Advances in the treatment of juvenile dermatomyositis

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Purpose of review

Juvenile dermatomyositis is a rare chronic inflammatory disease that primarily affects the muscles and skin. Immunosuppressive therapy has played a very important role in reducing mortality rates and morbidity. The review focuses on the spectrum of medications currently used in the treatment of juvenile dermatomyositis, highlighting new advances and unanswered questions.

Recent findings

Data regarding the treatment of juvenile dermatomyositis come almost entirely from retrospective studies with relatively small numbers of patients. Corticosteroids continue to be the accepted first-line therapy. Evidence that the addition of methotrexate at initiation of treatment allows corticosteroids to be tapered more rapidly with good outcomes exists. High-risk, refractory patients may benefit from intravenous cyclophosphamide. Results in refractory patients treated with rituximab are also encouraging. Topical immunosuppressant agents have been largely disappointing in treating rash. The effect and role of exercise in the treatment and rehabilitation of patients with juvenile dermatomyositis is an interesting new area of research.

Summary

Future research in the treatment of juvenile dermatomyositis should focus on improving the understanding of disease course and its predictors such that treatment protocols can be developed to provide the most benefit and least amount of medication toxicity for the individual patient.

Keywords

corticosteroids, juvenile dermatomyositis, methotrexate, rituximab, treatment

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Abbreviations

CYP	cyclophosphamide
IVIG	intravenous immunoglobulin
IVMP	intravenous methylprednisolone
JDM	juvenile dermatomyositis
MTX	methotrexate

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Introduction

Juvenile dermatomyositis (JDM) is a rare chronic inflammatory disease that affects primarily the muscles and skin, although other organ systems may be involved [1]. The typical clinical features are proximal muscle weakness and a characteristic rash. Although the cause of JDM is unknown (and likely has both genetic and environmental influences), it is felt that JDM is an autoimmune disease. Immunosuppressive therapy has therefore been the cornerstone of therapy and has changed the face of JDM over the decades. Over the past 50 years, mortality rates and morbidity have dropped substantially. Despite this, a proportion of children will continue to have evidence of active disease and require treatment many years after diagnosis [2].

While immunosuppression is generally agreed upon for the treatment of JDM, there is variability regarding the mode of administration, duration of treatment and the medication(s). The development of standard treatment protocols for JDM has been hindered by the lack of randomized trials and, until recently, a lack of outcome measures [3]. In addition, there is significant clinical heterogeneity within JDM, both in the manner in which the disease can present and in the disease course. The presentation of JDM can range from insidious onset with mild disease, to life-threatening weakness/ulcerative disease. The clinical course also appears to have a number of distinct patterns; currently, this cannot be predicted at disease onset. These include a monophasic, polyphasic and chronic persistent course [4,5].

The goals of treatment include controlling the underlying disease and preventing/treating complications. Complications such as calcinosis and contractures are felt to be related to disease, while osteoporosis and cataracts are primarily secondary to medication toxicity. The initial choice of therapy depends largely on the clinical presentation of the patient, while long-term therapy is influenced by both response to therapy and our knowledge of the natural history of the disease. This article will review the medications currently used in the treatment of JDM, highlighting new advances and unanswered questions.

Corticosteroids and methotrexate

Although there are no prospective randomized trials demonstrating the efficacy of corticosteroids in JDM, few would dispute their central role in the treatment of this disease. Early data came from series published in the 1980s suggesting that patients with JDM had better

outcomes when treated with corticosteroids [4–6]. Interestingly, in the study by Spencer *et al.* [5], published over 20 years ago, the authors make note of the controversy surrounding dose and duration of treatment; this is still an area of uncertainty today.

One approach to the treatment of JDM has been to treat aggressively and early with high doses of corticosteroids (2 mg/kg) [4]. This recommendation was derived from the observation that children in whom treatment was delayed for more than 12 months, and given less aggressive therapy, did more poorly in terms of ultimate level of function and severity of calcium deposits. In some patients, it was also recognized that second-line agents were required, as corticosteroids alone were insufficient to control disease.

Over the years, diverse treatment protocols have been proposed by different authors. These protocols include intravenous pulses of methylprednisolone (IVMP) [7,8] (as there is some evidence that gastrointestinal vasculopathy may impair enteral medication absorption [9]), low-dose oral corticosteroids [10,11], the addition of second-line agents early in the course of disease [12, 13,14••] and rapid weaning of corticosteroids while treating with a second-line agent [14••]. Apart from Lang and Dooley [7], who reported poor outcomes in patients treated with IVMP alone, most authors report favourable results despite the different protocols.

A number of second-line agents have been used in the treatment of JDM; however, methotrexate (MTX) appears to be the most widely accepted. A number of approaches to the use of MTX in JDM exist. One suggested approach is to use it at the outset for patients with manifestations suggesting severe disease, such as dysphagia and severe cutaneous vasculitis [10]. Another approach is to use MTX in those patients who fail to respond to corticosteroids within 6 weeks of initiation of high-dose prednisone [11].

The approach at our centre is to treat all patients with a diagnosis of JDM with high-dose oral corticosteroids (2 mg/kg/day in divided doses) and MTX [14••]. We reserve IVMP for patients who have poor response or worsen on oral corticosteroids, and those who have respiratory or gastrointestinal compromise. Part of the rationale for treating patients with MTX immediately is the potential to wean corticosteroids more rapidly and presumably cause fewer treatment-related side effects. In support of this, we have recently compared two cohorts followed at our centre – one which received first-line therapy with MTX, and an historical control group followed prior to the initiation of the MTX protocol. In brief, clinical outcomes were just as good with rapidly tapered prednisone supported by MTX but the duration and cumulative dose of corticosteroids was substantially less (10 compared with 26 months in the control group). As a result, there were fewer corticosteroid side effects in the MTX group.

As with the above study, all studies in JDM regarding treatment are limited by their retrospective nature. There have been no head-to-head trials comparing the protocols used in different centres. One problematic issue is the variability of the natural history of disease and our inability to predict the course at disease onset. Ultimately, the goal will be to find a balance between aggressively treating those patients who have a propensity for a more severe or chronic course, and not overtreating patients who have a predisposition to have a monophasic course.

Intravenous immunoglobulin

Intravenous immunoglobulin (IVIG) is used in the treatment of numerous autoimmune disorders [15]. IVIG appears to have an adjunctive role in the treatment of JDM [16,17]. Our experience parallels other studies in that we use IVIG for steroid-resistant or steroid-dependent cases of JDM. Over a 10-year period, we reported 18 such patients with IVIG in addition to corticosteroids (we have now treated over 40 this way). The majority of patients were able to reduce prednisone dose by more than 50% for more than 3 months. A proportion of these patients were also treated with additional steroid-sparing agents, so the number that responded to IVIG itself may have been overestimated [18]. Nevertheless, it is currently our practice to consider the addition of IVIG to the corticosteroid/MTX regimen (2 g/kg/dose initially every 2 weeks for five infusions and then every 4 weeks) in refractory patients. We have found it to be well tolerated and we believe it to be efficacious.

Cyclophosphamide

Cyclophosphamide (CYP) has been used to treat patients who are at high risk for significant morbidity and mortality. Markers of high-risk disease include ulceration of the skin and gastrointestinal tract, and respiratory disease. Historically, when mortality rates were higher, one series [6] reported gastrointestinal and respiratory complications as the cause of death in 10 patients who died with JDM.

Riley *et al.* [19] reviewed the efficacy and tolerability of intravenous pulse CYP for high-risk patients. Two of their 12 patients died from underlying pulmonary insufficiency early in the course of treatment, highlighting the severity of disease. The remaining 10 patients received a median of eight infusions with a mean cumulative dose of 4.6 g/m^2. Almost all patients received concurrent second-line treatment (MTX, cyclosporin) without dose reduction. The surviving 10 patients had improvement

after 6 months of treatment with respect to muscle function and strength, and reduction in extra-muscular disease. Interestingly, skin disease was the predominant extra-muscular manifestation that persisted despite treatment with CYP. The side effects associated with this treatment included one patient with febrile neutropenia, three cases of localized herpes zoster infections, and alopecia that resolved after cessation of CYP. As the risk of infection in these sick and likely immunocompromised patients is significant, it has been our practice to discontinue MTX or other disease-modifying anti-rheumatic drugs with the commencement of CYP.

Biologic agents

Etanercept and infliximab – two TNF-α antagonists – have been used in the treatment of various pediatric rheumatic conditions [20,21]. Evidence [22] suggests that TNF-α plays a role in the pathophysiology of dermatomyositis both in children and adults. While small series have suggested a beneficial role of anti-TNF-α agents in the treatment of dermatomyositis, ultimately, their role is still unclear [23,24]. Our very limited experience has not been favourable.

Rituximab – a monoclonal CD20+ B cell-depleting antibody – is a promising new biologic agent that is being investigated in a broad range of conditions involving B-cells [25]. Humoral immunity appears to play a role in the pathogenesis of idiopathic inflammatory myopathies, given the presence of autoantibodies in these illnesses. Levine [26••] has recently published an open-label pilot study of rituximab in the treatment of adults with dermatomyositis. Seven adults with refractory disease were treated with rituximab. Of the six who were available for evaluation, B-cell depletion coincided with an improvement in muscle strength, rash, vital capacity and enzyme markers. The few studies [27,28] of using rituximab in JDM also suggest a favourable response. While rituximab may represent a promising new therapy in the treatment of dermatomyositis, further study is needed.

Other second-line agents

There has been experience using a number of other second-line agents in JDM, including cyclosporin A [29,30], azathioprine [6], systemic tacrolimus [31], hydroxychloroquine [32] and mycophenolate mofetil [33]. The latter two medications have been employed specifically in the treatment of skin disease. Despite some positive studies, we do not routinely consider these agents in the initial therapy of JDM.

Topical therapy

Topical tacrolimus (0.1%) ointment has been used to treat patients with cutaneous disease. In an unblinded pilot study, six patients, in whom muscle disease was quiescent, applied ointment to the affected areas twice daily for 4–6 weeks. Three patients had dramatic improvements when assessed by their primary dermatologist, while the other three patients had only minimal improvement [34]. In a side-by-side comparison in another small study [35], results were more disappointing. None of the five treated patients showed evidence of improvement. We have used topical tacrolimus in a modest number of patients with both chronic skin disease and flare of skin disease. Overall, we have not been convinced of a dramatic benefit.

Other aspects of treatment

While this review has focused on the medications used in treating dermatomyositis, there are a significant number of other considerations that the clinician must take into account when treating a child with JDM. A multidisciplinary team consisting of nurses, physiotherapists, occupational therapists, dieticians and social workers is likely necessary for the optimal support of many of these patients.

Complications from active disease and its treatment represent a significant degree of morbidity for these patients. Fortunately, the incidence of calcinosis is decreasing but, for some patients, it remains a debilitating and disfiguring problem. Many treatments have been tried, including diltiazem [36], aluminum hydroxide [37], probenecid [38], bisphosphonates [39] and local corticosteroid injections, amongst others. No treatment has been proven to be effective. As calcinosis in many patients tends to regress over time (often years), any uncontrolled studies of efficacy may only reflect regression to the mean.

Physical disability represents a significant problem in patients who are profoundly weak or those with contractures. The role of exercise in the treatment and rehabilitation of patients with JDM has been receiving more attention recently. Historically, there has been concern regarding the potential of causing muscle fibre damage and inflammation with exercise and muscle strengthening. Maillard *et al.* [40••] recently reported no change in the degree of muscle inflammation in patients with JDM after a short bout of moderate exercise. Physiotherapy plays an important role in the rehabilitation of our patients with JDM; those patients who are so weak that they pose safety dangers (i.e. cannot get up from the ground without aid) are usually admitted to a rehabilitation centre for extensive physiotherapy and occupational therapy.

Toxicity from systemic corticosteroids is a major concern in patients with JDM. All of our patients are followed by a dietician and receive supplemental calcium and vitamin D while taking corticosteroids.

Conclusion

Fortunately, the overall outcome for patients with JDM has improved quite dramatically over the past five

decades. This presumably correlates with more aggressive treatment with corticosteroids and secondary immunosuppressive medications. While there are number of exciting new medications on the horizon, such as rituximab, many of the medications in our arsenal are the same as 30 years ago. Much research is still needed regarding the efficacy and tolerability of the biologic agents, before implementing them as routine therapy in JDM. Fine-tuning treatment protocols using the medications we have used for years should be the one of the goals of research. Further understanding about the disease course and early predictors of disease course is needed to accomplish this. International collaboration should continue in the development of validated outcome measures and prospective trials.

References and recommended reading

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 569).

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