Idiopathic Inflammatory Myopathy: Treatment Options

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Idiopathic inflammatory myopathy (IIM) comprises a group of rare disorders in which there is an immune-mediated attack on skeletal muscle, the consequence of which is muscle damage and weakness in the patient. As in other inflammatory diseases, the general approach to therapy is use of immunosuppressive agents. Many options exist for IIM treatment, but therapeutic approaches are based mostly on empirical evidence and small studies, many of which are uncontrolled. Recently, new agents have been designed to target specific components of the immune response, and they offer hope for more effective or safer IIM therapy.

Introduction

Idiopathic inflammatory myopathy (IIM) comprises the following entities: polymyositis (PM), dermatomyositis (DM), inclusion body myositis (IBM), juvenile DM, myositis associated with malignancy, and myositis associated with systemic inflammatory disease (overlap syndromes). Although these conditions are grouped together for academic purposes, they differ significantly in their individual clinical and histologic features. For example, although DM and PM are autoimmune conditions included in the same family as systemic lupus erythematosus, scleroderma, and rheumatoid arthritis, IBM appears to be a degenerative process [1]. Nevertheless, all of the IIMs share the theme of immune-mediated attack on skeletal muscle, which produces muscle damage and weakness in the patient. As in other inflammatory diseases, immunosuppressive agents are the general approach to therapy. However, several unique challenges await the physician treating IIM.

The first challenge is making the correct diagnosis. Because DM is often associated with a characteristic rash, this diagnosis is usually straightforward; however, diagnosing PM or IBM can be more difficult [2]. The following noninflammatory myopathies and neurologic conditions can also present with proximal muscle weakness: central and peripheral nervous system disorders, adult-onset muscular dystrophies (eg, limb-girdle muscular dystrophy, fascioscapulohumeral muscular dystrophy, Becker's muscular dystrophy), metabolic myopathies (eg, phosphofructokinase deficiency, acid-maltase deficiency, carnitine palmityl-transferase II deficiency, mitochondrial myopathies), endocrine myopathies (eg, hypo- or hyperthyroidism, Cushing's syndrome, acromegaly), neuromuscular junction disorders (eg, myasthenia gravis, Eaton-Lambert syndrome), viral myopathy, and toxic myopathy.

Today, statin myopathy is frequently considered in the differential diagnosis of weakness or myalgia given these agents' high use in clinical practice [3]. Differentiation among these entities often can be accomplished using a combination of clinical features, serologic studies, electromyography, MRI, and muscle biopsy. Due to the large differential diagnosis of myopathy, when referring patients for electromyography, MRI, or biopsy, it is essential to work with physicians who have experience with muscular disorders. Regardless, because all of the above studies have their own limitations, even a thorough work-up may yield an equivocal conclusion. Because the patient may be deteriorating quickly, time may be an important factor, and the physician will be pressed to make a treatment decision despite an unclear diagnosis. Furthermore, PM and DM can be associated with the presence of malignancy. In this scenario, the symptoms attributable to myositis may precede the discovery of the malignancy. Often these patients respond poorly to myositis therapy, but respond to treatment of the malignancy [4]. Signs and symptoms suggestive of IIM include arthritis, rash, elevated acute phase reactants, positive antinuclear antibody, family history of autoimmunity, lack of atrophy, lack of facial muscle involvement, and acute to subacute presentation. The presence of myositis-specific antibodies can suggest a defined clinical pattern such as the antisynthetase syndrome or may predict response to therapy [5].

The next challenge is the choice of therapy and its management. Due to the rarity of IIMs, few randomized placebo-controlled trials (RCTs) have been performed. Most studies exploring therapeutic options for IIM

(including the RCTs) use few patients, have varied outcome criteria, or include heterogeneous populations of patients with IIM, all of which make it difficult to draw conclusions and apply the results to individual patients. Indeed, treatment approaches remain empirical. In the last decade, the International Myositis Assessment and Clinical Studies (IMACS) Group has developed a set of outcome criteria to be used for RCTs [6,7]. This effort should help overcome many of the limitations of previous studies. Currently, many centers worldwide participate in observational and interventional trails. Due to the rarity of the disease, it is important to consider every patient with IIM for a clinical trial if logistically possible.

High-dose corticosteroids remain the first line of therapy. Because corticosteroids cause many serious side effects or worsen preexisting medical problems, numerous medical issues in addition to the myositis become active simultaneously; this requires coordination of care and good communication between several health care providers. Furthermore, treatment with steroids can cause myopathy, creating a paradox unique to IIM treatment.

The next challenge is to manage patients who respond partially to or are refractory to therapy. Due to issues discussed earlier, there is no clear definition of when a patient is refractory to therapy. A complete failure to respond or a minimal response after 4 to 6 weeks of appropriate therapy should prompt a reconsideration of the diagnosis. Noninflammatory myopathies, IBM, myositis associated with malignancy, and anti-SRP syndrome are not likely to respond as well as PM and DM. In patients with longstanding disease, it may be difficult to determine how much of the patient's weakness is due to active inflammation and how much is due to damage. Serum muscle enzymes, MRI, or repeat muscle biopsy may help determine if active inflammation is playing a role.

General Approach to Therapy

The patient is started on a high dose of corticosteroid and maintained on this dose until strength improves and muscle enzyme levels decrease (approximately 4–6 weeks), and then the dose is slowly tapered over months. Because some patients with IIM have a monocyclic disease course, patients who respond well to this therapy may eventually be tapered off steroids completely or may be maintained on a low dose. However, if the patient does not respond well to therapy or flares during the taper, the addition of second-line therapies and possibly third-line therapies (discussed later) are then considered. During treatment, patients are usually followed closely using a combination of serum muscle enzymes (creatine kinase [CK], aldolase, aspartate aminotranferase, alanine aminotransferase, myoglobin, lactate dehydrogenase), muscle strength testing, and attention to extramuscular manifestations of the disease. Of note, the muscle enzymes may return to normal before the patient has either a subjective or objective improvement in strength; furthermore, after disease has been controlled, a rise in muscle enzymes may predict subsequent worsening of clinical status [8].

Corticosteroids

Corticosteroids were first employed to treat another autoimmune condition, rheumatoid arthritis, in 1948 (reviewed by Neeck [9]). Since the 1950s, corticosteroids have been the first-line therapy for PM and DM. IBM tends not to respond well to any therapy, but a trial early in the disease course may result in some improvement [10]. Although no adequate trials have compared different steroid treatment protocols, the recommendations of physicians who have treated many IIM patients tend to be similar. The following are three examples of specific approaches to steroid therapy that have been published previously.

1. Maintain patient on approximately 1 mg/kg or 60 mg prednisone (or equivalent steroid dose) daily in a divided dose for at least 1 month and until the CK has normalized. Then decrease the dose by about 25% each month with a goal of a once-daily maintenance dose of 5 to 10 mg per day (by 4–6 months) [8].
2. Eighty to 100 mg prednisone once daily for 3 to 4 weeks, followed by tapering over 10 weeks to 80 to 100 mg every other day. This can be accomplished by reducing the "off day" dose by 10 mg/week (side effects may make a faster taper necessary) until it is down to zero. Assuming a response, follow with tapering 5 to 10 mg every 3 to 4 weeks until down to approximately 50 mg every other day. At this point, the rate of taper is slowed even further to a decrease of 2.5 mg every few months [11].
3. One to 1.5 mg/kg per day of prednisone (maximum, 100 mg/day), changing to every other day dosing in 2 to 4 weeks (or 2–3 months in patients with more severe disease). This regimen is continued until the patient has regained normal strength or until their strength has plateaued (approximately 4–5 months). Then taper by 5 mg every 2 weeks until at 20 mg every other day; then taper by no more than 2.5 mg every 2 weeks [12].

In a retrospective study of 113 patients with IIM, Joffe et al. [10] showed that after the first prednisone trial, 25% of patients had a complete remission, 61% of patients had a partial remission, and 14% of patients had no response. Patients who have known malabsorption or fail to show cushingoid features after many weeks of high-dose prednisone may benefit from a change to methylprednisone or dexamethasone. Patients who have a disease flare during the steroid taper may respond to one of the following: 1) a small increase in the steroid dose followed by a slower rate of dose reduction; 2) a large increase in the steroid

dose followed by a rapid reduction to a level just above where the patient flared, then followed by a slower rate of dose reduction; or 3) intravenous pulse methylprednisone (IVMP) (eg, 0.5–1 g daily for 3 days). The strategy used should depend on the severity of the flare and the patient's medical comorbidities.

Of note, it has been suggested that patients with milder disease may respond well to a lower initial starting dose of corticosteroids, although it is not clear if this requires early initiation of an immunosuppressive agent [13]. In addition, patients with overlap of another systemic inflammatory illness may need less corticosteroid [14]. In addition to serving as a second-line agent, IVMP has been suggested as a possible initial therapy [15,16]. In a study by Matsubara et al. [17], 11 patients with PM and DM were treated with three to nine courses of three consecutive daily infusions of 500 mg methylprednisone in addition to oral daily prednisone. When compared with a group that received only daily oral prednisone, the IVMP group had a higher remission rate and a faster time to normal CK levels. Differences in side effects were not discussed.

Several publications have suggested that patients who are treated earlier in their disease course tend to respond better to therapy [10,18]. This may be analogous to emerging paradigms in the treatment of rheumatoid arthritis, in which early aggressive therapy leads to better long-term outcomes [19]. The cellular and molecular abnormalities that cause some autoimmune diseases can exist years before the patient has symptoms and tend to evolve [20], which raises the possibility that patients early in their disease course may be more sensitive to therapy.

Immunosuppressive agents and other treatments

Immunosuppressive drugs or intravenous immunoglobulin (IVIG) are typically added if adequate steroid therapy is not effective, if the patient flares frequently during the steroid taper, if the side effects of the steroids are intolerable, if the patient is responding but needs a "steroid-sparing" agent, or if the disease is severe and rapidly progressive. In patients who have little or no response to an adequate steroid trial, it is always important to reconsider the diagnosis and possibly perform new diagnostic tests. If the patient does not respond to an adequate trial of a second-line agent (at an appropriate dose for a reasonable duration) or is intolerant, then another second-line agent or third-line agent is added or substituted.

Methotrexate and azathioprine

Methotrexate and azathioprine are the most commonly used second-line agents. Methotrexate is usually prescribed at 15 to 25 mg weekly, given orally, subcutaneously, or intramuscularly. In treating inflammatory myopathy, several publications have described higher doses and have employed the intravenous route. Folic acid or folinic acid is given in addition to the methotrexate to help minimize side effects. Azathioprine is typically prescribed at 1.5 to 2 mg/kg per day orally.

In a case series, Arnett et al. [21] treated five patients with steroid-resistant PM using oral or intravenous methotrexate in doses up to 50 mg weekly. Four of five patients improved, but two developed pneumonitis, which contributed to death in one patient. Metzger et al. [22] treated 22 patients with steroid-resistant PM or DM using prednisone and methotrexate (average maintenance dose, 42 mg weekly intravenously). Patients were treated for an average of 15 months, and 77% of patients achieved an improvement in muscle strength, a decrease in serum CK level, and significantly reduced steroid doses. Toxicity was minimal and reversible.

In a retrospective cohort study, 55 patients with IIM (including IBM) who were previously treated with an adequate trial of steroids were also treated with methotrexate (minimum, 5 mg/week for 8 weeks). In this study, 31 patients had a partial response and nine patients had a complete response [10]. In a randomized trial of methotrexate versus cyclosporine, 36 patients with DM and PM (newly diagnosed or a relapse of previously quiescent myositis) were randomized to either 7.5 to 15 mg of weekly oral methotrexate or 3 to 3.5 mg/kg per day of cyclosporine [23]. Both groups were also treated with prednisone at 0.5 to 1 mg/kg daily and were followed for 6 months. Both groups showed improvement without a significant difference in efficacy or toxicity.

In a randomized, controlled trial, Bunch et al. [24] treated 16 patients with prednisone 60 mg daily and either azathioprine, 2 mg/kg per day, or placebo. At 3 months, no significant difference was seen between the groups, but during the 3-year, uncontrolled follow-up, the group that received the azathioprine had less functional disability and required a lower prednisone dose for maintenance [25]. In a randomized, double-blind trial of methotrexate, 15 mg weekly, plus steroids versus azathioprine, 2.5 mg/kg per day, plus steroids, 28 patients with PM and DM were treated, and researchers found no significant difference in efficacy [26].

In a randomized cross-over study of 30 patients with steroid-refractory PM and DM (most patients had also failed a trial of one immunosuppressive agent), patients were randomized to either escalating oral methotrexate, 7.5 mg escalating to 22.5 to 25 mg/week, plus escalating azathioprine, 50 mg escalating to 150 mg/day, versus intravenous methotrexate at 500 mg/m^2 followed by leucovorin rescue [27]. Patients could cross over to the other arm at 3 or 6 months if they did not improve. Eight of 15 patients who received the oral combination therapy improved, whereas only 3 of 15 who received intravenous methotrexate improved. After crossover, four people improved with the oral combination therapy, whereas one person improved with intravenous methotrexate.

Intravenous immunoglobulin

IVIG preparations are purified from pooled human plasma obtained from thousands of donors. IVIG is usually given at a total 2 g/kg monthly. Because a common side effect, aseptic meningitis, appears to be related to the infusion rate, the above dose is often given over 3 to 4 days at approximately 0.5 g/kg per day. There are many available IVIG preparations, each with a varied amount of salt and sugar content, which may be a consideration in patients with medical comorbidities.

A placebo-controlled trial in 15 patients with DM showed improvement of both strength and rash following three monthly treatments of IVIG at 2 mg/kg [28]. Biopsies taken after treatment with IVIG compared with those taken before treatment showed reduction of major histocompatibility complex class I, transforming growth factor-β, and adhesion molecules, as well as a decrease in complement component deposition in muscle. In 35 patients with refractory PM, an uncontrolled study of IVIG, 2 g/kg monthly for 4 to 5 months, 71% of patients showed significant improvement in strength and significant reductions in serum CK levels [29]. Also, steroid doses in these patients were reduced.

Cyclosporine

Cyclosporine is an inhibitor of T-cell activation that has been used in transplant medicine (for the prevention of organ rejection) and as therapy for rheumatoid arthritis and psoriasis. Starting dose is usually 2 to 2.5 mg/kg per day and can be slowly increased to a maximum of 5 mg/kg per day.

Zeller et al. [30] published a retrospective study of six patients with juvenile DM who had failed corticosteroids; four patients had also failed second-line agents. Patients were treated with 5 to 6 mg/kg per day of cyclosporine, continued on corticosteroids, and were followed for a mean of 51.5 months. All patients exhibited improved disease control and could taper their steroids. Three patients relapsed after discontinuation of cyclosporine, but their disease came under control once the drug was reintroduced. Jones et al. [31] published a letter describing two patients who failed treatment with cyclosporine and experienced significant side effects. Qushmaq et al. [32] published their experience treating six patients (four PM, two DM) who had failed corticosteroids and at least one second-line agent. Doses used ranged from 2.4 to 4.2 mg/kg per day and patients were followed for 3 to 44 months. All patients saw reduced CK levels and improved strength, and all but one were able to taper their prednisone dose. In a randomized trial of methotrexate versus cyclosporine, 36 patients with DM and PM (either newly diagnosed or a relapse of previously quiescent myositis) were randomized to either 7.5 to 15 mg of weekly oral methotrexate or 3 to 3.5 mg/kg per day of cyclosporine [23]. Because cyclosporine was not superior to methotrexate over 6 months in this study, the authors concluded that methotrexate would be a better choice for a second-line therapy, due to its cost and the expectation of its long-term toxicity.

Mycophenolate mofetil

Mycophenolate mofetil (MMF) is used commonly in organ transplant medicine to suppress rejection. It is initiated typically at 250 to 500 mg twice per day and is escalated every few weeks to 1000 mg twice daily. In 2000, Gelber et al. [33] treated four patients with classic skin manifestations of DM (two patients also had muscle involvement) with MMF. All patients had failed hydroxychloroquine, and three of four also failed corticosteroids and methotrexate. Patients were treated with 1000 to 1500 mg twice daily for 6 to 20 months. All patients saw improvement in the skin findings, one patient had an improvement in strength, and three patients were able to taper their steroid dose. Majithia and Harisdangkul [34] published a case series of seven patients with biopsy-proven IIM who had inadequate responses to corticosteroids and other immunosuppressive agents. Patients were treated with MMF in doses up to 1000 mg twice daily. Six of seven patients had improvement in weakness, and all had a decrease in the levels of their muscle enzymes. Edge et al. [35] published a retrospective chart review of 12 patients with DM who had failed conventional therapy; patients were treated with MMF in doses up to 1000 mg twice daily. Ten of the patients had an improvement of skin findings and increased strength, and they were able to taper concomitant therapies. One patient developed B-cell lymphoma of the central nervous system.

Tacrolimus

Tacrolimus is an inhibitor of T-cell activation that has been used in transplant medicine. In 1999, Oddis et al. [36] reported treating eight patients with IIM (six of whom had anti–Jo-1 antibody) that had failed corticosteroids and at least one immunosuppressive agent. Patients were treated with oral tacrolimus at 0.075 mg/kg per day (target 12-hour plasma trough, 5–20 ng/mL) for a mean of 4 to 6 months. All patients experienced improved strength, and five of the six anti–Jo-1 patients achieved normal strength (in three of these patients, CK levels became normal within 1 month of therapy). One patient developed hypertension and worsening renal function. Wilkes et al. [37] published a retrospective study of 13 patients with antisynthetase syndrome and interstitial lung disease. Patients were treated with the same dosing described above for an average of 51.2 months. A significant improvement was observed in all pulmonary function test parameters. All patients had a decrease in their CK level, and strength in most patients was improved or unchanged despite a significant reduction of steroid dose.

Rituximab

Recently, the therapeutic benefit of rituximab in the treatment of autoimmune hemolytic anemia and immune thrombocytopenia purpura has led to its increased use in treating other autoimmune diseases. Trials of rituximab in rheumatoid arthritis, systemic lupus erythematous, and Wegner's granulomatosis have shown promising results.

Recently, Levine [38•] reported a small, open-label trial of rituximab in DM. In addition to standard therapy, seven adults were treated with four weekly infusions of rituximab; B cells were depleted in all patients. All patients had improved muscle strength, between 36% and 113%. In four patients, return of symptoms correlated with return of B cells. Other symptoms including rash, alopecia, and reduced forced vital capacity also showed improvement. Noss et al. [39] published three cases of IIM (two PM, one DM) that had failed corticosteroids and either methotrexate or azathioprine who were treated with 1000 mg intravenous rituximab on days 0 and 14. All three patients showed improved strength, with two patients achieving normal strength. CK levels became normal in all patients (average time to normal CK, 4.6 months). Corticosteroid dose was reduced in all. Two patients had disease flares manifested by weakness and increased CK at 6 and 10 months and were retreated. After retreatment, CK returned to normal, but changes in strength were not discussed. Mok et al. [40] published a report of four patients with active PM that was refractory to conventional therapy. Patients were treated with four consecutive, weekly doses of 375 mg/m^2 of intravenous rituximab. At 28 weeks, all patients had a reduction of CK level. Two patients returned to normal strength, whereas two patients had a mild improvement of strength. Chung et al. [41] treated eight patients with refractory DM with two infusions of intravenous rituximab (1000 mg for each infusion given 2 weeks apart). Three patients had improved muscle strength, but muscle enzymes and skin scores were not significantly changed at 24 weeks.

Tumor necrosis factor-α blockade

Tumor necrosis factor (TNF)-α has been implicated in the pathogenesis of inflammatory myopathy, which has led investigators to use TNF-α blockade in PM and DM.

Several reports that include either one or a few patients have shown that treated patients experience improved strength and decreased serum muscle enzyme activity [42–44]. Another report, however, described the development of myositis in a patient with rheumatoid arthritis treated with infliximab [45]. Efthimiou et al. [46] published a retrospective study of eight patients with DM or PM who had failed conventional therapy and were treated with etanercept (6 patients), infliximab (1 patient), or both (1 patient). After follow-up for an average of 15.2 months, six patients, all of whom were treated with etanercept, had an improvement of strength, and all of these patients had reduced CK. Hengstman et al. [47] published the results of an open-label trial of infliximab and methotrexate in drug-naïve patients with DM and PM. Six patients were treated, but the trial was terminated early because of a low inclusion rate and high drop-out rate (a result of disease progression). Dastmalchi et al. [48•] published the results of an open-label pilot study of infliximab in 13 patients with PM (5 patients), DM (4 patients), and IBM (4 patients) who had failed conventional therapy. Three patients withdrew due to adverse events (weakness, severe erythema, and severe cough, in one patient each). Of those who completed the study, three improved by greater than or equal to 20% in three of the six IMACS Group core variables for disease activity, four were unchanged, and two worsened.

Plasma exchange

Plasma exchange has been used to treat autoimmune conditions with the goal of reducing the levels of autoantibodies, cytokines, or circulating immune complexes. Miller et al. [49] published a randomized, controlled trial in which 39 patients with PM and DM were randomized to either plasma exchange, leukapheresis, or sham apheresis. During the study period, the dose of corticosteroids was held constant, and no immunosuppressive drugs were used. Patients received three treatments per week for 4 consecutive weeks and were assessed at 1 month, at which time, there was no significant difference in strength between groups. Cherin et al. [50] reported the treatment of 57 patients with PM and DM (38 acute cases, 19 subacute or chronic cases). Patients were treated with three sessions weekly for 3 weeks, then two sessions bimonthly for a mean of 14.8 treatments. Thirty-nine patients continued on corticosteroids and an immunosuppressive agent. Clinical improvement was observed in 54% of patients; all of the patients who improved were acute cases.

Conclusions

Although many options exist for treating IIM, therapeutic approaches are based, for the most part, on empiric evidence and small, often uncontrolled studies. The disease's rarity has made large, controlled studies extraordinarily difficult. The recent effort to create and validate criteria for disease activity and the introduction of new agents born from decades of work aimed at understanding the immune system and its dysfunction offer great promise for the future. Because the illness is rare, all IIM patients should be considered for participation in a clinical trial, if possible.

Disclosure

The author has reported no potential conflict of interest relevant to this article.

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