. The TNF $\alpha$ -308 polymorphism may be a more relevant risk-conferring gene than other associated HLA genes.<sup>[14]</sup> Some authors have argued that TNF polymorphisms are an integral part of the increased susceptibility to autoimmune disease conferred by carrying the 8.1 ancestral haplotype.<sup>[14]</sup> However, a recent study has shown that the TNF $\alpha$ -308 polymorphism is dependent on some of the ancestral haplotype alleles (specifically HLA-B\*08) and concluded that "it appears that excess TNF $\alpha$  production is more likely associated with possession of the AH (ancestral haplotype) rather than the TNF-308A allele alone."<sup>[13]</sup> This issue remains unresolved.

The finding that a TNF $\alpha$  polymorphism is associated with increased production of TNF is intriguing, and suggests a potential therapeutic target. Unfortunately, as discussed in section 3.1, there are little data available on the use of TNF inhibitors in JDM. The role of TNF in the pathogenesis of JDM requires additional investigation and may lead to a better understanding of JDM and its treatment.

### 1.3 Chimerism

The topic of chimerism has also been of recent interest in studies of the pathogenesis of JDM. It is well recognized that there is an exchange of living cells between the mother and fetus. It is possible to measure these cells, in small numbers, many years after birth by recognizing that they are genetically different than 'self cells.' This side-by-side persistence is called chimerism (or because of the small numbers of cells, microchimerism).<sup>[15]</sup> Reed et al.<sup>[16]</sup> were the first to describe the presence of chimerism in children with JDM, and have since gone

on to further characterize this finding. Since the initial report, Reed and other investigators have documented an increased risk of chimerism in children with JDM compared with their siblings, with the non-self cells being found in both blood and muscle tissue.<sup>[17-21]</sup> The cells appear to be dendritic and B cells, which has been suggested to imply involvement in the disease process.<sup>[19]</sup> This hypothesis is further strengthened by the observation that the maternally transferred chimeric T cells are responsive against the child's T cells in children with JDM.<sup>[21]</sup>

Of additional interest is the report that the maternal HLA genotype is associated with the presence of chimerism. Reed et al.<sup>[21]</sup> showed that the presence of HLA-DQA1\*0501 (which is already considered a risk factor for the development of JDM; section 1.1) in the mother is associated with an increased risk of chimerism in children with JDM as well as in well siblings and healthy controls. This may be at least a partial explanation for the HLA associations that have been described in JDM.

The details of the relationship between chimerism and JDM, and the interplay with the maternal HLA genotype remain unclear. While Reed et al.<sup>[21]</sup> have hypothesized that the presence of chimeric cells act as a 'second hit' in a genetically predisposed individual (in the case of JDM, most commonly by the presence of HLA-DQA1\*0501), this remains to be proven. However, this is a promising avenue of research.

### 1.4 Type I and II Interferons

Several recent studies have indicated the importance of the type I interferons in the pathogenesis of JDM. Type I interferons are recognized to be key to the regulation of the immune response to viruses and intracellular infections. One of the important lines of evidence has been the use of gene expression profiling, where the expression of large numbers of genes is compared between children with and without JDM. It has been shown that a large proportion of the genes that are differentially expressed in skeletal muscle tissue of JDM patients are induced by type I interferons;<sup>[22,23]</sup> this has been duplicated in adult DM (see Greenberg et al.<sup>[24]</sup>). This has been called the interferon signature or fingerprint. Increases in several specific interferon-inducible proteins with angiostatic properties have also been shown in muscle tissue of JDM patients.<sup>[25]</sup> This provides an intriguing link to the well documented vasculopathy of JDM, and may be a key step in the pathogenesis.<sup>[26,27]</sup>

Upregulation of type I interferon-induced genes has also been demonstrated in peripheral blood mononuclear cells. O'Connor et al.<sup>[28]</sup> reported that expression of a specific interferon-inducible enzyme called myxovirus resistance protein

A (MxA), which has the advantage of being tightly regulated by type I interferons and not other cytokines, was increased in peripheral blood mononuclear cells in both treated and untreated JDM patients. Furthermore, they showed that levels of MxA expression correlated with disease activity.<sup>[28]</sup> Finally, Baechler et al.,<sup>[29]</sup> in a study that included both adult DM and JDM, showed the presence of the interferon signature, and found that it was also associated with disease activity. These studies confirm the results obtained from muscle tissue, and also provide a potential marker of disease activity.

Type II interferons may also play a role in the pathogenesis of IIM. A recent report in adult-onset patients documented an association between adult-onset IIM and interferon- $\gamma$  polymorphisms.<sup>[30]</sup> It is not clear what relevance this may play in JDM, particularly considering that this study included a mixed group of 101 patients with polymyositis, 90 with DM, and 70 with myositis in association with another connective tissue disease. This is likely to be an area of ongoing investigation.

### 1.5 Plasmacytoid Dendritic Cells

When considering the apparent importance of proteins induced by type-I interferons in the pathogenesis of JDM (section 1.4), an obvious question is “what is the source of the interferons?” A lot of attention has been paid recently to a population of cells called plasmacytoid dendritic cells (PDCs). These cells are known to be capable of producing large amounts of type I interferons. They were first documented in adult-onset DM, localized to the perivascular infiltrates.<sup>[24,31]</sup> It was also shown that these cells were CD4 positive, and formed the majority of what were previously thought to be CD4-positive T cells.<sup>[24]</sup>

Subsequent work has documented PDCs in JDM muscle tissue.<sup>[32,33]</sup> Furthermore, Lopez de Padilla et al.<sup>[33]</sup> documented the presence of immature PDCs in normal muscle tissue of patients without JDM, and that the PDCs found in the muscle of JDM patients were predominantly mature. They also showed that while the immature PDCs were scattered through the normal muscle, the mature PDCs in JDM muscle were localized to areas of lymphocytic infiltrates. To explain their findings, they hypothesized that following a local insult (the nature of which is unknown), immature PDCs initiate a T-cell-mediated inflammatory response, leading to muscle damage. The ensuing inflammatory conditions result in maturation of the PDCs, leading to local production of type I interferons and production of interferon-inducible proteins, which in turn lead to further recruitment of inflammatory cells and persistence of the inflammatory response.

### 1.6 Infection

The possibility that JDM might be related to infection has been a topic of interest for some time. The reports of the importance of type I interferons (section 1.4) and PDCs (section 1.5) lends new impetus to research in this area, given the role of these pathways and cells in defense against viral and intracellular pathogens. However, despite this interest, compelling evidence of the role of infections in the pathogenesis of JDM has been lacking.

There have been a variety of studies attempting to study a potential link between specific infections and JDM. Implicated agents have included coxsackievirus B, group A  $\beta$  hemolytic streptococcus, hepatitis B virus, influenza, parainfluenza, *Borrelia* spp., *Toxoplasma gondii* and parvovirus (reviewed by Pachman<sup>[34]</sup>). However, these studies have not been consistent and, where attempts have been made, have not been able to be replicated (for example see Mamyrova and Rider<sup>[35]</sup>). It is reasonable to conclude from this work that if JDM is caused by an infectious agent, either the specific organism has not been found or JDM is not associated with a single agent.

Attempts have also been made to investigate the role of infection in JDM from a more epidemiologic methodology. Pachman et al.<sup>[36]</sup> reported that 63% of children presenting with JDM had a history of an infection in the preceding 3 months compared with 42% in a control group ( $p=0.013$ ). The nature of these infections was not specified. In a more recent study, Pachman et al.<sup>[37]</sup> again documented that infections are common in the 3 months preceding disease onset. In this study, which utilized a structured interview within 6 months of diagnosis, they found that 57% of children with JDM had respiratory infections, 30% had gastrointestinal infections, and 63% of the children with infectious symptoms had been administered antibiotics. Unfortunately, this study did not include a comparator population (it is not possible to determine if these children with JDM differed from normal, healthy children) and did not include testing for any specific infectious agents. Finally, Vegosen et al.<sup>[38]</sup> reported on seasonality of birth in patients with juvenile IIM. In their study, the overall birth distributions of juvenile IIM patients did not differ from controls. However, those of several subgroups did appear to, including Hispanic IIM patients, patients with a positive autoantibody called p155 antibody, and those with HLA-DRB1\*0301. The results suggested that early life exposures (presumably infectious) may influence the development of juvenile IIM.

A final and quite intriguing line of research is related to the possibility of molecular mimicry playing a role in the

pathogenesis of JDM. Massa et al.<sup>[39]</sup> have shown that cytotoxic T-lymphocytes from children with JDM react against autologous cells expressing a self peptide derived from myosin, and that this peptide has homology with peptides derived from group A streptococcus as well as several other infectious organisms. Somewhat related to this, Elst et al.<sup>[40]</sup> have shown that T cells autoreactive to a self protein called heat shock protein (Hsp) 60 are present in children with JDM. Expression of Hsp60 was upregulated in inflamed muscle tissue, but this can also be upregulated by other forms of muscle injury (such as infection). The role of these autoreactive T cells is not clear, as they may have both effector and regulatory effects. It is possible that infections induce an autoimmune response through these mechanisms, but this evidence is very preliminary.

Thus, the role of infection in the pathogenesis of JDM is not clear. However, studies have shown that infections are common prior to disease onset, and although an association with specific infections has not been consistently shown, the concept of cross reactivity to self-peptides that bear similarities to peptides from a variety of infectious organisms is an attractive way of reconciling these data. In addition, a prominent role of infection as an inciting event for the development of JDM would explain the apparent importance of type I interferons, which are key in the defense against viruses and other intracellular pathogens.

## 2. Evaluation

There have been few studies of therapy in JDM (see section 3). One reason for this has been the lack of validated measures with which to evaluate children with JDM. This also impacts clinical care, as it can sometimes be difficult to make clinical decisions without valid measurements of the various features of JDM. Fortunately, there has been much recent work on the evaluation of children with JDM. This will facilitate further research into new and better therapies.

### 2.1 Muscle and Skin Disease

Proximal muscle weakness is recognized to be one of the cardinal features of JDM. However, valid assessment of muscle strength has been elusive. The mainstay has been manual muscle testing (MMT), based on the Medical Research Council 5-point scale,<sup>[41]</sup> but this has subsequently been expanded and modified by a variety of investigators, resulting in a variety of related tools being used by researchers around the world. This has caused problems with comparability between studies and validity as each of these versions has not been independently

validated. Recently, Jain et al.<sup>[42]</sup> published reliability data on the 10-point scale applied to 26 muscle groups, and recommended this as the preferred form of MMT. This study was conducted in nine children with JDM and one with polymyositis. The authors documented acceptable inter- and intra-rater reliability of the 10-point MMT.

Although MMT is considered to be an important component of the assessment of children with JDM, it is clear that it is not a complete assessment of muscle function. For example, MMT does not assess the ability to perform tasks, nor is endurance addressed. For this reason, more functionally oriented assessments of muscle strength have also been considered important. The Childhood Myositis Assessment Scale (CMAS) is a 14-item, observational, performance-based tool that assesses a variety of tasks, including proximal, distal, and axial muscle strength as well as timed endurance items.<sup>[43]</sup> This has been validated and shown to exhibit inter-rater reliability, construct validity, and responsiveness.<sup>[44]</sup> The Childhood Health Assessment Questionnaire (CHAQ) is a 30-item self- or parent-report tool that assesses the ability to perform a variety of activities of daily living.<sup>[45]</sup> It was originally described for use in children with arthritis, but has also been validated for use in JDM;<sup>[46,47]</sup> these studies documented inter-rater reliability, construct validity, and responsiveness of the CHAQ in JDM.

The other cardinal feature of JDM is skin disease. Assessment of skin disease can be very complex, with numerous potential skin lesions being possible in any single patient. This can make determining the degree of skin activity or assessing whether skin disease has improved or deteriorated very difficult. Attempts have recently been made to address this problem by developing standardized assessment tools for skin disease.

The Cutaneous Assessment Tool (CAT) is a 21-item tool that assesses both the presence and severity of activity and damage lesions in JDM.<sup>[48]</sup> It has been shown to demonstrate inter-rater reliability, construct validity, and responsiveness.<sup>[48,49]</sup> The CAT has been criticized for being long and complex. This has led to a shortened version of the CAT being developed, which assesses the same 21 lesions, but only for their absence or presence. This shortened version of the CAT has been shown to have similar measurement characteristics to the full-length tool.<sup>[50]</sup> Another tool called the Dermatomyositis Skin Severity Index (DSSI), which assesses redness, induration, scaliness, and surface area of skin involvement, has also been developed.<sup>[51]</sup> It does not distinguish between different skin lesions of JDM. The DSSI has been shown to have good inter- and intra-rater reliability, and construct validity, but responsiveness has not been assessed.<sup>[51]</sup> A third tool that has been developed to assess skin disease in DM (both juvenile and

adult) is the Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI).<sup>[52]</sup> It assesses 16 body areas, scoring each for erythema, thickness, scaling, excoriation, and ulceration, as well as scoring Gottron's lesions, periungual changes, and alopecia. The authors of the CDASI compared the reliability for the CDASI, the CAT, and the DSSI, and found that the reliability was highest for the CDASI, in their hands.<sup>[52]</sup>

At present, there is no consensus regarding which of these tools performs the best, making this an important topic of future research. A consensus-based process to consolidate these tools or develop a single tool that incorporates their most important features is needed.

## 2.2 Other Clinical Assessments

Abnormalities in the visible capillaries of the digital nailfolds were described as early as 1971 in patients with a variety of connective tissue diseases.<sup>[53]</sup> Recent studies have emphasized the potential value of digital nailfold capillary assessments. Smith et al.<sup>[54]</sup> assessed 60 children with newly diagnosed JDM using video microscopy, looking for evidence of arboreal branching loops, dilated loops, and changes in loop density. They found that loop density was inversely related to duration of untreated disease and severity of skin disease, and concluded that active skin disease indicated underlying vasculopathy. Nascif et al.<sup>[55]</sup> examined 13 children with JDM and 5 with overlapping conditions, evaluating microhemorrhages, capillary enlargement, branching, and dropout. They reported that abnormalities correlated with disease activity, and that the best correlation was with dropout. Most recently, Christen-Zaech et al.<sup>[26]</sup> reported data on 61 children with JDM evaluated at diagnosis and at 36 months. They found that improvements in capillary density were associated with improvement in skin disease activity but not muscle disease activity, and were associated with a shorter duration of untreated disease and a monocyclic course. These studies document the importance of digital nailfold capillary assessment in the clinical evaluation of children with JDM.

Difficulties with swallowing can be seen in children with JDM. This is usually thought to be in the context of moderate to severe weakness. Detection of significant swallowing problems is critical to avoid the risks associated with aspiration, particularly in children with substantial weakness. However, in an abstract, Punaro et al.<sup>[56]</sup> documented that aspiration was more common than clinically appreciated in children with JDM. Subsequently, McCann et al.<sup>[57]</sup> studied 14 children with IIM, all of whom underwent a video-fluoroscopic swallowing

study. Surprisingly, they found no relationship between abnormalities on the swallowing study and symptoms of dysphagia – some children with no symptoms had evidence of aspiration and some children with dysphagia had normal studies. Also, there was no relationship between the findings of the swallowing study and other measures of disease activity, including muscle strength. This study suggests that swallowing dysfunction cannot be accurately predicted, leading to the reasonable conclusion that children with JDM require swallowing studies, regardless of strength or symptoms.

## 2.3 Measures of Overall Disease Activity and Damage

Assessment of disease activity and damage in JDM can be challenging, given the complex, multi-system nature of the illness. For example, some aspects of the disease (such as muscle strength) may improve, while at the same time other features (such as skin disease) may deteriorate. Because it is important, particularly in clinical trials, to be able to determine if patients have improved, or if one group of patients have had a better response than another group, recent work has focused on measuring overall disease activity and damage.

Rider et al.<sup>[58]</sup> reported on the use of visual analog scales (VAS) to assess disease activity and damage in patients with juvenile IIM. They reported that physician, parent, and patient global assessments of both disease activity and disease damage showed inter-rater reliability, while the global assessments of disease activity showed reasonable responsiveness. Unfortunately, one drawback of the use of global scores in the assessment of JDM is that they require considerable experience with the illness to appropriately integrate the various components of disease activity or damage that are being assessed.

In order to make the process of assessing disease activity and damage more transparent and standardized, several tools have been developed that attempt to explicitly consider and weight the various components of the illness. Bode et al.<sup>[59]</sup> described the JDM Disease Activity Score (DAS). This tool consists of a muscle disease domain (overall function plus eight items assessing strength) and a skin disease domain (ten items assessing skin disease). The authors reported good inter-rater reliability and some evidence of construct validity. More recently, the JDM DAS has been shown to demonstrate responsiveness, construct validity, and discriminant validity.<sup>[60]</sup> The Myositis Disease Activity Assessment (MYOACT) is a tool that uses a series of 10 cm VAS to assess global activity in ten areas: constitutional, cutaneous, skeletal, gastrointestinal, pulmonary, cardiac, other, extra-muscular, muscle and global.<sup>[60]</sup> The

Myositis Intention-to-Treat Activity Index (MITAX) assesses disease activity in each of these areas, but each area is graded by determining whether a change in treatment is warranted. This assumes that disease activity is directly related to the decision to increase or decrease therapy.<sup>[60]</sup> These latter tools, originally developed in adults, have not been extensively evaluated in children with JDM. However, good responsiveness for both tools in JDM has been reported.<sup>[60]</sup>

## 2.4 Core Sets

It is clear that there are many disease components that can be assessed in JDM. Previous research in JDM has been hampered by the inconsistent use of measures across studies, making it difficult to compare them. For this reason, some of the most important publications regarding clinical assessment in JDM have attempted to address the issue of which components should constitute a core set.

Somewhat unfortunately, this issue was taken on by two semi-independent groups (with some overlap of members). This has resulted in two similar but not identical recommended core sets of measures that should be reported in all clinical trials in JDM. Miller et al.,<sup>[61]</sup> representing the International Myositis Outcome Assessment Collaborative Study Group (IMACS), developed a recommended core set of outcome measures for both adult and pediatric IIM. The core set was developed by a review of the existing literature, followed by an international consensus conference and a second conference to refine the initial proposals using a Delphi technique. The resulting core set consisted of a measure of global disease activity (physician global and parent/patient global assessment using a Likert scale or VAS), a measure of muscle strength (MMT), a measure of physical function (CHAQ and/or CMAS, depending on age), a laboratory assessment (levels of at least two recognized muscle enzymes), and a measure of extraskeletal muscle disease activity (to be developed at the time of this review). A variety of other measures were also considered as part of an 'extended set.'

Ruperto et al.,<sup>[62]</sup> representing collaboration between the Pediatric Rheumatology International Trials Organization (PRINTO) and the Pediatric Rheumatology Collaborative Study Group (PRCSG), set out to develop core sets of outcome measures to be assessed in both JDM and juvenile systemic lupus erythematosus. They used questionnaires of involved physicians to develop candidate measures for a core set, followed by a consensus meeting where measures to be included were chosen using a nominal group technique. This core set consisted of a physician global assessment (Likert or VAS), patient/parent global assessment (Likert or VAS), a measure of

muscle strength (MMT, possibly CMAS as well), a measure of functional ability (CHAQ), a laboratory assessment (muscle enzyme levels), a global disease activity tool (the DAS or MYOACT/MITAX), and a measure of health-related quality of life (the Child Health Questionnaire [CHQ]).

The overall spirit of both of these core sets is very similar. Areas where they depart include use of the CMAS as a measure of strength by PRINTO/PRCSG and as a measure of function by IMACS, slightly different use of muscle enzymes (at least two for the IMACS core set, not specified in the PRINTO core set), use of an additional assessment of global disease activity and health-related quality of life by the PRINTO/PRCSG group, and inclusion of a measure of extraskeletal muscle disease activity by the IMACS group.

Once core sets were recommended, the next obvious step was to establish definitions for improvement. This is particularly important for clinical trials. Rider et al.,<sup>[63]</sup> for the IMACS group, reported the findings from 29 adult and pediatric myositis experts who evaluated 102 paper cases. Through nominal group techniques, a consensus definition of improvement in adult and pediatric myositis was achieved: three of the six core set measures improved by >20%, with no more than two being worse by >25% (which could not include MMT). More recently, the PRINTO/PRCSG group has also studied this issue.<sup>[60]</sup> They reported data derived from a prospective collection of data from 294 international patients with JDM. Response to therapy was determined by the treating physician, and the core set variables were then assessed in relation to this determination using logistic regression. This study did not generate a 'rule' as with the IMACS work. Rather, improvements that best predicted response to treatment were defined for each core set variable. These were 2.4 cm for the physician global assessment (10 cm VAS), 5 for the DAS, 3.7 cm for the parent global assessment (10 cm VAS), 5 for the CMAS, 1 for the CHAQ, and 17.3 for the CHQ.

This work on core sets is critical. It allows for consistency across published work, and provides guidance for investigators conducting clinical trials. It remains a concern that there are areas of disagreement between the published recommendations. This is an issue that will need to be addressed at some point in the future; given the relatively small differences, this should be possible.

## 2.5 Role of Magnetic Resonance Imaging

The use of magnetic resonance imaging (MRI) has become integral to the evaluation of children with JDM for several reasons: (i) it is non-invasive; (ii) it can be used in children too

young for MMT or other techniques of muscle testing to be valid; (iii) it does not depend upon cooperation or effort from the patient; (iv) it is generally thought that MRI is highly sensitive; and (v) because entire muscle groups can be the focus of examination, it is not susceptible to the patchiness that is recognized to characterize muscle biopsy results.

Recent work has clarified the role of MRI in caring for children with JDM. Maillard et al.<sup>[64]</sup> studied 10 children with active JDM, 10 children with inactive JDM, and 20 healthy controls. They showed that MRI (T2 relaxation time) scores were higher in the group with active disease, and that the abnormalities correlated well with measures of disease activity, including physician global assessment, CMAS, and CHAQ; this work is also important in that it provides a quantitative method for assessing muscle MRI. Kimball et al.<sup>[65]</sup> documented that MRI (and specifically short tau inversion recovery technique) was able to identify edema or inflammation of the skin, subcutaneous tissue, and fascia that was not detectable by the usual assessments. Interestingly, 5 of the 26 patients with JDM studied developed calcinosis in the same locations within 9 months, showing the clinical relevance of the imaging findings. These studies show the potential value of MRI in JDM. However, Summers et al.<sup>[66]</sup> have injected a note of caution. They found that moderate exercise (stair-stepping for up to 10 minutes) performed by children with juvenile IIM could produce MRI changes that mimicked inflammation, lasting for about 30 minutes.

The importance of MRI in the evaluation of JDM has been documented by Brown et al.<sup>[67]</sup> They conducted an international consensus survey of diagnostic criteria for JDM. These authors found that 58% of respondents used MRI as a criterion for diagnosis of JDM and that MRI, along with muscle biopsy, was considered to be the most useful or clinically relevant criteria after proximal muscle weakness, typical rash, and elevated muscle enzyme levels.

The development of new diagnostic criteria for JDM is an ongoing process, but it appears likely that MRI will be a component. However, to maximize the usefulness of MRI studies, consensus regarding the best types of scans, standardization of methodology, and development of a quantitative assessment of MRI to allow comparisons between patients and over time will be needed.

## 2.6 Laboratory Evaluation

Advances in the understanding of the pathogenesis of JDM have resulted in a number of potential laboratory tests that could be of value in the ongoing assessment of JDM. Addi-

tional tests would be helpful, given that it has been well documented that beyond the time of diagnosis, muscle enzyme levels fail to correlate with disease activity.<sup>[44,47]</sup> The role of many of these tests is as yet unclear.

The type I interferon signature (section 1.4) may provide candidates for new laboratory tests to monitor disease activity in JDM. Levels of MxA have been shown to be increased in peripheral blood mononuclear cells in JDM patients, and to correlate with disease activity.<sup>[28]</sup> Neopterin is another type I interferon-induced protein, released by macrophages, which has also been found to be elevated in the peripheral blood of active JDM patients, and to correlate with disease activity.<sup>[68,69]</sup> A variety of other type I interferon-induced molecules have also been shown to be upregulated in muscle tissue,<sup>[23,25]</sup> but these are less likely to be useful, given that monitoring by serial muscle biopsy is not appropriate. Future research may find additional molecules that can be monitored in peripheral blood and further clarify their role in the evaluation of JDM; at present these are of research interest only.

Eisenstein et al.<sup>[70]</sup> described the role of monitoring lymphocyte subsets in the evaluation of children with JDM. They showed that the percentage of CD19-positive cells (B cells) in peripheral blood was correlated with disease activity (with a higher percentage being associated with greater disease activity). Subsequently, they confirmed this result with the additional finding that natural killer (NK) cells were reduced in JDM patients with active disease.<sup>[71]</sup> The authors suggested that the relative increase in B cells may be related to the absolute decrease in NK cells. Mizuno et al.<sup>[72]</sup> studied peripheral blood T cells in two patients with JDM. Although very preliminary, due to the small number of patients, they found that the untreated patients had oligoclonal expansion of their CD8+ cells, with normalization in the patient who responded to treatment and persistence in the patient who failed to respond. Although the role of monitoring these lymphocyte subsets remains unclear, they may provide a promising method to monitor the status of immunologic activation in JDM patients. In some institutions, B cells/NK cells are currently being monitored as part of standard care.

Identification of myositis-specific antibodies (MSA) and myositis-associated antibodies (MAA) has become an important part of the evaluation of adults with IIM.<sup>[73,74]</sup> These antibodies have been shown to be associated with well defined clinical syndromes,<sup>[73,74]</sup> identify patients at increased risk of myositis associated with malignancy,<sup>[75]</sup> and provide guidance regarding treatment choices and prognosis.<sup>[73,74]</sup> In children with JDM, these autoantibodies have been much less helpful. Feldman et al.<sup>[76]</sup> studied 41 children with JDM and 9 with



other forms of IIM, but found only 2 children with anti-Mi-2 antibodies. Another report studied 77 children with IIM, and found only 12 children with MSA or MAA (9 with anti-Mi-2, 1 each with anti-PL-12, anti-Jo1 and anti-SRP).<sup>[77]</sup> In summary, small numbers of children have the traditionally recognized MSA or MAA, making their assessment unlikely to contribute to patient care.

Recently, a new autoantibody called anti-p155 has been identified, which is present in 23–29% of JDM patients studied.<sup>[75,78]</sup> Anti-p-155 appears to be specific for IIM (present in only 1 of 138 disease and healthy controls), but not specific for JDM (it is seen in adult DM, children and adults with myositis associated with another connective tissue disease, and malignancy-associated DM). The role of anti-p155 testing is unclear at this time.

## 2.7 Muscle Biopsy

As noted previously, muscle biopsy has fallen somewhat out of favor. This is partly because of the invasiveness of the procedure. It is also related to the ability to only sample a small part of the muscle, which in a patchy illness, may result in no abnormalities being documented. However, some recent work has helped to redefine the role of muscle biopsy in JDM.

Li et al.<sup>[79]</sup> studied the expression of MHC class I molecules in muscle biopsies of ten JDM patients and three controls. They found that even in biopsies that were histologically normal, with no evidence of lymphocyte infiltration and no muscle fiber injury, MHC class I expression was clearly increased compared with controls. The authors caution that this expression is not specific for JDM (it is described in other inflammatory myopathies as well as some muscular dystrophies), but they do show that it appears to be an early event in JDM, one that precedes visible muscle damage or inflammation. A very interesting follow-up to these findings is a report from the same group that reported a patient with amyopathic JDM who did not have overexpression of MHC class I.<sup>[80]</sup> The authors concluded that lack of MHC class I overexpression may reflect the lack of myositic involvement in this patient, although they acknowledge that sampling error may be another explanation. MHC class I overexpression may be a useful part of the evaluation of muscle biopsies of suspected JDM patients, but will require studies in additional patients.

Miles et al.<sup>[81]</sup> reviewed biopsies from 72 patients diagnosed with JDM, and attempted to correlate pathologic findings with clinical course. They found that extensive myopathic changes and central nuclei without basophilia predicted a chronic course, and that severe arteropathic changes, arterial direct immuno-

fluorescence, foci of capillary loss or endomysial fibrosis, and muscle infarcts predicted a chronic course with ulceration. These results are important because if they can be replicated, they demonstrate a potential role for muscle biopsy in all JDM patients. While muscle biopsy may not be necessary to make a diagnosis, it might be valuable in guiding initial therapy. In particular, if a chronic and/or ulcerative course can be predicted, much more aggressive initial therapy may be indicated.

Finally, Wedderburn et al.<sup>[82]</sup> have described a proposed scoring system for muscle biopsy in JDM. This international group of pediatric rheumatologists, other physicians with an interest in childhood myositis, and histopathologists with specific expertise in muscle biopsies developed this tool through a consensus process. The resulting tool consists of an inflammatory domain (staining and localization of CD3 and CD68 cells), a vascular domain (capillary dropout [CD31 stain], arteropathy, infarction), a muscle fiber domain (MHC class I overexpression, neonatal myosin staining, and several other changes in fiber appearance), and a connective tissue domain (fibrosis). These investigators also assessed inter-rater reliability of the tool, and showed that while many items performed well, reliability was poor for approximately half the items. Given that the assessors in this study were experts in the field, this suggests that the tool requires further work to refine and fully validate it. Nevertheless, this is an important step in standardizing the assessment of muscle biopsies, both for clinical use and in clinical trials.

## 3. Treatment

There have been very few clinical trials of treatment in JDM. This is largely related to the rarity of the illness and a lack of methodology to adequately assess it. However, as described in section 2, the last few years have seen considerable progress in the evaluation of JDM, facilitating the conduct of clinical trials to study new treatments. There remain significant challenges, as the studies will need to involve many centers to accrue adequate patients, but new treatments are badly needed. Standard treatment consists of high-dose corticosteroids, weaned slowly over 1–2 years, with frequent use of other corticosteroid-sparing medications, such as methotrexate or intravenous gammaglobulin. This prolonged course of corticosteroids has significant morbidity, and there remain a number of patients with chronic and/or refractory disease. Improved understanding of the pathogenesis of JDM (see section 1) should lead to new treatment targets and new classes of medications in the future.

### 3.1 Anti-TNF Therapy

Documentation of the association of JDM with TNF $\alpha$  polymorphisms (section 1.2) has led to consideration of anti-TNF medications as a potential therapy for JDM. Unfortunately, there has not been a completed clinical trial to date. Miller et al.<sup>[83,84]</sup> have presented results in abstract form for a small number of patients with JDM treated with etanercept. They treated ten children with chronic disease, despite intravenous pulse corticosteroids and other immunosuppressant medications. The dosage used was 0.4 mg/kg administered subcutaneously twice weekly. The authors reported a statistically significant improvement in disease activity (measured by DAS). However, the change appeared quite modest, improving from 9.89 to 8.72 ( $p=0.008$ ). In addition, the CHAQ actually increased (from 0.89 to 1.00;  $p$ -value not given), and there was no change in muscle enzyme levels or percent of B cells. This is consistent with the anecdotal statement of Stringer and Feldman,<sup>[85]</sup> who reported that their experience with etanercept in patients with JDM in a large tertiary care referral center has not been favorable.

Riley et al.<sup>[86]</sup> have recently reported on the open-label treatment of five JDM patients with infliximab. All patients were refractory to standard therapy, including intravenous corticosteroids, methotrexate, and at least one other disease modifying antirheumatic drug, and had progressive calcinosis. They were treated with 3 mg/kg, with follow-up doses administered at 2, 6, and then every 8 weeks after; doses and intervals were modified based on clinical evaluation. The authors reported that all patients had improvements in muscle strength and function (measured by CMAS), global disease activity (measured with a VAS), and joint contractures. All patients were able to reduce their intake of systemic corticosteroids, with three being able to discontinue them.

These data must be considered very preliminary, given the lack of blinding and a control group. However, there appears to be reasonable justification for a clinical trial to assess the efficacy of TNF-inhibitors in JDM. Infliximab is likely the most promising, although no data are available on other agents (adalimumab or others).

### 3.2 Rituximab

Rituximab is an anti-CD20 monoclonal antibody, which acts to deplete B cells. It is thought that B-cell depletion is important to achieving clinical response in patients with JDM. In children with JDM, the use of rituximab was first reported by Levine<sup>[87]</sup> who treated five patients, two of whom were children with refractory JDM. These patients received two weekly doses

of rituximab 100 mg/m<sup>2</sup>. They experienced B-cell depletion, but otherwise tolerated the treatment well. The JDM patients were reported to experience 40% and 45% improvements in muscle strength, but no other details were available.

Endo et al.<sup>[88]</sup> also reported their experience with rituximab in JDM (published as an abstract). They presented a patient with severe disease, who failed to go into remission despite treatment with high-dose corticosteroids, as well as hydroxychloroquine, methotrexate, mycophenolate mofetil, etanercept, infliximab, cyclophosphamide, and intravenous gammaglobulin. The patient had persistent weakness, rash, and severe calcinosis, and after 7 years of chronic disease, she was treated with rituximab (4 weekly infusions, total dose 2800 mg, weight not provided). The patient experienced a remission of disease, and at the time of this report, was only taking 5 mg of prednisone. Further follow-up was not available.

Recently, Cooper et al.<sup>[89]</sup> reported their results using rituximab in four JDM patients. Disease duration ranged from 5 weeks to 27 months, and all patients had markedly active disease despite treatment with corticosteroids, methotrexate, and other immunosuppressant agents. All patients received rituximab 375 mg/m<sup>2</sup> weekly for 4 weeks. Two patients were retreated 1 year later for disease recurrence. All patients had depletion of their B cells (one after a second dose). Three patients had excellent responses, with resolution of rash, normalization of strength, and weaning or discontinuation of other medications. Responses lasted for 12 months or more; two patients with flares responded well again. One patient had progression of her disease with no evidence of response, despite appropriate B-cell depletion.

Finally, Dinh et al.<sup>[90]</sup> have reported the use of rituximab for chronic cutaneous features of DM. Two of the three patients had JDM and had been treated with oral corticosteroids (40 and 50 mg maximum), methotrexate, hydroxychloroquine, and ciclosporin, with apparent response in muscle disease, but minimal improvement in chronic and marked skin disease. Both patients were treated with rituximab 375 mg/m<sup>2</sup> weekly for 4 weeks, and experienced dramatic improvements in their skin disease. They were also able to discontinue or markedly wean all other immunosuppressant medications.

In this small number of reports, rituximab has been well tolerated in JDM, with no serious adverse effects (including infections) reported. Responses have been dramatic, but a clinical trial is necessary to determine if these results are generalizable. There is an ongoing trial being conducted, with participating centers in North America and Europe, to determine the efficacy of rituximab in both adults and children with refractory DM.

### 3.3 Methotrexate

Although there has never been a clinical trial to support its use, methotrexate has become commonly used as a corticosteroid-sparing medication in JDM. Fisler et al.<sup>[91]</sup> reviewed their experience using what they describe as 'aggressive management.' Thirty-five patients with JDM seen over a 10-year period were all treated with a semi-standardized local protocol consisting of high-dose oral or intravenous corticosteroids, followed by initiation of methotrexate (0.5–1 mg/kg administered weekly, subcutaneously or intravenously) within 6 weeks if there was no improvement in muscle enzyme levels. At follow-up (time not clearly defined), 26 patients were in remission (no rash, weakness or elevation of enzyme levels) whether they could still be on medications was not stated and only five had developed mild calcinosis. They also noted that those who developed calcinosis had a longer disease duration before treatment, longer time to normalization of muscle enzyme levels, and a longer time to remission. The authors concluded that their stepwise approach was highly successful at both achieving rapid control of disease and preventing long-term complications. However, it must be recognized that this study did not compare this regimen with another, making it difficult to determine if these outcomes would have been achieved without methotrexate.

Ramanan et al.<sup>[92]</sup> have taken a somewhat different approach to the use of methotrexate in JDM. The authors, deriving data from one of the larger JDM clinics in the world, compared JDM patients before and after a change in clinical practice. Prior to the change, most patients were treated with oral corticosteroids (2 mg/kg/day), with weaning occurring approximately by 10% every 4 weeks depending on clinical status and response. After the change, most patients were treated with oral corticosteroids (2 mg/kg/day) but methotrexate was started at presentation (10–20 mg/m<sup>2</sup> weekly, maximum 25 mg); corticosteroids were weaned every 2 weeks depending on clinical status and response. This resulted in a markedly shorter period of exposure to corticosteroids (10 vs 27 months, cumulative dose 7574 vs 15 152 mg). Not surprisingly, the patients with the more rapid corticosteroid wean had a better growth velocity and less weight gain, and there were non-statistically significant trends towards fewer cataracts and insufficiency fractures. Otherwise, the authors did not detect any other differences in outcome, including muscle strength, physical function, persistence of rash, calcinosis, disease flare or need for other medications.

Interpretation of the Ramanan et al.<sup>[92]</sup> study is limited by the use of a non-randomized control group. It is possible that there is confounding by indication, with patients with more

severe disease receiving more aggressive therapy. It is not clear that the two groups were comparable. However, this important work does provide preliminary evidence that early use of methotrexate may allow much more rapid weaning of corticosteroid therapy than has been traditional. If these results are supported by further follow-up, this is an attractive step in reducing morbidity for children with JDM.

### 3.4 Other Medications

Although the majority of patients with JDM do well with standard treatment (corticosteroid therapy with or without methotrexate), there remains a smaller number of patients who have either very severe disease (in particular those with evidence of skin or bowel vasculitis) or disease that simply fails to respond. For these patients, additional medications are needed.

Riley et al.<sup>[93]</sup> have recently reported on their use of cyclophosphamide in JDM. In a 7-year period, 12 patients received intravenous pulse cyclophosphamide. Indications were severe weakness, skin ulcerations or serious internal organ involvement (gastrointestinal ulceration, interstitial lung disease or seizures). Patients were started with 500 mg/m<sup>2</sup>/dose, with increases up to 1000 mg/m<sup>2</sup> if tolerated, and received six to seven monthly doses, followed by 3-monthly doses until there was no further severe disease activity. Patients also received high-dose corticosteroids, and nine also received another immunosuppressant concurrently. Two patients died before the medication could be effective (interstitial lung disease and brain stem vasculitis, respectively). The other ten children responded to treatment to varying degrees, with stability or continued improvement after discontinuing cyclophosphamide. Side effects were generally mild and transient, with only one episode of febrile neutropenia and no serious infections. No children developed secondary cancers, infertility or gonadal failure, although follow-up continues. Interpretation of these results is limited once again by the lack of a direct comparator group. It is not possible to determine if another regimen may have been equally successful, or if these children would have improved without cyclophosphamide. However, clinical experience has shown that patients with severe weakness, skin ulcerations or serious internal organ involvement have a high risk of poor outcomes, and this work provides at least some evidence of the efficacy and safety of cyclophosphamide in these circumstances.

Tacrolimus (FK-506) is another medication for which there has been some recent information. Tacrolimus has similar activity to ciclosporin, a medication that is generally accepted to be effective in JDM, although with considerable toxicity.<sup>[85]</sup> Yamada et al.<sup>[94]</sup> reported the effectiveness of oral tacrolimus in a single JDM patient in whom ciclosporin had been ineffective

due to poor absorption. Martin Nalda et al.<sup>[95]</sup> subsequently reported the use of tacrolimus in six children with JDM with severe disease. These patients had been treated with tacrolimus for at least 1 year, and were reported to have experienced improvements in muscle and skin disease, and to have successfully weaned their corticosteroids. The use of topical tacrolimus has also been reported in adult DM, with mixed results,<sup>[96,97]</sup> but there is little evidence published in children to date. These small studies are far from adequate to establish the role of systemic tacrolimus in JDM, but may provide some preliminary evidence that warrants future investigation.

There are a variety of medications that are commonly used in JDM that have not been reviewed here. These include intravenous gammaglobulin, systemic ciclosporin, and azathioprine. These have not been considered because there have been no recent developments to warrant their inclusion. However, there is an ongoing large, international clinical trial being conducted by the Pediatric Rheumatology International Trials Organization, which will compare prednisone alone, prednisone plus methotrexate, and prednisone plus ciclosporin as initial therapy in JDM. This important study should definitively establish the role of both methotrexate and ciclosporin in JDM. Also, there are a variety of immunosuppressant medications, such as mycophenolate mofetil, which have been used in small numbers of patients with JDM, with occasional published abstracts, but no other data to indicate their role in the management of JDM. For this reason, their inclusion in a review such as this has been deferred until such time as more data are available.

#### 4. Conclusions

This article provides a review of the advances in the understanding of pathogenesis, evaluation, and treatment of children with JDM. This is indeed an exciting time to be involved in the care of these children. Studies on pathogenesis are providing important insights into the sequence of events that lead to JDM. These studies may, in the future, allow determination of patients at highest risk for poor outcomes, and point the direction to safer and more effective treatment. Considerable advances in the evaluation of JDM will facilitate clinical trials of new therapies, and help to standardize clinical measurement in both research and clinical contexts. Finally, new medications such as rituximab, and new ways of using older medications, such as methotrexate, promise to lead to improvements in treatment for children with JDM and associated reductions in morbidity. There remains much work to be done, but it is clear that research is leading to a much better understanding of this complex and fascinating disease.

#### Acknowledgments

No sources of funding were used to assist in the preparation of this review. The author has no conflicts of interest that are directly relevant to the content of this review.

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