Review - CME

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Progress and prognosis in juvenile dermatomyositis

Jeffrey A Dvergsten*,[1] & Ann M Reed[1]

[1]Duke University Medical Center, PO Box 3212, Durham, NC, USA

*Author for correspondence: jeffrey.dvergsten@duke.edu

With the advent of corticosteroids as a treatment option for autoimmune disease in the early 1960s, the course of juvenile dermatomyositis was altered from one of high mortality to one with various degrees of morbidity. Prior to treatment with corticosteroids, juvenile dermatomyositis resulted in recovery, recovery with chronic disability or death. Corticosteroids significantly decreased mortality and by modifying disease course, morbidity but introduced additional complications. Biomarkers of disease activity, as well as predictors of disease course and severity, are lacking but are a focus of current investigation. Improved understanding of pathogenesis has expanded medication choices to treat both new-onset and refractory disease. Published consensus treatment plans are being implemented, facilitating studies of comparative effectiveness and toxicity.

Keywords: biomarkers • consensus treatment plans • corticosteroids • morbidity • mortality • pathogenesis • refractory disease

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LEARNING OBJECTIVES

Upon completion of this activity, participants will be able to:

- Analyze the disease state of juvenile dermatomyositis
- Assess diagnostic tools for juvenile dermatomyositis
- Evaluate the prognosis of juvenile dermatomyositis
- Distinguish first-line therapy for juvenile dermatomyositis

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Author & credentials: ***Jeffrey A Dvergsten, MD,*** *Duke University Medical Center, PO Box 3212, Durham, NC, USA.*
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Why this review?

Although the prognosis of juvenile dermatomyositis (JDM) has improved dramatically since the introduction of corticosteroids, it remains a disease with significant morbidity with many patients on chronic immunosuppression years after diagnosis [1–3]. The goals of this review are: to give a historical and current perspective to the diagnosis, treatment and outcomes of JDM; present developments in our understanding of the mechanisms of JDM pathogenesis including the relationship of these mechanisms to disease measures; and, finally, describe the progress of multi-institutional collaborative efforts to improve our knowledge of JDM by building and characterizing large cohorts.

Juvenile dermatomyositis

Dermatomyositis (DM) is one of a group of rare systemic autoimmune diseases with the common characteristic of muscle weakness – the idiopathic inflammatory myopathies (IIM). In children, JDM is the predominant IIM with an annual incidence of approximately 1.9–3.2 cases per million [4,5]. Clinical, histopathologic and radiographic features are the results of a systemic, presumably autoimmune vasculopathy [6]. JDM is characterized by proximal muscle weakness with evidence of muscle inflammation and characteristic skin findings present in children before 18 years of age in North America or before 16 years of age in Europe (Table 1). JDM has similar histopathologic findings as adult DM, but JDM does not carry the same risk of malignancy and interstitial lung disease as is encountered in adult DM [7–9]. Currently, JDM has a 5-year survival of >95% [1], but morbidities secondary to disease (lipodystrophy, persistent weakness or calcinosis), as well as treatment remain significant challenges [10,11].

Historical perspective

The clinical features of DM were described independently in 1887 by Wagner, Hepp and Unverricht; however, in 1891, Unverricht first designated these findings as 'dermatomyositis' [12]. Children were initially believed to exist on the young end of a continuum of disease that primarily affected middle-aged persons and, as such, were included in early case series with adults [13,14]. Karelitz and Welt's review of the literature in 1931 revealed 75 cases of DM with 22 occurring in childhood [15]. In 1960, Banker [16] asserted her view that DM in children is a different entity from that affecting adults. In 1966, Pearson differentiated juvenile from adult DM in his classification [17]. Also in 1966, Banker and Victor described the pathologic findings in affected muscle being consistent with vasculitis [18]. Corticosteroids were used initially in treating adults with DM [17]; their use in children became more generalized in the late 1960s [18]. With increased use, there were studies into how to optimize therapy while minimizing treatment side effects [19,20]. These issues continue to be the focus of research efforts today even as our understanding of the intricacies of JDM increases.

Etiology & pathogenesis of JDM

As in many systemic autoimmune diseases, the etiopathogenesis of JDM is incompletely understood. Etiologic factors are multiple, based on a genetic predisposition that renders an individual susceptible to dysregulation of molecular and cellular processes involved in initiating and maintaining an immune response following inciting environmental exposures. In JDM, both the innate and adaptive immune systems are implicated in the development of an autoimmune vasculopathy that leads to complement activation, upregulation of MHC class I and inflammation in muscle and skin resulting in the clinical features of the disease (Figure 1) [21–24]. Current investigation is focused on elucidating the contribution of component parts of the immune system in initiating and perpetuating the disease, including the role of genetic risk loci in conferring disease and the interactions of cellular and soluble mediators of immunity in breaching regulatory mechanisms intended to keep the immune response in check. Advances in understanding the pathogenesis of JDM is opening up avenues for improved diagnosis, disease severity staging, prediction of disease course and better directed therapies.

Table 1. Clinical features of juvenile dermatomyositis.

Constitutional	Cutaneous/subcutaneous	Musculoskeletal	Pulmonary	Gastrointestinal
Fever Fatigue Weight loss Adenopathy	Malar rash Heliotrope rash Gottrons sign/papules Periungal telangiectasias Calcinosis Lipodystrophy	Proximal muscle weakness Myalgia Arthralgia/arthritis Pharyngeal/ hypopharyngeal/palatal weakness Flexion contractures	Respiratory muscle weakness	Esophageal dysmotility GI bleed/perforation Malabsorption Pancreatitis Cholecystitis

Single nucleotide polymorphisms in MHC & non-MHC regions

Genetic susceptibility to autoimmunity may be incurred by changes to genomic DNA; the most notable and extensively studied region being the MHC or in humans also known as HLA. MHC and non-MHC gene variants occur through changes in nucleotide sequences including those of a single nucleotide (single nucleotide polymorphisms [SNPs]).

The HLA 8.1 ancestral haplotype (HLA-B*08; DRB1*03; DQA1*05; DQB1*02) is recognized as the principal immunologic determinant in JDM conferring risk, as well as protective factors [25–27]. A recent multinational genome-wide association studies analysis of patients of European ancestry with either adult or JDM supported this conclusion as the genome-wide association studies identified the MHC as the strongest genetic risk locus [28]. In addition, examination of genetic regions outside the MHC identified three SNPs linked to three novel genes that associated with both adult and JDM. The proteins encoded by these genes, PLCL1, B lymphoid tyrosine kinase and CCL21, have roles in cell signaling, cell proliferation and differentiation and chemotaxis, respectively. Additional proteins with roles in cell signaling have been implicated in adult DM. In a Japanese population of adult DM, a SNP of the *STAT4*, re7574865, was associated with DM, specifically the re7574865T allele [29]. The presence of the *STAT4* gene is believed to be a risk factor in many autoimmune diseases including sytemic lupus erythematosus, rheumatoid arthritis and juvenile idiopathic arthritis [30]. A SNP at residue 620 (R620W) of the gene encoding PTPN22 has also been associated with susceptibility to adult and JDM [31]. Although these non-MHC associations did not reach a genome-wide level of significance, they may support the concept of quantitative thresholds of immune cell signaling which postulates that the sum effect of genetic polymorphisms is integral in the pathogenesis of autoimmune disease [32,33].

SNPs in genes encoding proinflammatory cytokines

Proinflammatory cytokines including TNFα and the interleukins (IL-1α, IL-1β and IL-6) are implicated in the pathogenesis of DM and JDM [34–36]. Polymorphisms in the TNFα-308A promoter region have been associated with an increased production of TNFα from peripheral blood mononuclear cells (PBMCs) [34]. Using a functional reporter cell assay, Niewold and colleagues examined serum expression of type I interferon (IFN)-induced genes in 39 patients with JDM; their results provided evidence that IFN-α activity was associated with the -308A allele [37]. Mamyrova *et al.* studied TNFα and IL-1 cytokine polymorphisms and identified risk as well as protective polymorphisms associated with JDM [35]. They confirmed the -308AG genotype as a specific risk factor for JDM, as well as TNFα-238GG. TNFα-238AG and the carriage of the TNFα-238A allele were protective. In addition, polymorphisms of IL-1α +4845TT and IL-1β +3953T were identified as risk factors and the presence of the IL-1α +4845G allele as being protective. In a study of adult Bulgarian patients with DM, the IL-6–174G/C promoter polymorphism was not found to be associated with DM [38]. Serum levels of IL-6 have been shown to be elevated in patients with adult and JDM suggesting a role in disease pathogenesis and perhaps a therapeutic target [36,39].

Cellular aspects of DM

Histiopathologic examination of tissues affected in the course of DM has directed investigations of various cell types believed to be important contributors to the pathogenesis of DM [40–42]. These cells, in nonpathogenic states, are primarily involved in innate and adaptive immunity and include dendritic cells (DCs), particularly, plasmacytoid DCs (pDCs); various phenotypes of T and B cells; natural killer (NK) cells, macrophages and mast cells [24,43,44]. The cells and their products are responsible for the histopathologic findings, as well as the cytokine signatures seen in DM.

In affected muscle from patients newly diagnosed with JDM, de Padilla and colleagues found that pDCs (identified by expression of CD4 and CD123) were found throughout inflamed muscle tissue, as well as in foci of cellular aggregates in the perimysium and perivascular areas [43]. These cells expressed CD83, a marker of pDC activation; in contradistinction, control

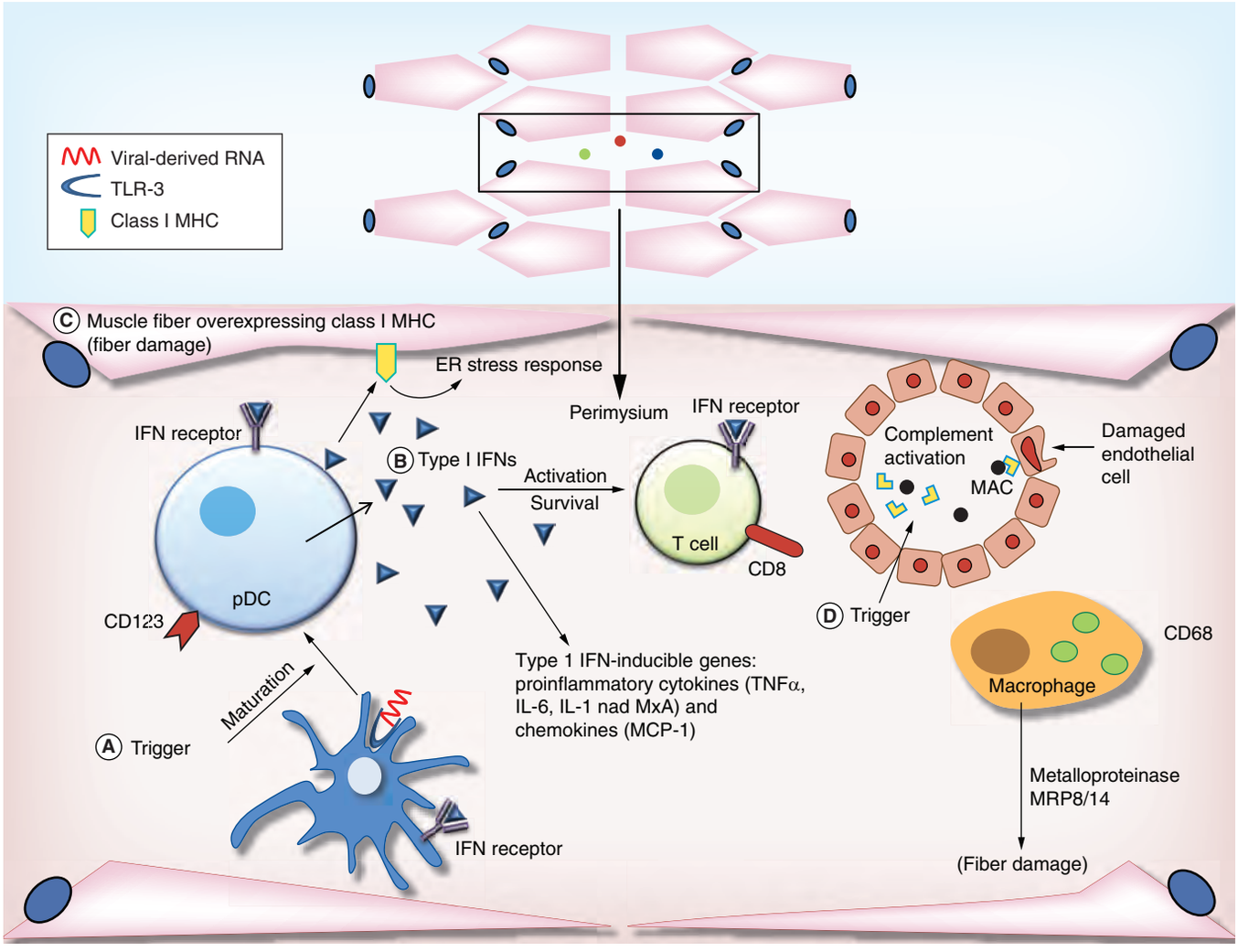

Figure 1. Proposed mechanisms of pathogenesis of juvenile dermatomyositis. (A) Activation of the innate immune system by an environmental trigger resulting in maturation of dendritic cell. **(B)** IFN produced by pDC has many effects including activation and survival of cytotoxic T cells, production of proinflammatory cytokines/chemokines and **(C)** upregulation of class I MHC with resultant ER stress and damage. **(D)** Immune complex deposition leads to inflammation of small muscular arteries and infarction of muscle. ER: Endoplasmic reticulum; IFN: Interferon; pDC: Plasmacytoid dendritic cell.

muscle specimens contained few CD123$^+$ cells with no co-expression of CD83. In skin, mature pDCs were identified by immunohistochemical analysis (presence of DC-LAMP) and found to be present throughout the epidermis and dermal layers, as well as perivascularly [24]. The expression of DC-LAMP was significantly greater in affected skin than in control skin. The pDC, through its ability to produce significant quantities of IFN-α, has numerous effects on systemic autoimmunity including stimulatory and regulatory roles, as will be discussed later. Furthermore, Nistala *et al.* reported that muscle biopsies from patients with JDM were infiltrated by CD68$^+$ (specific for cells of myeloid lineage) macrophages; these cells secreted the MRP8/14, a proinflammatory protein which leads to muscle damage [44]. The IFN-α-associated chemokine MCP-1 and IL-6 was also found to be present in JDM muscle tissue and serum, these believed to perpetuate inflammation through recruitment of inflammatory cells to affected muscle. MCP-1 and IL-6 have been proposed as biomarkers for disease activity [36]. Immature and mature CD4$^+$ T cells are a major component of cellular infiltrates and these cells have been found to form neolymphoid structures in JDM muscle along with pDCs and B cells suggesting a local maturation of T cells [43,45].

Mast cells affect multiple arms and functions of the immune system including immunosurveillance, as well as the generation, perpetuation and termination of an immune response [46]. It has been demonstrated that the number of mast cells infiltrating the skin from patients with JDM was significantly higher than

that in skin from nonaffected controls; however, there was no significant difference between infiltrations of affected versus control muscle tissue suggesting a specific role for mast cells in skin and a different mechanism for perpetuation of the immune response in skin compared with muscle [24].

Cells believed to have a role in DM pathogenesis are also found in patient serum [44,47,48]. In a study of peripheral blood lymphocytes (PBLs) from newly diagnosed, untreated children with JDM, the percentage of circulating total B cells ($CD19^+$) was significantly increased compared with age-matched controls [47]. However, the proportion of activated B cells was not different between the two groups. There was a decrease in the percentage of $CD3^-$ $CD16^+$ and/or $CD56^+$ (denoting NK cells) and $CD3^+$ $CD8^+$ suppressor/cytotoxic T cells. It was concluded that the increase in B cells was relative to the decrease of circulating $CD8^+$ T cells and/or NK cells co-expressing CD54 (ICAM-1), the decrease occurring as these cells were redirected to areas of inflammation. Increased numbers of $CD56^+$ NK cells have been found in affected muscle in children with JDM [43]. Longitudinal analysis of JDM PBL subsets has correlated PBL phenotypes with an improved clinical course; these phenotypes include $CD3^+$ $CD69^+$ T cells, HLA-DR^- $CD11c^+$ myeloid DCs and HLA-DR^- $CD123^+$ pDCs [48].

Type I IFN signature in DM

Type I IFNs (IFN-α, IFN-β and IFN-ω, among others) have multiple effects that bridge the innate and adaptive immune systems. They have important roles in the maintenance and regulation of immune processes such as antigen presentation (MHC class I expression, maturation of DCs), activation of signaling pathways involved in induction of genes encoding proinflammatory cytokines and chemokines, proapoptotic proteins, as well as differentiation of T cells. Type I IFN is difficult to measure in tissue and serum, therefore, assays have been developed that measure the expression of type I IFN-regulated genes including MxA [49,50]. Gene expression profiling in patients with adult and JDM has revealed differential type I IFN signature overexpression in muscle and serum [36,50–52]. Bilgic and colleagues found that a type I IFN gene expression signature was significantly upregulated in serum samples from a cohort of 56 DM patients (19 patients with JDM) [36]. Upregulation was significantly correlated with disease activity as measured by the physician's global visual analog scale. In an effort to better delineate which type I IFN initiated upregulation of these genes, Liao and colleagues measured serum levels of IFN-α, IFN-β and IFN-ω, as well as IFN-inducible gene expression in PBMCs of patients with adult DM [53]. They found that serum levels of IFN-β, but not IFN-α or IFN-ω, were highly associated with DM. They also found that IFN-β was significantly correlated with IFN gene signatures. IFN-α is believed to play a role in upregulation of MHC class I on myofibers. Accumulation of class I proteins in the endoplasmic reticulum (ER) results in ER stress leading to muscle injury [54]. In addition, cytokine and chemokine upregulation induced by type I IFNs may contribute to this injury [41,55]. Muscle biopsy specimens in JDM display a high level of IFN-α gene expression, which supports the correlation between muscle inflammation and levels of serum IFN activity [49,56]. Taken together, these findings suggest that specific IFN signatures may serve as biomarkers of disease activity in JDM [57].

Autoantibodies in JDM

The influence of autoantibodies in identifying a JDM disease phenotype, and determining disease course and severity is an active area of research [58]. Certain antibodies are found in autoimmune disease with myositis as a clinical feature and are called myositis-associated antibodies, with the most common being anti-Ro and anti-La. A second group of antibodies are termed myositis-specific antibodies (MSAs). MSAs target cytoplasmic or nuclear antigens involved in numerous molecular processes including protein synthesis and translocation, and gene transcription. 'Classic' MSAs include anti-synthetase (histidyl-tRNA synthetase [Jo-1]), anti-signal recognition particle and anti-Mi-2, a DNA helicase. Recently identified MSAs include anti-p155/140 (targeting transcription intermediary factor 1-γ protein) and anti-p140 (anti-MJ) targeting NXP2 [59]. Rider and colleagues reported results including demographic, clinical and laboratory characteristics among MSA subgroups from a large cohort of patients with JIIM including JDM [60]. They found that specific MSAs may define clinically distinct phenotypes, as well as predictors of disease severity and outcome. In their cohort of 374 patients (320 with JDM), 68% of patients with JDM had at least one MSA. In contradistinction to previous reports, more than one MSA was identified in approximately 2% of patients, the most common being anti-Mi-2 with anti-p140, anti-p155/140 or anti-MJ. The most common MSAs associated with JDM were anti-p155/140 (38%), anti-MJ (24%), anti-synthetase (Jo-1 being the most common at 5%) and anti-Mi-2 (3%).

Diagnosis

The diagnosis of JDM is made by meeting both clinical and laboratory criteria. Despite advances in the understanding of the etiopathogenesis of JDM and the

likely diversity of pathologic processes involved, the criteria proposed by Bohan and Peter in 1975 remain the standard for diagnosis and classification [61]. Based on these criteria, a diagnosis of definite JDM requires either a positive finding on electromyelogram (EMG) or by muscle biopsy. However, results from multicenter cohorts reveal utilization of muscle biopsy in approximately 50% of cases and EMG ranging from 32 to 61% [62,63], despite procedure accessibility (89 and 87%, respectively) [62], reflecting the move toward noninvasive measures such as MRI to aid in diagnosis. Changes in clinical practice have been the impetus for modification of the Bohan and Peter criteria both to address change in practice, as well as to develop uniform criteria for clinical studies [58,64,65].

MRI in the diagnosis of JDM

Currently MRI supports clinical and laboratory findings consistent with the diagnosis of JDM and detects affected muscle for biopsy. MRI is a sensitive tool for determining muscle inflammation and T2-weighted or short-tau inversion-recovery images demonstrate muscle and perimuscular edema, and fascial signal abnormalities; T1-weighted images may reveal fibrosis, atrophy and fatty infiltration of muscle [66]. However, these findings may be present in other muscle diseases. Despite the lack of specificity limiting its use as an independent diagnostic tool, MRI is an important adjunct in the diagnosis of JDM. In the analysis of diagnostic studies employed by clinicians contributing to the CARRA JDM cohort, MRI was the most commonly performed with 90% of patients imaged prior to enrollment [63]. Additionally, MRI was more likely to reveal findings consistent with disease as compared with muscle biopsy or EMG (91 vs 76 and 50%, respectively) although the timing of these investigations in the course of disease was unknown and prior therapy may have decreased the sensitivity of any given study. In a survey of members of the Network for JDM and the Paediatric Rheumatology International Trials Organization (PRINTO), MRI was utilized by 58% of respondents; accessibility to MRI for these respondents varied significantly ranging from 25% in Asia to 100% in the USA and Canada [62].

The changing role of muscle biopsy

Case series comprising patients from the 1960s through the 1990s report use of muscle biopsy for diagnostic purposes in approximately 85% of patients diagnosed with JDM [19,21,22,63,65]. Results consistent with myositis ranged from 87 to 92% [22,67,68]. More recently, Wargula *et al.* report 92% of 59 biopsy specimens as consistent with JDM [23]. The routine use of muscle biopsy in the diagnosis of JDM is waning [63], and currently its role diagnostically is in identifying disease not clearly distinguished by clinical, laboratory or radiographic features [62,69–72]. Due to the potential spotty involvement of the muscle, excisional biopsy is most often performed; however, improved ability to identify affected muscle with MRI guidance may increase the yield of needle biopsy [73]. Histopathologic findings characteristic for JDM are also seen in other myopathies, however, in such cases where conventional histologic features are not supportive of a diagnosis, additional findings such as MHC-I expression in muscle fibers have been proposed as an adjunct to establish the diagnosis with supporting clinical and laboratory data [72]. Varsani, reporting for the UK Juvenile Dermatomyositis Research Group describes the validation of a modified JDM biopsy score tool with high inter-and intra-observer agreement for a histological score estimating severity of pathological change. The scoring system includes inflammatory, muscle fiber, vascular and connective tissue domains; aspects of the scoring system were found to correlate with clinical disease activity [74]. Information gained from determining extent of histopathologic damage as a correlate of clinical course and outcome, as well as the utility of tissue markers in determining pathogenesis, course, treatment response and outcome of this disease make it difficult to deny the role of muscle biopsy in JDM [22–24,45,71,75].

Course

The heterogeneity of presentation of DM has been long appreciated with symptoms ranging from absence of weakness and rash to ulcerative skin disease with debilitating weakness. Prior to corticosteroid therapy, disease course tended to be one of chronicity with high morbidity and mortality [76]. Corticosteroids significantly altered the course of disease, revealing different patterns of disease, and led to attempts to categorize patients into groups based on histopathologic features and duration of disease activity [20,22,34,68,77]. Three courses, excluding death, are generally described in studies including: limited (mild, monocyclic), intermediate (moderate, polycyclic) and chronic (chronic ulcerative, chronic continuous, persistent) progression of disease [20,22,67,68,77,78]. Despite current interventions, most case series report chronic disease course [2,23,77,78]. Higher scores on the Childhood Assessment Questionnaire (CHAQ) were associated with a chronic continuous disease course [2]. Chronic disease course has been determined to be a predictor of poor outcome [1,79].

Disease inactivity & remission

Factors relevant to determination of disease course include achievement of clinically inactive disease and remission; however, there is currently no consensus as

to what defines these disease states and, presently, institutional practice is likely to designate the variables used to define these states [77]. However, as more information regarding clinical, laboratory and histopathologic features as determinates of disease course become available, distinct definitions are likely to evolve. Utilizing definitions of disease inactivity derived from the literature, Lazarevic *et al.* utilized the PRINTO database to develop multiple combinations of inactive disease criteria placing these in rank order as to their ability to characterize inactive disease [80]. Classification of a patient as having inactive disease was found to best be determined by a combination of three of four of the following variables: creatinine kinase ≤150, childhood myositis assessment scale (CMAS) score ≥48, manual muscle testing (MMT) score ≥78 and a physician global assessment of overall disease activity (PhyGloVas) ≤0.2 mm. The goal of developing such criteria is that these may be used in clinical practice (i.e., determining length of therapy), research (standardizing studies) and clinical trials (development of new therapies).

Measures of disease activity

Measures of disease activity are used clinically to determine response to treatment and also as research instruments to assess variables associated with, and proposed to be, predictors of disease course, activity and outcome. These measures include but are not limited to the Disease Activity Score (DAS), MMT, CMAS, Global Assessments of Disease Activity (physician, parent and subject) and CHAQ. Two international study groups, the International Myositis Assessment and Clinical Studies Group and PRINTO have developed consensus core set measures utilizing groups of individual measures to evaluate response to therapy in patients with JDM [81,82]. Measures employed in assessment of myositis activity and damage in adults and children are comprehensively summarized by Rider and colleagues [83].

Predictors of disease course, activity & outcome: demographic

Age and sex of patients with JDM have been investigated to determine their relationship to factors affecting course, activity and outcome [84,85]. Characteristics of disease at a young age of onset have been proposed to determine a different disease phenotype than later onset although there is no consensus among reports as to a specific phenotype and young age does not appear to predict a poor outcome [1,84,85].

Female sex has been associated with significantly higher CHAQ scores suggesting poorer outcome for females; however, the author stressed the importance of prospectively evaluating additional cohorts as poorer outcome has not been a consistent finding [2]. Niewold *et al.* report a gene–gene, gene–sex interaction in cytokine polymorphisms of osteopontin and TNFα-308A, two alleles associated with high serum IFN-α activity and JDM pathogenesis which may explain the female predominance of JDM [37].

Clinical features

Cutaneous findings have been proposed as predictors of disease course and severity. The presence of rash (most strongly indicated by Gottron's papules) at 3 months was the earliest predictor of a longer time to remission in a study examining early clinical features in determining course [81]. At 6 months, nailfold capillary abnormalities, in addition to rash predicted a longer time to remission in the same study. Early involvement of skin has also been associated with cardiac dysfunction in a long-term follow-up cross-sectional study of JDM patients using skin DAS [86]. Abnormal nailfold capillaries have long been recognized as a predictor of chronic disease in JDM [87]. Abnormal capillary findings have been considered a noninvasive measure of disease activity [87–90]. Schmeling *et al.* determined nailfold capillary density to be a marker of skin and muscle disease using the CMAS and a modified DAS incorporating three skin (SDAS) and three muscle (MDAS) criteria [91]. However, even though nailfold capillary density improved with treatment, it was not found to correlate with outcome or course of disease. The number of capillary end row loops has been found to correlate with length of untreated disease with a normal number associated with a shorter duration of symptoms [92].

Histopathologic features

One of the most consistent factors affecting disease course is degree of vasculopathy as evidenced by cutaneous and subcutaneous findings [22,77,93]. Wargula and colleagues, using Crowe's classification of disease course [22], investigated the correlation of specific muscle histopathology with disease course and severity in children with JDM [23]. They found that the presence of infarct and direct immunofluorescence staining of intramuscular arteries or capillaries for one or more of: IgA, IgG, IgM, C3c, C3d, C5, C1q and/or fibrinogen was associated with development of chronic ulcerative disease. Additional findings including perifasicular myopathy were not correlated with disease course. The muscle biopsy scoring tool evaluated by the UK DRG was developed to measure histological severity however morphologic changes were also found to correlate well with muscle strength and clinical measures of disease activity including the Physician Global Assessment and CMAS [74].

Radiographic features

Malattia *et al.* addressed the significant challenge of addressing disease activity versus chronic damage by utilizing a whole-body MRI (WB-MRI) muscle score combined with measures of disease activity including MMT and CMAS to compare WB-MRI with clinical exam and correlate results with disease activity measures [94]. Of 41 patients, seven did not demonstrate abnormal muscle signal intensity. The remaining 34, including one diagnosed as amyopathic, demonstrated signal abnormalities including focal and patchy distribution (n = 27) and diffuse, homogenous distribution (n = 7) typically in proximal muscles (n = 26), but also in clinically asymptomatic distal musculature (n = 19). The fact that WB-MRI was able to detect subclinical disease highlighted the importance of further investigating its role in prognosis and outcome. Also examined were signal abnormalities in subcutaneous tissue and myofascia. Use of MRI findings at diagnosis as a predictor of disease outcome has also been investigated in JDM [93]. Disease severity was classified subjectively by comprehensive MRI appearance as normal, mild, moderate or severe. Controlling for disease duration, the odds ratio for progressing to chronic disease was higher for those individuals with abnormal signal findings in the subcutaneous tissue. Involvement of subcutaneous tissue has been associated with dystrophic calcification [95].

Looking at MRI T2 relaxation times of thigh musculature from patients with JDM, Maillard and colleagues found a correlation between relaxation times and measures of muscle strength (MMT and myometry) and function (CMAS), as well as general function (CHAQ) [96]. In addition, they reported that the T2 relaxation time is significantly increased in patients with active versus inactive disease and controls, concluding that MRI T2 relaxation time can be used as a quantitative measure of inflammation in children with JDM.

Cellular/molecular factors

Investigations for sensitive biomarkers as indicators of disease activity, as well as measures of response to therapy have been augmented by advances in genomic and proteomic technology. In JDM, cytokine signatures, MHC molecules, MSAs, genomic modifications and PBMC phenotypes have all been identified as useful in determining disease characteristics [34,35,37,48,97].

TNFα and IL-1 genetic polymorphisms have been proposed as indicators of disease severity [35]. Additionally, the TNFα-308A polymorphism has been associated with the development of calcinosis, ulcerations and a chronic disease course [34,35]. Reed *et al.* calculated whole blood type I IFN and chemokine scores in patients with JDM, collecting information prospectively regarding disease activity and measuring serum levels of type I IFN-inducible genes, IFN-regulated cytokines and chemokines [58]. They concluded that changes in the type I IFN gene and chemokine scores as well as in cytokine levels of TNFα, IL-6 and IL-8 may serve as sensitive markers of change in disease activity.

The presence of the anti-p155/140 doublet in patients with JDM may determine a more severe course [59]. Anti-p155 autoantibody has been associated with development of lipodystrophy, a complication of JDM with a prevalence of 10–40% that results in a localized or generalized loss of subcutaneous fat [98]. Anti-p140 has been associated with calcinosis and determination of its presence at disease onset may provide information regarding risk and prognosis [59]. In patients with refractory JDM who received treatment with rituximab, a multivariable analysis was used to evaluate the association of individual predictive factors with improvement [99].

Outcomes

Mortality

Bitnum's hallmark report from 1964 is often cited when considering the mortality rate prior to the general use of corticosteroids in JDM [76]. At that time, the mortality rate was approximately a third; it was also noted, that if a child did not die in the first 2 years, they were likely to survive although with deformities and disabilities. In evaluating a large cohort of pediatric patients with rheumatologic diagnoses, Hashkes and colleagues described the limitations of studies obtained prior to the 1990s [100]. They report on a cohort of 39,221 patients with data collected prospectively from 1992 to 2001, with 662 (2.8%) having a diagnosis of JDM. They note 5 deaths (0.8%) in these patients but a standardized mortality ratio, comparing observed deaths to expected deaths of 2.64. Four deaths were related to JDM complications including two from heart disease, one from aspiration pneumonia and one from gastrointestinal perforation. Huber, for the Childhood Myositis Heterogeneity Study Group, reported a rate of JDM mortality of 2.4% with cause of death primarily related to pulmonary causes (n = 4) with one patient succumbing to gastrointestinal hemorrhage [101]. Mortality risk factors identified in univariable analysis included presence of anti-synthetase autoantibodies, interstitial lung disease and older age at diagnosis.

Morbidity

As current therapy has improved overall mortality the question of impact on morbidity remains, including the contribution of treatment-related morbidity. Noted previously, most patients follow a chronic course of disease which exposes them to the effects

of ongoing inflammation, as well as the effects of medications that have significant short-term and long-term effects. Recent studies report that approximately 30% of patients continue on medications at long-term follow-up [1–3]. In the Norwegian cohort, patients diagnosed before 1990 were less commonly treated with MTX (38 vs 65%; p = 0.039), methylprednisolone (3 vs 26%; p = 0.027) and anti-malarial agents (21 vs 61%; p = 0.001) [3]. Patients treated before 1990 also had more accumulated organ damage. Disease-related morbidities include: calcinosis, cutaneous scarring, lipodystrophy, muscle atrophy, joint contractures and persistent weakness [1,3]. Calcinosis remains a significant morbidity and there has not been any consistently effective treatment and despite aiming therapies at various physiologic pathways there is no evidence beyond case reports and case series to support any as a standard therapy [102–106].

Treatment of JDM

There is currently little evidence on which to base treatment for JDM. The lack of randomized controlled trials has led to treatment strategies dictated by factors including disease phenotype, regional experience and results from treatment of adult DM. Corticosteroids are the mainstay of therapy but adverse effects of long-term use lead to significant morbidity including growth suppression, osteoporosis, avascular necrosis and metabolic derangement. Small studies have been performed investigating dose, route of administration and length of therapy with corticosteroids in an effort to minimize overall exposure and limit side effects [107–109]. Ramanan *et al.* investigated the use of methotrexate as a steroid-sparing agent allowing a more aggressive wean of corticosteroids in a retrospective cohort study of 31 patients with JDM [110]. They reported a decrease in mean duration of corticosteroid use from 27 to 10 months as compared with historical controls.

Methotrexate is now generally considered to be first-line therapy along with corticosteroids. Stringer and colleagues presented North American pediatric rheumatologists (CARRA members) with clinical cases of varying severity (mild to severe, including ulcerative) [69]. Methotrexate, in combination with corticosteroids, was the most common combined therapy at disease onset (range 30–44% depending on disease severity). Methotrexate was also the most common second-line agent used, alone or in combination with other agents, in up to 84% of cases. In a PRINTO study to evaluate response to therapy in an international cohort of an intent-to-treat population of 275 patients (174 patients completed the study), Hasija *et al.* reported data on geographic treatment practices in four regions, Western Europe, Eastern Europe, North America and Central and South America [111]. Patients were divided into two groups, recent-onset disease versus disease flare, and treatment was evaluated at baseline, 6, 12 and 24 months. There was no significantly different use of methotrexate at baseline in the four regions for both recent-onset and disease flare groups; however, patients in North America were more likely to have been treated with methotrexate during disease course compared with the other three regions. Cyclosporine A use in Western and Eastern Europe was greater than in South, Central and North America in both groups with use greatest in disease flares. Preliminary results of a multisite, randomized trial comparing prednisone alone, prednisone and methotrexate and prednisone with cyclosporine A reported that both combinations were superior to therapy with prednisone alone. There were fewer adverse effects with methotrexate/prednisone versus cyclosporine/prednisone but response was similar [80].

Additional agents for treating severe or refractory disease have been reported in retrospective case series including intravenous immunoglobulin [112], mycophenolate mofetil [113,114], azathioprine [115], tacrolimus [116] and cyclophosphamide [117], as well as biologic agents including etanercept, infliximab [118] and rituximab [119,120]. The efficacy and safety of rituximab in refractory myositis – JDM, adult DM and polymyositis – was evaluated in a prospective, randomized controlled cross-over study [121]. There was no significant difference in time to improvement between treatment groups; however, 83% of patients met the definition of response. Of importance, the addition of rituximab was noted to have a significant steroid-sparing effect. This study suggested that rituximab may be effective and warrants further investigation. Figure 2 summarizes current medications used in treatment of JDM based on disease phenotype.

Consensus treatment plans

Using information gathered from the JDM treatment survey [69] and expert opinion, CARRA members developed three consensus plans for the treatment of moderately severe JDM [121,122]. These include combinations of methylprednisolone, prednisone, methotrexate and intravenous immunoglobulin (Figure 3). The goal of the consensus treatment plans (CTPs) is to collect prospective data regarding the efficacy and toxicity of the various regimens with the potential of developing evidence-based recommendations for the treatment of JDM.

Conclusion

The use of corticosteroids have significantly reduced the mortality and morbidity associated with JDM. Current understanding of the impact of genetic predisposition, genetic polymorphism and the pleiotrophic

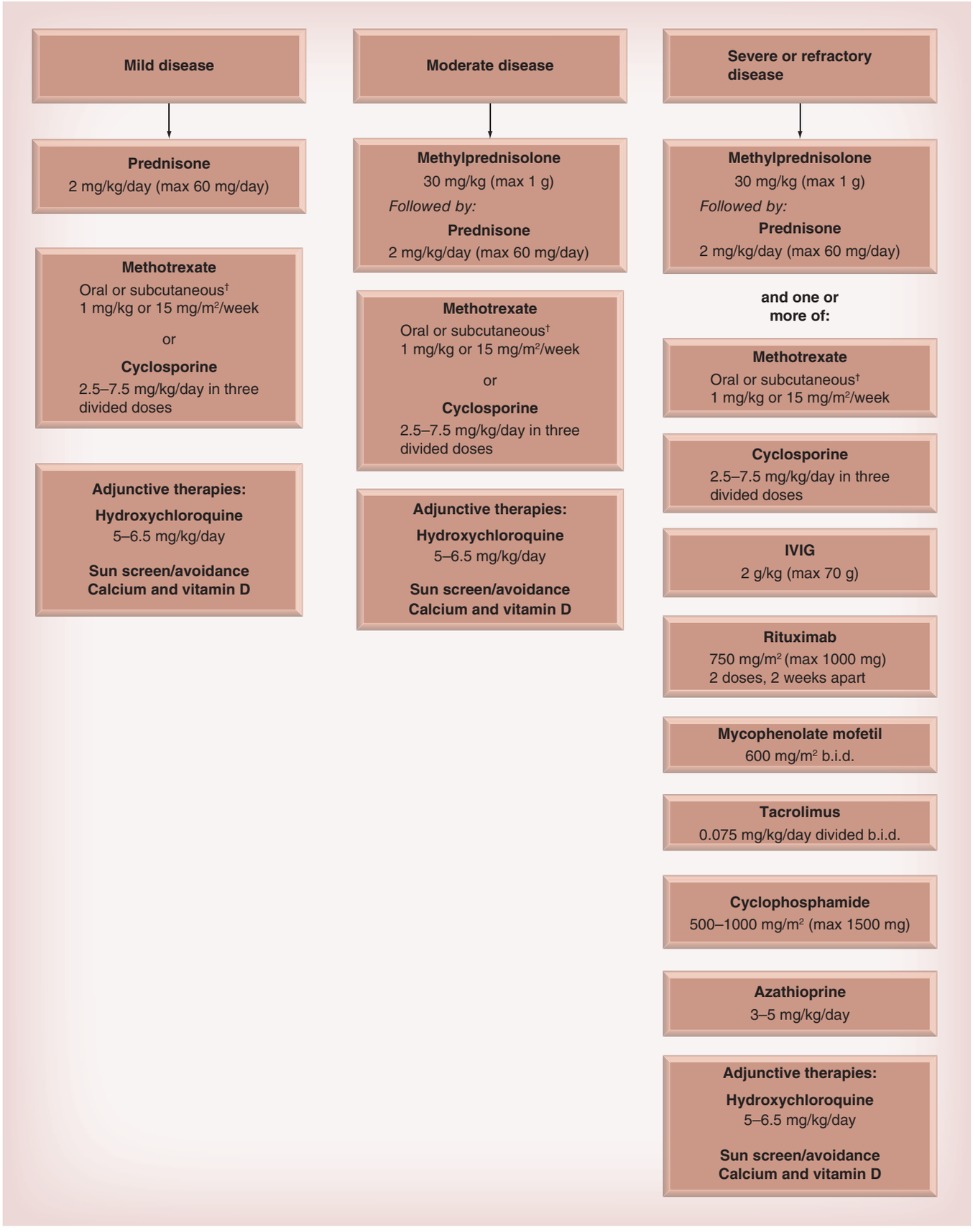
Mild disease
Prednisone
2 mg/kg/day (max 60 mg/day)
Methotrexate
Oral or subcutaneous†
1 mg/kg or 15 mg/m²/week
or
Cyclosporine
2.5–7.5 mg/kg/day in three divided doses
Adjunctive therapies:
Hydroxychloroquine
5–6.5 mg/kg/day
Sun screen/avoidance
Calcium and vitamin D
Moderate disease
Methylprednisolone
30 mg/kg (max 1 g)
Followed by:
Prednisone
2 mg/kg/day (max 60 mg/day)
Methotrexate
Oral or subcutaneous†
1 mg/kg or 15 mg/m²/week
or
Cyclosporine
2.5–7.5 mg/kg/day in three divided doses
Adjunctive therapies:
Hydroxychloroquine
5–6.5 mg/kg/day
Sun screen/avoidance
Calcium and vitamin D
Severe or refractory disease
Methylprednisolone
30 mg/kg (max 1 g)
Followed by:
Prednisone
2 mg/kg/day (max 60 mg/day)
and one or more of:
Methotrexate
Oral or subcutaneous†
1 mg/kg or 15 mg/m²/week
Cyclosporine
2.5–7.5 mg/kg/day in three divided doses
IVIG
2 g/kg (max 70 g)
Rituximab
750 mg/m² (max 1000 mg)
2 doses, 2 weeks apart
Mycophenolate mofetil
600 mg/m² b.i.d.
Tacrolimus
0.075 mg/kg/day divided b.i.d.
Cyclophosphamide
500–1000 mg/m² (max 1500 mg)
Azathioprine
3–5 mg/kg/day
Adjunctive therapies:
Hydroxychloroquine
5–6.5 mg/kg/day
Sun screen/avoidance
Calcium and vitamin D

Figure 2. Treatment of juvenile dermatomyositis based on disease phenotype (see facing page). Disease severity is based upon physician assessment.
†GI absorption may be decreased early in disease course therefore intravenous/subcutaneous route is preferred.
b.i.d.: Twice daily; IVIG: Intravenous immunoglobulin.

effects of type I IFN in the dysregulation and perpetuation of inflammation has provided inroads into determining biomarkers of disease activity, as well as predictors of disease course and severity. Collaborative registries are providing information regarding clinical practice including diagnosis and treatment; the effects of these are prompting discussions regarding revised diagnostic criteria, use of minimally invasive measures of disease severity and activity as well as standardization of treatment.

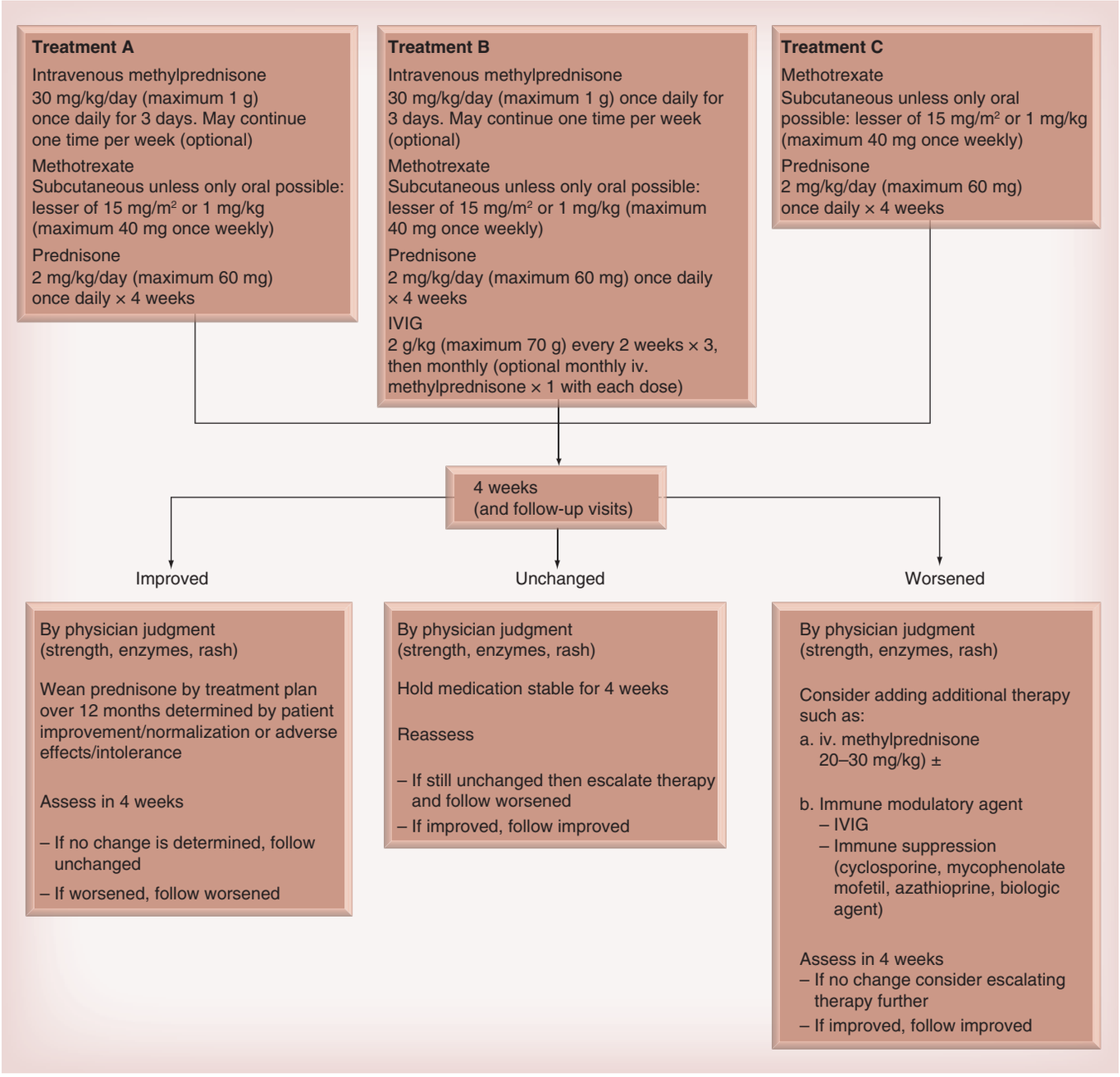

Figure 3. Consensus treatment protocols for moderate juvenile dermatomyositis.
iv.: Intravenous; IVIG: Intravenous immunoglobulin.
Adapted with permission from [121,122].

Future perspective

Forthcoming work will consist of further elucidation of the mechanisms of pathogenesis contributing to the clinical signs and symptoms of JDM including those involved in initiation and perpetuation of disease. Advances in identification and confirmation of biomarkers for diagnosis and disease activity will enable clinicians to tailor therapy thereby improving outcomes by limiting disease and medication related morbidities. Ongoing collaborative efforts will determine which treatment protocols are most effective in managing JDM including the roles of newer biologic agents.

Executive summary

Juvenile dermatomyositis

- Juvenile dermatomyositis (JDM) is the most prevalent idiopathic inflammatory myopathy of childhood, with an annual incidence of approximately 3.2 cases per million children.
- Disease is typified by proximal muscle inflammation with evidence of muscle inflammation and characteristic skin findings.
- With the initiation of corticosteroids in the 1960s, mortality decreased from approximately 33% to less than 5%.

Etiology & pathogenesis

- The etiopathogenesis of JDM is incompletely understood.
- Clinical findings, including pathognomonic skin findings, are the result of a systemic, presumably, autoimmune vasculopathy involving cellular and soluble constituents of both the innate and adaptive immune system.
- Genetic risk loci, primarily within MHC but also non-MHC regions, have been identified and are implicated in the pathogenesis of JDM.
- Interferon-inducible gene signatures may serve as biomarkers of disease activity and may guide therapeutic decisions in the future.

Diagnosis

- Criteria proposed by Bohan and Peter in 1975 remain the standard for diagnosis and classification of JDM.
- MRI has become an accepted, noninvasive modality for determining muscle involvement and is used in lieu of muscle biopsy and electromyelogram in diagnosis by a significant number of pediatric rheumatologists.
- Changes in clinical practice have raised interest in developing criteria based on current practice.

Course

- JDM has varied presentations and disease courses, which are likely dictated by extent of influence from genetic and environmental factors.
- Clinical, histopathologic and radiologic features have been proposed as predictors of disease course and severity.

Outcomes

- While mortality has decreased dramatically since the initiation of corticosteroids as treatment for JDM, morbidity continues to be significant related to both disease (calcinosis, lipodystrophy), as well as pharmacologic therapy (long-term effects of corticosteroids).

Treatment

- Consensus treatment protocols are currently available for investigating the efficacy and toxicity of various regimens in the treatment of moderate JDM.
- Future therapy may include use of anticytokine biologics as the role of these proteins in pathogenesis is better understood.

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Progress and prognosis in juvenile dermatomyositis

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Activity evaluation: where 1 is strongly disagree and 5 is strongly agree.					
	1	**2**	**3**	**4**	**5**
The activity supported the learning objectives.					
The material was organized clearly for learning to occur.					
The content learned from this activity will impact my practice.					
The activity was presented objectively and free of commercial bias.					

1. You are seeing a 7-year-old girl for findings suspicious for juvenile dermatomyositis (juvenile DM). As you evaluate this patient, what should you consider regarding the disease entity of juvenile DM?

- ☐ **A** It is characterized by an even balance between both proximal and distal muscle weakness
- ☐ **B** Juvenile DM shares histopathologic findings with adult DM
- ☐ **C** Juvenile DM is associated with a higher risk for interstitial lung disease compared with adult DM
- ☐ **D** Only the adaptive immune system is implicated in the pathogenesis of juvenile DM

2. Which of the following modalities is most often used to help make the diagnosis of juvenile DM?

- ☐ **A** Magnetic resonance imaging (MRI)
- ☐ **B** Clinical strength testing
- ☐ **C** Electromyography
- ☐ **D** Muscle biopsy

3. The parents of this patient are very concerned about her prognosis. What can you tell them?
- ☐ **A** Male gender portends a worse prognosis
- ☐ **B** Higher density of nailfold capillary abnormalities portends a longer time to remission
- ☐ **C** Younger age at onset is the most important risk factor for a poor prognosis
- ☐ **D** MRI findings are not helpful in establishing a prognosis

4. Which of the following is considered first-line treatment of juvenile DM?
- ☐ **A** Methotrexate and corticosteroids
- ☐ **B** Azathioprine and methotrexate
- ☐ **C** Infliximab or rituximab
- ☐ **D** Etanercept or anakinra