Selected aspects of the current management of myositis

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James Lilleker, Sean Murphy and Robert Cooper

Abstract: The idiopathic inflammatory myopathies (IIM) are a rare and heterogeneous group of acquired autoimmune muscle disorders, often referred to as 'myositis'. Clinical assessment, together with muscle biopsy findings and autoantibody status are key factors to consider when making a diagnosis of IIM, and in stratification of the 'IIM spectrum' into disease subgroups. Treatment stratified according to serotype (and in the future, likely also genotype) is increasingly being used to take account of the heterogeneity within the IIM spectrum. Subgroup classification is also important in terms of monitoring for complications, such as malignancy and interstitial lung disease. Disease monitoring should include the use of standardized tools such as the IMACS disease activity outcome measures. Other tools such as muscle MRI can be useful in identifying areas of active muscle inflammation. Treatment outcomes in IIM remain unsatisfactory. The evidence base to guide treatment decisions is remarkably limited. In addition to muscle inflammation, a number of noninflammatory cell-mediated mechanisms may contribute to weakness and disability, and for which no specific treatments are currently available.

Keywords: Myositis, myopathy, myositis specific antibodies, myositis subgroups, myositis disease activity, myositis damage, outcome assessment tools

Introduction

The idiopathic inflammatory myopathies (IIM) are a rare and heterogeneous group of acquired autoimmune muscle disorders, often referred to as 'myositis'. This review will focus on selected aspects of the current management of adult-onset IIM, but largely omit sporadic inclusion body myositis (IBM), for which no effective disease-modifying treatments currently exist.

For many years, IIM has been classified simply as either polymyositis (PM) or dermatomyositis (DM). However, the definition of IIM subtypes is currently undergoing upheaval as a consequence of our increased understanding of the genetic and serological associations with certain clinical phenotypes. Emphasis is now on defining clinicoserological syndromes that can inform treatment response, predict the likelihood of developing certain clinical features and thus guide therapeutic decision making [Betteridge and McHugh, 2015].

Underlying pathological mechanisms remain poorly understood in IIM and the mainstay of treatment continues to be the unfocused 'immunosuppression'. Little progress has been made towards a more stratified (precision medicine) approach targeting specific pathological processes, as is occurring in other autoimmune disorders such as rheumatoid arthritis [Okada *et al.* 2014]. Additionally, fully standardized and validated methods for monitoring disease activity and treatment response remain elusive [Miller, 2012]. As a consequence, outcomes in IIM treatment continue to be generally poor. Patients can suffer refractory muscle weakness and fatigue, in addition to extramuscular manifestations (e.g. skin disease, cardiac and respiratory involvement, etc.) that can be difficult to control. Furthermore, mortality rates are increased compared with normal individuals, and the association of adult DM with malignancy remains a significant additional concern [Dobloug *et al.* 2015].

Another issue is that patients can sometimes 'fall between stools' and the differing approach of neurologists and rheumatologists has been noted [Christopher-Stine, 2010]. In fact, IIM patients will often need input from respiratory physicians, dermatologists, rehabilitation specialists, pain

Correspondence to:
Robert Cooper, MD, FRCP
Salford Royal NHS Foundation Trust, Stott Lane, Salford M6 8HD, UK
robert.cooper@liverpool.ac.uk

James Lilleker, MB/ChB, MRCP
Salford Royal NHS Foundation Trust, Salford, UK

Sean Murphy, MB/ChB, MRCP
University of Manchester, Manchester, UK

specialists and other allied health professionals (e.g. pharmacist, physiotherapist, occupational therapist, and speech and language therapist) in additional to their parent physician. Treating patients with IIM is complex, and thus requires close cooperation between these care providers.

Classification

IIM is heterogeneous, and accurate subtype classification is fundamental if one is to treat the disease effectively. Accurate diagnosis relies upon a combination of clinical characteristics, muscle biopsy histopathology findings and serology. Traditionally, reliance was made upon the Bohan and Peter diagnostic criteria [Bohan and Peter, 1975a, 1975b], which does show good discriminatory ability when distinguishing between PM/DM and systemic lupus erythematosus or systemic sclerosis (sensitivity 93%, and specificity 93%) [Oddis and Medsger, 1995].

However, these criteria have a number of limitations. In particular, no reference is made to IBM, which was still being referred to as 'steroid-resistant PM' at the time the criteria were envisioned. Reliance on the Bohan and Peter criteria means that patients with IBM, and other PM mimics such as muscular dystrophy, risk being misdiagnosed as having PM. Furthermore, these criteria do not make reference to serological or muscle-imaging findings, both of which are increasingly used in the diagnostic work-up of IIM patients. In summary, it is now clear that the Bohan and Peter criteria are outdated and should not be relied upon. The more recent criteria developed by Hoogendijk and colleagues added important exclusion criteria, to avoid misdiagnosis of IBM as PM and to reduce the likelihood of noninflammatory muscle disease being misclassified as IIM [Hoogendijk *et al.* 2004]. Serology (the presence of myositis-specific antibodies) and myo-oedma on magnetic resonance imaging (MRI) were also added, although only to support a 'probable' rather than 'definite' diagnosis of either PM or DM.

Further criteria are being developed using a multicentre data-driven approach and are currently undergoing an ACR/EULAR approval process. The criteria (for which an online calculator is available at: http://www.imm.ki.se/biostatistics/calculators/iim/) were produced after analysis of pooled demographic, clinical and laboratory data on 976 IIM patients and 624 controls. The calculator can be used with or without the availability of muscle biopsy data and produces a probability that the patient has IIM as well as a suggested subgroup (e.g. DM, PM or IBM). A predetermined minimum probability of 50% is suggested to define IIM cases, but a more stringent threshold of 90% is suggested for inclusion in clinical trials.

Importantly, pure PM now appears to be a distinctly rare entity [Dalakas, 2015]. It is more common, for instance, for muscle inflammation to occur as a feature of the antisynthetase syndrome (which also includes features such as fever, arthralgias, Raynaud's phenomenon and 'mechanics hands'), for which separate diagnostic criteria have been proposed [Connors *et al.* 2010]. 'PM' may also form part of an overlap syndrome with other connective tissue diseases (CTD), such as mixed CTD or systemic sclerosis. Thus, features of these CTDs should be sought to aid classification and guide management. Necrotizing autoimmune myositis (NAM, also referred to as immune-mediated necrotizing myopathy (IMNM)) has also become recognized as a distinct entity, which in the past may have been classified as PM. In NAM, antibodies against signal recognition particle (SRP) and 3 hydroxy-3 methylglutaryl- coenzyme A reductase (HMGCR) are usually identified and the muscle biopsy is characterized by the presence of myonecrosis with a relative paucity of inflammatory features [Hamann *et al.* 2013].

It is becoming clear that each clinical phenotype within the IIM spectrum is associated with a distinctive genetic and serological signature [Miller *et al.* 2015; Rothwell *et al.* 2015]. These developments are being gradually translated in to clinical practice. For example, the presence of anti-TIF1-gamma antibodies, which in adult DM patients strongly associates with the presence of malignancy, necessitates vigilant cancer screening [Trallero-Araguás *et al.* 2012]. Other antibody profiles can be used to predict treatment responses. For example, DM patients with anti-Mi-2 antibodies tend to respond well to immunosuppression [Aggarwal *et al.* 2014]. Further tools that allow a more accurate stratification of the heterogeneity of IIM are desirable in order to focus management efforts and exploit new therapeutic targets.

Clinical trials and the therapeutic evidence base

Recent efforts have led to the production of the semivalidated International Myositis Assessment and Clinical Studies Group's (IMACS) 'core-set' outcome measures [Rider *et al*. 2011] and 'definition of improvement' [Rider *et al*. 2003]. These are increasingly utilized in clinical trials as primary outcome measures. Also, there is now an international consensus statement regarding the conduct of clinical trials in IIM [Oddis *et al*. 2005].

The major strength of using the IMACS outcome measures is the multifaceted nature of the assessment, which takes account of laboratory measures of muscle-enzyme levels [usually creatine kinase (CK)], manual muscle testing (MMT), as well as patient- [Health Assessment Questionnaire (HAQ) and global visual analogue scale] and physician-completed [Myositis Disease Activity Assessment Tool (MDAAT) and global visual analogue scale] scoring tools.

Difficulties in using these measures in clinical trials do, however, remain. Not all measures are completely validated and some aspects exhibit a 'ceiling effect', especially in patients with relatively mild disease at the outset [Rider *et al*. 2011]. Furthermore, differentiating between disease *damage* (i.e. irreversible change to muscle such as fatty replacement with or without fibrosis) and disease *activity* (which is amenable to treatment) remains difficult. This distinction is of key relevance when defining inclusion and exclusion criteria for clinical trials in IIM [Miller, 2012].

Any discussion of the treatment of IIM must highlight that the evidence base is remarkably limited. Clinical trials for IIM have most often been small and underpowered, and until recently have not utilized standardized outcome measures. Another issue is that inclusion criteria have often been based on outdated definitions of IIM, and which did not take into account recent developments regarding serological associations with certain IIM phenotypes.

These strictures have resulted in an uninformative knowledge base and a lack of clear evidence-based treatment algorithms. In the UK, there are, for instance, no licensed treatments for IIM, which are instead 'borrowed' from other diseases such as the CTDs. This issue was highlighted in a recent Cochrane review [Gordon *et al*. 2012]. Treatment decisions in IIM are thus usually based on local expert options, or consensus of opinions, rather than on the results of randomized controlled trials.

In other disease where the evidence base is lacking, consensus statements and 'standards of care' have been produced to guide practice. However, in the UK, no such statements exist. This is gradually being addressed and there is ongoing work to produce a patient-derived standard of care statement for IIM [Lilleker *et al*. 2015] as well as consensus statements on treatment of IIM according to the phenotype observed [Tansley *et al*. 2014].

Magnetic resonance imaging of muscle

MRI is used increasingly in IIM for diagnostic purposes, to optimize diagnostic biopsy-site choice and to assess disease activity and damage during treatment. From a diagnostic perspective, MRI has identified differences between PM, DM and IBM, as well as between inflammatory disease of muscle *versus* noninflammatory mimics [Sekul *et al*. 1997; Tomasová Studynková *et al*. 2007]. Performing targeted muscle biopsies based on the identification of areas of muscle inflammation on MRI has the potential to increase diagnostic yield [Tomasová Studynková *et al*. 2007].

Muscle MRI can indicate the degree of fatty replacement of muscle (e.g. using T1-weighted sequences) as well as estimate the intensity and extent of disease activity. The latter is inferred from the presence and extent of myo-oedema, as detected on short tau inversion recovery (STIR) sequences [Miller, 2012; Tomasová Studynková *et al*. 2007]. The distinction between irreversible disease damage and disease activity is critical when considering the likelihood of success of any therapeutic intervention.

Quantitative assessment of MRI findings is the focus of much research effort, with potential benefits over the rather subjective approach currently taken which involves the use of semiquantitative scoring systems [Mercuri *et al*. 2007]. These semiquantitative scoring tools currently lack validation, and different scales may be utilized in different centres. In contrast, quantitative MRI analysis [Yao *et al*. 2015] has the potential to provide a robust objective outcome measure for use in clinical trials, and also has the potential to feed automated image-analysis techniques that could be deployed in future clinical practice.

Treatment

Treatment of IIM will often focus on skeletal muscle disease. However, IIM is a multisystem disorder and concern should be given to extra-muscular aspects of the disease, particularly the skin in DM and the potential for respiratory and cardiac involvement. Also of relevance is the occurrence of other complicating issues, including pain, fatigue, dysphagia and depression, which should be addressed for each patient.

Whilst the IMACS outcome measures can also be used in clinical practice, a more holistic approach is often utilized which exploits the clinical expertise of the treating physician as well as a number of other investigational modalities for assessing disease activity and damage, including MRI of muscle. A common mistake is to make treatment decisions based on change in an individual measure. For example, serum CK can fall without improvement in muscle strength, and levels can be normal even in those with obviously active disease [Dalakas and Hohlfeld, 2003]. The overall message is to 'treat the patient, not the numbers' and despite advances in technology, clinical examination remains vital if one is to successfully assess and treat IIM patients.

One aspect that needs highlighting is the issue of 'steroid resistance'. Very few accurately diagnosed PM or DM patients will resist response to corticosteroid therapy. Thus, when an individual case proves truly unresponsive to corticosteroids, the IIM diagnosis should be reviewed. This is particularly so in cases that are seronegative for all IIM-specific or -associated autoantibodies (MSA/MAA). In this situation, there is a significant possibility that either the patient has IBM or another IIM mimic, such as a muscular dystrophy. Importantly, a number of dystrophic conditions (e.g. limb girdle muscular dystrophy 2B, a dysferlinopathy) are associated with an inflammatory appearance on muscle biopsy, which can lead to diagnostic confusion [Hilton-Jones, 2014]. The diagnostic review will usually include a repeat diagnostic muscle biopsy, as with the passage of time, degenerative features of non-PM/DM diseases can accumulate and become more conspicuous [Brady *et al.* 2014].

Treating skeletal muscle disease

Given that the IIM pathological process involves autoimmune inflammation, it is no surprise that current treatment approaches focus on the use of immunosuppression. Corticosteroids remain the mainstay of initial treatment, despite the absence of good-quality evidence to support their use. Where there is clinical urgency, intravenous methylprednisolone can be used instead. A steroid-sparing agent is then usually commenced (e.g. azathioprine, methotrexate or mycophenolate). There is little to guide drug choice in this aspect, although mechanism of action may be considered and treatment tailored according to prominent aspects of disease. Intravenous immunoglobulins (IVIg) are also commonly used, particularly in accurately diagnosed but truly steroid-resistant cases.

This review does not discuss all potential treatment options, but instead highlights some more novel considerations. A broader review of the pharmacological options for treating IIM can be found in the Cochrane review by Gordon and colleagues [Gordon *et al.* 2012], and in a more recent systematic review by Vermaak and colleagues [Vermaak *et al.* 2015]. It is important to remember that noninflammatory mechanisms also contribute to muscle damage. There is, therefore, a potential role for intervention targeting these pathways, which will briefly be discussed.

Tacrolimus. The safety and efficacy of tacrolimus is well documented. There are sound biological reasons to consider the use of tacrolimus in IIM, although the evidence base supporting its efficacy is small and of low quality. There has recently been one prospective, open-label study and two retrospective controlled studies investigating its use in IIIM.

In the prospective open label study, tacrolimus was used in nine patients with refractory IIM [Matsubara *et al.* 2012]. Eight of these patients were found to show clinical improvements after 6 months with minimal adverse effects. A retrospective controlled study of 49 previously untreated patients with IIM complicated by interstitial lung disease, involved 25 patients receiving tacrolimus and 24 receiving conventional therapies [Kurita *et al.* 2015]. After adjustment, the tacrolimus group had significantly longer event-free (death or other adverse event) survival as compared with the conventional therapy group [weighted hazard ratio (HR) 0.32, 95% confidence interval (CI) 0.14–0.75, $p = 0.008$]. In addition, the tacrolimus group had significantly longer disease-free survival as compared with the conventional therapy group (weighted HR 0.25, 95% CI 0.10–0.66, $p = 0.005$). A further retrospective controlled study examined 23 patients with IIM treated with prednisolone plus tacrolimus compared with 19 treated with prednisolone plus conventional therapy [Yokoyama *et al.* 2015]. A steroid-sparing effect of tacrolimus over conventional therapy was identified, which persisted over the 36 months of the study; at completion the median prednisolone dose was 4.75 mg in the tacrolimus group *versus* 10 mg in the conventional-therapy group, $p = 0.02$.

Rituximab. A large ($n = 200$, although 48 had juvenile DM) randomized controlled trial examining the efficacy of rituximab administered early *versus* late in the treatment of refractory IIM has recently been completed [Oddis *et al.* 2005]. There was no difference in the time to reach the IMACS definition of improvement between the two groups (the primary outcome). However, most patients (83%) did improve. It is argued that the result reflects a lack of statistical power to distinguish between the benefits of early *versus* late treatment, rather than a failure of rituximab *per se*.

Tociluzimab. Tocilizumab is an interleukin-6 (IL-6) receptor blocker and as such, has potential use in the treatment of IIM. IL-6 has been found at increased levels in IIM muscles [Lepidi *et al.* 1998] and serum IL-6 levels have been shown to correlate with the Myositis Intention-to-Treat Activity Index (MITAX) disease activity score [Gono *et al.* 2014]. The use of tocilizumab has previously been described in two patients with PM [Narazaki *et al.* 2011] and one with DM [Kondo *et al.* 2014] with a suggestion of promise. A randomized controlled trial of tocilizumab in refractory IIM is ongoing [ClinicalTrials.gov identifier: NCT02043548].

Other ongoing clinical trials. There are a number of ongoing phase II and phase III clinical trials of novel therapies for IIM:

1. Belimumab [ClinicalTrials.gov identifier: NCT02347891] is an inhibitor of B-cell activating factor (BAFF) which is currently used in the treatment of systemic lupus erythematosus and is the subject of a phase II/III trial in PM and DM.
2. BAF312 [ClinicalTrials.gov identifier: NCT01801917] is a sphingosine 1-phosphate (S1P) receptor modulator, which inhibits lymphocyte egress from lymph nodes and is currently the subject of a phase II trial in patients with PM.
3. A phase II trial of IMO-8400 [ClinicalTrials.gov identifier: NCT02612857], an antagonist of Toll-like receptors (TLRs) 7, 8 and 9 is ongoing in patients with DM.
4. Gevokizumab [EudraCT number: 2012-005772-34], which binds to interleukin-1-beta, is the subject to a phase II trial in patients with PM, DM or NAM.

Interestingly, the inclusion criteria in some ongoing clinical trials in IIM still refer to the Bohan and Peter diagnostic criteria.

Creatine supplementation. Reduced skeletal muscle total creatine and increased urinary creatine excretion (suggesting muscle catabolism) are observed in patients with neuromuscular disorders, including IIM [Chung *et al.* 2007]. A recent study ($n = 37$) has demonstrated improved functional performance in PM and DM patients receiving dietary supplementation with creatine in combination with a home exercise programme, compared with those receiving placebo and exercise over 6 months [Chung *et al.* 2007]. The use of creatine supplementation in IIM has been reviewed by Cochrane, with the authors concluding that there is evidence supporting the suggestion that creatine supplementation can improve functional outcomes in IIM [Kley *et al.* 2013].

Exercise. The role of exercise as a potential therapeutic modality in IIM has recently been reviewed [Lightfoot and Cooper, 2016]. In the past, there was concern that exercise may be dangerous in those with IIM, perhaps generated as a result of the observation that CK can rise after exercise. However, reassurance is provided by results from a number of studies examining aerobic and resistive exercise programmes in patients with IIM. In patients with PM and DM, increased muscle strength, improved disease-activity scores and gene expression profiles showing a reduction in proinflammatory and profibrotic gene networks has been observed in response to a supervised 7-week resistance exercise programme [Alexanderson *et al.* 2007; Nader *et al.* 2010]. It is suggested that exercise may therefore exert a disease-modifying effect at a molecular level through modification of gene expression. In further support of this hypothesis, Munters and colleagues recently reported downregulation of genes related to inflammation and endoplasmic reticulum (ER) stress in a group of seven patients with DM or PM that underwent a 12-week endurance exercise programme compared with a nonexercised control group [Munters *et al.* 2016].

Endoplasmic reticulum stress and reactive-oxygen species. To the frustration of many of those treating IIM patients, outcomes with immunosuppressive therapy remain unsatisfactory. Even with aggressive immunosuppression, significant and irreversible disease damage often remains. The reasons for this are poorly understood, but mechanisms are thought to involve noninflammatory cell-mediated pathways. Recent work has focused on the role ER stress and subsequent downstream effects potentially detrimental to muscle function, including the generation of toxic reactive-oxygen species and mitochondrial dysfunction [Lightfoot *et al.* 2015]. Further work on elucidating the exact mechanisms at play will be important in the identification of new therapeutic targets in IIM.

Myositis is a multisystem disorder

In treating a patient with IIM, one must look beyond the skeletal muscle. Disease of the skin, heart, lungs and the association with malignancy are key issues that need addressing. In many cases, screening for subclinical disease must be instituted to ensure expeditious detection of potential complications so that appropriate intervention might take place. Importantly, these extramuscular manifestations can be predicted by a patient's serological profile. A full review of treating the extra-muscular aspects of IIM will not follow, but we will mention a few key aspects to consider.

Cardiac disease. Myocardial disease in IIM is under-recognized and is associated with high levels of morbidity and mortality [Lundberg, 2006]. Most cardiac disease is subclinical, and feasible methods of screening are limited in many clinical settings (e.g. poor access to cardiac MRI). The use of a panel of biochemical assays accounting for markers released differentially from skeletal and cardiac muscle may offer accurate screening for cardiac involvement in IIM in the clinical setting [Hughes *et al.* 2015]. Importantly, it is now recognized that troponin-T can be released from regenerating skeletal muscle and as such, is not a reliable marker of cardiac involvement in IIM [Bodor *et al.* 1997].

Malignancy. Whilst the association of adult DM with malignancy is well established, it is now possible to refine the assessment of malignancy risk using serology. In particular, the presence of anti-TIF1-gamma antibodies is highly associated with malignancy and intense initial and regularly repeated screening is likely warranted in this group.

Malignancy screening is often performed at the discretion of the treating physician and there are no firm recommendations dictating which investigations should be performed (e.g. endoscopy, abdominal ultrasound, PET/CT) and the interval between them. In the Lambert-Eaton myasthenic syndrome, prediction scores have been produced which allow a tailored approach for screening for small cell lung cancer [Titulaer *et al.* 2011]. There is currently no similar work in DM, although it would be assumed that serological testing for TIF1-gamma antibodies would form part of the scoring system.

A practical approach to managing myositis

Whilst bearing in mind the heterogeneity of IIM and the limited evidence base, a number of practical recommendations can be made about the general management. It is our view that patients with IIM should be referred to a specialist clinic for ongoing care. The experienced teams of healthcare professions in such clinics can minimize the risk of diagnostic error and also have access to clinical trials of potential new IIM therapies. Access to physiotherapy and other allied health professionals is also of key importance. The use of long courses of high-dose corticosteroids requires care regarding the potential for complications, including effects on bone health.

Depending upon the severity of presentation, particularly in terms of the degree of muscle weakness, corticosteroids should be commenced either orally (e.g. prednisolone 1 mg/kg up to 100 mg) or intravenously (e.g. methylprednisolone, 1 g/day for 3 days, then converting to oral prednisolone). IVIgs are also occasionally used in this setting, although practice differs between specialists. Around 4 weeks of high-dose corticosteroid treatment may be required to induce disease suppression. This should include improvements in a variety of disease-activity clinical-outcome measures including muscle strength, and not just a fall in the CK level. At this time (or before, if preferred), a steroid-sparing agent is usually commenced and the corticosteroid dose is gradually tapered. Commonly prescribed options include azathioprine, methotrexate, mycophenolate, cyclosporin and tacrolimus. A failure of treatment response necessitates review of the diagnosis and consideration of other therapies, including rituximab or cyclophosphamide, the latter being of particular use in those with coexisting interstitial lung disease.

Conclusions

1. Clinical assessment, together with muscle biopsy findings and autoantibody status, are key factors to consider when making a diagnosis of IIM, and in stratification of the 'IIM spectrum' into disease subgroups.
2. Treatment stratified according to serotype (and in the future, likely also genotype) is increasingly being used to take account of the heterogeneity within the IIM spectrum. Subgroup classification is also important in terms of monitoring for complications, such as malignancy and interstitial lung disease.
3. Disease monitoring should include the use of standardized tools such as the IMACS' disease-activity outcome measures. Other tools such as muscle MRI can be useful in identifying areas of active muscle inflammation.
4. Treatment outcomes in IIM remain unsatisfactory. The evidence base to guide treatment decisions is remarkably limited.
5. In addition to muscle inflammation, a number of noninflammatory cell-mediated mechanisms may contribute to weakness and disability, and for which no specific treatments are currently available.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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