Diagnosis and treatment of inflammatory myopathy: issues and management

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Abstract: The idiopathic inflammatory myopathies include polymyositis (PM), dermatomyositis (DM) and inclusion body myositis (IBM). The specific etiologies of these muscle diseases are not well known and are thought to involve components of the humoral and cellular immune system as well as other nonimmune factors. Diagnosing these myopathies involves a laboratory evaluation, imaging studies, multidisciplinary consultations, histologic examination and potentially genetic studies. Despite all that we currently know about inflammatory muscle disease with these studies, we find that our current concept of muscle disease is changing. In the cases of immune-mediated necrotizing myopathy and inclusion body myositis, the concept of inflammation needs to be rethought. Moreover, the classification schemes for these idiopathic myopathies may need updating to include current research findings that relate to pathogenesis. With ongoing discoveries, classification and appropriate treatment is becoming increasingly challenging. This paper discusses the inflammatory myopathies, the challenges to diagnosis, classification controversies and potential treatment options.

Keywords: inflammatory, myopathy, treatment, vacuoles, muscle biopsy

Introduction

In the era of genomics, defining disease states through genetic studies becomes a powerful tool to better understand disease pathophysiology and disease classification. This is the case as we learn more about muscle disease, particularly for rheumatologists who care for patients with idiopathic inflammatory myopathies (IIMs).

For example, a 52-year-old man comes to your office complaining of weakness in his legs. This weakness has been present for the past 6 months and is worsening. He has otherwise been healthy, is not taking myotoxic drugs, has no rash, and is up to date with his cancer screening. Your examination finds that he is weak, not only in the thighs but in his upper arms as well. Laboratory testing shows an elevated serum creatine kinase (CK) level and a muscle biopsy of the vastus lateralis reveals classic inflammatory myositis.

The term myopathy best describes this patient's muscle disease because it is not clear what the underlying pathology may be. When classifying myopathies, the presence of a heliotrope or

Gottron's rash favors the diagnosis of dermatomyositis (DM). In the absence of a rash, as with our patient, polymyositis (PM) may be the preferred diagnosis. However, the differential diagnosis for muscle disease without a rash is extensive (Table 1). As we learn more about muscle pathophysiology through research, we are able to better differentiate inflammatory *versus* noninflammatory disease, and therefore, target our treatment appropriately.

PM, DM and inclusion body myositis (IBM) constitute the IIMs. Cellular and humoral immune dysfunction are involved in muscle damage. But a specific etiology has not been found and the lack of full understanding of disease pathogenesis makes proper classification challenging.

The classification challenge

In 1975, Bohan and Peter developed a classification scheme for PM and DM that continues to be used today [Bohan and Peter, 1975a, 1975b]. However, new information gained in recent years suggests additional information can be useful in

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Table 1. Differential diagnosis of muscle disease.

Inflammatory myopathies	Noninflammatory myopathies
Infectious myopathies Bacterial (egs. Staph, Strep, M. tuberculosis) Viral (egs. Influenza, EBV, HBV, HCV, HIV, HTLV-1) Fungal (egs. Candida, Coccidiomycosis) Protozoal (egs. Toxoplasma, malaria) Cestode (egs. Cysticercosis) Nematode (egs. Trichinosis) Toxic myopathies (egs. Cocaine/heroin, cimetidine, D-penicillamine, adulterated rapeseed oil, amiodarone, L-tryptophan, colchicine) Lipid-lowering agents Myositis associated with graft versus host disease Myositis ossificans Myositis associated with the vasculitides Macrophagic myofasciitis Inflammatory dystrophies (fascioscapulohumeral dystrophy (FSHD), dysferlin deficiencies) Idiopathic inflammatory myopathies (egs. PM, DM) Malignant hyperthermia Myotonia Neuromuscular junction disorders (egs. Eaton-Lambert Syndrome, myasthenia gravis) Periodic paralyses Rhabdomyolysis Tendonitis-fasciitis syndromes	Congenital (nemaline rod, central core) Mitochondrial (acid maltase, McArdle's, phosphofructokinase (PFK), carnitine and carnitine palmityltransferase deficiency) Endocrine (hypo- & hyperthyroidism, acromegaly, diabetes, hypo- & hyperparathyroidism) Toxic (drugs – egs. Ethanol, AZT, corticosteroids) Nutritional (vitamin E deficiency, malabsorption syndromes) Muscular dystrophies (egs. Duchenne's, Becker's, FSHD, LGMD (limb-girdle muscular dystrophy), Distal, Oculopharyngeal) Neuropathies Denervating conditions (spinal muscular atrophy, amyotrophic lateral sclerosis) Proximal neuropathies (Guillan-Barre syndrome, autoimmune polyneuropathy, diabetic plexopathy, acute intermittent porphyria) Overuse syndromes Paraneoplastic syndromes (egs. carcinomatous neuropathy, cachexia, myonecrosis) Rheumatic syndromes (egs. Giant cell arteritis/polymyalgia rheumatica (GCA/PMR), granulomatosis with polyangiitis, polyarteritis nodosa (PAN), fibromyalgia syndromes) Trauma

classification, and the possibility of reclassification should be considered. Several examples of suggested additions to diagnostic criteria include using myositis-specific autoantibodies [Love *et al.* 1991] which were not known when Bohan and Peter published in 1975. The use of autoantibodies to classify myositis was expanded upon through extensive serologic testing to demonstrate the heterogeneity of the disease in terms of overlap with clinical features and to predict therapeutic outcomes [Koenig *et al.* 2007]. More recently, in 2003, Dalakas put forth the notion that inflammatory cells infiltrating muscle-bearing surface markers such as CD4, CD8 and major histocompatibility complex (MHC) class I be used to help classify PM *versus* DM [Dalakas and Hohlfeld, 2003]. These important findings should be incorporated into clinical thinking when diagnosing the patient.

However, other types of myositis need improved criteria to properly classify the disease. Sporadic IBM presents such a challenge. Physical, electrodiagnostic, serologic and histologic results cross over between neurologic and rheumatologic findings. We typically think of patients with IBM as

older men that have asymmetric, distal weakness with a muscle biopsy showing minimal to moderate inflammation that shows characteristic red-rimmed vacuoles on Gomori trichrome stain. Healthcare providers that care for patients with IBM know that vacuoles can be seen in many other myopathies and are knowledgeable of these mimics (Table 2). A second example of difficult to classify myositis is immune-mediated necrotizing myopathy (IMNM) [Dalakas, 2011c]. These patients can have a dramatic myopathy with high serum CK levels, profound weakness and a non-inflammatory necrotic biopsy. Recent studies suggest that an autoimmune process may underlie disease pathology of immune-mediated necrotizing myopathy, but this is not the entire picture.

Understanding pathogenesis

Inflammatory muscle diseases are characterized by symmetric proximal weakness, increases in serum muscle enzyme levels, characteristic electromyography (EMG) findings, and a muscle biopsy demonstrating inflammation. Rheumatologists label IIMs as autoimmune disease and therefore immune self-reactivity should be present in the

Table 2. Muscle diseases containing vacuoles on biopsy.

Lysosomal Acid maltase deficiency Batten's disease Autophagic Danon disease X-linked myopathy with excessive autophagy Infantile autophagic vacuolar myopathy Childhood autophagic vacuolar myopathy Adult-onset autophagic vacuolar myopathy with multiorgan involvement LGMD 1A Toxic myopathy Inflammatory myopathies Hypokalemic myopathy Peroxisomes Lafora disease Phosphorylase deficiency	Rimmed vacuoles present Inclusion body myositis Oculopharyngeal muscular dystrophy Oculopharyngeal muscular dystrophy Distal myopathies (Welander, Finnish-Markesberry, distal dystrophy, distal myopathy with vocal cord and pharyngeal weakness [MPD2]) Hereditary IBMs Hereditary inclusion body myopathy (HIBM) 1, 2, 3 Inclusion body myopathy with Paget's disease and Frontotemporal dementia (IBMPFD) Miscellaneous Periodic paralysis Glycogen storage Lipid storage Centronuclear myopathy Lipofuscin (aging) Freezing artifact Desmin storage
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<http://neuromuscular.wustl.edu/lab/mbiopsy.htm#vacuoles>
 IBM, inclusion body myositis; LGMD, limb-girdle muscular dystrophy.

biopsy, and ideally, self-reactive T lymphocytes should be reacting to myocytes that have increased expression of MHC class I. Myocyte death occurs causing the above signs and symptoms. A recent review by Dalakas describes three observations in the immunopathogenesis of PM [Dalakas, 2006, 2011c]. First, CD8+ T cells are responsible for myocyte invasion in PM. B cells and natural killer cells are not abundant in this disease. Immunoelectromicroscopy studies show that CD8+ T cells and macrophages send out spike-like projections into the non-necrotic muscle fibers, which then displace or compress the muscle fiber [Dalakas, 2011c]. The major cytotoxic effector mechanism in PM is the perforin pathway. Second, increased expression of MHC class I on affected muscle fibers is also a major finding in disease pathogenesis. And lastly, the formation of the immunologic synapse occurs between the MHC class I expressing muscle fibers and the cytotoxic CD8+ T cells with costimulatory support [Dalakas, 2011c].

DM mimics PM in its muscle distribution, but presents with skin rashes such as the heliotrope rash, Gottron's papules, V-sign and/or shawl sign. Pathogenesis differs from PM as the main target in DM is the vascular endothelium of capillaries [Dalakas, 2006, 2011c, 2011d]. Activation of complement, C3, with subsequent formation of the macrophage activation complex is seen early in the disease. Complement-mediated changes result in vacuolization and necrosis of capillaries, perivascular inflammation, and ischemic muscle

fiber damage with marked reduction in the number of capillaries per myocyte. Lymphocytic infiltrates consisting of B cells and CD4+ T cells are found in the perimysial and perivascular regions and plasmacytoid dendritic cells are located in the perifascicular regions.

Sporadic IBM is the most common form of myopathy in patients over age 50. Clinical features are different from those seen in PM or DM. The disease tends toward an indolent course and is resistant to therapy. Immunopathologic findings can be similar to those seen in PM [Dalakas, 2011c], despite the fact that the disease is treatment resistant. Most recent studies [Dalakas, 2011d; Malicdan *et al.* 2007] suggest an autophagic cell death of the myocyte. One suggested mechanism is the build up of misfolded MHC glycoproteins within the autophagosome, leading to endoplasmic reticulum stress and a subsequent inflammatory response to the obstructed cell. However, the nature of this process is unknown and heavily debated.

In IMNM, patients have an acute or subacute onset of severe muscle weakness, serum CK levels in the high thousands, and muscle histopathology characterized by necrosis mediated by macrophages [Benveniste *et al.* 2011; Christopher-Stine *et al.* 2010; Dalakas, 2011c; Mammen *et al.* 2011]. As we learn more about IMNM, it does appear to be influenced by many factors that include malignancy, viral infection, and statin

ingestion. Upregulation of MHC class I can be seen in some patients and response to immunomodulatory therapy can occur. Serum autoantibodies have been observed in IMNM and recently studies by Christopher-Stine and Mammen and their coinvestigators suggest the importance of statin therapy as a possible etiology in patients with autoantibodies to 3-hydroxy-3-methylglutaryl-coenzyme A reductase [Christopher-Stine *et al.* 2010; Mammen *et al.* 2011].

Myositis mimics/differential diagnosis

The mimics of myositis are many and present challenges to both the clinician and to the patient. Drugs, food supplements, endocrinopathies, dystrophies and psychiatric conditions are just some of the causes for myalgias and weakness. Myositis-overlap syndromes also present with myalgias and weakness in conjunction with other rheumatologic diseases such as rheumatoid arthritis or systemic lupus erythematosus [Gherardi, 2011]. Malignancy must also be considered in patients presenting with weakness and myalgias because the incidence of new cancer is higher in patients with IIM [Selva-O'Callaghan *et al.* 2010; Zahr and Baer, 2011]. Drug-induced or toxic myopathies can present with acute or subacute muscle weakness, myalgia, elevated CK levels and/or myoglobinuria [Valiyl and Christopher-Stine, 2010]. These drugs include colchicine, cholesterol-lowering agents (statins, red yeast rice, ezetimibe), HIV therapies (particularly zidovudine), antiviral therapies (interferon), antimalarials (hydroxychloroquine), immunosuppressive agents (glucocorticoids, leflunomide, tumor necrosis factor-alpha inhibitors), and voriconazole (an antifungal drug). Endocrine disorders such as hypo- and hyperthyroidism, hyperparathyroidism, Cushing's disease (steroid myopathy), Addison's disease, and pituitary gland disorders can present with proximal muscle weakness and/or myalgias, but not necessarily always increasing CK levels [Markenson, 2010].

Increasingly recognized in adults with new onset weakness are muscular dystrophies. These acquired hereditary muscle diseases cause myalgias, weakness, and are progressive. Dystrophies such as limb-girdle muscular dystrophy (LGMD), nemaline myopathy, and dyferlinopathies are examples of these disorders. Chronic pain syndromes and fibromyalgia can present with significant muscle pain that may appear to cause weakness [Assumpcao *et al.* 2010] but will lack specific

inflammatory findings. Generalized anxiety disorders and unipolar depression can present with significant muscle pain as well [Aldao *et al.* 2010].

Tools for making the diagnosis

To properly diagnose the patient with muscle weakness, testing should include a thorough history and physical examination, routine laboratory tests (complete blood count, complete metabolic panel, muscle enzymes, thyroid-stimulating hormone and other targeted studies as necessary), autoimmune serologies, imaging studies, neurologic evaluation, EMG, nerve conduction velocities and muscle biopsy. The history and physical examination allows the patient to describe the onset of disease, pattern of presentation, and possible inciting or environmental factors. Environmental factors to review include recent infections, drugs (licit or illicit), work exposures, and nutritional supplements. A detailed family history can help to decide the possible genetic pattern of disease. Close attention should be paid to the physical exam to look for the pattern of weakness (distal *versus* proximal, symmetric *versus* asymmetric, or bulbar involvement). A detailed neurologic exam is important to look for neuropathic disease. With this information, one can broaden a differential to include other myopathic processes like dystrophies or metabolic processes.

Muscle enzymes

Levels of serum muscle enzymes (CK, ALT, AST and lactate dehydrogenase [LDH]) are often elevated, although serum CK levels can test at the near normal level for some patients with DM or longstanding disease when most of the muscle has been damaged and is replaced by fat. Remember that AST, ALT and LDH actually reflect both muscle disease and liver disease. Think twice about the need for a liver biopsy in a patient with IIM with elevations of ALT and/or AST.

Myositis-specific antibodies

Myositis-specific antibodies (MSAs) are found in approximately 50% of patients with IIM [Waschbisch *et al.* 2010]. Several MSAs have been well described in the literature, are commercially available for testing, and knowing the presence of a MSA, are helpful in treating the patient. There are pitfalls when testing for the presence of a MSA. This is because of current day assay techniques used to determine the presence or absence

of a MSA. With the newer immunosorbent assay methods, the sensitivity and specificity of the results may differ from the original techniques used to find and describe the autoantibody. This can sometimes confuse the interpretation of a test result. Examples of MSAs include antisynthetase, anti-signal recognition particle (SRP), anti-Mi-2 and anti-PM/Scl. The positive finding of a MSA is helpful in predicting the future course and prognosis [Aldao *et al.* 2010; Castro and Gourley, 2010]. For example, anti-tRNA synthetase antibodies (e.g. anti-JO-1 antibodies) are strong predictors of interstitial lung disease. Anti-SRP autoantibody correlates with high serum levels of CK in patients with necrotizing myopathy [Benveniste *et al.* 2011]. Mi-2 autoantibodies can be found in classic DM and patients tend to have a good prognosis after therapy. There are several less well understood antisynthetase autoantibodies that include anti-PL12, anti-EJ, anti-OJ, anti-PL7, and anti-KS. These antibodies are reportedly more common in patients with PM than in patients with DM and are rare in children.

As per our earlier discussion about classification, MSA status can be very useful to clinicians. Patients with autoantibodies to anti-tRNA synthetases tend to have the antisynthetase syndrome. This syndrome consists of myositis, interstitial lung disease, fever, polyarthritis and skin changes (mechanic's hands). Antisynthetase syndrome is amenable to therapy so that muscle strength can recover, often worsening when therapy is decreased or withdrawn. In contrast, patients with anti-SRP often present with profound muscle weakness, myalgias, and cardiac involvement. Anti-SRP-associated myopathy usually requires very intensive therapy and even in the face of aggressive immunosuppression, patients may not recover strength.

Imaging

Imaging studies with magnetic resonance imaging (MRI) or ultrasound can be extremely useful. T1-weighted and short tau inversion repeat (STIR) images on MRI distinguish the location of muscle involvement, extent of fatty replacement and muscle loss, and severity of disease activity. We customarily perform MRI of the bilateral thighs to aid in detecting disease activity and disease damage. MRI of tissue with STIR sequencing is very sensitive to changes in water content and inflammation can be seen as an increase in signal intensity. T1-weighted imaging is useful to identify

anatomy and evaluate the extent of disease damage. MRI is an excellent imaging tool to determine the most appropriate site for muscle biopsy. More recently, ultrasound can also be used to look at specific sites of interest in real time and also to evaluate for signs of active disease, atrophy and/or hypertrophy [Botar-Jid *et al.* 2010; Oskarsson, 2011]. The procedure is quick and noninvasive. Contrast-enhanced ultrasound can provide information on the blood flow in a particular muscle area of interest and can give an indirect measure of active muscle disease. Because this is done in real time, fasciculations can be visualized in affected muscle. However, its use relies on an experienced ultrasonographer and so it is not routinely performed at many centers.

Neuromuscular evaluation

Neurologic evaluation is central to help distinguish between myopathic and neuropathic disease and provides useful insight into the characteristics of myopathies *versus* neuropathies [Koopman, 2005]. Thorough manual muscle testing, reflex evaluation and detailed histories and physicals are helpful. The use of EMG and nerve conduction velocity testing provides details to distinguish muscle disease from neurologic disease. EMG findings of short, small, low-amplitude polyphasic motor unit potentials, fibrillation potentials even at rest, and bizarre high-frequency repetitive discharges support findings of myopathic disease.

Muscle biopsy

Muscle biopsy can be very useful to define the etiology of muscle disease. We favor biopsies for histologic study when it is feasible; there is an experienced histopathology laboratory that can satisfactorily process the sample with standard and special staining and an experienced pathologist to interpret the histologic findings. Textbook teaching states that PM typically demonstrates a lymphocytic infiltration seen mostly within the fascicles (endomysial inflammation), some fiber necrosis, degenerative and regenerative fibers. CD8+ T cells are identified in PM and IBM muscle cells expressing MHC class I antigens. In patients with DM, perifascicular atrophy is common. The main features of IBM include endomysial inflammation, vacuolization ('red rimmed vacuoles' on Gomori trichrome stain), and loss of muscle fibers. Large, atrophic, or angulated fibers are also present. Necrosis and macrophage invasion are seen on the IMNM biopsies.

To properly diagnose muscle disease, one should use all the clinical, laboratory, imaging and histologic information available.

The dilemma of inclusion body and immune-mediated necrotizing myopathy

How does a rheumatologist think about IBM and IMNM? This discussion revolves around whether the diseases truly represent an autoimmune, inflammatory illness. Opponents to the idea that these are autoimmune diseases use evidence that the diseases are not responsive to aggressive immunosuppression, there can be sparse inflammation in muscle biopsy and a deficiency of autoantibodies in most patient's serum. Proponents cite the increased association of IBM/IMNM with other autoimmune diseases, upregulation of MHC class I markers on myocytes and the finding of autoantibodies in a subgroup of patients [Dalakas, 2006]. In the case of IMNM, it is interesting to find in the sera of some patients exposed to statin therapy a newly found 200/100 kD autoantibody against 3-hydroxy-3-methylglutaryl-coenzyme A reductase [Christopher-Stine *et al.* 2010].

IBM is unique among the inflammatory myopathies in that the typical muscle biopsy can show inflammatory cells but the numbers are often low and the degree of inflammation relatively mild. This lack of significant inflammation in the biopsy may surprise the clinician that observes the clinical picture of weakness, elevation of serum CK and edema signal on STIR images. In contrast to patients with IBM, patients with IMNM present with acute weakness, very high levels of serum CK and abundant edema by STIR MRI. Again, expecting a large inflammatory process in the muscle, the biopsy typically lacks a lymphocytic infiltrate; rather there is myocyte swelling and rupture with muscle necrosis.

Certainly classification schemes that better define the wide range of myopathies will help clinicians to gain a better understanding of how to think about these patients. Continued research efforts to help appreciate the pathophysiology will improve our ability to render the most appropriate therapy.

Treatment and management

'I know it when I see it' is often used to define something that is frequently nebulous. However,

when considering treatment options for patients with muscle disease, it becomes very important to make sure we are using therapies that have a good chance of helping the patient (Table 3). We have observed many referrals for cases of suspected PM when the patient had a dystrophy or other cause of myopathy, not amenable to treatment. Therefore, proper diagnosis is the first step to successful treatment.

The mainstay of therapy for inflammatory and autoimmune (IIM) myopathies is immunosuppression, physical therapy and avoidance of complications [Dalakas, 2010]. Nonmedication modalities are employed to maintain strength and overall function. Most of the medication treatment regimens are currently not approved by the US Food and Drug Administration, which in turn can present another obstacle to patient care. Another consideration to therapy is proper monitoring for adverse events (Table 3). Because liver-associated enzymes also come from inflamed muscles, it is necessary to watch closely and discriminate between potential liver toxicity from active muscle disease.

First-line therapy for IIMs includes corticosteroids with subsequent second-line therapy using steroid-sparing agents [Dalakas, 2011a; Distad *et al.* 2011]. High-dose corticosteroids, generally starting with prednisone at 1 mg/kg per day, with eventual taper after several months to the lowest dose to maintain a remission is the current standard of care. In patients with severe disease (e.g. significant lung impairment, inability to swallow, profound motor strength loss or extreme body rash), methylprednisolone at 1 g per day given intravenously for 3–5 days is used at the onset. Monitoring strength and serum muscle enzyme levels (CK, AST, and ALT) should be used to evaluate response to treatment. Watching carefully for potential adverse events is very important and prophylaxis should be strongly considered (e.g. osteoporosis, immunizations). Coadministration of steroid-sparing agents can be considered if patients continue to have poor or partial response to first-line treatment.

Second-line treatments can be added to the therapeutic regimen several months after the start of prednisone, or in severe disease, begun immediately. Data are limited regarding what agent to use but choices include azathioprine, methotrexate, intravenous immunoglobulin (IVIG), mycophenolate mofetil, cyclophosphamide, immunophilin inhibitors and rituximab.

Table 3. Therapeutic regimens for idiopathic inflammatory myopathies.

Agent	Typical doses	Side effects and toxicities
First line		
Methylprednisolone (IV)	1 g/day for 3–5 days	Increased susceptibility to infection, osteoporosis, hypertension, diabetes, weight gain, steroid-induced myopathy, mood changes, skin fragility, avascular necrosis, glaucoma
Methylprednisolone or Prednisone (oral)	1 mg/kg/day for at least 4–8 weeks, then taper	
Second line and steroid sparing		
Azathioprine	2–3 mg/kg/day, orally	Fever, abdominal pain, nausea, vomiting, anorexia; combination with allopurinol increased myelosuppression and hepatotoxicity; TPMT activity may need to be checked in certain patients prior to initiation of medication or in those with poor reaction to treatment
Methotrexate	15–25 mg/week, should be given with folate 1 mg/day; orally or intramuscularly	Hepatotoxicity, interstitial lung disease (caution in those with anti-JO-1 antibody positivity), interstitial pneumonitis, myelosuppression, renal toxicity, alopecia, stomatitis, oncogenicity, teratogenicity
Mycophenolate mofetil	1–1.5 mg twice daily, 500 mg twice daily in renal impairment, orally	Diarrhea, myelosuppression, tremors, hypertension
Intravenous Immunoglobulin (IVIg)	2 g/kg total dose given over 2–5 days (1 g/kg/day over 2 days or 0.4 g/kg/day over 5 days), repeated monthly for at least 3 months, intravenously; may need premedication with diphenhydramine 25–50 mg, orally, plus/minus acetaminophen 650 mg, orally	Flu-like symptoms, myalgias, fever, headache, fluid overload, rash, aseptic meningitis, caution in patients with cardiac conditions, risk of renal failure or thrombosis
Rituximab	1 g intravenously, repeat in 2 weeks; then subsequent doses 6–9 months after second dose	Fever, nausea, infection susceptibility, rare infusion reactions, rare progressive multifocal leukoencephalopathy
Tacrolimus	2–3 mg twice daily, orally	Increased susceptibility to infection, lymphoma, alopecia, skin erythema, pruritis, constipation, diarrhea, nausea, anemia, leukocytosis, thrombocytopenia, headache, hypertension, paresthesia, tremor, renal failure
Cyclophosphamide	1–2 mg/kg/day, orally or 1 g/m ² monthly, intravenously	Gastrointestinal (GI) upset, alopecia, risk of malignancy, hemorrhagic cystitis, teratogenicity, sterility, increased risk of infection
Cyclosporine	3–4 mg/kg/day in two divided doses, orally, then increase up to 6 mg/kg/day	Hypertension, renal failure, gingival hyperplasia, GI upset, hypertrichosis, oncogenicity, tremor, risk of infection

(Continued)

Table 3. Continued

Agent	Typical doses	Side effects and toxicities
Nonpharmacologic interventions		
Physical therapy, occupational therapy, and rehabilitation	Strength training, assist with/ modifications for activities of daily living	
Assistive devices	Cane, wheelchair, motorized scooter, ankle braces, rolling walker, shower chair, commode	
Diet and lifestyle modification	Modification of home, swallowing precautions, fall prevention	
Emotional and psychiatric support	Concern for depression	

Azathioprine has a long history of use in treating IIMs at doses of 1.5–3 mg/kg daily [Dalakas, 2011b]. The goal of therapy is to allow the corticosteroid doses to be lowered while preserving or improving muscle strength. Results may take many months to observe. The major toxicity is gastrointestinal, hepatic and bone marrow. Monthly monitoring of liver function tests and blood counts should be performed until a stable dose of azathioprine is reached. One advantage of azathioprine is that pulmonary toxicity is rare and therefore it makes an appropriate choice for use in patients with pulmonary involvement. Similar to azathioprine is methotrexate, which can be administered orally or subcutaneously. A dose up to 25 mg per week is usual. Response to methotrexate should become evident in 2–3 months. The most common adverse effects are elevation in liver function tests and myelosuppression. Coadministration of azathioprine and methotrexate is helpful for severe disease [Villalba *et al.* 1998]. Mycophenolate mofetil is administered orally at doses of 2–3 g per day. Potential response is usually seen after 2–3 months. The medication is generally well tolerated. Major side effects include gastrointestinal symptoms and leucopenia. Cyclosporine administered in divided doses from 3 mg/kg per day to 6 mg/kg per day is another option. Response can usually be seen in less than 6 months. Major adverse effects include hypertension, renal toxicity, hepatotoxicity and bone marrow suppression.

Inadequate response to steroids and oral steroid-sparing agents has necessitated the use of biologics and newer immunosuppressive agents. Some myositis experts suggest that when beginning therapy in severely affected patients or in rapidly progressive disease with high doses of prolonged

corticosteroids, IVIG is preferred. Best studied in DM, IVIG has been particularly effective [Dalakas *et al.* 1993]. In our experience, some PM can also respond. Doses up to 2 g/kg over the course of 1–5 days with repeated monthly infusions has demonstrated improvement in muscle strength, skin rash and lowering of the serum CK level.

Rituximab is the best studied of all therapeutic agents. The results of the largest IIM trial to date (see <http://www.edc.gsph.pitt.edu/rimstudy/referphys.html>) were presented at a national rheumatology meeting in November 2010 [Aggarwal *et al.* 2010]. In this randomized, blinded, placebo-controlled clinical study, 161 of 195 (83%) randomized patients (78% PM, 82% DM, 83% JDM (Juvenile Dermatomyositis)) met the definition of improvement during the course of the trial. Patients were treated with two 1 g intravenous doses 2 weeks apart. The medication is generally well tolerated but severe infusion reactions can occur and infection risk is increased.

IBM presents a quandary in treatment and management because the hallmark of disease is resistance to treatment. The list of published clinical treatment trials for IBM is small and outcomes that show significant improvements in strength are lacking. These trials include the above-listed therapies in addition to beta-interferon-1a, anti-T-lymphocyte globulin, and azemtuzumab. Reasons for treatment failure or resistance are only speculative.

Conclusions

The next generation of treatment for patients with IIMs may need more than suppression of the

immunologic response. The other avenues for therapeutic targets that can lead to potential therapeutic success may include regenerative therapies such as gene therapy, or the use of stem cells. A gene therapy clinical trial is proposed at the Children's Hospital in Ohio (see <http://www.nationwidechildrens.org/gene-therapy-clinical-studies>) for muscular dystrophy and sporadic IBM.

Nonpharmacologic therapies must also be integrated into the care of patients. Most important to IIM treatment is physical therapy to improve aerobic capacity and attempt to maintain motor function [Johnson *et al.* 2009]. Diet and lifestyle changes and modifications can have a positive effect. Dietary modifications need to be undertaken by patients receiving corticosteroids. Low-fat, low-carbohydrate, and low-salt diet should be initiated to aid in decreasing weight gain, hypertension, hyperglycemia and edema. To prevent or treat osteoporosis, calcium and vitamin D supplementation should be started and bisphosphonate therapy should be considered. As disease progresses and weakness and/or muscle atrophy may increase, assistive devices and home modifications need to be considered to aid with activities of daily living and preventions of falls and other injuries. Individuals experiencing dysphagia should be evaluated by speech/swallow therapy and have aspiration precautions and dietary modifications to prevent choking. Emotional support is also very important in maintaining ongoing health [Dalakas, 2010].

In rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease and other autoimmune inflammatory diseases, great strides have been made in advancing the treatment of patients. However, these strides have not yet been fully seen in patients with IIMs. As newer biologic therapies come to the market for autoimmune disease, it makes sense that small exploratory trials are set up to test responsiveness in IIMs. Nevertheless, newer therapies for IIMs should address the wide disease heterogeneity and more specific classification schemes need to be in place to properly identify patients who can benefit from intervention.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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