Abstract

Since idiopathic inflammatory myositis is relatively uncommon, randomized placebo controlled trials are rare. Although corticosteroids have not been tested in randomized controlled trials, general clinical consensus among physicians has accepted it as effective therapy. However, corticosteroid toxicity leads to significant disability in many patients. For patients with refractory dermatomyositis, intravenous immunoglobulin is an effective short-term treatment but its long-term effect remains unknown. Immunosuppressants are commonly used in refractory inflammatory myositis; evidence for their efficacy, with very few exceptions, has been derived from case reports and open studies with small numbers of patients. Even in randomized trials, the lack of validated and generally accepted outcome measures makes it difficult to compare the effect of interventions in different studies. Although the balance of evidence suggests that immunosuppressants are equally effective in dermatomyositis and polymyositis, there are no randomized controlled trials to show if any of these drugs, individually or in combination, is best. For uncommon diseases, such as inflammatory myositis, only multicentre randomized controlled trials involving rheumatologists and neurologists will define the optimal therapy.

Idiopathic inflammatory myositis is a group of acquired conditions characterized by inflammation of skeletal muscles. Bohan and Peter proposed that these conditions be divided into primary idiopathic polymyositis, primary idiopathic dermatomyositis, dermatomyositis/polymyositis associated with neoplasia, childhood dermatomyositis/polymyositis, dermatomyositis/polymyositis associated with vasculitis, and polymyositis/dermatomyositis associated with collagen vascular disease [1, 2]. Dalakas [3] has more recently proposed that inclusion body myositis be included in the classification of inflammatory myopathy, and this is widely accepted, as is the preferred use of the term ‘autoimmune rheumatic disease’ to replace ‘collagen vascular disease’.

Although the aetiologies of these six categories are likely to differ, they share some common features, notably striking proximal muscle weakness, histological evidence of endomysial inflammation and activation of the immune response. Current therapy for inflammatory myositis is broadly similar but patients with inclusion body myositis are more refractory to therapy. Furthermore, the inclusion bodies themselves have been shown to contain a variety of proteins, including amyloid and tau, which suggests that this condition may be more degenerative in nature. Recent reviews of the treatment of inclusion body myositis have concluded that corticosteroids give only a modest benefit and that azathioprine and methotrexate have been shown to be effective in only eight out of 35 trials [4, 5]. In this review we will focus on the treatment of dermatomyositis and polymyositis.

The estimated annual incidence rate of polymyositis and dermatomyositis varies between 1.9 and 7.7 per million [6–15]. In a 20-yr study of inflammatory myositis in America from 1963 to 1982, the annual incidence was 5.5 per million [6]. Interestingly, the incidence was higher (10 per million) in the last decade. A similar study in Israel showed an annual incidence of 2.2 per million [7]. In this study, the annual incidence increased from 0.47 per million in the third decade to a peak of 6.32 per million in the seventh. Disease was more common in females in both studies, with a female:male ratio of 2:1. However, most of these reports describe retrospective hospital-based studies with limited searches in which the true incidence of idiopathic inflammatory myositis may have been underestimated. Furthermore, different diagnostic criteria were employed in these studies, so that comparing their results is problematic. Data on the prevalence of polymyositis and dermatomyositis are
very limited. Estimates from the USA [14] and Japan [16] range between 50 and 63 per million; however, these were also retrospective studies and may have underestimated the true disease prevalence.

The prognosis of dermatomyositis and polymyositis was poor before the availability of corticosteroids. In the first literature review in 1903, Steiner [17] described 28 patients. While noting that patients could recover from dermatomyositis, he also stressed the gravity of the condition; 17 of these patients had died. The beneficial effects of steroids have been re-emphasized by a recent Italian study of 63 patients. The authors reported that half of their patients were managed with steroids alone [18]. After the introduction of corticosteroids in the 1950s, 12 studies examined the mortality of inflammatory myositis, which ranged between 11 and 45% [13, 19–29]. The variation in mortality rate in these studies may have been due to the use of different inclusion criteria, such as the inclusion of patients with inflammatory myositis associated with malignancies. Poor prognostic factors common to many studies include old age, race, bulbar involvement, delayed treatment and cardiovascular and pulmonary involvement. Interestingly, the creatine phosphokinase level, grade of disability and degree of muscle weakness at presentation do not correlate with prognosis. In one study in the UK carried out between the 1950s and 1970s, 33% of survivors had significant disability after 3 yr, and in half of these patients the disease remained active [30]. In a further UK study in the 1980s, of 25 patients followed for up to 10 yr, approximately one-third returned to normal function but one-third died or were left severely incapacitated and the remainder were left with significant weakness [31].

A more recent national inception cohort study in Canada examined 257 patients with polymyositis and dermatomyositis. Disability, as measured by the health assessment questionnaire, increased with disease duration and the side-effects of corticosteroids were major contributors to disability [32].

Treatment of dermatomyositis and polymyositis

As dermatomyositis and polymyositis are uncommon, there have been few randomized controlled trials, and those that have been completed enrolled small numbers of patients. Consequently, optimal therapy has not been defined adequately.

Corticosteroids

Corticosteroids are the standard treatment for idiopathic inflammatory myositis, but their efficacy has not been tested fully in randomized, placebo-controlled trials [33] and is unlikely ever to be tested in this way. There is a strong consensus among physicians that corticosteroids improve disease significantly in the majority of patients with inflammatory myositis [30, 34–37]. Different treatment regimens have been advocated, but most suggest using oral high-dose therapy with prednisolone 60 mg/day initially. The prednisolone dose should then be tapered to either daily or alternate-day therapy [36]. One retrospective review suggested that the prognosis of dermatomyositis and polymyositis had been improved by high-dose corticosteroid therapy [30]. There was considerable improvement in average disability with time in the high-dose corticosteroid therapy group. The maximum improvement occurring within the first three years. The degree of improvement in disability was considerably less in those who were treated inadequately. In contrast, another study has shown that the mortality and morbidity associated with dermatomyositis and polymyositis remained high despite treatment with corticosteroids [20].

The major drawbacks of long-term corticosteroid treatment are its side-effects and, in some patients, insufficient efficacy. Side-effects of corticosteroid affected 32% [38] to 41% [28] of treated patients with polymyositis and dermatomyositis. Furthermore, in long-term studies, disability was associated with corticosteroid side-effects, especially osteonecrosis and osteoporotic vertebral fractures [32]. In an attempt to reduce the side-effects of corticosteroids, Nzeusseu et al. [39] studied the effect of a lower starting dose than is recommended classically in 25 patients with polymyositis and dermatomyositis. Fifteen patients were treated with a high-dose regimen (> 0.5 mg prednisolone/kg/day) and 10 with a low-dose regimen (≤ 0.5 mg prednisolone/kg/day). The functional outcome of the low-dose regimen group did not differ from that of patients given higher doses, although the sample size of the study was small and the lack of a statistically significant difference may have been the result of a type II error. Interestingly, vertebral fractures were less common in patients treated with lower doses of corticosteroids. With the widespread availability of dual X-ray absorptiometry and the introduction of effective prophylactic bisphosphonate therapy, this is one therapeutic area in which genuine improvement in outcome can be expected.

Pulsed intravenous methylprednisolone has also been advocated for the treatment of refractory inflammatory myositis [40, 41] without evidence from randomized control trials. In an open study, the numbers of macrophages, CD8+ T cells and B lymphocytes in the inflammatory infiltrate of muscle biopsies decreased after treatment [42]. There were also reductions in the expression of intercellular adhesion molecules and major histocompatibility complex antigens on endothelial cells [42]. However, it is unclear whether these histological changes correlated with the clinical response.

Immunosuppressants

Immunosuppressive agents, especially methotrexate and cyclosporin, are often used in refractory cases of polymyositis and dermatomyositis, but, once again, their use is based on clinical experience rather than
randomized controlled trials. Based on a literature search using Medline, a range of immunosuppressants has been used in polymyositis and dermatomyositis. These include azathioprine [5, 34, 37, 43–46], methotrexate [5, 43, 44, 47–63], cyclosporin A [3, 33, 35, 36, 63–70], cyclophosphamide [41, 44, 71–78] and chlorambucil [79].

Azathioprine. Azathioprine is used commonly as a steroid-sparing agent in chronic inflammatory diseases. It has been recommended by some as the preferred immunosuppressant in polymyositis and dermatomyositis [80]. Its efficacy in idiopathic inflammatory myositis is supported by a small number of reported cases [34, 37, 44, 45]. Up to 75% of patients treated with azathioprine showed a good response in retrospective reviews [5, 37, 44]. Disappointingly, a small randomized placebo controlled trial of azathioprine (2 mg/kg per day) in 16 inflammatory myositis patients showed no significant difference in muscle strength, creatine phosphokinase or histopathological features between the active and placebo groups [46]. However, the sample size was small and a follow-up period of 3 months may be too short to detect a statistically significant improvement in muscle function. In contrast, a subsequent open study of the same patients and corticosteroid- and azathioprine-treated patients had a better long-term outcome after 3 yr than corticosteroids alone [45]. A recent trial of azathioprine in combination with methotrexate showed that combination therapy was not superior to intravenous methotrexate alone in refractory inflammatory myositis, although there was a trend favouring the combination therapy [43]. In a retrospective review of 113 consecutive patients treated at the National Institutes of Health, the authors found that methotrexate therapy may be superior to either azathioprine or further steroid treatment alone in certain patients who do not respond completely to an initial adequate course of prednisolone [5].

Methotrexate. The use of intravenous methotrexate was first reported in refractory dermatomyositis in 1968 [63]. Subsequently, a few case reports and retrospective reviews have suggested that methotrexate is effective in childhood and adult idiopathic inflammatory myositis [5, 43, 44, 47–62]. Oral low-dose methotrexate is the commonest second-line treatment for rheumatoid arthritis. It suppresses inflammation and improves function. Although it is associated with side-effects that require regular monitoring by blood tests, it has one of the best benefit/risk ratios among second-line drugs in rheumatoid arthritis [81]. Bohan et al. [29] treated 25 patients with steroid-resistant inflammatory myositis with oral methotrexate; 88% had significant disease improvement and 43% were able to reduce their corticosteroid dose. Miller et al. [52] reviewed the clinical course of 16 children with recalcitrant dermatomyositis who were treated with oral methotrexate in addition to corticosteroids. Twelve patients who received methotrexate for at least 8 months regained normal muscle strength. Furthermore, the prednisolone dose in 11 patients could be reduced to \( \leq 5 \) mg/day. Complications during methotrexate treatment required discontinuation of methotrexate in five patients, and were unrelated to the cumulative dose of the drug. Active disease recurred in five patients in whom methotrexate had been discontinued after apparent clinical remission had been achieved [52]. In dermatomyositis, two reviews suggested that cutaneous disease responded well to methotrexate, with improvement in all patients, and allowed reduction in the corticosteroid dose [48, 50], although methotrexate-induced side-effects were common [50]. A recent randomized trial compared the efficacy and tolerability of cyclosporin A with those of methotrexate in 36 patients with active polymyositis and dermatomyositis [57]. Clinical improvement and decreased creatine phosphokinase were seen in both groups. Patients treated with methotrexate showed a better response than patients who received cyclosporin A, although the difference was not statistically significant.

Cyclosporin A. Cyclosporin A is a T-cell immunosuppressant that has been used extensively in the prevention and treatment of transplant rejection. Bendtzen et al. first reported the use of cyclosporin A in polymyositis [83]. Numerous case reports and small open series have suggested that cyclosporin A, like methotrexate, may be efficacious in dermatomyositis and polymyositis [3, 33, 35, 36, 63–70, 83–91]. In some cases, cyclosporin A was effective in patients with inflammatory myositis who had failed combination therapy with corticosteroids and other immunosuppressants [65, 69]. The dose used was high and ranged from 3 to 10 mg/kg/day. In three reviews of paediatric patients with dermatomyositis and polymyositis, cyclosporin A increased muscle strength and decreased muscle enzyme levels [63, 65, 67].

Chlorambucil. Clinical experience with chlorambucil in inflammatory myositis is extremely limited. One study in five patients with dermatomyositis who had failed azathioprine and methotrexate suggested that chlorambucil at a dose of 4 mg/day had some beneficial effects [79]. Improvement occurred in all patients and four patients achieved disease remission after 13–30 months of therapy.

Cyclophosphamide. The role of cyclophosphamide in inflammatory myositis is controversial. There are reports of success [72–75] and failure [71] in open studies. Cyclophosphamide is toxic and predisposes patients to malignancies after long-term treatment. Its use should be restricted to patients who are refractory to corticosteroids and other immunosuppressants.

Combination therapy. In idiopathic inflammatory myositis, there are a few reports of combination therapy, such as azathioprine plus methotrexate [43] and methotrexate plus cyclosporin A [92]. A recent randomized cross-over trial compared the effect of weekly oral methotrexate and daily azathioprine with that of intravenous methotrexate with leucovorin rescue given fortnightly [43]. Thirty patients, most of whom had an
inadequate response to immunosuppressants, were studied. Of the 15 patients initially randomized to oral methotrexate and azathioprine, 12 improved with oral therapy and four improved with intravenous methotrexate. The difference between the two treatments was not statistically significant. Although the study lacked the power to compare the two treatments directly, intention-to-treat analysis showed a trend in favour of those patients who first received oral combination therapy.

Cyclosporin A plus methotrexate also appears to be beneficial in refractory juvenile dermatomyositis and juvenile rheumatoid arthritis [63]. In five patients with refractory juvenile dermatomyositis, muscle strength increased and creatine phosphokinase levels decreased with combination therapy. Furthermore, combination treatment permitted the dose of prednisolone to be reduced.

**Immunoglobulin**

Intravenous immunoglobulin is used for the treatment of many autoimmune diseases, including autoimmune thrombocytopenia and Kawasaki’s disease. Although its mechanism of action remains unknown, its efficacy in autoimmune diseases suggests it is immunomodulatory. In a pilot study, Gelfand [93] suggested that it may be used for the treatment of idiopathic inflammatory myositis, and reported its efficacy. Patients with dermatomyositis and polymyositis were treated with 1 g/kg/day of immunoglobulin for 2 days every 4 weeks. There was increased proximal muscle strength and reduction in the creatine phosphokinase level. Subsequently, two open studies in patients with refractory dermatomyositis and polymyositis [94, 95] reported improvement in cutaneous disease and muscle power. In 1993, Dalakas et al. [96] reported the result of a randomized, double-blind, placebo-controlled trial in 15 patients with refractory dermatomyositis. Patients were randomly assigned to receive either 2 g/kg of immunoglobulin or placebo monthly for 3 months, with the option of crossing over to the alternative therapy for 3 more months. Muscle strength was assessed with a modified Medical Research Council score. Eight patients assigned to the immunoglobulin group, but none of the patients in the placebo group, showed a statistically significant improvement in muscle strength score. After the cross-over phase, 12 patients in total received immunoglobulin and nine showed a major improvement. Mean muscle strength score increased from 74.5 to 84.7, which was statistically significant. In the placebo-treated group, only three patients had improvement. Muscle biopsies in the immunoglobulin-treated patients also showed improvement and there was an increase in muscle fibre diameter, a decrease in the diameter of capillaries and reduced complement deposits, especially C3b and the membrane attack complex on capillaries [96, 97]. Sera from immunoglobulin-treated patients also inhibited C3 uptake *ex vivo* [97], suggesting that immunoglobulin may act by inhibiting complement activation. Other open studies of immunoglobulin in inflammatory myositis, especially dermatomyositis, reported similar efficacy [66, 98–100]. All these studies, except one in which two patients with juvenile dermatomyositis were treated for more than 12 months, only assessed short-term clinical efficacy. More long-term data are needed to assess the long-term safety and efficacy of intravenous immunoglobulin in idiopathic inflammatory myositis.

**Plasmapheresis**

Plasmapheresis is used in the treatment of refractory autoimmune diseases to remove circulating autoantibodies and immune complexes. Since idiopathic inflammatory myositis is associated with the production of autoantibodies, plasmapheresis has been tried in refractory cases. In open studies [101, 102], the results appeared promising. Thirty-five patients with inadequate clinical responses to corticosteroids and/or immunosuppressants were treated with plasmapheresis, chlorambucil and cyclophosphamide [101]. Muscle strength improved in 32 patients during therapy and some patients experienced improvement that approached remission. However, the results of a subsequent randomized, double-blind controlled trial in 39 patients with polymyositis or dermatomyositis were disappointing [103]. Patients were randomized to receive plasma exchange, leukapheresis or sham apheresis. Twelve treatments were given over a 1-month period. In each treatment group, three patients improved, with increased muscle strength and functional capacity. There was no statistically significant difference in the clinical response among the three treatment groups. Given the lack of efficacy, the cost and the potential for complications, there is little justification for using plasma exchange in patients with myositis, with the possible exception of those patients who have an accompanying monoclonal gammopathy [104].

**Other therapies**

Whole-body irradiation, usually in fractionated doses, over approximately 1 month has been reported to be beneficial in a small number of patients with drug-resistant myositis [105–107]. In addition, total lymphoid irradiation with around 200 rads, delivered over a period of 5–6 weeks, has been reported to be beneficial in some patients with myositis [109]. No double-blind control trials using sham irradiation have been reported. Adverse events are common with lymphoid irradiation, and a long-standing concern about the development of malignancy remains.

There are also case reports describing thymectomy and extracorporeal photochemotherapy for refractory myositis and dermatomyositis, but the number of cases is small and the efficacies of the treatments remain uncertain.

In this review, we have focused on the drug treatment of myositis. However, it is important to recognize that drug therapy is only one aspect of the management.
of patients with these diseases. Other aspects of management, including the use of sun-blocking agents for the skin in patients with dermatomyositis, the appropriate use of physiotherapy, occupational therapy and occasionally surgery, are described elsewhere [109, 110].

References

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