

# DIAGNOSIS AND TREATMENT OF INFLAMMATORY MUSCLE DISEASES

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The inflammatory myopathies are rare. No accurate figures for incidence or prevalence are available but if one takes the two most common conditions, dermatomyositis and inclusion body myositis, their combined annual incidence is probably less than 200 new cases per annum in the UK (population ~60 million). Given that patients with inflammatory myopathy may present to, and be managed within, one of several specialties (for example, dermatology, rheumatology, neurology, general medicine), and that there are about 250 neurologists in the UK, it is apparent that most general neurologists are going to see these conditions on average probably no more than once every couple of years. In perhaps 70% of cases, the diagnosis and management are straightforward and successful early experience may encourage a sense of competence that is only shaken when things do not go as expected. There is no doubt that patients are best served by somebody with specific expertise and interest in these rare conditions, and ideally there should be such a specialist in each region to whom they can be referred.

This article will consider the classification of the inflammatory myopathies, the clinical features of the so-called idiopathic inflammatory myopathies, and approaches to their diagnosis and management. With respect to drug treatment there is an absolute dearth of randomised controlled trials and the best advice that can be offered is based on “expert opinion”. Multicentre trials are desperately needed. Emphasis will be placed on pitfalls in diagnosis and management. Current views on pathogenesis will be noted, but many areas of ignorance remain and it is likely that the next few years will see a major revision of opinions.

Some fundamental issues and take home messages are summarised in box 1.

## CLASSIFICATION

In brief, the inflammatory myopathies (box 2) are simply those disorders in which the primary pathological process is inflammation within muscle. In most, the main clinical consequence is weakness, much less frequently pain. This definition thus excludes myopathies with secondary inflammation in muscle, such as some of the muscular dystrophies, and conditions in which the inflammatory process is in associated tissues rather than muscle itself, such as polymyalgia rheumatica. These latter conditions are particularly important as they may be misdiagnosed and mistreated as being forms of myositis. In some conditions, such as sarcoidosis, rheumatoid arthritis, and Sjögren’s syndrome, inflammatory infiltrates in muscle are probably relatively common, but clinical consequences, such as weakness, are rare. Macrophagic myofasciitis, a recently defined disorder seen mainly in France, is probably secondary to aluminium, used as an adjuvant in some vaccines.

This review will be confined to four disorders, because of their relative frequency and importance to the general neurologist. *Dermatomyositis* (DM) is the most common form of classical inflammatory myopathy. Isolated *polymyositis* (PM) is rare, but a frequent misdiagnosis. But PM is relatively frequently associated with various manifestations of connective tissue disease, a situation for which many use the term “overlap syndrome”. Some argue that there is a difference between “overlap” and “association” but in truth we are currently ignorant of the true relationship between these various conditions. Debate continues as to whether *inclusion body myositis* (IBM) is a primary inflammatory myopathy, or whether the inflammatory changes are a secondary phenomenon. One of the strongest arguments in favour of the latter is that IBM responds poorly, if at all, to immunosuppressant/anti-inflammatory treatments. IBM is often initially wrongly diagnosed and treated as PM, usually because of failure to appreciate the specific clinical and pathological features of the condition.

## PATHOGENESIS

For a long time, DM and PM were considered to be essentially identical disorders, differing only by the presence or absence of skin involvement. There is now overwhelming evidence that they are fundamentally different disorders in term of pathogenesis and that their clinical similarities simply reflect muscle’s limited repertoire of response to disease. It is likely that in the future their

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**Box 1: Ten important points to ponder**

- (1) Pain and discomfort are rarely prominent in myositis
- (2) The normal upper limit for serum creatine kinase is higher than you think
- (3) Failure to appreciate points 1 and 2 leads to many patients being wrongly diagnosed, and treated, as having polymyositis
- (4) Pure polymyositis is a rare condition
- (5) Inflammatory infiltrates in a muscle biopsy may be a secondary phenomenon and failure to appreciate this is a common reason for wrong diagnosis and inappropriate treatment
- (6) Absence of inflammatory infiltrates in a biopsy does not exclude myositis
- (7) Despite their clinical similarities, dermatomyositis and polymyositis are fundamentally different disorders in terms of pathogenesis
- (8) Inclusion body myositis, the most common acquired myopathy over the age of 50 years, is frequently misdiagnosed as polymyositis. Whether it is a true "myositis" remains hotly debated
- (9) Dermatomyositis may be a paraneoplastic disorder, particularly in the elderly
- (10) Long term morbidity and mortality relate to interstitial lung disease, myocardial involvement, and associated malignancy

**Box 2: Classification of the inflammatory myopathies**

- ▶ Idiopathic
  - dermatomyositis (DM)
  - polymyositis (PM)
  - inclusion body myositis (IBM)
- ▶ Associated with connective tissue diseases
  - systemic lupus erythematosus
  - mixed connective tissue disease
  - scleroderma
  - Sjögren's syndrome
  - rheumatoid arthritis
- ▶ Infective
  - viral (Coxsackie, influenza, HIV, HTLV I)
  - parasitic
  - bacterial
  - fungal
- ▶ Miscellaneous
  - eosinophilic myositis
  - associated with vasculitis
  - granulomatous (for example, sarcoid)
  - orbital myositis
  - graft v host disease
  - macrophagic myofasciitis

differing pathogeneses will lead to specific immunomodulatory treatments for each disorder, but that is not so at present and treatment, as for other autoimmune disorders, takes the form of a "blunderbuss" approach to immunosuppression.

DM is a humorally mediated autoimmune disorder. Complement dependent attack leads to destruction of capillaries in muscle and other tissues. In muscle, the resulting microangiopathy leads to the characteristic pathological features of infarction and perifascicular atrophy. Whether it is deposition of circulating immune complexes or the binding of an antibody to an endothelial antigen which triggers this lytic complement pathway is unknown.

PM is caused by a cell mediated immune phenomenon. Autoinvasive CD8+ T cells, recognising an unknown muscle antigen, invade non-necrotic muscle fibres expressing class I major histocompatibility complex antigen (MHC-1) and lead to their destruction.

In IBM, although there is some similarity with the immunocytological findings seen in PM, there is evidence that the fundamental pathological process is different and that at least some of the inflammatory and immune changes seen in IBM may be epiphenomena. Similarities have been drawn between the pathological findings in muscle in IBM and those in the brain in Alzheimer's disease, but again whether these are primary or secondary phenomena has yet to be determined.

The detection of so called myositis specific antibodies in the blood of many patients with DM, PM and, less frequently, IBM raises further questions about immunopathogenesis, although there is no evidence that these antibodies are pathogenic. A consistent finding in all three disorders is expression of MHC-1 antigen (which is not constitutively expressed) on the surface of undamaged muscle fibres, and indeed this may be used as a pointer to the diagnosis of an idiopathic inflammatory myopathy even in the absence of inflammatory infiltrates. Potentially bringing these two observations together, it has recently been shown in an animal model that inducing muscle fibre surface expression of MHC

1 is alone sufficient to trigger an inflammatory myopathy, although not exactly paralleling PM or DM, and the production of circulating anti-synthetase antibodies.

Clearly, we still have a great deal to learn about the afferent and efferent limbs of the immune process in each of these disorders, and until we do so there must be uncertainty as to the best approach to classification, never mind specific treatment, and there will be continuing use of unsatisfactory terms such as "overlap syndrome".

**CLINICAL FEATURES**

Many inherited myopathies (for example, the muscular dystrophies) are characterised by highly selective involvement of specific muscles, with physically adjacent muscles showing notably different degrees of involvement. Thus, in facioscapulothoracic muscular dystrophy the proximal upper limb wasting and weakness affects the periscapular and humeral (that is, biceps and triceps) muscles, but spares deltoid. There may even be differential involvement within a muscle, so that in several limb-girdle muscular dystrophies one may see areas of both atrophy and hypertrophy within quadriceps. This selectivity, which is a powerful diagnostic tool for the appropriately experienced clinician, is **not** a feature of DM or PM, but is evident in many cases of IBM.

In DM and PM, as in so many acquired myopathies (for example, endocrine and drug induced myopathies), the characteristic feature is generalised proximal muscle wasting and weakness, with the pelvic girdle musculature nearly always being more severely affected than the shoulder girdle muscles (presentation with shoulder girdle weakness is unusual). The typical symptoms include difficulty climbing stairs and rising from a low chair, and difficulty with tasks at and above shoulder height such as self grooming and lifting objects onto shelves. Distal weakness is a late feature and is never as severe as proximal weakness.

In contrast, IBM often shows remarkably selective muscle involvement, with the most characteristic pattern being wasting and weakness of quadriceps (and it is almost certainly the

most common cause of what used to be called “isolated quadriceps myopathy”) and of the long finger flexors. The clinical consequences are falling, caused by the knees giving way, and weakness of grip. In other words, the most fundamental functions of the lower and upper limbs, respectively, are compromised and the disease can cause profound functional disability. We have yet to find satisfactory mechanical aids or other approaches to help with these problems.

In addition to these general observations about the pattern of muscle involvement, each disease also has additional clinical characteristics and associations.

### Dermatomyositis

DM can affect all ages but the disease in children differs somewhat from that in adults; general misery rather than obvious weakness may be the presenting feature, subcutaneous calcification is more common, the face may be flushed without the more specific characteristics of the rash seen in adults, and the bowel may be involved. Associated malignancy in childhood is rare.

In adults the disease usually presents subacutely with symptoms evolving over several weeks, but less commonly the onset can be very acute with widespread muscle and subcutaneous oedema. Patients with severe disease may develop respiratory failure. Dysphagia, with risk of aspiration, is also common in severe disease.

About 20% of cases, more in the older population, are associated with an underlying malignancy and, as with other paraneoplastic disorders, the neoplasm may not reveal itself until some considerable time (possibly 2–3 years) after first presentation. Unlike, for example, Lambert-Eaton myasthenic syndrome, there is not a close association with one particular site or type of tumour.

Skin rash is evident in most patients and is often the first symptom. It may be absent throughout (dermatomyositis sine dermatitis), the diagnosis then resting on the characteristic muscle biopsy findings in DM, be fleeting and rather non-specific (for example, facial or chest erythema), or be difficult to see in dark skinned individuals (and note that the incidence of DM is higher in those of Afro-Caribbean origin). Dermatologists may see DM without apparent muscle weakness (dermatomyositis sine myositis) but in most of those patients muscle biopsy will show characteristic abnormalities.

The rash has many similarities with that seen in systemic lupus erythematosus, and indeed there are pathological features in common including the presence of undulating tubules in capillary endothelial cells. Both show photosensitivity. The typical cutaneous features of DM include erythema over the light exposed cheeks (malar distribution), upper anterior chest (V sign), upper posterior chest (shawl sign), and knuckles. The eyelids may be oedematous and show purple (heliotrope) discolouration, but this is a less constant feature than the less specific erythema and the hand signs. As well as erythema there may be a scaly eruption (Gottron’s sign) over the knuckles, but the phalanges are spared. Dilated capillaries may be seen at the base of the fingernails. A dry, cracked, appearance to the hands is referred to as “mechanic’s hands”; it is often, but not invariably, associated with the presence of anti-synthetase antibodies, including anti-Jo-1.

Interstitial lung disease is seen in about 10%, and is occasionally the presenting problem. Here there is a strong association with the presence of anti-synthetase antibodies, particularly anti-Jo-1. It may potentially be confused with methotrexate induced pneumonitis when that drug is used to

### Box 3: Diseases commonly misdiagnosed as polymyositis

- ▶ Inclusion body myositis
- ▶ Dermatomyositis sine dermatitis
- ▶ Muscular dystrophy
  - limb-girdle muscular dystrophy type 2B (dysferlinopathy)
  - Becker (especially when adult onset)
- ▶ Endocrinopathy
- ▶ Drug induced myopathy
- ▶ Metabolic myopathies
  - acid maltase deficiency
  - McArdle’s deficiency (myophosphorylase deficiency)
- ▶ Neurogenic disorders
  - late onset spinal muscular atrophy
  - motor neurone disease
- ▶ “Fatigue” syndromes

treat the myositis. Myocarditis and conduction abnormalities may be seen, particularly in severe acute disease. Morbidity and mortality in DM relate mainly to interstitial lung disease, myocardial involvement, and the complications of respiratory failure secondary to respiratory muscle weakness.

### Polymyositis

Evolution of weakness is slower than in DM, typically over months, but generally faster than in IBM. Dysphagia and facial weakness are uncommon. It is a disease of adult life. It is uncertain whether PM is associated with malignancy, but if it is the link is less strong than for DM, and on current evidence extensive searching for an underlying malignancy is not justified. The uncertainty is because earlier studies used obsolete criteria to distinguish between PM and DM.

PM is never associated with the cutaneous features of DM. As in DM, interstitial lung disease is associated with anti-Jo-1 and other myositis specific antibodies. Myocardial involvement may occur.

“Pure” PM is rare, but as noted below PM may be associated with other manifestations of connective tissue disease. A diagnosis of PM is frequently made in error (box 3). “Treatment resistant” PM is usually the result of an incorrect diagnosis, most often IBM, and indeed many patients with IBM have finally been correctly diagnosed only after failure to respond to immunosuppression. Failure to diagnose IBM at the outset is typically due to not appreciating the specific pattern of muscle weakness, in particular missing finger flexion weakness, and failing to appreciate the specific pathological features, notably rimmed vacuoles and filamentous inclusions. Muscular dystrophy may be mistaken for PM, most often when the duration of symptoms appears to be short. The pattern of weakness may be very helpful in making a distinction. Secondary inflammatory infiltrates may cause pathological confusion, especially in dysferlinopathy and facioscapulo-humeral muscular dystrophy. In endocrine myopathies other features of the endocrinopathy are usually evident. Statin induced myopathy is increasingly common with the wider use of these drugs. Acid maltase deficiency is frequently initially misdiagnosed as a limb-girdle muscular dystrophy or PM, unless the characteristic early involvement of the diaphragm is present. McArdle’s disease, especially if fixed proximal weakness is present and a clear history of exercised induced exacerbation is not obtained, may be misdiagnosed as PM. Neurogenic disorders may cause confusion if it is not appreciated that active denervation may be accompanied by elevation

of the serum creatine kinase (SCK) and that neurophysiological findings can be confusing.

Finally, the diagnosis of PM is often wrongly made in the rather common situation of a patient with pain, symptomatic but not objective weakness, and modest elevation of the SCK. Muscle biopsy may show minor “abnormalities” which are wrongly taken to confirm the diagnosis of PM. Steroids may offer a brief honeymoon period of improvement. Looking at such patients more carefully, one notes that their pain is not entirely in the muscles, but also affects their joints and sometimes their skin and bones. What they describe as weakness is more a difficulty in sustaining effort. Initial examination may suggest weakness, but with encouragement and functional tests such as rising from a squat it becomes apparent that there is no true weakness. Most laboratories quote an upper normal concentration of SCK that is too low. Values are higher in men than women, and in blacks than whites. A normal male undertaking modest physical activity may have concentrations as high as 600 IU/l. Somebody undertaking more vigorous exercise, and particularly if black, may have values up to 1000 IU/l. The difficulty, of course, is knowing whether a concentration of, say, 450 IU/l in somebody complaining of muscle pain is relevant or not. Patients with this type of problem should never be put on steroids without a muscle biopsy. But they are, and when their symptoms continue and they then have a biopsy it may be impossible to interpret the findings. The correct diagnosis in this rather common group of patients may prove to be elusive. Rheumatologists send them to neurologists with a diagnosis of ?polymyositis, and they get sent back with a label of polymyalgia-like syndrome, ?fibromyalgia, or chronic fatigue syndrome.

#### Inclusion body myositis

This is the most common acquired myopathy in those over 50 years of age. It is substantially more common in men, an unusual feature for an autoimmune disease and another factor that has cast some doubt as to whether it is a true primary inflammatory myopathy. Infrequently, it can present as early as the third decade. Familial instances have been recorded. It is more correctly designated as sporadic IBM to distinguish it from the much rarer inherited IBM. This includes dominant and recessive forms, which share clinical and pathological features with sporadic IBM, with the notable exception of absence of inflammatory infiltrates.

The major clinical features of IBM have already been discussed, but it merits repetition to emphasise that the presence of distal weakness that is as severe or more pronounced than the proximal weakness in the same limb is highly characteristic. This is usually most evident for the finger flexors, but ankle dorsiflexion weakness may also be pronounced. Another feature of IBM, but not PM or DM, is asymmetric muscle involvement, sometimes pronounced. Mild facial weakness may be seen even when limb weakness is relatively mild (rare in DM and PM), and dysphagia can be an early or late feature.

The rate of progression is typically slower than in PM. Elderly patients frequently cannot easily date the onset of the problem, as they attribute early symptoms to the normal effects of aging. Substantial quadriceps wasting and weakness is frequently evident on first presentation. A major practical problem is falling caused by an inability to lock the knees.

Myositis specific antibodies are much less frequent in IBM compared with DM and PM. Similarly, associated conditions are less frequent, but there are reports of IBM in association with Sjögren’s syndrome, hepatitis C, HTLV-1 infection, and sarcoidosis.

#### Overlap/associated syndromes

Rather than trying to define specific associations (“splitting”), on the basis of our current somewhat limited knowledge, it is perhaps best to simply note that patients with myositis may also be found to have features of other connective tissue disorders (“lumping”). Many of these associations have been described above. DM may be associated with features of scleroderma (often with circulating anti-PM-Scl antibodies) and mixed connective tissue disease. PM is associated with many systemic autoimmune diseases and indeed isolated PM is rare. DM and PM may be associated with non-specific symptoms such as fever and arthralgia, and with Raynaud’s phenomenon. These various phenomena, together with interstitial lung disease, when associated with anti-synthetase antibodies, form the main components of the *anti-synthetase syndrome*. In such patients, the myositic component may be slight and initially overlooked. Finally, to avoid diagnostic confusion, it is worth noting that DM is often associated with the presence of anti-nuclear antibodies (ANA), often at substantial titre, but without other clinical features or specific immunological findings associated with SLE. On the other hand, patients with SLE may have an associated myositis.

#### DIAGNOSIS

Skilled clinical assessment, taking into account all of the factors already discussed, is arguably the most powerful diagnostic tool, but laboratory confirmation of the diagnosis is required in most cases. The “gold standard” is muscle biopsy. Electromyography, estimation of SCK, and detection of myositis specific antibodies may be helpful. Arguably, a patient with all of the classical clinical features of DM, elevation of the SCK, and typical neurophysiological changes does not need a confirmatory muscle biopsy, but overall few cases of suspected myositis should escape biopsy. If management difficulties arise, there is often regret if a biopsy was not performed before initiation of treatment.

#### Serum creatine kinase

Despite its lack of specificity this is an extremely useful test in both diagnosis and management. In the vast majority of patients with DM or PM the concentration is elevated, typically to several thousand IU/l. It tends to be higher in those with acute onset and substantial weakness, and lower in those with more chronic disease, but there is considerable variability. For unexplained reasons, the SCK occasionally remains stubbornly normal. Most patients with IBM have an increased SCK, but typically rather lower than in DM and PM, often around 1000 IU/l. In all of these diseases there may be substantial fluctuation from day to day, even without treatment.

#### Electromyography

Electromyography typically shows spontaneous “irritative” activity (fibrillation potentials and positive sharp waves) and a myopathic pattern of motor unit potentials. In IBM “neurogenic” changes in the form of large amplitude long duration motor unit potentials are often seen.

#### Muscle biopsy

Some care is needed in selecting an appropriate muscle for biopsy. The usual choice, largely because of convenience and familiarity with normal findings, is between deltoid and quadriceps (vastus lateralis). The ideal muscle to biopsy is one that is moderately weak. A very weak atrophic muscle may



**Table 1** Major muscle biopsy findings

Pathological feature	Dermatomyositis	Polymyositis	Inclusion body myositis
Inflammatory infiltrates	<b>Perivascular</b>	Endomysial	Endomysial
T cells > B cells	–	+	+
B cells > T cells	+	–	–
Partial invasion of fibres	–	++	++
Microinfarcts	++	–	–
Scattered necrotic fibres	–	+	+
Perifascicular atrophy	++	–	–
Zonal myofibrillar loss	+	–	–
Rimmed vacuoles	–	–	++
1° capillary loss	+	–	–
1.5 nm filaments	–	–	++
MHC-1 expression	+	++	++

Particularly important distinguishing features are emphasised either in bold or with ++.

simply show end stage changes (fibrosis and fatty replacement) of no diagnostic value. This can be a particular problem in IBM when the quadriceps may already be very wasted at presentation and deltoid may show no weakness. Deltoid may still show typical pathological changes, but if not and diagnostic doubt remains then another muscle may need to be sampled.

The key issues for the interpretation of muscle biopsy findings are appropriate sample handling and processing, and an experienced assessor. At present, in the UK, there is inadequate training of pathologists in the field of myology. In addition, except in specialist centres, the small throughput of samples adds little to their already limited experience. The combination of a clinician and a pathologist, both with little interest or experience in neuromuscular disease, is a common reason for misdiagnosis.

The major pathological features in DM, PM, and IBM are summarised in table 1.

### Antibodies

These are of limited value in diagnosis and management. The presence of anti-Jo-1 antibody might alert one to the possibility of the development of interstitial lung disease, but that possibility should in any case be considered and can occur in the absence of detectable antibody. Anti-PM-Scl may indicate the possibility of the development of sclerodermatous changes, and is also associated with interstitial lung disease. Anti-SS-A/Ro antibodies are associated with Sjögren's syndrome.

### MANAGEMENT

DM and PM will be considered together, IBM separately. With respect to drug treatment, and also to some extent to general management issues, it must be reiterated that there is little guidance from the literature in the form of randomised controlled trials and that much of what is presented here is based on personal experience and "expert opinion".

A few general, but often neglected, principles apply to the management of all of these disorders. Exercise is important, not only to maintain whatever residual muscle strength there is, but also to help muscle recover following suppression of the inflammatory process. In addition, both active and passive exercise can reduce the risk of the development of contractures. Thus, the advice of a suitably experienced physiotherapist is required. Depending on the severity and pattern of muscle weakness, the patient may also need the services of an occupational therapist and orthotist. These are major issues in IBM, in which the disease is going to progress relentlessly

with time. Nutrition is important. Inadequate calorie intake will lead to catabolism and further loss of muscle. This is a particularly important issue in acute DM associated with dysphagia, when tube feeding may be required, and in IBM associated with dysphagia.

### Dermatomyositis and polymyositis

Although their drug management will be considered together, there are two issues specific to the management of DM. Firstly, except in children, the possibility of an associated malignancy must be excluded, particularly in the older patient and those with a higher risk of malignancy (for example, smoker, strong family history, other predisposing illness). Where appropriate, examination should include breast, vaginal, and rectal examination. Imaging should include the chest, abdomen, and pelvis. More detailed investigations may be suggested by the history—for example, colonoscopy in somebody with altered bowel habit. Reassessment is necessary for 1–2 years. Secondly, although the skin rash is likely to respond to systemic immunosuppressant therapy, there are situations when topical treatment may also be of value—for example, for a severe local skin eruption. Furthermore, the rash is photosensitive and a sun blocking cream can be very effective in reducing cutaneous manifestations.

Corticosteroids are the mainstay of treatment. Unanswered questions relate to the specific preparation and dosage regimens, the selection, use, and timing of introduction of other immunosuppressant drugs ("steroid sparing agents"), and the place for intravenous immunoglobulin treatment.

### Corticosteroids

The vast majority of patients respond to steroids. Failure to respond is most often caused by inadequate initial dosage or duration of treatment, less often to lack of compliance because of worry about side effects. A few patients appear to be truly resistant, but respond to other immunosuppressant regimens. Experience suggests that early aggressive treatment tends to be associated with a faster response and better outcome, so all but the most indolent cases are given intravenous methylprednisolone 500 mg daily for five days, followed by oral prednisolone 1 mg/kg body weight per day, given as a single morning dose. Once the SCK has returned to normal and the patient is improving, the dosage is reduced by 5 mg on alternate days, so that after 1–2 months the patient will be on 1 mg/kg body weight on alternate days. Thereafter, the dose is slowly reduced, depending on clinical response and SCK (see below), to determine the minimal maintenance dose.

Open studies have suggested that other steroid regimens might offer a better benefit/side effect ratio, but none has been

proven in an appropriate randomised controlled trial. These have included pulsed high dose oral and intravenous regimens, and the use of dexamethasone rather than prednisolone.

Osteoporosis prophylaxis (we use calcium, vitamin D, and weekly alendronate) should be used from the outset, and a bone density scan performed as a baseline and thereafter at intervals as long as the patient remains on steroids.

### Immunosuppressants

There is enough evidence from the literature and personal experience to leave no doubt that such drugs can be effective. There is currently inadequate data to suggest that any one drug is superior to another, and choice is largely determined by personal experience, often from using the drug to treat other diseases. Thus, rheumatologists and dermatologists tend to use methotrexate (up to 30 mg weekly), as they have experience of its use in arthritis and psoriasis respectively, whereas many neurologists favour azathioprine (2.5 mg/kg body weight per day), having gained experience of its use in myasthenia gravis and immune neuropathies. Methotrexate can cause a pneumonitis, and possibly this could be confused with the interstitial lung disease associated with myositis. Cyclosporin (up to 5 mg/kg body weight per day) has been advocated for use in childhood DM, but is also used in the adult form of the disease. Mycophenolate mofetil (2 g daily) is currently in vogue. Cyclophosphamide has been given as intravenous pulses (up to 1 g/m<sup>2</sup> body surface area) and as oral treatment (up to 2 mg/kg body weight per day). There is some evidence to suggest that it is particularly helpful in the treatment of associated interstitial lung disease.

A further question relates to the timing of the introduction of these drugs. It is often suggested that they be used if the patient fails to respond adequately to prednisolone, has serious side effects from prednisolone, or the required maintenance dose of steroids is unacceptably high. The practical problem is that it may take many months, possibly of continuing deterioration, before the patient can be identified as falling into one of these categories. The various immunosuppressant drugs listed above are all slower to act than prednisolone. Azathioprine is probably the slowest—experience from myasthenia gravis shows that it takes 9–12 months to become effective. All of the other drugs probably work faster than this, but even so probably take many months to exert their maximal effect. Because of these issues, and paralleling our experience in myasthenia gravis, it is reasonable to start an immunosuppressant drug (our choice is azathioprine) at the same time as prednisolone, in the expectation that it will eventually allow a lower maintenance dose of prednisolone. This hypothesis has yet to be proven in a randomised controlled trial.

### Intravenous immunoglobulin

There have been enough studies to conclude that intravenous immunoglobulin is effective in both DM and PM, but not sufficient data to define its exact position versus steroids and immunosuppressant drugs. At present its use is probably best reserved for those with disease that is resistant to steroid and immunosuppressant drug treatment.

### Monitoring response

This involves elements of art as well as science. The aim is to taper the prednisolone to find the minimum dose required to hold the disease in remission, which in some patients on an

additional immunosuppressant drug may be zero. Although it is often emphasised that one should treat the patient, not the blood test, a rising SCK is a cause for concern and may herald recurrence. On the other hand, recurrence, with increasing weakness, can occur with no increase in SCK. Steroid induced myopathy is a theoretical concern, but appears to be rare on an alternate day dosage regime. As with many other autoimmune diseases, the disease may be held in pharmacological remission, but “cure” is more elusive. In our experience, long term drug-free remission is more common in DM than PM.

### Inclusion body myositis

Most patients with typical IBM do not have a useful response to steroids, immunosuppressant drugs, or intravenous immunoglobulin. If after informed discussion they are keen to attempt drug treatment, then I would use an 18–24 month trial of prednisolone and azathioprine (or methotrexate) as outlined above. The prednisolone would be tapered until the SCK started to rise. Treatment would only continue if there was unequivocal benefit. The potential side effects should not be underestimated and in the last year we have seen death from cytomegalovirus pneumonia, and salmonella infection in an artificial hip.

Atypical cases make me more inclined to propose a trial of treatment, but as yet the evidence base for doing this is lacking. Features might include onset in early adult life, pronounced inflammatory infiltrates on biopsy, exceptionally high SCK, and associated immune disorders.

### SUMMARY

The most common inflammatory myopathies are dermatomyositis, polymyositis (which rarely occurs as an isolated entity, more often associated with other features of connective tissue disease), and inclusion body myositis. They each present diagnostic and therapeutic challenges and are best managed in a unit with particular interest and experience in these disorders. Most patients require long term specialist supervision. Multicentre trials are desperately required to determine the best approaches to drug treatment. Non-drug aspects of management are very important, but frequently neglected.

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- Discusses the similarities between the pathological findings in IBM and those in Alzheimer's disease. Not everybody agrees with the proposed pathological mechanisms.
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- ▶ **A very interesting paper, in which upregulation of MHC 1 in mice was shown to induce an inflammatory myopathy and the production of myositis specific antibodies. Not yet clear of the significance of this for idiopathic inflammatory myopathies in man.**
- 10 **Peng A, Koffman BM, Malley JD, et al.** Disease progression in sporadic inclusion body myositis: observations in 78 patients. *Neurology* 2000;**55**:296–8.
- ▶ **Useful natural history study. Important when considering therapeutic trials for this disorder.**

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