Inflammatory Myopathies

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Opinion statement

The mainstay of treatment for the idiopathic inflammatory myopathies currently and traditionally has been therapeutics aimed at suppressing or modifying the immune system. Most therapies being used are directed towards polymyositis (PM) and dermatomyositis (DM), as there is yet to be efficacious treatment of any kind for inclusion body myositis (IBM), However, there are few randomized controlled studies supporting the use of such therapies even in PM and DM. Even in the absence of controlled studies, oral corticosteroids (in particular high-dose prednisone) continue to be the first-line medications used to manage these conditions. Second-line therapies include the addition of chronic, steroid-sparing immunosuppressive drugs such as azathioprine, methotrexate, cyclosporine, cyclophosphamide, and mycophenolate mofetil. These drugs are typically added when patients are on corticosteroids for an extended period or when the disease is refractory. Such medications often allow corticosteroid dosages to be reduced, but monitoring is required for their own side effects, such as bone marrow suppression, kidney dysfunction, and respiratory concerns. Small controlled studies also support the role of intravenous immunoglobulin therapy as an alternative therapy, particularly for DM, though the cost of this treatment is sometimes prohibitive. Rituximab, a monoclonal antibody that depletes B cells, has also shown efficacy in uncontrolled studies in DM and holds promise for the treatment of this disease. Other promising immunotherapies currently under study are inhibitors of interferon-α and tumor necrosis factor-α. Unfortunately, though a number of immunomodulatory treatments have been investigated in IBM, none has convincingly demonstrated benefit.

Introduction

The idiopathic inflammatory myopathies largely comprise dermatomyositis (DM), polymyositis (PM), and inclusion body myositis (IBM). These are clinically and histopathologically distinct diseases with many clinical features in common [1, 2, Class IV]. A fourth inflammatory myopathy subtype, called necrotizing myopathy (NM), has more recently been described [3–5, Class III]; it may be related to malignancy, other autoimmune diseases, or toxic exposure (eg, statins), or it can be idiopathic. Given the lack of randomized controlled trials in NM, this review will focus on DM, PM, and IBM. Although DM and PM are usually responsive to immunotherapies, IBM is typically refractory. Much of the original literature describing the clinical differences and associations of DM and PM used Bohan and Peters' criteria [6, 7, Class III]. Using Bohan and Peters' criteria, DM is differentiated from PM by the presence of a rash, rather than by histopathologic differences. The likely result is overdiagnosis of PM, with many cases of DM without obvious skin manifestations (as well as muscular dystrophies) wrongly classified as PM [7, Class III]. Sporadic IBM is frequently misdiagnosed, even though it is the most common inflammatory myopathy in patients older than 50 years of age. Accurate diagnosis is important because IBM is the least likely to improve with immune therapy [8, Class III].

Diagnosis

Patients with DM and PM often present with subacute onset of progressive, symmetric proximal weakness. Patients typically complain of difficulty arising from low chairs, as well as difficulties going up and down stairs. Muscle pain or tenderness is rare. Unlike PM, DM is associated with a number of characteristic skin manifestations, including heliotrope rash, a macular, erythematous rash seen over the face, upper trunk, and limbs, and Gottron's nodules, papular erythema of the metacarpophalangeal and interphalangeal joints. Tiny capillary telangiectasias around the nail beds also are often seen. The rash may precede or accompany the development of muscle weakness, and occasionally the typical rash appears without muscle weakness, known as *DM sine myositis* (or amyopathic DM) [9, Class III].

Sporadic IBM presents with the insidious onset of slowly progressive proximal and distal weakness. The slow evolution of the disease process probably accounts in part for the delay in diagnosis, which can be delayed up to 6 to 8 years from the onset of symptoms [10, Class III]. Patients with IBM have a unique pattern of weakness, which is often asymmetric, with early weakness and atrophy of the quadriceps, the forearm flexor muscles (ie, wrist and finger flexors), and the ankle dorsiflexors. At least 60% of patients develop dysphagia, which can be the presenting symptom and at times is so severe as to require cricopharyngeal myotomy [11, 12, Class III].

PM is characterized histologically by the presence of endomysial inflammatory cells (mainly CD8+ T cells and macrophages), which surround and invade non-necrotic muscle fibers, and the expression of major histocompatibility complex antigen-1 on many muscle fibers, including those distant from inflammatory cell infiltrate (Fig. 1). Pathologically, DM is, in part, a microangiopathy. Early findings on muscle biopsy demonstrate deposits of membrane attack complex (MAC) on endomysial capillaries and a reduction in capillary density, but whether the MAC deposition is a primary or secondary event is unclear [13–15, Class III]. As the disease progresses, muscle biopsies demonstrate inflammatory cells (mainly
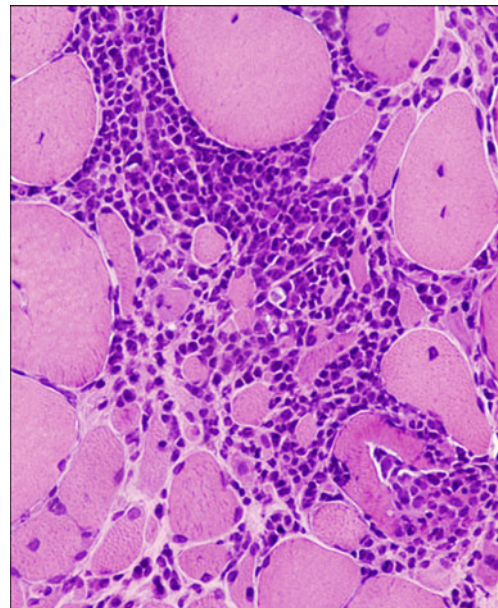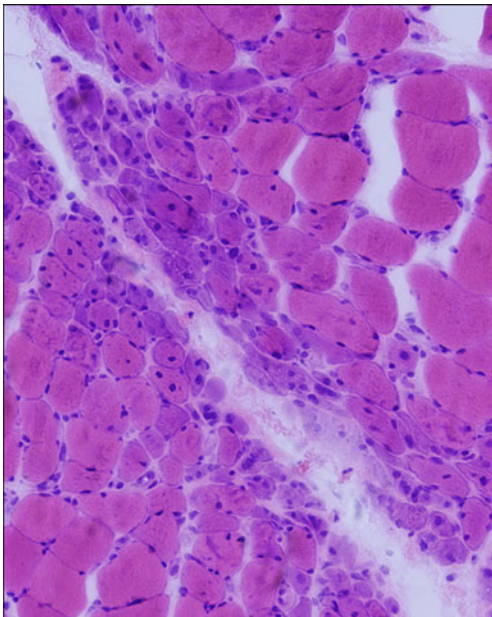

Figure 1. Prominent inflammatory cells are shown surrounding nonnecrotic muscle fibers in polymyositis (H & E, original magnification ×20).
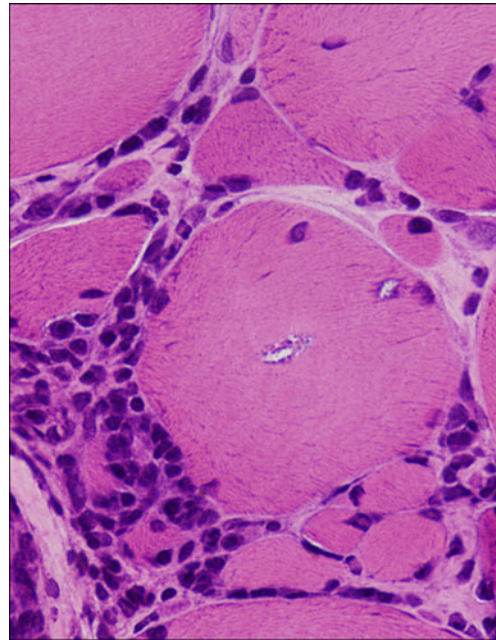
plasmacytoid dendritic cells and B cells) around blood vessels, primarily in the perimysium, and characteristic perifascicular atrophy (Fig. 2). Recent studies suggest that plasmacytoid dendritic cells may oversecrete type-1 interferons, which are toxic to capillaries and nearby perifascicular muscle fibers, leading to their degeneration [16, 17, Class III]. Endomysial inflammation and fibers with one or more rimmed vacuoles are characteristically seen in muscle biopsy specimens in IBM (Fig. 3). Within the rimmed vacuoles, amyloid deposition is evident on Congo red staining using polarized light or fluorescence techniques [18, Class III]. Electron microscopy typically demonstrates 15-nm to 21-nm cytoplasmic and intranuclear tubulofilaments within muscle fibers. The poor clinical response to various immunosuppressive therapies argues against a primary autoimmune basis for IBM [19•, Class III].

Principles of Treatment
First-Line Therapy   Thus far, well-designed, randomized controlled treatment trials in PM, DM, and IBM have been limited, and none exist for NM [20••, Class III]. A few uncontrolled studies suggest that patients with NM may respond to immunosuppression [3, 5, Class III]. Although no prospective, ran-

Figure 3. Rimmed vacuoles are noted in a few muscle fibers in inclusion body myositis (H & E, original magnification ×40).

domized, controlled clinical trials have studied the efficacy of corticosteroids in PM and DM, clinical experience suggests that their use clearly results in moderate to significant improvement in most patients. Currently, the authors recommend prednisone as the first-line treatment of DM and PM, with most patients demonstrating clinical improvement within 3 to 6 months of starting therapy. Adjustments of prednisone and other immunosuppressive agents should be based on an objective clinical examination and functional gains, not on serum creatine kinase (CK) levels or the patient's subjective response. A maintenance dose of prednisone or one of the second-line agents may be required to sustain a clinical response.

Second-Line Therapy   If a patient does not significantly improve after 4 to 6 months of prednisone, a second-line agent is added (usually methotrexate, mycophenolate mofetil, or azathioprine). In a randomized, placebo-controlled trial, Bunch et al. [21, Class II] compared the effects of prednisone with the addition of azathioprine (2 mg/kg) to prednisone and placebo in 16 patients with DM and PM. No significant difference was demonstrated between

Figure 2. Evidence of perifascicular atrophy in dermatomyositis (H & E, original magnification ×20).

the two groups at the end of 3 months. However, in a longer follow-up study [22, Class II], patients maintained on both prednisone and azathioprine demonstrated a significant benefit in measures of strength testing and a lower prednisone requirement compared with the patients receiving prednisone and placebo. In the authors' experience, methotrexate works faster than azathioprine, though there has been no prospective placebo-controlled trial of methotrexate alone and no trial comparing these two agents in inflammatory myopathies.

In patients with severe weakness, interstitial lung disease (ILD), cardiomyopathy, diabetes, osteopenia or osteoporosis, or in women who are postmenopausal, often a second-line agent is started concomitantly with prednisone. Because methotrexate can cause pulmonary fibrosis, it is best avoided in patients who already have ILD. In these patients, mycophenolate mofetil may be a better choice. In very weak patients, sometimes a short course of intravenous methylprednisolone, such as 1 gram per day for 3 days, is helpful prior to initiating prednisone or other immunosuppressant therapies.

If patients do not respond adequately to the combination of prednisone and methotrexate, mycophenolate, or azathioprine, the authors give a 3-month trial of intravenous immunoglobulin (IVIg). The efficacy of IVIg in patients with refractory DM was first demonstrated by Dalakas et al. [23, Class II], and several other studies have since suggested its efficacy and safety in both PM and DM [24, 25, Class III].

IVIg may influence the immune system in inflammatory myopathies in a number of ways. A prospective, placebo-controlled trial of IVIg in 15 patients with DM who were unresponsive to other agents demonstrated not only clinical improvement but also a reduction of complement consumption; interception of MAC formation; downregulation of inflammation, fibrosis, cytokines, chemokines, and adhesion molecules; and alterations in thousands of immunoregulatory genes [26, Class III].

Third-Line Therapy Third-line agents include tacrolimus, cyclosporine, and cyclophosphamide, based mostly on case reports or small series. A trial and literature review of cyclosporine in resistant DM and PM demonstrated a modest response rate, with three of six patients achieving normal strength [27, Class III]. How-

ever, cyclosporine toxicity, including renal insufficiency and hypertension, though reversible, was a substantial problem. In the authors' experience, patients who fail prednisone, methotrexate, azathioprine, mycophenolate mofetil, and IVIg usually do not respond to these third-line agents. In patients with PM or DM, intravenous cyclophosphamide has been studied mostly as therapy for interstitial pneumonitis and has shown efficacy and only mild toxicity in a recent small series [28, Class IV]. A few uncontrolled studies have shown that rituximab, which transiently depletes B cells, is beneficial in the treatment of DM. In one study of eight patients with DM [29, Class III], three patients had partial remission in regard to their muscle strength. There was no impact on the dermatologic manifestations of the disease. In a study by Levine [30, Class III], all six DM patients treated had a marked improvement in strength, forced vital capacity measurements, and skin lesions. Rituximab is largely well tolerated, although its cost limits its use. The results of a large NIH trial of rituximab in PM and DM were negative, although modest benefit was seen in treated patients [31].

Treatment of Inclusion Body Myositis Unfortunately, patients with IBM do not significantly improve with immunosuppressive treatment. A small, uncontrolled study using prednisone did not show any benefit, as subjects had no improvement in strength following treatment, despite reduction of inflammation on muscle biopsy specimens [32, Class III]. Other such studies using corticosteroids alone have also been unsuccessful. Similar uncontrolled studies of prednisone in combination with methotrexate [33, Class III] or methotrexate plus azathioprine [34, Class III] suggested partial improvement or stabilization of strength and substantial reductions of serum CK levels. An initial uncontrolled study of IVIg suggested a benefit in three of four patients [35, Class III]. However, subsequent double-blind, placebo-controlled trials of IVIg have not shown efficacy [36–38, Class II]. Numerous additional randomized controlled studies in IBM have all been unsuccessful, including treatment trials of methotrexate [39, Class II], the anabolic steroid oxandrolone [40, Class II], anti-T-lymphocyte globulin therapy [41, Class II], and high-dose beta interferon-1a [42, Class II]. Given the lack of evidence for any benefit, the authors do not routinely prescribe immunomodulatory or immunosuppressant therapy for the treatment of IBM.

Treatment

Diet and Lifestyle

- Dietary supplementation currently plays a limited role in treating the inflammatory myopathies, but the nutritional supplement creatine may be of potential benefit. In a 6-month, double-blind, randomized, placebo-controlled trial, 29 patients with DM or PM improved significantly with oral creatine supplements (20 g/d for 8 days, then 3 g/d) in conjunction with exercise as compared with exercise alone, based on functional performance times and changes on magnetic resonance spectroscopy [43, Class II.]
- Patients taking chronic corticosteroid therapy also need to make dietary modifications to minimize effects such as fluid retention, hyperglycemia, and weight gain. Patients on prednisone therapy should adhere to a low-salt, low-carbohydrate, and low-fat diet. They should also take calcium (1 g/d) and vitamin D (400–800 IU/d) supplementation to decrease the risk of osteopenia.

Pharmacologic Therapy

Corticosteroids

Standard dosage	In patients with severe weakness or with severe systemic involvement, methylprednisolone sodium succinate (Solu-Medrol) (1 g) is given intravenously daily for 3 days, and then patients are started on oral prednisone, as outlined. In patients with mild to moderate weakness, patients are started on 0.75 to 1.5 mg/kg of prednisone orally (usually 60 mg/d), taken once every morning for 2 to 4 weeks before switching to alternate-day dosing (60 mg every other day). Patients with more severe disease are slowly tapered to alternate-day dosing over 2 to 3 months by decreasing the dose by 10 mg each week (ie, 60 mg alternating with 50 mg daily for 1 week, then 60 mg alternating with 40 mg daily for 1 week, and so forth, until the patient is taking 60 mg every other day). Patients are then kept on alternate-day, high-dose prednisone until their strength returns to normal or until improvement plateaus (usually 4–6 months). Subsequently, the prednisone dose is tapered by 5 mg every 2 to 3 weeks. Once the dose is reduced to 20 mg every other day, prednisone is tapered no faster than 2.5 mg every 2 weeks. A maintenance dose of prednisone is often required to sustain the clinical response.
Contraindications	Systemic fungal infections.
Main drug interactions	None.
Main side effects	Increased susceptibility to infection, diabetes, osteoporosis, cataracts, glaucoma, avascular necrosis, weight gain, hypertension, steroid myopathy, hypokalemia, peptic ulcer disease, impaired wound healing, fragile skin, alteration in mood, and psychosis.
Special points	If a patient does not significantly improve after 4 to 6 months of prednisone, or if there is an exacerbation during the taper, the authors add a second-line agent (methotrexate, azathioprine, or IVIg). At the same time, the prednisone dose is doubled and given daily (≤100 mg/d) for at least 2 weeks before

switching back to every-other-day dosing. Once patients have regained their strength, the prednisone taper is resumed at a slower rate. High-dose, long-term steroids and lack of physical activity can cause type 2 muscle fiber atrophy with proximal muscle weakness, which needs to be distinguished from weakness because of relapse of the myositis. Patients who become weaker during prednisone taper, have increasing serum CK levels, and have abnormal spontaneous activity on electromyography are more likely to be experiencing a flare of the myositis. In contrast, patients with normal serum CK and electromyography and other evidence of steroid toxicity (eg, Cushingoid appearance) may have type 2 muscle fiber atrophy and could benefit from physical therapy and a reduction in the dose of steroids.

Concurrent management. A chest radiograph and a purified protein derivative (PPD) skin test with controls should be performed on all patients before initiating immunosuppressive medications. Patients with a history of tuberculosis or those with a positive PPD may need to be treated prophylactically with isoniazid. Measure bone density with dual-energy x-ray absorptiometry (DEXA) at baseline and every 6 months while patients are receiving corticosteroids. A bone density less than 2.5 SD below normal is considered positive for osteoporosis. The authors give alendronate (35 mg orally once per week) to postmenopausal women without evidence of osteoporosis. However, because the long-term side effects of bisphosphonates are not known, especially in men and in young, premenopausal women, this type of prophylactic treatment is started in these patients only if DEXA scans show bone loss at baseline (1.0 SD below normal but not as yet enough to diagnosis osteoporosis) or if there is significant loss on follow-up scans. If DEXA scans demonstrate osteoporosis at baseline or during follow-up studies, patients are started on alendronate at 70 mg per week. Alendronate can cause severe esophagitis, and absorption is impaired if taken with meals. Therefore, patients must be instructed to remain upright and not to eat for at least 30 min after taking a dose of alendronate.

Though evidence is lacking, empiric therapy with double-strength trimethoprim/sulfamethoxazole (160 mg once a day) may also be warranted to prevent *Pneumocystis carinii* pneumonia, especially in patients taking other concurrent immunosuppressant therapies.

Cost	Relatively inexpensive: 5 mg (100 ea): $11.99; 10 mg (30 ea): $11.99. Cost is increased if alendronate is added to the regimen: 5 mg daily (100 ea): $255.98; weekly: 35 mg (1 package, 4 ea): $49.99; 70 mg (1 package, 4 ea): $32.99.

Methotrexate

Standard dosage	Begin methotrexate orally at 7.5 mg per week, given in three divided doses 12 h apart. The dose is gradually increased by 2.5 mg each week up to 20 mg per week. If there is no improvement after 1 month of 20 mg per week of oral methotrexate, a switch to weekly parenteral (intramuscular or intravenous) methotrexate is made, and the dose is increased by 5 mg every week up to 60 mg per week. In patients with severe muscle weakness or myocarditis, methotrexate is initiated parenterally in doses of 20 to 25 mg per week, in combination with corticosteroids.
Contraindications	Interstitial lung disease or presence of anti-Jo-1 antibody, severe renal or hepatic impairment, pregnancy, and breastfeeding.
Main drug interactions	Trimethoprim (may increase risk of myelosuppression).
Main side effects	Myelosuppression, renal or hepatic toxicity, interstitial pneumonitis, alopecia, stomatitis, teratogenicity, oncogenicity, and increased risk of infection.

Special points	Start folate 1 mg daily. Doses greater than 50 mg per week require leucovorin rescue. Monitor pulmonary function at baseline and check approximately every 6 months. Complete blood counts and liver function tests (AST, ALT, and gamma-glutamyl transpeptidase [GGT]) are followed closely. It is important to check the GGT, because elevations are specific for hepatic dysfunction, whereas AST and ALT may be elevated from myositis.
Cost	Relatively inexpensive: 2.5 mg (30 ea): $31.99; 25 mg/mL (1 vial, 2 mL): $15.11.

Azathioprine

Standard dosage	50 mg per day in adults, increasing by 50 mg per week to a total dose of 2 to 3 mg/kg per day.
Contraindications	Pregnancy and breastfeeding.
Main drug interactions	Allopurinol increases risk of myelosuppression and hepatic toxicity; trimethoprim.
Main side effects	A systemic reaction characterized by fever, abdominal pain, nausea, vomiting, and anorexia occurs in 12% of patients and requires discontinuation of the drug. The systemic reaction generally occurs within the first few weeks of therapy and resolves within a few days of discontinuing the azathioprine. Rechallenge with azathioprine usually results in recurrence of the systemic reaction. Other major complications of azathioprine are myelosuppression, hepatic toxicity, pancreatitis, teratogenicity, oncogenicity, and risk of infection.
Special points	Monitor complete blood count and liver function tests (AST, ALT, bilirubin, and GGT) every 2 weeks until the patient is on a stable dose of azathioprine, then monitor once per month. If the leukocyte count falls below 4000 per mm^3, the dose is decreased. Azathioprine is held if the leukocyte count declines to 2500 per mm^3 or the absolute neutrophil count falls to 1000 per mm^3. Leukopenia can develop as early as 1 week or as late as 2 years after initiating azathioprine. Leukopenia usually reverses in 1 month, and it is possible to then rechallenge the patient with azathioprine without recurrence of the severe leukopenia. Discontinue azathioprine if the liver function tests increase to more than twice the baseline values. Liver toxicity generally develops within the first several months of treatment and can take several months to resolve. Patients can occasionally be successfully rechallenged with azathioprine after liver function tests return to baseline without recurrence of hepatic dysfunction. Again, it is important to check the GGT, which is specific for the liver, as opposed to just AST and ALT, which can be elevated secondary to hepatotoxicity or exacerbation of the myositis. Thiopurine methyltransferase (TPMT) activity can also be checked prior to initiating azathioprine, as reduced activity is associated with an increased risk of bone marrow suppression that may prohibit its use.
Cost	Relatively inexpensive: 50 mg (30 ea): $27.99.

Mycophenolate Mofetil

Standard dosage	1 to 1.5 g twice daily (500 mg twice daily if evidence of renal insufficiency).
Contraindications	Myelosuppression, pregnancy, breastfeeding.
Main drug interactions	Antacids, oral contraceptives.

Main side effects	Diarrhea, myelosuppression, hypertension, tremors.
Cost/cost-effectiveness	Relatively expensive: Tablet, 500 mg (100 ea): $129.99. Capsule, 250 mg (30 ea): $35.99.

Rituximab

Standard dosage	750 mg/m^2 (up to 1 g) once, then repeated in 2 weeks, with repeat dosing every 6 to 9 months.
Contraindications	Live vaccine.
Main drug interactions	None.
Main side effects	Fevers, nausea, shivering, asthenia, headache; rare infusion reaction, progressive multifocal leukoencephalopathy (PML).
Special points	In other diseases, it appeared that clinical responses to rituximab were not as long-lasting when it was combined with methotrexate. With other biologic agents, combination therapy with methotrexate has afforded synergistic clinical efficacy and, in some cases, beneficial pharmacokinetic interactions.
Cost/cost-effectiveness	Expensive: two-dose course of therapy at 1,000 mg per course is about $12,000.

Intravenous Immunoglobulin

Standard dosage	2 g/kg total dose given over 2 to 5 days (1 g/kg per day over 2 days or 0.4 g/kg per day over 5 days), repeated monthly for at least 3 months.
Contraindications	Immunoglobulin A deficiency (risk of anaphylactic reaction), renal insufficiency, significant atherosclerotic disease, history of deep vein thrombosis.
Main drug interactions	None, but added caution should be applied with nephrotoxic medications.
Main side effects	Flu-like symptoms, headaches, myalgias, fever, chills, nausea, and vomiting are common. Rash and aseptic meningitis may also occur. More serious side effects include the risk of renal failure and risk of thrombosis with subsequent myocardial infarction or stroke.
Special points	Premedication with acetaminophen (650–1000 mg) and diphenhydramine (25–50 mg) appears to decrease the risk of developing flu-like symptoms.
Cost	Very expensive. Cost varies, but approximately $10,000 per treatment.

Tacrolimus

Standard dosage	2 mg orally twice daily. The dose is titrated according to clinical response, tolerance, and levels.
Contraindications	Interstitial lung disease or presence of anti-Jo-1 antibody, severe renal or hepatic impairment, pregnancy, breastfeeding.
Main drug interactions	Posaconazole, voriconazole, itraconazole, ziprasidone, nifedipine.
Main side effects	Increased susceptibility to infection and the possible development of lymphoma, alopecia, erythema of skin, pruritus, constipation, diarrhea, nausea, anemia, leukocytosis, thrombocytopenia, headache, insomnia, paresthesia, tremor.
Special points	Whole blood trough concentrations of tacrolimus should be checked periodically.
Cost	Moderately expensive. Capsule: 1 mg (100 ea): $345.97.

Cyclophosphamide

Standard dosage	1.0 to 2.0 mg/kg per day orally or 1 g/m^2 per month intravenously.
Contraindications	Myelosuppression, pregnancy, breastfeeding.
Main drug interactions	Allopurinol, digoxin, succinylcholine.
Main side effects	Gastrointestinal upset, myelosuppression, alopecia, hemorrhagic cystitis, teratogenicity, sterility, increased risk of infections and secondary malignancies.
Special points	It is important for the patient to maintain high fluid intake to avoid hemorrhagic cystitis. Urinalysis and complete blood counts should be observed closely (every 1 to 2 weeks at the onset of therapy and then at least monthly). Cyclophosphamide should be decreased if the leukocyte count falls below 4000 per mm^3. Cyclophosphamide is held if the leukocyte count falls below 3000 per mm^3, if the absolute neutrophil count falls below 1000 per mm^3, or if there is evidence of hematuria. Cyclophosphamide can be restarted at a lower dose once the leukopenia has resolved, but the authors do not restart the medication in patients with hematuria.
Cost	Moderately expensive. Intravenous solution: $51.43 for 1 g. Tablets: 25 mg (30 ea): $62.82; 50 mg (30 ea): $110.20.

Cyclosporine

Standard dosage	Start at a dose of 3 to 4 mg/kg per day in two divided doses, and gradually increase to 6 mg/kg per day as necessary. (Aim to maintain trough serum cyclosporine levels of 50–200 ng/mL.)
Contraindications	Hypertension, renal dysfunction, malignancy, pregnancy, breastfeeding.
Main drug interactions	Statins, methylprednisolone, aminoglycosides, vancomycin, erythromycin, trimethoprim with sulfamethoxazole, azoles, calcium channel blockers, amiodarone, digoxin, ticlopidine, other drugs metabolized via cytochrome P450, St. John's wort, grapefruit and grapefruit juice.
Main side effects	Hypertension, renal failure, gastrointestinal upset, hypertrichosis, gingival hyperplasia, oncogenicity, tremor, risk of infection.
Special points	Monitor blood pressure, electrolytes, renal function, and trough cyclosporine levels.
Cost	Moderately expensive. 25 mg (1 box, 30 ea): $33.99; 100 mg (1 box, 30 ea): $140.96.

Assistive Devices

- If patients are sufficiently weak, they may require an assistive device such as a single-prong cane, rolling walker, or wheelchair to prevent falls. They may need elevated toilet seats and a shower chair. Uncommonly, patients may also require assistance with transfer to the commode, such as a Hoyer lift.

Physical Therapy

- Physical therapy is virtually always indicated to help patients maintain their strength and to address activities of daily living, such as the need for assistive devices. Such therapy can be performed in parallel with immunomodulatory therapies.

Emerging Therapies

Anti-Tumor Necrosis Factor-α Blockers

- As tumor necrosis factor-α (TNF-α) has been shown to play a role in the pathogenesis of both PM and DM [44, Class III], blockers of TNF-α, including infliximab and etanercept, continue to be studied for their potential therapeutic effects in these diseases. A recent open-label, controlled study of infliximab in combination with weekly methotrexate in DM and PM showed improvement in manual muscle testing, hand dynamometry, disease activity assessments, and CK levels in the few patients who completed the study [45, Class III]. The trial was terminated prematurely because of a high dropout rate due to disease progression and the occurrence of an infusion reaction. A phase II, randomized controlled study of etanercept for the treatment of DM was recently completed, but results have not yet been published. A phase II study is also under way to test the effects of etanercept in IBM.

Stem Cell Transplantation

- A recent study suggests that autologous stem cell transplantation may play a role in the treatment of refractory severe juvenile DM. Holzer et al. [46, Class IV] reported on two patients with severe, progressive juvenile DM who had developed contractures and were wheelchair dependent despite the use of a number of therapies, including methotrexate, steroids, immunoglobulins, cyclosporine, and rituximab. The patients underwent autologous stem cell transplantation using a CD3/CD19-depleted graft after immunoablative conditioning with fludarabine, cyclophosphamide, and anti-thymocyte globulin. Both patients experienced dramatic improvement and sustained remission of the disease. Though the treatment was reasonably well tolerated, the significant morbidity noted in other studies using this therapy would make this a viable treatment for only a few severely debilitated patients.

Disclosure

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- Of major importance

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