Inflammatory Myopathy

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Opinion statement

Patients with polymyositis or dermatomyositis should be treated with prednisone (approximately 1 mg/kg/d) for an initial period of 4 to 6 weeks. Once improvement occurs, the dose should be tapered and converted to an alternate-day regimen, which should be continued for at least 12 months. Methotrexate or azathioprine should be administered concomitantly to patients in whom there is inadequate control. The early introduction of one of these drugs allows more rapid reduction in the dose of prednisone and helps to avert serious side effects. Intravenous immunoglobulin therapy is indicated for patients who have immunodeficiency, who are unable to tolerate immunosuppressive drugs, whose conditions are deteriorating, or who have severe relapses. Cyclosporine or cyclophosphamide may be effective for resistant disease. Patients with inclusion body myositis should undergo a 3- to 6-month trial of prednisone, alone or in combination with methotrexate or azathioprine. Maintenance doses of these drugs should be continued if the patient's condition improves or stabilizes.

Introduction

Since the publication of the definitive monograph on polymyositis by Walton and Adams in 1958 [1], classification of the inflammatory myopathies has evolved progressively (Table 1), as has our understanding of the underlying pathogenic mechanisms in the different forms of immune-mediated inflammatory myopathy.

The majority of cases encountered in neurologic practice fall into three main categories: polymyositis, dermatomyositis, and inclusion body myositis. Polymyositis and dermatomyositis may develop in isolation or in association with systemic connective tissue disease (*eg*, progressive systemic sclerosis, systemic lupus erythematosus, mixed connective tissue disease, Sjögren's syndrome), retroviral infection (human immunodeficiency virus or human T-cell lymphotrophic virus type I), or malignancy (in adult dermatomyositis) (*see* Table 1). In dermatomyositis, the immune process is directed against vascular endothelial cells in skin and muscle with the deposition of immune complexes and of the C5b9 membrane attack complex of complement [2,3], leading to depletion of the muscle capillary bed and to ischemic change [4]. On the other hand, in polymyositis, there is cytotoxic necrosis of muscle fibers as a result of invasion by sensitized $CD8^+$ T cells and macrophages [5].

The term *inclusion body myositis* was introduced by Yunis and Samaha in 1971 [6] to describe inflammatory myopathy associated with distinctive muscle fiber inclusions [7]. It is now known that this accounts for as many as one third of patients with inflammatory myopathy referred to neuromuscular clinics [8]. The condition is characterized clinically by a selective pattern of limb muscle involvement and histologically by the presence of rimmed vacuoles, tubulofilamentous inclusions, mitochondrial abnormalities, and deposits of amyloid and other associated proteins in muscle fibers [9,10]. In addition, there is invasion of nonnecrotic muscle fibers by $CD8^+$ T cells and macrophages [5], but it is unclear whether this represents a primary immune attack on muscle fibers or an epiphenomenon associated with an underlying degenerative process [11].

Although they have never been subjected to controlled clinical trials, glucocorticoids remain the standard first-line treatment in polymyositis and

Table 1. Immune-mediated inflammatory myopathies

Disease	Associations
Polymyositis, isolated	Connective tissue diseases (progressive systemic sclerosis, systemic lupus erythematosus, mixed connective tissue disease, Sjögren's syndrome)
	Other autoimmune diseases
	Other systemic diseases (sarcoidosis, hypereosinophilic syndrome)
	Drug-induced causes (D-penicillamine)
Dermatomyositis, isolated	Vasculitis*
	Malignancy†
	Connective tissue diseases
Inclusion body myositis, isolated	Other autoimmune diseases
	Connective tissue diseases
	Human immunodeficiency virus infection

*Juvenile dermatomyositis.
†Adult dermatomyositis.

Table 2. Treatment options for inflammatory myopathies

First-line
Glucocorticoids
Second-line
Methotrexate
Azathioprine
Intravenous immunoglobulin*
Third-line
Intravenous immunoglobulin
Cyclosporine
Cyclophosphamide
Plasmapheresis
Last option
Whole body/lymphoid irradiation
Thoracic duct drainage
Thymectomy

*In patients who are immunodeficient or who have other contraindications to the use of cytotoxic agents.

dermatomyositis, and they may be administered as oral prednisone or as pulse therapy with intravenous methylprednisolone [12•, Class IIIc]. Combined therapy with prednisone and methotrexate or azathioprine is recommended for patients with severe myositis or when there has been a long delay before treatment is begun. It has also been recommended as a steroid-sparing measure if there is particular concern about glucocorticoid side effects [12•, Class IIIc]. If patients do not go into remission with glucocorticoid therapy, a second-line agent such as methotrexate or azathioprine should be added at an early stage, before glucocorticoid side effects develop (Fig. 1; Table 2). Although there have not been any comparative trials of these two agents, methotrexate is preferred because it can be given in a single weekly dose and it carries a lower risk of development of malignancy than azathioprine [13]. Intravenous immunoglobulin therapy (IVIG) has been shown to be effective in treating dermatomyositis [14, Class IIa], polymyositis, and overlap syndromes [15•,16, Class IIIa1] but is not effective as first-line therapy [17, Class IIIa1]. Therefore, it is reserved as third-line therapy, in combination with prednisone and immunosuppressive agents, for patients whose conditions are not well controlled or who are unable to tolerate these agents (Fig. 2) and as second-line treatment for patients who have immunodeficiency [18, Class IIIb1]. Additional controlled trials of IVIG are required to refine the indications for its use and to determine the optimal dosage regimens.

Combined with ongoing glucocorticoid and immunosuppressive therapy, plasmapheresis was reported to be effective for patients with resistant polymyositis and dermatomyositis in an uncontrolled trial [19, Class IIIa1]. This was not confirmed, however, in a subsequent double-blind crossover trial comparing plasmapheresis, leukapheresis, and sham apheresis after discontinuance of immunosuppressive therapy [20, Class IIa]. IVIG is now preferable to plasmapheresis and appears to be equally or more effective, though there have been no comparative studies of the two treatment modalities.

Other immunosuppressive agents that have been reported in uncontrolled trials to be effective in resistant polymyositis and dermatomyositis include cyclophosphamide and cyclosporine. Cyclosporine has been shown to be particularly effective in juvenile dermatomyositis [21, Class IIIa1]. There have also been reports of the efficacy of chlorambucil, hydroxychloroquine, low-dose whole-body or lymphoid irradiation, thymectomy, and thoracic duct drainage for severely disabled patients who did not respond to any other form of treatment, but none of these has been formally evaluated in controlled trials [12•, Class IIIc; 22–24, Class IIIb].

Patients with inclusion body myositis are usually resistant to treatment with glucocorticoids and immunosuppressive agents, and their muscle weakness progresses. In a small proportion of patients, however, there has been some improvement in muscle strength or the condition stabilizes [25, Class IIIb2; 26, Class IIIa1]. A 3- to 6-month trial of prednisone alone or in combination with a steroid-sparing agent

such as methotrexate or azathioprine is recommended once the diagnosis has been established [12•, Class IIIc]. If there is improvement in or stabilization of muscle strength, treatment is continued with maintenance doses of these drugs (Fig. 3). Results of one controlled [27•, Class IIa] and two of three small uncontrolled [15•,28,29, Class IIIa1] trials of IVIG therapy have shown mild improvement in muscle strength in some muscles of some patients with inclusion body myositis. This is not usually sufficient to be of functional benefit, however; therefore, IVIG is not recommended for routine use. Anabolic agents such as clenbuterol may help to preserve muscle strength and warrant further evaluation in a controlled trial.

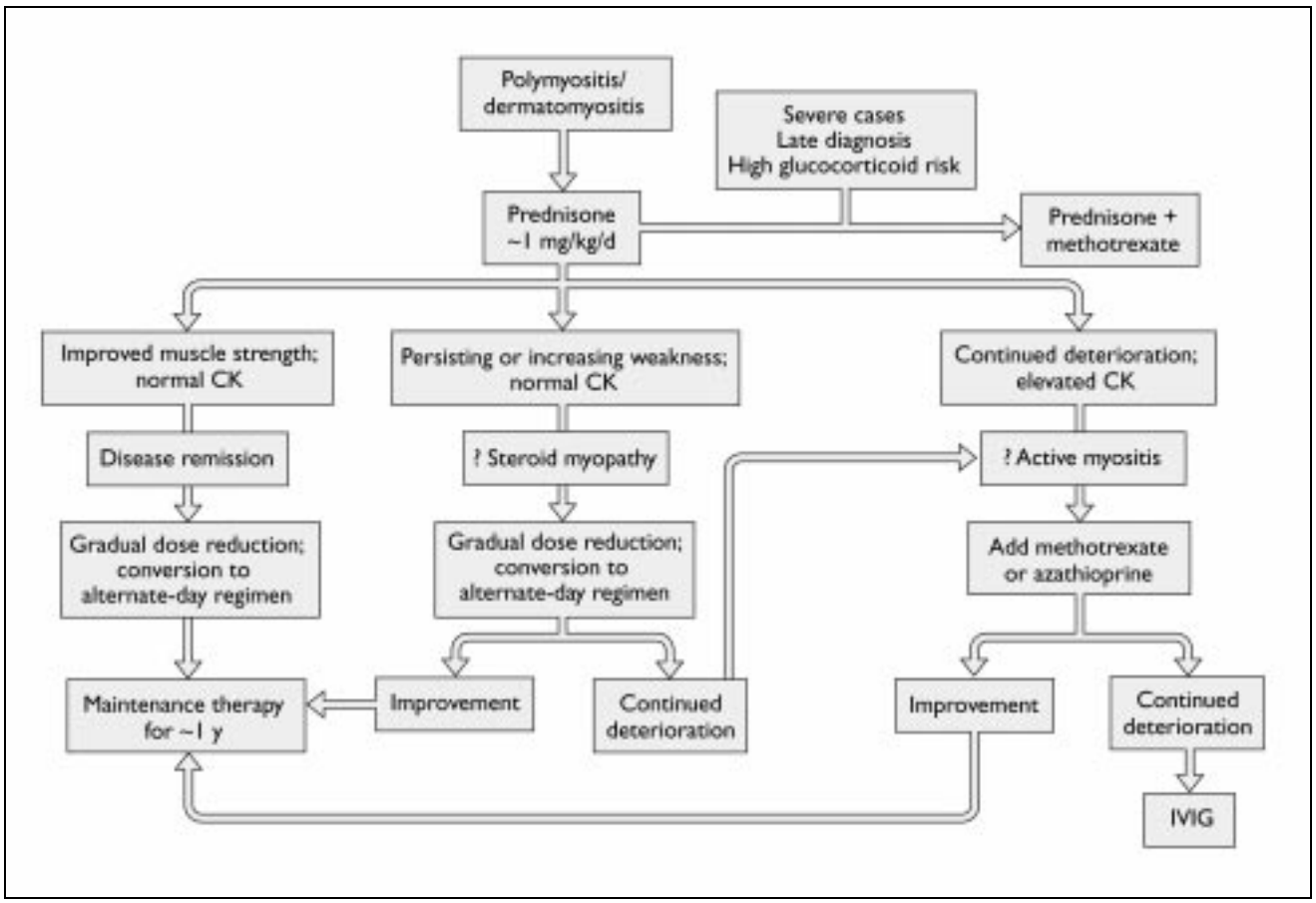

Figure 1. Treatment algorithm for patients with polymyositis and dermatomyositis. CK—creatine kinase; IVIG—intravenous immunoglobulin.

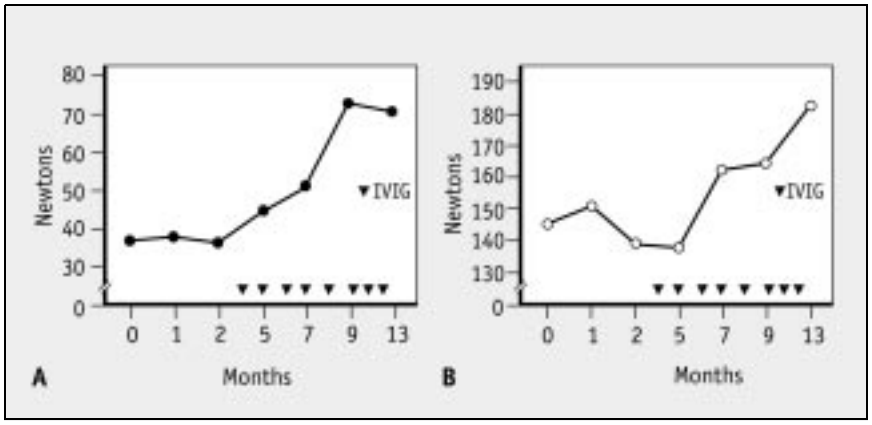

Figure 2. Isometric muscle strength in the neck flexors (*A*, normal >65 newtons) and hip flexors (*B*, normal >210 newtons) in a 52-year-old man with polymyositis and systemic sclerosis before and after the initiation of intravenous immunoglobulin therapy (IVIG). Prednisolone (30 mg/d reducing to 7.5 mg/d) was continued during the period of IVIG therapy.

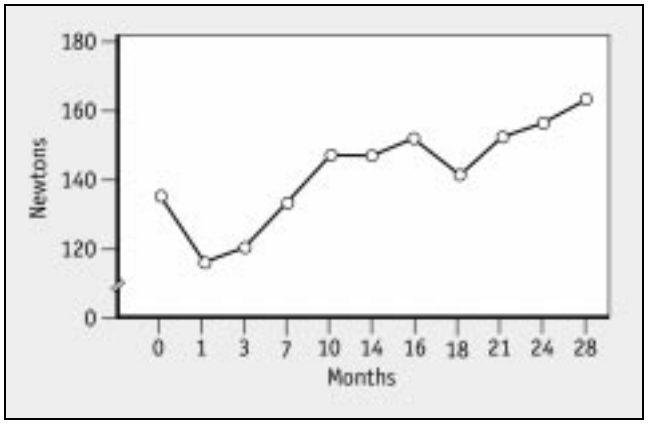

Figure 3. Sixty-one-year-old woman with inclusion body myositis of 5 years' duration. Progressive improvement in isometric muscle strength in the left hip flexors (normal >130 newtons) after the initiation of treatment with prednisolone (50 mg/d reduced to 20 mg on alternate days by 20 months) and methotrexate (10 mg/wk reduced to 7.5 mg/wk at 12 months).

Treatment

Pharmacologic treatment

- Used to induce early remission with improvement in muscle strength, physical endurance, skin changes, and general well-being.
- Indicated to maintain control of the underlying autoimmune process and to prevent disease reactivation.
- Employed to regain prompt control of the disease process when clinical relapses occur.

Glucocorticoids: prednisone, methylprednisolone

Oral prednisone or prednisolone is the standard first-line treatment for patients with polymyositis or dermatomyositis, and it may induce complete or virtually complete remission in most of them. Prednisone itself is inactive and undergoes conversion to prednisolone in the liver. The potency of prednisolone is approximately five-fourths that of prednisone. Intravenous pulse therapy with methylprednisolone has been reported to be effective as initial therapy [30, Class IIIa1], but its relative efficacy and incidence of side effects have not been compared with those of oral therapy. In patients with severe myositis, treatment may be started with intravenous methylprednisolone and may be followed by oral prednisone. A 3- to 6-month trial of oral prednisone is also recommended for patients with inclusion body myositis.

Standard dosage Treatment is initiated with oral prednisone or prednisolone in a single or a divided daily dose of approximately 1 mg/kg and is continued for 4 to 6 weeks before tapering. There are no reliable guidelines for the rate of reduction, but this should be determined on the basis of the clinical response and the degree of concern about the side effects of glucocorticoids in each patient. It is usually possible to reduce the dose of prednisone by 5 to 10 mg/d/wk during the second month of treatment and to convert to an alternate-day regimen to reduce the degree of adrenal suppression and glucocorticoid side effects. A maintenance dose of prednisone of less than 10 mg/d (or less than 20 mg on alternate days) should be continued for at least 12 months after muscle function recovers and the serum creatine kinase level returns to normal. Pulse methylprednisolone is administered intravenously, 1000 mg/d for 3 consecutive days, or the same dose may be administered on 3 alternate days.

Contraindications Although glucocorticoids involve no absolute contraindications, they should be administered with caution to the elderly and to patients with diabetes mellitus, osteoporosis, or any kind of infection; it may be necessary to use lower doses in these groups of patients. In patients with hepatic dysfunction, conversion of prednisone to prednisolone is inhibited; it is therefore preferable to use prednisolone in these patients.

Main drug interactions A higher dose of prednisone may be required for patients treated with drugs that cause the induction of hepatic enzymes (*eg*, anticonvulsants) because of the increased metabolic rate of the glucocorticoid.

Main side effects Cushingoid features, hypertension, diabetes mellitus, infections, cataracts, glaucoma, osteoporosis, aseptic necrosis of the femoral and humeral head, steroid myopathy.

Special points Patients should undergo assessments of muscle strength and serum creatine kinase activity and examinations for side effects on a regular basis [31]. If muscle strength continues to deteriorate, particularly in proximal lower limb muscles, and the creatine kinase activity has returned to normal, the possibility of steroid myopathy should be suspected. At times, it is difficult to know whether progressive deterioration in muscle strength is due to active myositis or to steroid myopathy, and in some patients it is necessary to repeat electromyography and muscle biopsy. When steroid myopathy is suspected, the dose of prednisone should be gradually reduced and an alternate-day regimen initiated, with implementation of a regular exercise program.

Calcium supplements (1 to 1.5 g/d) should be administered routinely, particularly in the elderly. In addition, in postmenopausal women with reduced bone density and a high risk for fracture, a vitamin D preparation (*eg*, calcitriol) or one of the bisphosphonates (etidronate or alendronate) should be administered to prevent additional bone loss and fractures [32,33, Class 1]. For patients with a history of peptic ulcers, an H_2-receptor blocker should be prescribed to prevent ulcer reactivation. To prevent the risk of reactivation of tuberculosis or the development of miliary tuberculosis, antituberculosis therapy should be initiated before glucocorticoid therapy for any patient with a history of tuberculosis or changes on chest imaging.

Cost effectiveness Glucocorticoid therapy is very cost effective because it reduces patient disability, precludes the need for hospitalization, and allows the patient to return to work. Glucocorticoid preparations are relatively inexpensive (approximately $0.10 to $0.20 per 20-mg tablet of prednisone; $10 to $20 per 400-mg methylprednisolone) and are available as generic formulations.

Methotrexate

The effectiveness of this drug has not been evaluated in controlled clinical trials, but retrospective studies have indicated that it may be beneficial and more effective than azathioprine in some groups of patients [34, Class IIIb2].

Standard dosage Methotrexate is administered orally in a starting dose of 7.5 to 10 mg once a week, which can be increased, if necessary, by 2.5 mg/wk to a maximum dose of 20 mg/wk. Dosages as high as 30 to 40 mg/wk may be prescribed. They are more likely to cause gastrointestinal side effects, however, and are best administered by the intramuscular or the intravenous route.

Contraindications Hepatic disease, renal failure, blood dyscrasia, active peptic ulcer, pregnancy. In addition, the drug should be used with caution in the elderly and in patients with diabetes, alcoholism, or severe obesity.

Main drug interactions Salicylates, nonsteroidal anti-inflammatory drugs, sulfonamides, phenytoin, tetracyclines, chloramphenicol, other antibiotics, and hepatotoxic drugs.

Main side effects Bone marrow depression, fever, pruritus, skin rash, ulcerative stomatitis, diarrhea, hepatic and renal dysfunction, interstitial pneumonitis, infection. Although there are no controlled data for humans, methotrexate does not appear to have oncogenic effects, at least not with short- to medium-term administration.

Special points Patients should be advised to reduce their intake of alcohol to a minimum. A folic acid supplement (5 mg folic acid) should be administered once a week, 4 days after the dose of methotrexate, to reduce the risk of bone marrow depression. Blood counts and liver function studies should be monitored at 4- to 8-week intervals. The dose of methotrexate should be adjusted if there is elevation of the aminotransferase levels or depression of the serum albumin level. Routine liver biopsy after a fixed period of administration or a specific cumulative dose of methotrexate is no longer recommended by the American College of Rheumatology [35].

Cost effectiveness The cost of methotrexate is approximately $1.70 per 2.5-mg tablet; its cost effectiveness has not been evaluated.

Azathioprine

	A controlled trial of azathioprine in combination with prednisone as a first-line therapy in polymyositis and dermatomyositis showed no additional benefit at 3 months, but it did indicate a better long-term outcome than did prednisone alone [36, Class IIa]. There have not been any trials comparing azathioprine with prednisone or with the other immunosuppressive agents.
Standard dosage	The drug is given orally, with food, in a daily dose of 2 to 3 mg/kg body weight in divided doses.
Contraindications	Pregnancy and hypersensitivity to the drug. Patients with rheumatoid arthritis previously treated with alkylating agents are at high risk for malignancy.
Main drug interactions	Allopurinol (the dose of azathioprine should be reduced to one quarter for patients taking a xanthine oxidase inhibitor); neuromuscular blocking agents; other bone-marrow-suppressive drugs; hepatic enzyme inducers or inhibitors; captopril.
Main side effects	Transient leukopenia, macrocytosis (approximately 20%); idiosyncratic reaction with fever, rash, myalgia, and abdominal symptoms (approximately 10%); hepatotoxicity; pancreatitis. The risk of malignancy is low with periods of administration of less than 5 years [37].
Special points	Blood counts and liver function studies should be monitored monthly. Patients who have mutations in the thiopurine methyltransferase gene are prone to severe and even fatal hematopoietic toxicity if administered azathioprine. They can be identified by genotyping [38]. Mutations were found in 9% of an unselected group of azathioprine-treated patients attending rheumatology clinics in Scotland [38].
Cost effectiveness	The cost of azathioprine is approximately $1.17 per 50-mg tablet; its cost effectiveness has not been evaluated.

Cyclophosphamide

	There have been no controlled trials of cyclophosphamide for the treatment of inflammatory myopathy, but its effectiveness in the treatment of steroid-resistant polymyositis and dermatomyositis has been reported [39, Class IIIb].
Standard dosage	The drug may be administered orally in a dose of 2 to 2.5 mg/kg/d or intravenously as a pulse dose of 500 to 1000 mg every 2 to 4 weeks.
Contraindications	Pregnancy; depressed bone marrow function; untreated infection; recent surgery.
Main drug interactions	Concomitant use of allopurinol increases the risk of bone marrow depression. Cyclophosphamide potentiates the effect of suxamethonium during anesthesia.
Main side effects	Bone marrow depression (transient neutropenia is usual), alopecia, gastrointestinal symptoms, hemorrhagic cystitis, infertility, and increased incidence of malignancy, especially bladder cancer.
Special points	Bladder toxicity can usually be avoided if the patient maintains a high fluid intake (more than 2 L/d) while on oral therapy or if the patient is administered equivalent doses of 2-mercaptoethane sodium sulphonate with pulse doses [40].
Cost effectiveness	The cost of cyclophosphamide is approximately $1.80 per 25-mg tablet and $8.45 per 100-mg vial. Its cost effectiveness has not been evaluated.

Cyclosporine

	No controlled studies have been published of cyclosporine administration in inflammatory myopathy. In a noncontrolled retrospective study of 26 patients with refractory juvenile dermatomyositis, however, low-dose cyclosporine induced remission and usually allowed the discontinuation of glucocorticoids [21, Class IIIa1; 41, Class IIIb2]. There have also been reports of benefit in adult patients with resistant polymyositis and dermatomyositis [42, Class IIIb2] and of the use of cyclosporine as first-line therapy in patients with early dermatomyositis [43, Class IIIb2].
Standard dosage	Cyclosporine is given orally in a starting dose of 3 mg/kg/d in divided doses. The dose is then adjusted according to the clinical response and the occurrence of side effects. It should be kept in the range of 2 to 3 mg/kg/d to reduce the likelihood of side effects. Plasma cyclosporine trough levels can be measured in the morning,

	12 hours after the last dose of the drug was administered. In our experience, however, routine monitoring of plasma levels is not necessary when using doses in the abovementioned range.
Contraindications	Infections, uncontrolled hypertension, renal insufficiency, immunodeficiency.
Main drug interactions	Danazol, diltiazem, doxycycline, erythromycin, ketoconazole, nicardipine, verapamil, and oral contraceptives all increase blood levels of cyclosporine. Carbamazepine, phenytoin, phenobarbitone, rifampicin, and isoniazid all reduce blood levels of cyclosporine. Nephrotoxicity is enhanced by aminoglycosides, amphotericin B, trimethoprim, and nonsteroidal anti-inflammatory drugs.
Main side effects	Nephrotoxicity, hypertension, hepatic dysfunction, hirsutism, skin rashes, gingival hypertrophy, headache, gastrointestinal symptoms, acute pancreatitis, hemolytic anemia, tremor, fatigue.
Special points	Blood pressure and serum creatinine levels should be monitored at least monthly. The dose of cyclosporine should be reduced if there is persistent elevation of the blood pressure or if the serum creatinine level rises to 30% or more above the pretreatment baseline level.
Cost effectiveness	The cost of cyclosporine is approximately $1.44 per 2.5-mg capsule. No formal analysis of its cost effectiveness has been performed.

Intravenous immunoglobulin

	High-dose IVIG therapy was shown to be effective in the treatment of dermatomyositis in a double-blind crossover trial of 12 patients with drug-resistant disease [14, Class IIa]. There have also been a number of uncontrolled studies demonstrating the efficacy of IVIG therapy in polymyositis and overlap syndromes [15•,16, Class IIIa1]. IVIG was not found to be effective when administered as first-line therapy, however [17, Class IIIa1]. A double-blind, placebo-controlled, crossover trial of IVIG therapy in 19 patients with inclusion body myositis showed only minor functional benefit in some patients and no significant improvement in muscle strength [27•, Class IIa]. Two of three small open studies did not show any significant benefit [15•,29, Class IIIa1].
Standard dosage	A total dose of 2 g/kg body weight is administered over a 5-day period (*ie*, 0.4 g/kg/d) in the initial course. Monthly 3-day courses (0.4 g/kg/d) are then administered for the next 3 to 6 months [15•, Class IIIa1]. Improvement usually begins after the first or second course. Treatment should be discontinued if there is no improvement after the third course. There have been no trials to determine the efficacy of lower doses or the optimal interval between courses.
Contraindications	Immunoglobulin A deficiency, hyperviscosity syndromes, severe vascular disease, renal insufficiency.
Main drug interactions	None.
Main side effects	Headache, nausea, fever, pruritus, myalgia. Rare side effects are anaphylactic reactions (especially in patients with IgA deficiency), aseptic meningitis, thromboembolism, and acute renal failure. Transmission of hepatitis C was associated with the use of some immunoglobulin preparations in the United States [44]. There is no longer a significant risk for the transmission of hepatitis C or human immunodeficiency virus infection because of current serum screening procedures and preparative techniques.
Special points	Because of the risk of thromboembolism, IVIG should be used with caution in the elderly and in patients who have a history of vascular disease.
Cost effectiveness	Immunoglobulin preparations are expensive; the cost of a 5-day course is approximately $10,000. There have been no analyses of the cost effectiveness of IVIG therapy.

Physical therapy and exercise

- Patients with inflammatory myopathies should be encouraged to undertake regular physical activity. Shortly after treatment begins and during acute relapses, range-of-motion exercises should be performed to prevent the development of joint contractures.
- Once the activity of the disease has been controlled, an isometric or lightweight isotonic exercise program for key muscle groups, such as the quadriceps, can be recommended [45]. Resistive exercise has been shown to improve muscle strength in patients with polymyositis or dermatomyositis [46, Class IIa], and a regular isokinetic training program has been shown to help reverse steroid myopathy [47, Class IIa]. At a later stage, a low-intensity aerobic bicycle, step, or pool program may be started and has been shown to improve muscle performance [45;48, Class IIa].
- An isometric exercise program should also be recommended for patients with inclusion body myositis and has been shown to improve the strength of some muscle groups [49, Class IIIa1].

Surgery

- Paraneoplastic dermatomyositis may improve after the removal of the primary malignancy, if this is possible [50].
- Surgery may be necessary for the removal of foci of subcutaneous calcinosis in patients with dermatomyositis when the foci become infected and ulcerate through the skin.
- Cricopharyngeal myotomy may be required for patients with inclusion body myositis who have severe dysphagia [51].

Other treatments

- A number of other uncontrolled forms of treatment have been reported to be effective in small numbers of patients with resistant myositis. These include low-dose, whole-body, or lymphoid irradiation [22,24, Class IIIb], thymectomy, and thoracic duct drainage [22, Class IIIb].
- Various forms of treatment, including local and systemic glucocorticoids, probenecid, colchicine, diltiazem, bisphosphonates, aluminum hydroxide, and low-dose warfarin, have been recommended for the subcutaneous calcinosis that develops, particularly in children and young adults with dermatomyositis. None has proven to be uniformly effective, however, and none has undergone formal evaluation in controlled trials [12•, Class IIIc].

Emerging therapies

- Hematopoietic stem cell transplantation may have a role in the treatment of severe, life-threatening cases of polymyositis and dermatomyositis, but this requires further evaluation [52].
- More specific forms of immunotherapy for inflammatory myopathy are not yet available. They await the identification of the target antigens against which the autoimmune process is directed and a more detailed understanding of the immune effector mechanisms in the different forms of myositis.

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