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Therapeutic Advances in Neurological Disorders 2008; 1; 157

DOI: 10.1177/1756285608097463

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Therapeutic advances and future prospects in immune-mediated inflammatory myopathies

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Neurological Disorders
(2008) 1(3) 157–166

DOI: 10.1177/
1756285608097463

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Los Angeles, London,
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Abstract: The inflammatory myopathies include three distinct entities: polymyositis (PM), dermatomyositis (DM), and inclusion body myositis (IBM). A T-cell-mediated cytotoxic process in PM and IBM and a complement-mediated microangiopathy in DM are the hallmarks of the underlying autoimmune processes. The most consistent therapeutic problem remains the distinction of PM from the difficult-to-treat mimics such as s-IBM, necrotizing myopathies and inflammatory dystrophies. This review provides a step-by-step approach to the treatment of inflammatory myopathies, highlights the common pitfalls and mistakes in therapy, and identifies the emerging new therapies. In uncontrolled studies, PM and DM respond to prednisone to some degree and for some period of time, while a combination with one immunosuppressive drug (azathioprine, cyclosporine, mycophenolate, methotrexate) offers additional benefit or steroid-sparing effect. In contrast, IBM is resistant to most of these therapies, most of the time. Controlled studies have shown that IVIg is effective and safe for the treatment of DM, where is used as a second, and at times first, line therapy. IVIg seems to be also effective in the majority of patients with PM based on uncontrolled series, but it offers transient help to a small number of patients with IBM especially those with dysphagia. *Bona fide* patients with PM and DM who become resistant to the aforementioned therapies, may respond to rituximab, tacrolimus or rarely to a tumor necrosis factor alpha inhibitor. For IBM patients, experience with alemtuzumab, a T-cell-depleting monoclonal antibody, is encouraging.

Keywords: inflammatory myopathy, polymyositis, dermatomyositis, inclusion body myositis, immunosuppressive drugs, intravenous immunoglobulin, rituximab, tacrolimus, tumor necrosis factor alpha inhibitors, alemtuzumab

Clinical characteristics

The inflammatory myopathies comprise three major and distinct subsets: polymyositis (PM), dermatomyositis (DM) and inclusion-body myositis (IBM). Although the presence of moderate-to-severe muscle weakness, endomyxial inflammation and variable creatine kinase elevation are common features in all of these conditions, unique clinical, immunopathologic and histologic criteria that bear on the different response to immunotherapies characterize each subset [Dalakas, 2004a, 1991; Engel and Hohlfeld, 2004; Dalakas and Hohlfeld, 2003; Mastaglia and Phillips, 2002]. A rare form of myositis, acute necrotizing myopathy, has emerged as a distinct subset that needs to be distinguished from the other three because of poor response to therapies.

DM affects all ages and presents with subacute onset of skin changes and proximal muscle weakness. The skin manifestations accompany or precede muscle weakness and include: a heliotrope rash (blue–purple discoloration) on the upper eyelids with edema; a flat red rash on the face, knees, elbows, malleoli, neck, anterior chest (in a V sign), or on the back and shoulders (shawl sign); and erythema of the knuckles with a raised, violaceous, scaly eruption (Gottron rash). Dilated capillary loops at the base of the fingernails with irregular, thickened and distorted cuticles, or cracked, ‘dirty’ horizontal lines at the lateral and palmar areas of the fingers (mechanic’s hands) are characteristic of the disease [Dalakas, 2004a, 1991; Engel and Hohlfeld, 2004; Dalakas and Hohlfeld, 2003; Mastaglia and Phillips, 2002].

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PM almost always begins above the age of 16, has a subacute onset, affects proximal muscles and spares facial and eye muscles. As a standalone entity, polymyositis is an uncommon disorder. Because it mimics many other myopathies, it remains a diagnosis of exclusion. A patient with presumed PM should not have positive family history of a neuromuscular disease, exposure to myotoxic drugs, a concurrent endocrine disease or the clinical signs of IBM as described below. Adult-onset inflammatory dystrophies, such as those owing to mutations in dysferlin, caveolin, dystrophin or calpain, are very often misdiagnosed and treated as PM. These constitute the largest group of patients below the age of 40 years labeled as 'polymyositis unresponsive to therapy'.

IBM has slow onset and progression, affects proximal and distal muscles, and results in significant weakness and atrophy. The facial and swallowing muscles are frequently affected resulting in choking episodes. Although IBM is commonly suspected when a patient with presumed PM does not respond to therapy, involvement of distal muscles, especially foot extensors and deep finger flexors, in almost all cases may be a clue to early diagnosis [Dalakas, 2004a, 1991; Engel and Hohlfield, 2004; Dalakas and Hohlfield, 2003; Mastaglia and Philips, 2002]. The weakness and atrophy may be asymmetric, with selective involvement of the quadriceps, iliopsoas, triceps, biceps, and forearm flexor muscles. Patients with IBM account for the majority of the patients above the age of 50 years labeled as 'polymyositis unresponsive to therapy'.

The diagnosis of these disorders is based on the combination of clinical history, serum muscle enzymes, electromyography and muscle biopsy. Creatine kinase levels are elevated in all three subsets but may be normal or only slightly elevated in DM and IBM. The electromyograph (EMG) is myopathic in all three and, although useful to exclude neurogenic disorders, it cannot to differentiate an inflammatory myopathy from other toxic or dystrophic myopathic processes. The muscle biopsy shows inflammatory features distinct for each subset and remains the most sensitive diagnostic tool. In DM the inflammation is perivascular or at the periphery of the fascicle and is often associated with perifascicular atrophy; in PM and IBM the inflammation is in multiple foci within the endomysial parenchyma and consists predominantly of CD8+ T cells that invade healthy muscle fibers expressing the

MHC-I antigen. The MHC/DC8 complex is characteristic and useful for the diagnosis of PM and IBM [Dalakas, 2004a, 1991; Dalakas and Hohlfield, 2003]. Plasma cells and dendritic cells are frequent among the infiltrates in all three disorders [Greenberg, 2007]. An additional feature in IBM is the presence of vacuoles containing 12–16 nm tubulofilaments with tiny deposits of amyloid and amyloid-related proteins [Askanas and Engel, 1998; Mendel *et al.* 1991].

Main immunopathologic characteristics

The cause of PM, DM and IBM is unknown, but an autoimmune pathogenesis is strongly implicated. In DM, there is activation of complement which leads to the formation and deposition of membranolytic attack complex on the endomysial capillaries leading to their destruction and resulting in muscle ischemia [Greenberg, 2007; Dalakas, 2004a, 1995, 1991; Engel and Hohlfield, 2004; Dalakas and Hohlfield, 2003; Mastaglia and Phillips, 2002; Emslie-Smith and Engel, 1990; Kissel *et al.* 1986]. Chemokines and cytokines are strongly upregulated. Activation of B cells and plasma cells is prominent while the upregulation of adhesion molecules and their receptors on the endothelial cell wall facilitates cell transmigration to the endomysial and perimysial spaces. In PM and IBM, antigen-driven, CD8+ cytotoxic T cells clonally expand *in situ* and invade healthy muscle fibers leading to muscle fiber necrosis via the perforin pathway [Salajegheh *et al.* 2007; Dalakas, 2004a, 1995, 1991; Engel and Hohlfield, 2004; Dalakas and Hohlfield, 2003; Mastaglia and Phillips, 2002]. Upregulation of costimulatory molecules, adhesion molecules, metalloproteinases, cytokines and chemokines on the muscle fibers and the autoinvasive T cells is a consistent finding. In IBM, in addition to the aforementioned immunopathology which is identical to PM, there are prominent degenerative features consisting of vacuoles and accumulation of amyloid or amyloid-related proteins, especially in fibers not invaded by T cells, suggesting the presence of two processes acting independently or in concert with each other, a primary immune process and a degenerative one. Recent data suggests that there is cross-talk between inflammation and degeneration and that proinflammatory mediators enhance degeneration and accumulation of amyloid-related proteins [Dalakas, 2008; Schmidt *et al.* 2008]. Theoretically, successful inhibition of inflammatory molecules can halt the

degenerative process and stop the disease progression [Dalakas, 2008].

Goals of therapy

The goal of therapy in inflammatory myopathies is to improve muscle strength and activities of daily living. Although when strength improves the serum creatine kinase level falls concurrently, the reverse is not always true because most of the immunosuppressive therapies can result in a decrease of serum muscle enzymes without necessarily improving muscle strength [Dalakas, 2006, 2003]. Unfortunately, this is commonly interpreted as a positive sign and when associated with a patients' subjective sense of feeling better (but not stronger) gives the erroneous impression of improvement, and forms the basis for the common habit of 'chasing' or 'treating' the creatine kinase level instead of muscle weakness [Dalakas, 2006, 2003]. It is essential therefore, to discontinue the applied therapies if an adequate trial has led only to a reduction in creatine kinase and not to an objective improvement in muscle strength. The level of creatine kinase is only helpful as an auxiliary measure and not as a guide to start or monitor therapy.

On assessing strength, it is essential in addition to using routine Medical Research Council (MRC) scales, to ask the patients specific questions about changes in performing routine physical tasks at home or work and activities of daily living. The patients need to be also informed from the onset that these are chronic disorders and a long-term therapy is anticipated. The potential long-term side effects of the drugs need to be explained and the patients' cooperation should be sought from the outset. This is especially useful when steroids are used and the patients need to adhere to a strict dietetic regimen.

Patients with DM have a high incidence of malignancy especially in older-age groups. In these circumstances, a thorough work-up is needed from the outset and yearly thereafter, especially the first 3 years. The most common cancers are those of the ovaries, gastrointestinal tract, lung, breast, non-Hodgkin lymphomas and, in Asian populations, nasopharyngeal cancer. In patients without risk factors, an expensive, blind radiological search for occult malignancy is not practical or fruitful [Dalakas, 1991]. A complete annual physical examination with pelvic, breast (mammogram, if indicated), rectal (colonoscopy

according to age or family history) and chest X-ray should suffice. If cancer is suspected, PET imaging may be considered.

Treatment for PM and DM

In spite of the progress in elucidating the specificity of the immune response, a number of fundamental issues remain unanswered hindering the prospects of specific immunotherapy. Accordingly, none of the available therapies are selective or antigen-specific but rather attack indiscriminately the various T-cell or B-cell functions.

Starting therapy: the role of corticosteroids

Prednisone is the first in-line drug whose use is based on experience but not on controlled trials. Because the effectiveness and relative safety of prednisone therapy determines the future need for stronger immunosuppressive drugs, my preference has been to start with a high-dose prednisone beginning early in the disease [Dalakas, 2006, 2003]. A high dose, at least 1 mg/kg or 60–80 mg/day, as a single daily morning dose (after breakfast) for an initial period of 3–4 weeks is preferable. In patients with severe PM or DM and systemic manifestations, I prefer to start treatment with IV methylprednisolone 1 g/day for 3–5 days and then continue with the oral prednisone regimen, as mentioned above. After 1 month of high-dose oral daily prednisone, I switch to an alternate-day dose. This is accomplished by gradually reducing the alternate 'off-day' dose by 5–10 mg per 1 or 2 weeks, or faster if necessitated by side effects. When reaching the every-other-day regimen without serious adverse effects, the dosage is reduced gradually by 5–10 mg every 3–4 weeks until the lowest possible dose that controls the disease is reached. The single-dose, alternate-day program minimizes adverse effects while adequately maintaining control of the underlying disease. It has been my preference to give the prednisone as a single dose in the morning because it is less likely to suppress the evening secretion of ACTH and more likely to secure a normal endogenous cortisol secretion the next morning.

The ultimate goal in a patient who responds to steroid therapy is to find the lowest dose that controls the disease with the least adverse effects. This is often accomplished by adding a steroid-sparing drug, while lowering the amount of steroid, without a breakthrough of disease. We do not

advocate a concurrent use of steroids with another immunosuppressant from the outset of treatment except if the disease has a very aggressive course and the patient is rapidly worsening. On the other hand, if by the time the steroid dosage has been reduced to 60–80 mg every other day (approximately 14 weeks after initiating therapy), there is no objective benefit (defined as increased muscle strength and not as lowering of the creatine kinase level or a subjective feeling of increased energy), the patient may be considered unresponsive to prednisone, and tapering is accelerated while the next in-line mode of therapy is started.

To minimize side effects, every patient should be requested from the beginning of steroid therapy to start a strict low-carbohydrate, low-salt, high-protein diet. Antacids, or one of the histamine H₂-receptor antagonists may be used if patients experience stomach upset. Co-administration of calcium supplements (1 g/day) and vitamin D (50,000 units per week) may be useful for long-term steroid administration. In postmenopausal women, when long-term therapy is required, I consider adding alendronate once weekly based on its proven efficacy in the prophylaxis of steroid-related osteoporosis.

Steroid myopathy versus disease activity

The long-term use of prednisone may theoretically cause worsening of muscle strength associated with a normal or unchanged CK level, referred to as 'steroid myopathy'. The term steroid myopathy is a misnomer because steroids do not cause histological signs of myopathy but, rather, selective atrophy of type II muscle fibers. Contrary to what is believed, the condition is not common. Rarely, it may be difficult to distinguish a developing steroid-induced myopathic weakness, from the increased weakness related to disease activity or to other factors such as decreased mobility, infection, or a concomitant systemic illness. The decision to adjust the prednisone dosage in a patient with myositis who has previously responded to treatment may be influenced by reviewing the past 1–2 month history of strength, mobility, serum creatine kinase, medication changes and associated medical conditions [Dalakas, 2006, 2003]. For example, in a patient who for the past 1–2 months has had increased creatine kinase levels, no new overt signs of steroid toxicity with reduced or unchanged dosage of steroids, and no evidence of a systemic illness or infection, increasing

muscle weakness is most likely due to worsening of the disease that may either require more prednisone or has become steroid-resistant requiring another dose [Dalakas, 2006, 2003]. When these signs are not clear, one may arbitrarily raise the prednisone dosage and wait for the answer, which can be evident in about 2–8 weeks, according to the change in the patient's strength. A clinical sign that I have found to be of some help in a few patients is the strength of neck extensor muscles, which usually worsens with exacerbation of the disease but remains unchanged with steroid-induced muscle intoxication. Electromyography, when shows increased spontaneous activity, is also useful to explore evidence of active disease.

Relapses while on maintenance steroid therapy

Relapses may occur while the steroid dose is decreased below a 'critical for a given patient' level, or in patients who are seemingly stable but decompensate after a viral illness, a concurrent infection or due to disease worsening. Many such patients can be controlled if the dose of prednisone is increased to a high single-daily dose (as high as the initial), or to a high alternate day (if the relapse is mild), for a month followed by a slow taper. More often however, relapses require more aggressive strategies, such as intravenous immunoglobulin (IVIg) or addition of an immunosuppressant, as described below.

Use of steroid-sparing regimens in steroid-responsive patients

The decision to start an immunosuppressive drug is based on its 'steroid-sparing' effect when, in spite of steroid responsiveness, the patient has developed significant complications or when attempts to lower a high steroid dosage have resulted in worsening of muscle strength. The preference for selecting an immunosuppressive drug for these circumstances is empirical because control studies have not been conducted. The choice is usually based on our prejudices or personal experience with each drug, and our own assessment of the relative efficacy/safety ratio. My own preference depends on disease severity, clinical setting and other conditions. The following immunosuppressive drugs are used [Dalakas, 2006, 2004b, 2003, 1999; Gold *et al.* 2003; Halloran, 2000; Hohlfeld and Dalakas, 2003; Mastaglia *et al.* 1998; Dalakas *et al.* 1993].

Azathioprine Although lower doses (1.5–2 mg/kg) are commonly used, I prefer higher doses up to 3 mg/kg for effective immunosuppression.

Because azathioprine is usually effective after 6 months of treatment, patience is required before it is concluded that the drug is ineffective. The major toxicity of azathioprine includes thrombocytopenia, anemia, leucopenia, pancytopenia, drug fever, nausea and liver toxicity. An elevation of liver enzymes, if slight, needs only observation. Azathioprine, which is metabolized by xanthine oxidase, if given concurrently with allopurinol can be severely toxic to the liver or bone marrow and combined use of these two drugs is not recommended. The susceptibility to toxicity is genetically dependent on interindividual variations in thiopurine S-methyl transferase (TPMT) enzyme activity based on the genetic polymorphism of high- versus low-metabolizing alleles. Patients with low enzyme activity concentrations have an increased risk of bone marrow suppression. Because of these side effects I prefer to use Cellcept, which acts also faster.

Mycophenolate mofetil (Cellcept) This is a morpholinoethyl ester of mycophenolic acid that blocks *de novo* purine synthesis and acts on both B and T cells. It is an antipurine antimetabolite, like azathioprine, but it does not cause significant bone marrow suppression or hepatotoxicity. It is a well-tolerated drug when used at doses up to 3 g/day. It does not work as fast as we initially thought and it may take up to 2–3 months to see any clinical benefit. In organ rejection, Cellcept works fast because it inhibits the production of new B and T cells; in autoimmune diseases however, the initial goal is to affect the autoreactive, existing lymphocytes which is accomplished with other drugs such as prednisone, while Cellcept acts later.

Methotrexate An antagonist of folate metabolism, methotrexate is a useful drug. I prefer the oral route starting at 7.5 mg weekly for the first 3 weeks (given in a total of three doses, 2.5 mg every 12 hours), increasing it gradually by 2.5 mg per week up to a total of 25 mg weekly. A rarely reported side effect (admittedly never seen by this author) is methotrexate pneumonitis, which can be difficult to distinguish from the interstitial lung disease seen in some patients with inflammatory myopathies. Other adverse effects include stomatitis, gastrointestinal symptoms, leukopenia, thrombocytopenia, renal toxicity, hepatotoxicity and malignancies. Because it acts faster

than azathioprine it might be preferable to use as a steroid-sparing agent.

Cyclosporine Cyclosporine affects T-cell-mediated immunity by inhibiting transcription of certain genes, mostly the IL-2 gene, resulting in reduced IL-2 and other cytokines. At doses of 150 mg twice a day (not more than 5 mg/kg/day) and frequent monitoring of the optimal trough serum level (100–200 ng/ml), this drug can be given without major complications. The kidney function should be closely monitored and non-steroidal anti-inflammatory drugs (e.g. Motrin) are avoided. When creatinine increases more than 30%, the drug should be discontinued. The concomitant use of ketoconazole (which inhibits the P450 cytochrome enzyme in the liver) allows for a lower (up to 80%) dose with less toxicity [Dalakas, 2006, 2003; Gold *et al.* 2003; Halloran, 2000; Hohlfeld *et al.* 2003]. The advantage of cyclosporine compared to azathioprine is that it acts faster.

What to do when steroids are inadequate: the use of high-dose IVIg

In my experience when corticosteroids have failed to induce remission, or in rapidly progressive cases with evolving severe weakness, the aforementioned immunosuppressive agents used only for 'steroid-sparing' toxicity, are inadequate alone to substantially increase strength. In these circumstances, the choice is IVIg.

IVIg has multiple mechanisms of action, most of which include inhibition of cytokines, competition with autoantibodies, inhibition of complement deposition, interference with Fc receptor binding on macrophages or the immunoglobulins on B cells, blocking the Fc receptors on target antigens, interaction with sialic acid-specific receptors on regulatory macrophages exerting an anti-inflammatory effect, or interference with antigen recognition by sensitized T cells. More than one of these actions is probably responsible for the observed benefit [Dalakas, 2004b, 1999]. The dose is 2 g/kg, given in 2–5 divided daily doses, every 5–8 weeks, as clinically required. In a double-blind study conducted in patients with refractory dermatomyositis, IVIg significantly improved the patients' strength compared with placebo [Dalakas *et al.* 1993]. The improvement becomes noticeable about 15 days after the first IVIg infusion, and it is clear and definitive after the second infusion. Marked improvement is also noticed in the active

violaceous rash or the chronic scaly eruptions on the knuckles. Repeated infusions may be required every 6–12 weeks to maintain improvement. In several patients we have been able to lower the prednisone and keep only a low maintenance dose. Some patients with DM, who had become unresponsive to steroids, may respond again to prednisone after a few IVIg infusions.

Because DM responds to steroids, IVIg therapy is best reserved for steroid-resistant patients, either as a second-line therapy or as a third-line add-on therapy in patients who are not adequately controlled with combination of steroids and methotrexate or azathioprine, and for patients who are immunodeficient or in whom immunosuppressants are contraindicated. In children and in older patients we use it as a second-line drug after steroids.

The beneficial effect of IVIg in PM has been documented only in open-label trials. A controlled study we had started 15 years ago was never completed. In our own and others experience, however, IVIg is effective in the majority of patients with PM [Dalakas, 1999; Mastaglia *et al.* 1998; Dalakas *et al.* 1993].

What to do if steroids and IVIg are ineffective or inadequate to induce remission

In most of these cases, it is prudent to evaluate the patients' diagnosis. If the diagnosis is secured (based on the unique clinical features, as in DM, or with new muscle biopsy, as in PM) or the patient had clearly responded to steroid and IVIg early in the disease course, the following can be used.

Rituximab This is a monoclonal antibody against CD20+ B cells resulting in B-cell depletion that lasts for at least 6 months. There is evidence based on number of reports that rituximab at 375 µg/m² once a week for 4 weeks or 2 g (divided in two biweekly infusions) can be beneficial to patients with DM and PM resistant to therapies [Kaposztas *et al.* 2008; Chung *et al.* 2007; Levine, 2005]. A NIH-sponsored multicenter trial is now in progress.

Cyclophosphamide In patients who have interstitial lung disease and severe clinical myopathy unresponsive to other agents, this drug can be

used at doses 0.5–1 g/m² monthly intravenously. Adequate hydration the day before and antiemetics are helpful. Adverse reactions include nausea, vomiting, alopecia, hemorrhagic cystitis, bone marrow suppression, secondary malignancies and sterility. Contraceptives are recommended for women and concomitant testosterone in men. It is critical to monitor the neutrophil count (no less than 1500–2000) and the lymphocyte count (no less than 1000) at 7, 10, 14 and 21 days and perform frequent urinalysis even after the drug is stopped.

Tacrolimus Formerly known as FK 506, tacrolimus is structurally different from cyclosporine although both share the ability to selectively inhibit the transcription of cytokines and specifically IL-2 [Halloran, 2000]. There is evidence that tacrolimus is effective in some difficult cases of polymyositis, especially when there is interstitial lung disease [Shimajima *et al.* 2004; Yamada *et al.* 2004; Oddis *et al.* 1999].

Other, newer agents In difficult cases other agents have been used with limited success. These include tumor necrosis factor alpha inhibitors and sirolimus [Nadiminti and Arbiser, 2005; Labioche *et al.* 2004; Hengstman *et al.* 2003].

Step-by-step approach

The excellent effect of IVIg in many DM and PM patients and the limited beneficial effect achieved by the other immunosuppressants have changed the order by which I personally use these agents. If steroids are inadequate, I go directly to IVIg followed by the addition of one of the aforementioned immunosuppressants. A step-by-step approach to the treatment of DM and PM is as follows:

1. Prednisone (in aggressive cases, combination with another agent listed in steps 2 and 3 is preferred by some practitioners).
2. IVIg (the use of IVIg as a second-line therapy is justified based on the observation that the immunosuppressants listed in step 3 have a mild effect alone and mostly a steroid-sparing effect).
3. Immunosuppressants, such as azathioprine, methotrexate, mycophenolate or cyclosporine only as steroid-sparing agent. These drugs are ineffective in steroid-resistant cases.

4. Newer agents (rituximab, tacrolimus, rapamycin).

Treatment of IBM

In spite of immunopathological features identical with PM, IBM patients are difficult to treat. Although a number of patients may transiently respond to steroids, the majority do not. Methotrexate in a controlled study was not better than placebo. Cyclosporine, azathioprine or mycophenolate mofetil are mostly ineffective although some patients may initially respond to some degree [Mowzoon *et al.* 2001; Mastaglia, 2000; Mastaglia *et al.* 1997]. IVIg may provide some benefit to a small number of patients for a period of time, especially in dysphagia, as demonstrated with controlled studies [Walter *et al.* 2000; Dalakas *et al.* 1997]. Although no statistically significant differences were overall noted, regional difference in certain muscle groups, especially the muscle of swallowing were observed [Dalakas *et al.* 1997]. Dysphagia appears to be the main symptom that improves consistently, as documented on subsequent open-label trials [Cherin *et al.* 2002]. Because dysphagia is life-threatening, IVIg can be considered in patients with significant swallowing difficulties and choking episodes [Dalakas, 2006, 2003; Mastaglia *et al.* 1998]. Cricopharyngeal myotomy may be another option [Verma *et al.* 1991] although in our experience it does not always work. Collectively, my approach to the treatment of patients with IBM is sequentially as follows:

1. Inform the patient that there is no proven effective therapy. I prescribe co-enzyme Q₁₀, even though there is no demonstrable benefit as a means to enhance endurance, given the mitochondrial changes in the biopsy. I also advocate a systematic non-fatiguing exercise program which we have shown to be of benefit [Spector *et al.* 1997].
2. Administer low-dose prednisone every other day combined with mycophenolate in some patients hoping for disease stability with a clear explanation that the benefit from this regimen is anecdotal and short-lived [Mowzoon *et al.* 2001], and is not based on controlled studies.
3. A trial with IVIg if there is significant worsening of muscle strength or life-threatening dysphagia.

4. Encourage them to participate in one of experimental trials. Our recently completed trial with alemtuzumab has been promising [Dalakas *et al.* 2007].

Prognosis

DM responds more favorably to therapy than PM. Overall, most patients improve, and many of them make a full functional recovery, which is sustained with maintenance therapy [Dalakas, 2001]. However, up to 30% of the patients may be left with residual muscle weakness or calcifications. The 5-year survival rate for treated patients with PM and DM is now approaching 80%. On the other hand, IBM is predictably disabling. Most of these patients will require use of an assistive device such as a cane, walker, or wheelchair. The older the age of onset, the more rapidly progressive the course of IBM appears to be.

Supportive therapy

I recommend physical therapy early in the disease to preserve existing muscle function, avoid disuse atrophy of the weak muscles and prevent joint contractures. Evaluation of swallowing function is also recommended because dysphagia is common, especially in IBM. Speech pathologists provide practical tips on how to prevent choking episodes and diminish the anxiety of an impending aspiration, not only for the patient but also for the immediate family [Dalakas, 2005, 1995].

Occupational and rehabilitation therapists help the patients with their ambulation by providing canes, braces or wheelchairs according to the stage of their disease, or by teaching them how to walk without falling; for example, by 'locking' on the knees or by using light braces, and how to perform easier fine motor tasks. Proper emotional support to accept these aids is essential; the patients and their families should be convinced that these means are not demoralizing but realistic approaches to improve transportation and socialization. Emotional support is also fundamental for young women with DM who are discouraged by a disfiguring rash, calcifications and steroid side effects. Reassurance that these symptoms improve with aggressive therapies and many steroid side effects are short-lived is important [Dalakas, 2005, 1995].

Practical therapeutic considerations

In light of the information presented earlier regarding the efficacy of these therapies, the following observations and practical tips may be useful [Dalakas, 2006, 2005, 2003, 2001]:

1. Patients with *bona fide* PM and DM should almost always respond to prednisone to a certain degree and for some period of time.
2. A patient with presumed PM, who has not responded to any form of immunotherapy, most likely has IBM or an inflammatory dystrophy. In these cases, a repeat muscle biopsy and a more vigorous search for the other disease are recommended.
3. Calcinosis, a manifestation of DM, does not resolve with immunotherapies. New calcium deposits, however, may be prevented if the primary disease responds to the available therapies. Diphosphonates, aluminum hydroxide, probenecid, colchicines, low doses of warfarin, and surgical excision have all been tried without success.
4. If prednisone or the other immunosuppressive therapies have not helped or have become ineffective in improving the patients' strength, they should be discontinued to avoid severe, irreversible adverse effects because, contrary to common belief, there is no evidence that their continuation maintains stability or prevents further disease progression.
5. In patients with cancer-associated myositis, the treatment should be aggressive to treat the cancer. Searches for possible cancer in DM patients should be a consideration the first 3 years.
6. Patients with interstitial lung disease may have a high mortality rate, and require aggressive treatment with cyclophosphamide, cyclosporine or tacrolimus.
7. Physical therapy to preserve existing muscle function, avoid disuse atrophy of the weak muscles, and prevent joint contractures should start early in the disease.
8. When treatment of PM is unsuccessful, the patient should be re-evaluated and the muscle biopsy re-examined. A new biopsy might be considered to make sure that the diagnosis is correct and that IBM or one of the inflammatory dystrophies have not been overlooked. The disorders most commonly mistaken for PM are: IBM, an inflammatory sporadic limb-girdle dystrophy with endomyrial inflammation resembling polymyositis, (such as dysferlinopathies, calpainopathy, caveolinopathy, sarloglyconopathy), metabolic myopathy (such as phosphorylase or acid maltase deficiency), endocrinopathy,

drug-induced myopathies with some secondary inflammatory features (such as the one due to statins), and neurogenic muscular atrophies.

The major pitfalls leading to failure of steroid or immunosuppressive treatment include:

1. inadequate initial dose of prednisone or cytotoxic drugs
2. short duration of therapy or quick tapering
3. early discontinuation of prednisone without keeping a 'maintenance' low-dose therapy
4. early development of preventable side effects necessitating early discontinuation of prednisone
5. wrong diagnosis.

Future directions

Advances in biotechnology have promoted the development of a new class of biotechnological products for immunotherapy [Dalakas, 2006; Gold *et al.* 2003; Hohlfeld and Dalakas, 2003]. These biotechnological agents are used to manipulate the immune system by selectively mimicking, inhibiting or depleting specific immune cells or otherwise interacting with naturally occurring polypeptides or oligonucleotides. However, these agents also present a number of specific problems, of intolerance, toxicity and high cost.

It is to be hoped that new techniques will continue to advance our understanding of the immunopathogenesis of PM, DM and IBM, and that these advances in knowledge will be rapidly translated into therapeutic applications. Agents that could be cautiously selected considering their cost and safety profile, include those against T-cell and B-cell growth factors or transduction molecules, co-stimulatory molecules, against chemokines and cytokines or adhesion molecules [Dalakas, 2006]. If promising in small pilot trials, they should be tested in controlled studies. For IBM, strategies to inhibit muscle degeneration by aggressively suppressing inflammation or inhibiting the myofiber cell-stress response by targeting the molecules implicated in major histocompatibility complex (MHC) activation and protein misfolding, may be rewarding [Dalakas, 2008]. The newly introduced concept of 'neuroinflammation' using IBM as a model [Dalakas, 2008] may open new avenues of investigating new anti-inflammatory agents in an effort to suppress

indirectly the potentially toxic proteins accumulated within the muscle fibers.

Conflict of interest statement

None declared.

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