Diagnosis and treatment of the idiopathic inflammatory myopathies

David J. Gazeley and Mary E. Cronin

Ther Adv Musculoskel Dis

(2011) 3(6) 315–324

DOI: 10.1177/
1759720X11415306

© The Author(s), 2011.
Reprints and permissions:
[http://www.sagepub.co.uk/
journalsPermissions.nav](http://www.sagepub.co.uk/journalsPermissions.nav)

Abstract: The idiopathic inflammatory myopathies (IIMs) are rare disorders with the unifying feature of proximal muscle weakness. These diseases include polymyositis (PM), dermatomyositis (DM) and inclusion body myositis (IBM) as the most common. The diagnosis is based on the finding of weakness on exam, elevated muscle enzymes, characteristic histopathology of muscle biopsies, electromyography abnormalities and rash in DM. Myositis-specific antibodies have been helpful in defining subsets of patients with different responses to treatment and prognosis. The cornerstone of therapy is corticosteroids with the addition of other immunosuppressives in severe or refractory disease or patients with intolerable side effects. IBM is particularly difficult to treat but is more slowly progressive as compared with PM or DM. There is still a great need to find more effective and less-toxic therapies.

Keywords: dermatomyositis, inclusion body myositis, idiopathic inflammatory myopathies, polymyositis

Introduction

The idiopathic inflammatory myopathies (IIMs) are a group of rare, acquired disorders with primary features of muscle weakness and inflammatory lesions identified in skeletal muscle specimens. While similar presentations may occur in muscle diseases associated with underlying connective tissue diseases, malignancy, infection or toxic exposures, three clear and distinct idiopathic, immune-mediated varieties exist: dermatomyositis (DM), polymyositis (PM) and inclusion body myositis (IBM).

The prevalence and incidence of these muscle diseases varies and is dependent on definitions and diagnostic criteria. Early epidemiologic studies often did not distinguish IBM as a separate entity. Overall annual incidence rates for the IIMs vary from 2.18 to 7.7 per million [Mastaglia and Phillips, 2002]. Incidence rates also change with age and gender. There is a bimodal age distribution with peaks at age <15 and another between ages 45–54. There is a slight female predominance (F:M = 1.5:1.0). Furthermore, IBM is the most common subtype in men over the age of 50 [Cox *et al.* 2010]. Under age 50, DM is more common than PM [Dalakas and Hohlfeld, 2003]. Incidence seems to be increasing, but this may reflect changes in disease

awareness, medical billing codes, medical record technology, and more sensitive diagnostic tools.

Etiopathogenesis of these diseases is not fully understood. An autoimmune etiology of the IIMs is supported by the presence of serum auto-antibodies, complement deposition in muscle tissue (in DM patients), lymphocyte-mediated cytotoxicity, and general clinical improvement in response to immunosuppression. Environmental triggers and genetic susceptibility are likely also involved with clear HLA gene associations and geographic case clusters. For example, HLA gene DRB1*0301 allele is associated with PM and IBM [Shamin *et al.* 2000].

The 5-year survival rates for IIM patients range from 63% to 95%. The broad range of survival rates is likely secondary to the variable presence of extramuscular manifestations particularly involving the lungs and heart as well as the increased risk of an underlying malignancy all of which are associated with a worse prognosis [Ng *et al.* 2009]. For example, while epidemiological data is limited, several authors suggest cardiac involvement is the cause of death in 10–20% of PM cases and conduction disturbances represent a poor prognostic finding [Bazzani *et al.* 2010].

Correspondence to:
Mary E. Cronin, MD
Professor of Medicine,
Rheumatology Division,
Medical College of
Wisconsin, 9200 West
Wisconsin Avenue,
Milwaukee, WI 53226, USA
mcronin@mcw.edu

David J. Gazeley, MD
Rheumatology Fellow,
Medical College of
Wisconsin, Milwaukee, WI,
USA

In this review we focus on the clinical features, diagnostic approach and treatment of these IIMs. This review does not explore the detailed pathogenesis, genetics or epidemiology of these disorders. Furthermore, we only address the adult onset forms of these diseases leaving juvenile onset DM for a separate review.

Clinical features

Muscle disease

As DM, PM and IBM all represent primary muscle diseases they share the common clinical manifestation of weakness, but there are characteristic muscle and extramuscular features unique to each subgroup. The myopathy symptoms, in general, are characterized by a gradual onset of proximal, usually symmetric muscle weakness but may present acutely. Patient often identify weakness, and seek medical care, when daily activities such as standing from chairs, climbing stairs, combing hair or bringing food to their mouth becomes difficult. Falls often become more frequent, particularly in IBM patients. Fine motor movement weakness involving the more distal muscles is usually reserved for more advanced disease, but can be seen relatively early in IBM. Associated muscle atrophy and myalgias may occur. The facial and extra-ocular muscles are typically spared, but respiratory and pharyngeal muscles can be affected. In DM and PM, weakness typically progresses over weeks or months with slower progression seen in IBM.

Muscle group involvement and the rate of disease progression are important clues to distinguish between the disease subtypes as well as differentiating inflammatory myopathies from primary neurologic disease or other etiologies of myopathy.

Skin disease

Unique to DM are characteristic cutaneous manifestations. In fact, an estimated 20% of DM cases do not have identified muscle involvement, a subtype otherwise known as amyopathic DM or DM sine myositis [Bendewald *et al.* 2010]. Cutaneous signs or symptoms more often precede muscle weakness and some skin changes correlate with the presence of malignancy [Callen, 2010]. A heliotrope rash presents as a purple or erythematous skin discoloration on eye lids and/or periorbital tissues. A nonpalpable brightly erythematous rash on face, trunk and proximal extremities can be seen and often

called a shawl (shoulders, trunk) sign or holster (lateral thighs) sign. Violaceous raised lesions on extensor surfaces of fingers overlying the articular surfaces are called Gottron's papules/sign. In contrast to Gottron's papules, other digital rashes associated with connective tissue disease (i.e. lupus) will typically manifest on the skin between articular surfaces. Skin changes on palms and lateral digits may be roughened, dry, with cracking appearance similar to a 'mechanics hand'. Mechanics hands represent one of the features of the antisynthetase subtype of disease. Finally, subcutaneous calcifications can be particularly bothersome and debilitating, particularly in juvenile patients and may erode through the skin causing recurrent infections.

Extramuscular disease

Constitutional symptoms including low-grade fever, malaise, and weight loss are most frequently seen in cases of myositis associated with connective tissue disease but can be seen in PM, DM and malignancy associated disease.

Potential pulmonary symptoms include dyspnea and cough. In addition to interstitial lung disease (ILD), lung disorders can include thoracic chest wall muscle weakness and diaphragm weakness. Aspiration pneumonitis and pneumonia is common when pharyngeal muscles are involved. Moreover, during therapy, changes in respiratory symptoms may represent medication toxicity (i.e. methotrexate-induced lung injury) or infectious pneumonia secondary to immunosuppression. The presence of ILD, seen in about 10% of PM and DM patients, worsens prognosis and often requires more aggressive therapy. Patients who present with fever seem to have a higher frequency of IIM-associated ILD [Ji *et al.* 2010]. Screening all patients with PM and DM for evidence of ILD with serial diffusing capacity of the lung for carbon monoxide (DLCO) and spirometry measurements is reasonable.

Approximately half of patients with IIM will have dysphagia with inflammatory muscle disease affecting the muscles of the oropharyngeal complex and esophagus [Dalakas, 1991]. The dysphagia can vary from minor symptoms to severe with frequent aspiration.

Cardiac conduction delays, arrhythmias, and cardiomyopathy are seen in patients with PM and DM.

Periungual vessel changes and Raynaud's phenomenon may be seen. Nailfold capillary microscopy may allow for early diagnosis and provide prognostic value. For example, disease activity and severity has been associated with increased number of nailfold capillary changes. Moreover, specific microscopy patterns are associated with paraneoplastic myositis and higher capillary scores correlate with the presence of ILD [Selva-O'Callaghan *et al.* 2010a].

Laboratory abnormalities

Identification of elevated muscle enzymes including creatine kinase (CK), lactate dehydrogenase (LDH), aspartate aminotransferase, alanine aminotransferase, and aldolase is a marker of muscle cell degeneration or cell membrane damage. CK is the most sensitive although not specific enzyme marker and may be elevated to 50× normal levels in setting of active DM or PM. CK level typically correlates with disease activity; however, levels may be normal even in setting of active disease and levels do not necessarily correlate with muscle dysfunction. CK levels in IBM are more often normal or less elevated, perhaps 10× normal levels [Dalakas, 1991]. An isolated elevated aldolase, in the absence of elevated CK level, will occasionally identify muscle injury and may be due to an inhibitor to CK activity [Kagen and Aram, 1987]. Myoglobinuria without identified urine red blood cells (RBCs) is consistent with myopathy.

Autoantibodies

The myositis-specific autoantibodies (MSAs) against ribonucleoproteins, RNA synthetases of the protein synthesis pathways are present in 20–30% of IIM patients [Dalakas and Hohlfeld, 2003]. The MSAs might best be divided into three broad groups that include (1) anti-tRNA synthetases, (2) anti-signal recognition particle (anti-SRP), and (3) others that includes anti-Mi-2 directed against a component of the nucleosome remodeling deacetylase, anti-polymyositis-scleroderma (anti-PM-Scl) directed against peptides of a nucleolar RNA processing complex, and anti-CADM-140 directed against an important receptor involved in innate immunity.

The role of autoantibodies in the pathogenesis of these inflammatory myopathies is uncertain, but they have clinical value in identifying certain disease subsets and prognosis. For example, the most commonly identified autoantibody is anti-Jo-1 (anti-histidyl-tRNA synthetase), and its

presences is associated with a clinical presentation that includes myositis, ILD, nonerosive arthritis, mechanics hands and Raynaud's phenomenon. Moreover, other antisynthetase antibodies are frequently associated with ILD and similar features as anti-Jo-1 positive disease, the 'antisynthetase syndrome' [Dalakas and Hohlfeld, 2003].

The anti-SRP antibody is associated with an acquired necrotizing myopathy and may confer poor prognosis as a marker of cardiomyopathy and aggressive, refractory disease [Valiyil *et al.* 2010]. Recently, a new anti-200/100-kd anti-HMG CoA reductase antibody has been identified and is associated with a necrotizing, immune-mediated myopathy that may be linked to prior statin therapy and typically responds to immunosuppression [Christopher-Stine *et al.* 2010]. The presence of a myositis-specific autoantibody against protein 155/140 seems to confer increased risk of underlying cancer or cancer-associated myositis [Chinoy *et al.* 2007].

Histopathology

Diagnosis remains dependent on histologic features on muscle biopsy. However, the affected muscle may have a patchy distribution leading to sampling errors. In addition, specimen processing problems and pathology interpretation may lead to variability and diagnostic confusion. While histologic criteria have been established there remains overlapping features on microscopy that makes distinguishing between IBM and PM, in particular, quite challenging [Chahin and Engel, 2008].

Light microscopy demonstrates inflammatory cell proliferation, necrosis, atrophic fibers, muscle fiber regeneration and increased connective tissues. Histologic differences between the DM, PM and IBM exist. In DM, the inflammatory infiltrates are typically in the perivascular spaces with endothelial cell hyperplasia and microvascular changes including capillary deposition of the complement C5b-9 membrane attack complex (MAC), presence of endothelial tubuloreticular inclusions and microinfarcts. In contrast, PM inflammatory infiltrates, composed of invading CD8+ T cells in response to strong MHC-1 myofiber expression, typically involve the fascicles [Gherardi and Romain, 2011]. Moreover, perifascicular atrophy is a characteristic of DM and absent in PM and IBM.

As the name implies, IBM is characterized by basophilic granular inclusions near rimmed vacuoles and eosinophilic cytoplasmic inclusions [Dalakas and Hohlfeld, 2003]. Inclusions are not specific to IBM and also may be seen in metabolic myopathies.

In the appropriate scenario that includes clinical features typical of an IIM, a muscle biopsy may possibly be avoided if cutaneous clues of DM are present. This is commonly more appropriate in juvenile DM and, in general, all adult patients should have a muscle biopsy. Skin biopsy of all DM lesions typically reveals atrophy of the epidermis with vacuoles in the basal keratinocyte layer with perivascular lymphoid cells found in the dermis. Immunofluorescence microscopy is important to distinguish DM lesions from systemic lupus erythematosus (SLE) lesions [Dourmishev and Wollina, 2006].

A muscle biopsy should be performed in all patients with suspected PM. Biopsy is important to distinguish PM from IBM and from many potential disease mimics including adult onset muscular dystrophies and other neuromuscular disorders such as amyotrophic lateral sclerosis (ALS) and myasthenia gravis. Moreover, repeat biopsies may be required if diagnosis remains uncertain due to an unexpected or limited response to therapy.

Electromyography

While often included in diagnostic criteria, electromyography (EMG) abnormalities are not diagnostic of DM or PM and similar findings may be seen in other noninflammatory myopathies. However, many myopathic and neuropathic diseases may share a similar clinical presentation. For example, both ALS and IIMs may present with weakness and elevated CK levels, and EMG provides an important tool to illuminate the true site of underlying pathology [Chahin and Sorenson, 2009]. The additional value of EMG includes identifying the highest yield biopsy sites and assessing response to therapy. EMGs typically show evidence of muscle irritability. Nonspecific EMG findings associated with myopathy include increased insertional activity, spontaneous fibrillations, positive sharp waves and complex repetitive discharges. Low-amplitude/short-duration polyphasic motor potentials are typical. EMG results may demonstrate mixed potentials with features of both myopathic as well as neurogenic disease particularly

in setting of long-standing disease with muscle fiber regeneration but neuropathic findings make IBM a more likely diagnostic choice [Dalakas and Hohlfeld, 2003]. Approximately one third of patients with IBM will have evidence of axonal neuropathy characterized by large-amplitude and long-duration potentials [Amato and Barohn, 2009].

Imaging

Many imaging modalities have been used in the evaluation of skeletal muscle in the setting of inflammatory myopathies with the dual goals of identifying abnormal muscle based on decrease muscle bulk, abnormal signal intensity and/or destruction of normal muscle morphology and identifying high-yield biopsy sites. Involvement of muscle with inflammation is not uniform and selection of the muscle to be biopsied must be one with activity and not fibrosis. Both CT and ultrasound are able to identify muscle atrophy and soft tissue calcifications. Fatty infiltration can manifest as focal areas of increased echogenicity on ultrasound [Kuo and Carrino, 2007].

Ultrasound benefits include real-time imaging and the high resolution without radiation exposure. Conventional myosonography has been evaluated in 61 patients with histologically proven IIM and compared with 102 control persons. The sensitivity of muscle ultrasound in detecting myositis (83%) was not significantly different from electromyography (92%) or serum CK activity (69%). The positive predictive value of ultrasound was 95%, whereas the negative predictive value was 89%. Using contrast-enhanced ultrasound with microbubbles, patients with PM and DM were found to have muscle edema and inflammatory hypervascularization that normalized following treatment and recovery. Furthermore, the results suggest that contrast enhanced ultrasound may have a role following 'positive' MR to identify true myositis [Weber *et al.* 2006].

The main advantage of magnetic resonance imaging (MRI) in muscle imaging is detection of muscle edema. Fat-suppressed T2 or short tau inversion recovery (STIR) sequences are the most sensitive and specific method of imaging PM/DM [Walker, 2008]. Fat-suppressed T2 or STIR images are necessary to distinguish fatty infiltration, as can be seen in chronic autoimmune myositis, and edema seen in active muscle inflammation. The use of intravenous

contrast does not add to the evaluation of non-infectious myositis [Kuo and Carrino, 2007]. MRI criteria have been established to distinguish IBM and PM. Functional imaging, blood oxygenation level dependent (BOLD) imaging, diffusion imaging and phosphorus magnetic resonance spectroscopy are MRI techniques that may ultimately play a role in inflammatory myopathy, but have not yet been standardized [Dion *et al.* 2002].

Diagnosis

Diagnosis is dependent on a combination of clinical presentation, exam features, laboratory studies, imaging, electrical studies and, ultimately, histopathology. Several diagnostic criteria have been developed. For example, Bohan and Peter published a diagnostic and classification criteria in 1975 to be used primarily for research purposes. Exclusion criteria for neurological and inherited diseases were included. The criteria did not include the subgroup of IBM nor did they include required, measurable thresholds of weakness or elevation of muscle enzymes. The criteria did include EMG and histopathologic criteria [Bohan and Peter, 1975]. In 1997, Targoff and colleagues incorporating new imaging modalities and biotechnology, added MRI findings and the presence of myositis-specific antibodies to the diagnostic criteria [Targoff *et al.* 1997].

While clearly a subgroup of the IIM, IBM has distinct clinical features. In particular, compared with DM or PM, IBM has a different rate of disease progression, unique muscle group involvement and a much poorer response to therapy. Thus, new diagnostic criteria for IBM have been established by the European Neuromuscular Centre that depend heavily on histopathology and include a few clinical features, such as slow progressive course and more distal muscle involvement [Verschuuren *et al.* 1997].

Differential diagnosis

Neurological, congenital, metabolic, endocrine, infectious and iatrogenic causes of muscle weakness and elevated muscle enzymes must be considered.

Acquired neurological conditions include a large proportion of the differential diagnosis when evaluating muscle weakness. For example, the neuromuscular junction disorder myasthenia

gravis should be considered, but typical features including muscle fatigability, involvement of facial muscles, EMG changes, normal muscle enzymes, and presence antiacetylcholine receptor antibodies help distinguish the disease from IIMs. Amyotrophic lateral sclerosis often presents with distal, nonsymmetric muscle weakness with exam featuring long track signs. Muscle enzymes are usually, although not always, normal and EMG demonstrates a neuropathic pattern.

Inherited metabolic myopathies such as adult acid maltase deficiency, carnitine deficiency and myoadenylate deaminase deficiency typically present with intermittent, often postexertion, symptoms of myalgias and muscle tenderness and rhabdomyolysis.

Common drug-induced myopathies include those caused by steroids, colchicine, statins, antimalarials and antiretroviral drugs. Potential myopathic toxins secondary to lifestyle decisions include cocaine and alcohol.

Inherited muscular dystrophies, HIV infection, rhabdomyolysis, viral/bacterial pyomyositis, sarcoid and parasitic infections should also be considered in the differential diagnosis of muscle weakness.

Risk of underlying malignancy

Although cancer occurs in a minority of cases of IIMs, the risk of associated malignancy is elevated. Moreover, the risk seems highest among DM patients and has been consistent among several different patient populations [Sigurgeirsson *et al.* 1992]. Approximately 70% of cancers associated with IIMs are solid organ tumors including ovarian, lung, cervix, bladder and stomach [Hill *et al.* 2001]. Unfortunately, no pattern of clinical presentation or CK level seems to correlate with the presence of underlying malignancy. The presence of a myositis-specific autoantibody against protein 155/140 seems to confer increased risk of underlying cancer or cancer-associated myositis [Chinoy *et al.* 2007].

The best approach to identify malignancy in newly diagnosed IIMs has not been established. A common general approach is to ensure that a patient is up to date on age-appropriate cancer screening (i.e. mammography, colonoscopy, prostate-specific antigen [PSA]) and to use history and physical examination (including rectal

and pelvic examinations) to guide further occult malignancy evaluation.

A Spanish study of 55 consecutive patients with IIMs (6 PM/49 DM) underwent [18F]-2- fluorodeoxy-D-glucose positron emission tomography/computed tomography (FDG-PET/CT) and conventional cancer screening to investigate the presence of an occult malignancy. Conventional cancer screening included a history, physical examination, laboratory tests (complete blood count and serum chemistry panel), chest and abdominal CT, tumor markers (i.e. CA-125 and PSA), mammography and gynecologic examination in women. The study finds FDG-PET/CT is equivalent to conventional cancer screening in finding occult malignancy in patients with previously identified IIMs and the authors argue that a single study is better for patients [Selva-O'Callaghan *et al.* 2010].

Treatment

There is a paucity of controlled clinical trials to support treatment decisions in the idiopathic inflammatory myopathies. Therapy in DM, PM and IBM should focus on improving weakness, and, most importantly, functional level and ability to perform activities of daily living. Treating extramuscular manifestations of IIMs, including dyspnea and rash, often will require additional inhaled and topical therapies and may require consultation with other specialties.

As discussed below, DM and PM typically follow a similar treatment approach, but IBM, unfortunately, has few proven beneficial therapies.

Glucocorticoids remains the mainstay, first-line therapy for the IIMs with a standard prednisone dose of 1 mg/kg/day (high dose) to gain control of disease followed by a taper to the lowest possible dose to keep disease controlled. No placebo-controlled studies exist. Response to therapy should be monitored by an objective measurement of exam strength rather than patient reported improvement in strength, fatigue or malaise. In addition, improvement of CK levels alone is not a reliable marker to determine response to therapy [Dalakas, 1991]. Most patients with PM/DM have a response to corticosteroids. The majority of these patients will have a partial response. If there is no response to oral corticosteroids within the first 3 months of therapy, the diagnosis should be questioned, an alternative therapy should be initiated, and steroids tapered.

Regarding resistant IBM disease, only small retrospective studies have demonstrated mild response to prednisone and response was not based on any objective improvement in muscle strength [Amato and Barohn, 2009].

The best type of oral corticosteroids has not been definitely determined. A randomized control study comparing dexamethasone with prednisone found no difference in efficacy, but high-dose dexamethasone caused fewer side effects [van de Vlekkert *et al.* 2010]. Chronic steroid use can be complicated by a painless steroid myopathy without elevations in CK levels. Thus, a common clinical dilemma is determining active myositis *versus* steroid-induced myopathy symptoms. Distinguishing between the two is often based on historical review, paying special attention to the temporal relationship among worsening symptoms, medications changes and CK level changes. Some clinicians advocate use of EMG to differentiate active inflammatory myopathy from glucocorticoid-associated myopathy. For example, in contrast to IIM, EMG in corticosteroid-associated myopathy typically lacks spontaneous fibrillation potentials [Engel and Franzini-Armstrong, 2004]. Patients may also develop corticosteroid-associated myopathy before the inflammatory disease is controlled so EMG may not definitively indicate which process is present.

The timing of when to begin a steroid sparing agent is debatable and dependent on initial response to corticosteroids, inability to taper steroid dose, significant steroid side effects or rapidly progressive weakness, particularly involving the respiratory/pharyngeal muscles. The two most frequently used medications are azathioprine and methotrexate. A small controlled trial of azathioprine (2 mg/kg/day plus oral corticosteroids) *versus* steroid alone did not demonstrate any improvement in weakness or CK levels in the azathioprine group at 3 months, but long-term data did demonstrate improved functional outcomes and lower maintenance prednisone doses in the azathioprine-treated group [Bunch, 1981].

A 48-week, moderate sized randomized, placebo-controlled study using oral methotrexate (5–20 mg) in IBM demonstrated reduced CK levels, but no improvement in objective muscle strength, activity level or patient reported assessments [Badrising *et al.* 2002].

Intravenous immunoglobulin (IVIG) infusions have demonstrated efficacy in biopsy-proven, treatment-resistant DM. A double-blind placebo-controlled study treated 15 patients with oral corticosteroids (mean daily prednisone dose 25 mg) and either IVIG (2 g/kg every month) or placebo infusions for 3 months with an additional crossover portion. Clinical response measured by muscle strength testing and a neuromuscular symptom scale (a score based on 20 activities of daily living that test specific muscle groups). Each group included a few patients also taking traditional steroid-sparing immunosuppressive agents. After 3 months, the patients receiving IVIG had a significant improvement in muscle strength ($p < 0.018$) and higher neuromuscular symptom scores ($p < 0.035$). Repeat muscle biopsy from the IVIG group demonstrated improved muscle histology findings. Mean duration of the efficacy of IVIG was limited to 6 weeks. Adverse events were limited to infusion-related headaches [Dalakas *et al.* 1993]. The use of IVIG remains controversial and many insurance companies will not cover the costs of this treatment in the inflammatory myopathies. The use of IVIG is probably best limited to severe disease as a bridge until the onset of response to other medications.

Similar to the response of IBM to oral steroids and other immunosuppressive drugs, IVIG is not an effective therapy for IBM as demonstrated by a double-blind, placebo-controlled study [Dalakas *et al.* 1997]. In contrast, a small proof of principle study of 13 IBM patients treated with alemtuzumab, a humanized monoclonal antibody directed against CD52 T cells, demonstrated slowed muscle strength decline, depletion of peripheral T cells and reduction of CD3+ lymphocytes in repeat muscle biopsies [Dalakas *et al.* 2009].

A role for cyclophosphamide infusions in refractory IIMs has been explored. Six patients from an original recruitment of 11 patients completed seven monthly cyclophosphamide infusions ($0.75\text{--}1.357\text{ g/m}^2$). Only one patient met criteria for improvement in strength and function and, moreover, therapy was complicated by two serious infections and one death. The authors concluded that intravenous cyclophosphamide should not be used in refractory IIM [Cronin *et al.* 1989]. Cyclophosphamide may still have a role in severe rapidly progressive disease or associated ILD.

Case reports and case series of mycophenolate mofetil use in refractory IIM demonstrate mixed, although mostly promising, results [Majithia and Harisdangkul, 2005].

Small case series of IBM treated with mycophenolate mofetil have reported improved objective muscle strength but two patients had underlying autoimmune disorders [Quartuccio *et al.* 2007].

As discussed previously, most anti-SRP-positive patients present with a rapidly progressive disease and often have a poor response to traditional immunosuppressive medications. Case series of these positive anti-SRP patients have been successfully treated with B-cell depletion therapy with rituximab [Valiyil *et al.* 2010] and tacrolimus [Oddis *et al.* 1999]. Tacrolimus was effective in other refractory patients, not only SRP-positive cases. Cyclosporine A has been reported as effective treatment in anecdotal reports.

Rituximab was reported in case series as effective treatment for IIMs [Levine, 2005]. Preliminary results from a large, multicenter controlled trial (the RIM trial) were recently reported in abstract form. The trial did not achieve the primary end point of a difference in time to definition of improvement between the two groups receiving rituximab at different time points but over 80% of the refractory patients enrolled in this trial did meet the definition of improvement.

Sustained disability is common and physical therapy and exercise is both safe and critical to prevent or limit muscle contractures and atrophy. Moreover, there is evidence that exercise reduces disease activity, improves exercise capacity, changes muscle fiber type (increased type I following exercise regimen) and increased muscle fiber area in patients with IIMs [Alexanderson, 2009; Dastmalchi *et al.* 2007].

Despite anecdotal reports, small pilot studies have demonstrated that tumor necrosis factor (TNF) blocking agents (infliximab) were not effective in refractory cases of inflammatory myopathy. After four infliximab infusions, no patients demonstrated improved objective muscle strength and most had evidence of increased muscle inflammation identified on MRI [Dastmalchi *et al.* 2008]. Moreover, there are case reports of TNF inhibitors being implicated in the development in DM [Klein *et al.* 2010].

A possible future direction in therapy for IIMs may include bone marrow transplantation. There are several case reports of anti-SRP-positive PM patients treated with autologous stem cell transplantation [Henes *et al.* 2009].

The rash of DM can be particularly difficult to control. The mainstay of therapy has been hydroxychloroquine in addition to topical corticosteroids and topical tacrolimus.

Future biological therapies that may show promise in the IIM include those manipulating T-cell signaling and B-cell growth factors such as daclizumab, alemtuzumab, and anti BAFF or APRIL agents. In addition, agents that block or limit lymphocyte migration are also being explored for use in IIMs [Dalakas, 2010].

Conclusion

The IIM represent a rare, but potentially life threatening group of diseases characterized by muscle weakness and often extra-muscular manifestations. Differential begins broad but with a careful history and examination combined with focused blood tests, serology results, imaging, electrical studies, and tissue sampling the appropriate diagnosis can be made and immunosuppressive therapy initiated. While corticosteroids remain the mainstay, use of alternative steroid sparing agents, immunotherapies and future biologic therapies are critical given variable patient response as well as potential drug toxicities. Moreover, no clearly efficacious therapies for the IBM subtype currently exist. Larger, randomized, controlled clinical studies are necessary to improve care of patient inflicted with these debilitating diseases.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

Dr Gazeley has no conflicts of interest to declare. Dr Cronin was a subinvestigator in the Rituximab in Myositis (RIM) Trial. She has no other conflicts of interest to declare.

References

Alexanderson, H. (2009) Exercise effects in patients with adult idiopathic inflammatory myopathies. *Curr Opin Rheumatol* 21: 158–163.

Amato, A.A. and Barohn, R.J. (2009) Inclusion body myositis: old and new concepts. *J Neurol Neurosurg Psychiatr* 80: 1186–1193.

Badrising, U.A., Maat-Schieman, M.L., Ferrari, M.D., Zwinderman, A.H., Wessels, J.A.M. and Bredveld, F.C. *et al.* (2002) Comparison of weakness progression in inclusion body myositis during treatment with methotrexate or placebo. *Ann Neurol* 51: 369–372.

Bazzani, C., Cavazzana, I., Ceribelli, A., Vizzardi, E., Dei Cas, E. and Franceschini, F. (2010) Cardiological features in idiopathic inflammatory myopathies. *J Cardiovasc Med* 11: 906–911.

Bendewald, M.J., Wetter, D.A., Li, X. and Davis, M.D. (2010) Incidence of dermatomyositis and clinically amyopathic dermatomyositis: a population-based study in Olmsted County, Minnesota. *Arch Dermatol* 146: 26–30.

Bohan, A. and Peter, J.B. (1975) Polymyositis and dermatomyositis. Part I and II. *N Engl J Med* 292: 344–407.

Bunch, T.W. (1981) Prednisone and azathioprine for polymyositis: long-term follow up. *Arthritis Rheum* 24: 45–48.

Callen, J.P. (2010) Cutaneous manifestations of dermatomyositis and their management. *Curr Rheumatol Rep* 12: 192–297.

Chahin, N. and Engel, A.G. (2008) Correlation of muscle biopsy, clinical course, and outcome in PM and sporadic IBM. *Neurology* 70: 418–424.

Chahin, N. and Sorenson, E. (2009) Serum creatine kinase levels in spinobulbar muscular atrophy and amyotrophic lateral sclerosis. *Muscle Nerve* 40: 126–129.

Chinoy, H., Fertig, N., Oddis, C., Ollier, W. and Cooper, R. (2007) The diagnostic utility of myositis autoantibody testing to predict the risk of cancer-associated myositis. *Ann Rheum Dis* 66: 1345–1349.

Christopher-Stine, L., Casciola-Rosen, L.A., Hong, G., Chung, T., Corse, A.M., Mammen, A.L. *et al.* (2010) A novel autoantibody recognizing 200-kd and 100 kd proteins is associated with an immune-mediated necrotizing myopathy. *Arthritis Rheum* 62: 2757–2766.

Cox, S., Limaye, V., Hill, C., Blumbergs, P. and Roberts-Thomson, P. (2010) Idiopathic inflammatory myopathies: diagnostic criteria, classification and epidemiological features. *Int J Rheum Dis* 10: 117–124.

Cronin, M.E., Miller, F.W., Hicks, J.E., Dalakas, M.C. and Plotz, P.H. (1989) The failure of intravenous cyclophosphamide therapy in refractory idiopathic inflammatory myopathy. *J Rheumatol* 16: 1225–1228.

Dalakas, M. (1991) Polymyositis, dermatomyositis, and inclusion-body myositis. *N Engl J Med* 325: 1487–1496.

- Dalakas, M. and Hohlfeld, R. (2003) Polymyositis and dermatomyositis. *Lancet* 362: 971–982.
- Dalakas, M., Illa, I., Dambrosia, J.M., Soueidan, S.A., Stein, D.P., Otero, C. *et al.* (1993) A controlled trial of high dose intravenous immune globulin infusions as treatment for dermatomyositis. *N Engl J Med* 329: 1993–2000.
- Dalakas, M., Rakocevic, G., Schmidt, J., Salajeghah, M., McElroy, B., Harris-Love, M. *et al.* (2009) Effect of alemtuzumab (CAMPATH 1-H) in patients with inclusion-body myositis. *Brain* 132: 1536–1544.
- Dalakas, M.C. (2010) Immunotherapy of myositis: issues, concerns and future prospects. *Nat Rev Rheumatol* 6: 129–137.
- Dalakas, M.C., Sonies, B., Dambrosia, J., Sekul, E., Cupler, E., Sivakumar. *et al.* (1997) Treatment of inclusion-body myositis with IVIG: a double-blind, placebo-controlled study. *Neurology* 48: 712–716.
- Dastmalchi, M., Alexanderson, H., Loell, L., Stahlberg, M., Borg, K., Lundberg, I.E. *et al.* (2007) Effect of physical training on the proportion of slow-twitch type I muscle fibers, a novel nonimmune-mediated mechanism for muscle impairment in polymyositis or dermatomyositis. *Arthritis Rheum* 57: 1303–1310.
- Dastmalchi, M., Grundtman, C., Alexanderson, H., Mavragani, C.P., Einarsdottir, H., Helmers, S.B. *et al.* (2008) A high incidence of disease flares in open pilot study of infliximab in patients with refractory inflammatory myopathies. *Ann Rheum Dis* 67: 1670–1677.
- Dion, E., Cherin, P., Payan, C., Fournet, J.C., Papo, T., Maisonobe, T. *et al.* (2002) Magnetic resonance imaging criteria for distinguishing between inclusion body myositis and polymyositis. *J Rheumatol* 29: 1897–1906.
- Dourmishev, L.A. and Wollina, U. (2006) Dermatomyositis: immunopathologic study of skin lesions. *Acta Dermatovenereol Alp Panonica Adriat* 15: 45–51.
- Engel, A. and Franzini-Armstrong, C. (2004) *Myology*, 3rd edn, McGraw-Hill: New York, pp. 1716–1719.
- Gherardi, R. and Romain, K. (2011) Pathogenic aspects of dermatomyositis, polymyositis and overlap myositis. *Presse Med* 40: e209–e218.
- Henes, J.C., Heinzlmann, F., Wacker, A., Seelig, H.P., Klein, R., Bornemann, A. *et al.* (2009) Antisignal recognition particle-positive polymyositis successfully treated with myeloablative autologous stem cell transplantation. *Ann Rheum Dis* 68: 447–448.
- Hill, C.L., Zhang, Y., Sigurgeirsson, B., Pukkala, E., Møllemeijer, L., Airio, A. *et al.* (2001) Frequency of specific cancer types in dermatomyositis and polymyositis: a population-based study. *Lancet* 357: 96–100.
- Ji, S.Y., Zeng, F.Q., Guo, Q., Tan, H.F., Tang, H.F., Luo, Y.J. *et al.* (2010) Predictive factors and unfavourable prognostic factors of interstitial lung disease in patients with polymyositis or dermatomyositis: a retrospective study. *Chin Med J* 123: 517–522.
- Kagen, L.J. and Aram, S. (1987) Creatine kinase activity inhibitor in sera from patients with muscle disease. *Arthritis Rheum* 30: 213–217.
- Klein, R., Rosenbach, M., Kim, E.J., Kim, B., Werth, V.P., Dunham, J. *et al.* (2010) Tumor necrosis factor inhibitor-associated dermatomyositis. *Arch Dermatol* 146: 780–784.
- Kuo, G.P. and Carrino, J.A. (2007) Skeletal imaging and inflammatory myopathies. *Curr Opin Rheumatol* 19: 530–535.
- Levine, T. (2005) Rituximab in the treatment of dermatomyositis: an open-label pilot study. *Arthritis Rheum* 52: 601–607.
- Majithia, V. and Harisdangkul, V. (2005) Mycophenolate mofetil (CellCept): an alternative therapy for autoimmune inflammatory myopathy. *Rheumatology* 44: 386–389.
- Mastaglia, F. and Phillips, B. (2002) Idiopathic inflammatory myopathies: epidemiology, classification, and diagnostic criteria. *Rheum Dis Clin N Am* 28: 723–741.
- Ng, K.P., Ramos, F., Sultan, M.F. and Isenberg, D.A. (2009) Concomitant diseases in a cohort of patients with idiopathic myositis during long-term follow-up. *Clin Rheumatol* 28: 947–953.
- Oddis, C.V., Scurba, F.C., Abu Elmagd, K. and Starzl, T.E. (1999) Tacrolimus in refractory polymyositis with interstitial lung disease. *Lancet* 353: 1762–1763.
- Quartuccio, L., De Marchi, G., Scott, C.A., Ferraccioli, G., Beltrami, C.A., De Vita, S. *et al.* (2007) Treatment of inclusion body myositis with cyclosporine-A or tacrolimus: a successful long term management in patients with earlier active disease and concomitant autoimmune features. *Clin Exp Rheumatol* 25: 246–251.
- Selva-O'Callaghan, A., Fonollosa-Pla, V., Trallero-Araguas, E., Martínez-Gómez, X., Simeon-Aznar, C.P., Labrador-Horrillo, M. *et al.* (2010a) Nailfold capillary microscopy in adults with inflammatory myopathy. *Sem Arthritis Rheum* 39: 398–404.
- Selva-O'Callaghan, A., Grau, J.M., Gamez-Cenzano, C., Vidaller-Palacin, A., Martínez-Gómez, X., Trallero-Araguas, E. *et al.* (2010b) Conventional cancer screening versus PET/CT in dermatomyositis/polymyositis. *Am J Med* 123: 558–562.
- Shamin, E.A., Rider, L.G. and Miller, F.W. (2000) Update on the genetics of the idiopathic inflammatory myopathies. *Curr Opin Rheumatol* 12: 482–491.
- Sigurgeirsson, B., Lindelof, B., Edhag, O. and Allander, E. (1992) Risk of cancer in patients with dermatomyositis or polymyositis—a population-based study. *N Engl J Med* 326: 363–367.

Targoff, I.N., Miller, F.W., Medsger Jr, T.A. and Oddis, C.V. (1997) Classification criteria for the idiopathic inflammatory myopathies. *Curr Opin Rheumatol* 9: 527–535.

Valiyil, R., Casciola-Rosen, L., Hong, G., Mammen, A. and Christopher-Stine, L. (2010) Rituximab therapy for myopathy associated with anti-signal recognition particle antibodies: a case series. *Arthritis Care Res* 62: 1328–1234.

Van de Vlekkert, J., Hoogendijk, J.E., de Haan, R.J., Algra, A., van der Tweel, L., van der Pol, W.L. *et al.* (2010) Oral dexamethasone pulse therapy *versus* daily prednisolone in sub-acute onset myositis, a randomized clinical trial. *Neuromusc Disord* 20: 382–389.

Verschuuren, J.J. (1997) Inclusion body myositis, In: Emery, A. (ed.). *Diagnostic Criteria for Neuromuscular Disorders*, Royal Society of Medicine, European Neuromuscular Centre: Baarn, the Netherlands, pp. 81–84.

Walker, U.A. (2008) Imaging tools for the clinical assessment of idiopathic inflammatory myositis. *Curr Opin Rheumatol* 20: 656–661.

Weber, M.A., Krix, M., Jappe, U., Huttner, H.B., Hartman, M., Meyding-Lamade, U. *et al.* (2006) Pathologic skeletal muscle perfusion in patients with myositis: detection with quantitative contrast-enhanced US—initial results. *Radiology* 238: 640–649.

Visit SAGE journals online
<http://tab.sagepub.com>

SAGE JOURNALS
Online