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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 standardised 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 non-inflammatory cell-mediated mechanisms may contribute to weakness and disability, and for
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Selected aspects of the current management of myositis

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Keywords:
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 clinico-serological syndromes which 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 remains unfocussed ‘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 standardised and validated methods to monitor disease activity and treatment response remain elusive [Miller, 2012]. As a consequence, outcomes in IIM treatment generally remain poor. Patients can suffer refractory muscle weakness and fatigue, in addition to extra-muscular manifestations (e.g. skin disease, cardiac and respiratory involvement etc.) which 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 specialists and other allied health professionals (e.g. pharmacist, physiotherapist, occupational therapist and speech and language therapist), in addition 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%, 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 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 Hoogendijk et al criteria added important
exclusion criteria to avoid misdiagnosis of IBM as PM and to reduce the likelihood of non-inflammatory muscle disease being misclassified as IIM [Hoogendijk et al., 2004]. Serology (the presence of myositis specific antibodies) and myo-oedema 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 multi-centre data-driven approach and are currently undergoing an ACR/EULAR approval process. The criteria, for which an online calculator is available (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 anti-synthetase 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. Necrotising autoimmune myositis (NAM, also referred to as immune-mediated necrotising myopathy) has also become recognised as a distinct entity which in the past may have been classified as PM. In NAM antibodies against SRP and HMGCR are usually identified and the muscle biopsy is characterised 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 into 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 semi-validated International Myositis Assessment and Clinical Studies Group (IMACS) ‘core-set’ outcome measures [Rider et al., 2011] and ‘definition of improvement’ [Rider et al., 2003]. These are increasingly utilised in clinical trials as a primary outcome measures. There is also now an international consensus statement regarding the conduct of clinical trials in IIM [Oddis, Rider, Reed, Ruperto, Hermine I. Brunner, 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 (Myositis Disease Activity Assessment Tool [MDAAT] and global visual analogue scale) completed 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 and/or 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 utilised standardised 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 randomised 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 optimise 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 non-inflammatory 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 semi-quantitative scoring systems [Mercuri et al., 2007]. These semi-quantitative scoring tools currently lack
validation, and different scales may be utilised 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 which could be deployed in future clinical practice.

**Treatment**

Treating IIM will often focus skeletal muscle disease. However, IIM is a multisystem disorder and concern should be given to extramuscular 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 individual patient.

Whilst the IMACS outcome measures can also be used in clinical practice, a more holistic approach is often utilised 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 required to be specifically highlighted is the issue of “steroid-resistance”. Very few accurately diagnosed PM or DM patients will not at least partly respond to corticosteroid therapy. Thus, when an individual case proves truly resistant to corticosteroids the IIM diagnosis should be reviewed. This is particularly so in cases which are seronegative for all IIM specific/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 range of pharmacological options for treating IIM can be found in the Cochrane review by Gordon et al [Gordon et al., 2012] and in a more recent systematic
review by Vermaak et al [Vermaak et al., 2015]. It is also important to remember that non-inflammatory 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 IIM.

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% 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 to 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 4.75mg in the tacrolimus group, versus 10mg in the conventional therapy group, p=0.02).
**Rituximab:** A large (n=200, although 48 had juvenile DM) randomised controlled trial examining the efficacy of rituximab administered early versus late in the treatment of refractory IIM has recently been completed [Oddis, Rider, Reed, Ruperto, Hermine I Brunner, 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.

**Tocilizumab:** 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 randomised controlled trial of tocilizumab in refractory IIM is ongoing ([https://clinicaltrials.gov/ct2/show/study/NCT02043548](https://clinicaltrials.gov/ct2/show/study/NCT02043548)).

**Other ongoing clinical trials:** There are a number of ongoing phase two and phase three clinical trials of novel therapies for IIM.

- Belimumab ([https://clinicaltrials.gov/ct2/show/NCT02347891](https://clinicaltrials.gov/ct2/show/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 two/three trial in PM and DM.

- BAF312 ([https://clinicaltrials.gov/ct2/show/NCT01801917](https://clinicaltrials.gov/ct2/show/NCT01801917)) is a sphingosine 1-phosphate (S1P) receptor modulator which inhibits lymphocyte egress from lymph nodes and is currently the subject of a phase 2 trial in patients with PM.

- A phase 2 trial of IMO-8400 ([https://clinicaltrials.gov/ct2/show/NCT02612857](https://clinicaltrials.gov/ct2/show/NCT02612857)), an antagonist of Toll-like receptors (TLRs) 7, 8 and 9 is ongoing in patients with DM.

- Gevokizumab (EudraCT number 2012-005772-34), which binds to interleukin-1-beta, is the subject to a phase two 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 to 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 programs 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 pro-inflammatory and pro-fibrotic 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 et al 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 program compared to a non-exercised 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 non-inflammatory cell-mediated pathways. Recent work has focussed 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 which must be addressed. 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 extra-muscular manifestations can be predicted by patients’ 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 recognised 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 recognised 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 regular 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 minimise 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 1mg/kg up to 100mg) or intravenously (e.g. methylprednisolone, 1g per day for three days, then converting to oral prednisolone). Intravenous immunoglobulins (IVlg) are also occasionally used in this setting occasionally, although practice differs between specialists. Around four weeks of high dose corticosteroid treatment may be required to begin 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, ciclosporin 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 co-existing interstitial lung disease.
Conclusions

- 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 standardised 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 non-inflammatory cell-mediated mechanisms may contribute to weakness and disability, and for which no specific treatments are currently available.

Conflict of interest statement

The authors have no conflicts of interest.

References


Selected aspects of the current management of myositis


