The management of myasthenia gravis

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Practical Neurology, 2005, 5, 18–27
INTRODUCTION

This is a pragmatic guide to the management of myasthenia gravis. We will assume the diagnosis is correct (Hilton-Jones 2002) and the reader understands the pathogenesis of the disorder (Newsom-Davis & Beeson 2001), and we will deal only with pharmacological and surgical management. The mode of action of different pharmacological treatments will not be discussed, but their adverse effects will be.

At the time of diagnosis, time must be set aside to adequately explain to the patient the nature of the disease and its management. The treatment strategy, the likely time-course of response, the long-term prognosis, potential complications of therapy, and the undoubted uncertainties about some areas of ‘best practice’ must all be discussed – this is clearly more difficult if the clinician sees relatively few cases of myasthenia, but is nonetheless crucial in optimizing patient adherence to therapy, and so outcome. Many countries have a patient support group – e.g. the Myasthenia Gravis Association in the UK (http://www.mgauk.org/) and the Myasthenia Gravis Foundation of Amer-
ica in the USA (http://www.myasthenia.org/) - which provides literature (typically less sensational than some of the information on the internet); this is a useful starting point for patients and their primary care physician on what is often going to be a very long journey.

PRINCIPLES OF MANAGEMENT
The management of myasthenia gravis confined to the extraocular muscles (ocular myasthenia) differs somewhat from that of generalized myasthenia (and later the two conditions will be discussed separately). However, the principles of management are similar, and for both there are three fundamental approaches:

- Symptomatic treatment;
- Immunomodulatory therapy;
- Immunosuppressant therapy.

Symptomatic treatment
Anticholinesterases
Most patients will respond, often quite dramatically, to an anticholinesterase, but in only a very small proportion will this be adequate long-term therapy. It must be emphasized to the patient that once the disease has been brought under control by other treatments, then it should be possible to withdraw the anticholinesterase. Not making this clear at the outset partly explains why some patients have such difficulty withdrawing their anticholinesterase at a later date when they are in remission. One can understand their reluctance to withdraw a drug that, sometimes after months of uncertainty about diagnosis often tinged with suggestions of non-organicity, had dramatically improved their weakness. The drug may also have a non-specific stimulatory effect that patients particularly notice if the drug is suddenly withdrawn, so gradual withdrawal over several weeks is the best strategy.

There is no reason to use any anticholinesterase other than pyridostigmine. Although a ‘retard’ formulation is now widely available, and has been much talked about on the web, there have been no trials demonstrating its superiority over the standard preparation. There is also some anxiety, based on theory rather than experience, that the longer duration of action and thus accumulation may precipitate cholinergic crisis. If the patient is struggling to adequately control symptoms with pyridostigmine, then it is probably time to move on to other therapeutic strategies.

Pyridostigmine should be introduced slowly (Box 1) to reduce the risk of adverse effects, which are essentially restricted to smooth muscle stimulation causing abdominal cramping, increased flatus, diarrhoea and, less frequently, urinary frequency and incontinence. If abdominal symptoms develop, they can be treated by propantheline - 15 mg tds, or 15 mg before each dose of pyridostigmine, or once daily, whatever is required for symptomatic control. For those who have difficulty swallowing, the pyridostigmine tablets can be crushed.

Cholinergic crisis should be largely confined to the history books – it was caused by excessive doses of anticholinesterases, which were not that uncommon when no other treatment options were available. It is still very occasionally seen as a result of physician or patient ignorance. If the maximum dose of pyridostigmine is confined to six tablets (= 360 mg) daily in adults, our experience is that cholinergic crisis never occurs.

Extra-ocular muscle surgery
Rarely, ptosis may be the only significant persisting symptom of myasthenia gravis, in which case ptosis-correction surgery may be a more attractive proposition than immunosuppressant therapy if pyridostigmine alone isn’t adequate. In our experience, few patients tolerate ptosis-bars fitted to their glasses. Similarly, some patients may be left with isolated diplopia due to fixed weakness of one or more extra-ocular muscles and the use of a prism or surgical correction may be appropriate (and preferable to the introduction of a steroid sparing immunosuppressant drug in those with pure ocular myasthenia).

**BOX 1 ANTICHOLINESTERASE (PYRIDOSTIGMINE) THERAPY**
- Pyridostigmine tablets are 60 mg.
- They are scored and so can be divided into quarters (15 mg).
- Start with 15 mg qds.
- Increase (if necessary) after 2 days to 30 mg qds.
- Increase (if necessary) after 2 days to 60 mg qds.
- Maximum dose 360 mg daily.
- Usually 90 mg qds.
- But some patients may benefit from 60 mg x 6 daily.
- Add propantheline if gastrointestinal adverse effects.
Any drug which had been introduced shortly before a relapse should be considered a possible cause. In practice, \( \beta \)-blockers are probably the most common culprit.

**Immunomodulatory therapy**

We use this term to describe those treatments (intravenous immunoglobulin, plasma exchange, and thymectomy) that alter the body's immune system without frankly suppressing it. Intravenous immunoglobulin (IVIg) or plasma exchange (PE) are used as quick acting but temporary measures to improve function whilst waiting for other therapies to take effect, whereas thymectomy is intended to offer long-term benefit. IVIg and PE may lead to improved function within days of starting treatment, but their beneficial effect lasts no longer than 6–8 weeks.

IVIg and PE

Both of these (expensive) treatments are widely used despite a paucity of evidence of benefit. It is perhaps easiest to summarise the situation by quoting the recent Cochrane review:

‘One randomised controlled trial did not show a significant difference between intravenous immunoglobulin and plasma exchange for treatment of severe exacerbations of myasthenia gravis. There is no evidence from randomised controlled trials to determine whether intravenous immunoglobulin for moderate or severe myasthenia gravis improves functional outcome or has a sparing effect on steroid dosage, nor is there sufficient evidence to favour intravenous immunoglobulin over steroids in moderate exacerbations. Further randomised controlled trials are needed’ (Gajdos et al. 2003).

Other smaller trials and anecdotal reports suggest there is no significant difference between the apparent benefits of IVIg and PE, so it is appropriate to consider them together.

Of course, the lack of trials does not necessarily mean that the treatments are ineffective and indeed few experienced observers doubt their efficacy. What is unanswered is whether they are superior (in terms of clinical benefit and cost) to other treatment options, such as simply increasing the dose of steroids in a myasthenic relapse. Our practice, paralleled by many others, is to use IVIg in preference to PE except when an individual patient has been intolerant of IVIg, or has previously responded better to PE than IVIg. IVIg is simpler to administer and can be used in the presence of systemic infection, the latter point being particularly important as sepsis is often a trigger for myasthenic crisis.

The main indications for IVIg/PE are:

- newly diagnosed patient with substantial weakness requiring a quick therapeutic effect;
- myasthenic relapse/crisis in a previously diagnosed patient.

In the newly diagnosed patient who is clearly going to need more than pyridostigmine (i.e. inadequate benefit after increasing up to 6 \times 60 mg tablets a day in 2–3 weeks), the main treatment options (see below) are thymectomy or immunosuppression. IVIg may improve the patient prior to thymectomy – and reduce their perioperative risk. Patients starting prednisolone, even when introduced gradually, may show an initial deterioration of their myasthenic symptoms in the first few weeks of therapy. Furthermore, the full response to prednisolone may take many months. IVIg is given in the hope of giving early improvement in function, carrying the patient through until the prednisolone starts to become effective, and lessening the likelihood of any initial prednisolone-induced deterioration. Whilst this practice is now quite widely established, the need for a formal trial is readily apparent. IVIg is expensive, not only in terms of the product itself, but also the need to admit the patient to hospital.

Deterioration in a patient whose myasthenia was previously controlled (a relapse, or if very marked referred to as myasthenic crisis) may be:

- spontaneous (which is not that uncommon and reflects the spontaneous fluctuation seen in many autoimmune disorders);
- induced by ‘stress’ (e.g. infection, surgery, emotional issues, hormonal factors);
- caused by reduction or withdrawal of previously effective therapy;
- precipitated by recent introduction of a drug that interferes with neuromuscular transmission. Although many drugs are known to do this (Newsom-Davis & Beeson 2001), lists are not exhaustive and any drug which had been introduced shortly before a relapse should be considered a possible cause. In practice, \( \beta \)-blockers are probably the most common culprit.

Any underlying cause must be treated or removed (e.g. infection) and immunosup-
pressive therapy may need to be increased, particularly if the relapse was due to reduction of therapy. Within the limitations already noted, IVIg is widely used as a short-term measure to improve function whilst waiting for any infection, for example, to settle, and any increased immunosuppressive therapy to become effective.

The main practical problem with IVIg is aseptic meningitis. If patients develop typical symptoms we do not perform a lumbar puncture, but just stop the IVIg and treat with analgesics and the problem usually settles within 3–5 days. This reaction may be product-specific and we have sometimes, with the patient’s consent, successfully used an alternative product without reaction on subsequent occasions. Prior to first use of IVIg many believe the patient should have a blood test to exclude IgA deficiency (patients with IgA deficiency produce antibodies against the IgA in the IVIg). In all cases the patient must be counselled about the potential hazards from a blood-donor-derived product.

Thymectomy

Few doubt that thymectomy works for some people – but which ones? Despite having been used widely for over 50 years the definitive trial is still now only in the planning stages – that it is going to happen at all is largely the result of a recent review (Gronseth & Barohn 2000). On the available, not very good, evidence, including personal experience, our current practice is as follows.

Most patients with thymoma identified on chest MRI or CT undergo thymectomy, all of ours being performed via the sternal split approach. An exception is the very elderly patient in whom serial scanning to monitor progress may be more appropriate. The patients are advised that their myasthenia is very unlikely to respond to thymectomy, but surgery is required to treat the thymoma, because there is significant morbidity associated with local and intrathoracic spread of the tumour. As an aside, it must be noted that there are recent data concerning tumour stage and histological subtype and the need for adjuvant therapies (radiotherapy and chemotherapy) that any department conducting thymectomy for tumour must be aware of (Chen et al. 2002). MRI and CT are probably about equal in detecting thymoma and the choice is up to local availability and radiologist preference. Occasionally there may be uncertainty as to whether or not a thymoma is present, in which case the scan should be repeated after a year. Scans are not used to diagnose hyperplasia, which is a pathological diagnosis (Fig. 1).

For patients without thymoma who fulfill the following criteria, we advise that thymectomy gives a 25% chance of remission, a 50% chance of improvement but still having to take long-term medication, and a 25% chance of no benefit:

- generalized (rather than purely ocular) myasthenia gravis;
- age under 45 years;
- anti-acetylcholine receptor antibody positive;
- within 1–2 years of onset.

Benefit may sometimes be apparent within weeks of thymectomy, but can be delayed for up to two years. We recognize that it is very difficult to determine whether any benefit accrues from the surgery, or from other changes in therapy, or indeed because of spontaneous fluctuation of the disease, which is well documented, hence our support for the proposed international trial of thymectomy.

We do not advise thymectomy for older patients, in whom the thymus is typically atrophic, or for patients who are anti-acetylcholine receptor antibody negative (no antibody negative cases have been reported with true thymic hyperplasia), although we are aware that some recognized authorities do. There is

Figure 1 Thymic hyperplasia: CD22 anti-B-cell antibody stained section of a hyperplastic thymus showing two germinal centres (arrows) surrounded by B-lymphocytes.
as yet inadequate experience in patients who are anti-MuSK antibody positive to make useful comment.

**Immunosuppressant therapy**

Prednisolone is the mainstay of immunosuppressive therapy. Other immunosuppressant drugs (e.g., azathioprine, methotrexate, ciclosporin, mycophenolate mofetil) are generally considered ‘second-line’ or ‘steroid-sparing’, but occasionally they are used alone (e.g., when a patient is intolerant of, or refuses, steroids). With one exception — azathioprine — there is a dearth of randomised trials, and practice is based on personal experience and prejudice.

Pregnancy merits comment. There is no evidence that either prednisolone or azathioprine are teratogenic, but there have been reports of premature birth and low birth-weight following exposure to azathioprine, particularly in combination with steroids. All the other immunosuppressant drugs are relatively contraindicated in pregnancy, mainly because of lack of evidence rather than certain evidence of problems. Methotrexate is also contraindicated in males who wish to become fathers because it can lower the sperm count; whilst there is no certain evidence of teratogenesis it is recommended that males stop taking the drug at least three months before attempted conception. But it must be emphasized that the contraindication in pregnancy is relative — the risks need to be balanced against the benefits. Additionally, maternal transfer of antibodies is more likely to occur in inadequately treated myasthenia. The key is informed discussion.

**Prednisolone**

The symptoms of myasthenia gravis may undoubtedly deteriorate following introduction of prednisolone but how much this is due to the drug, how much to the mode of introduction (e.g., starting at a high dose rather than gradually increasing), and how much to unrelated causes such as the natural history of the disease after first presentation, is unclear. Few people advocate the use of high-dose oral or intravenous methylprednisolone as used in multiple sclerosis (e.g., 2.5 g over 2–5 days) — a few small studies have given contradictory results with either evidence of benefit or deterioration (there may be scope for further study, perhaps combined with IVIg, of the potential benefit for earlier remission).

When surveying the Myasthenia Centres planning to take part in the international thymectomy trial, about 80% used alternate-day prednisolone. The evidence in adults that adverse effects are fewer than when using daily steroids is dubious but that is still our practice. Early fluctuation (i.e., worse on the non-steroid day) seems to be a good prognostic feature of steroid responsiveness and usually settles with time as strength improves. An occasional exception to persevering with an alternateday regime is for those patients with diabetes whose diabetic control proves difficult because of daily fluctuations. We always introduce prednisolone gradually (Box 2). Steroids take weeks to months to work and there is no good reason to

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**BOX 2 IMMUNOSUPPRESSION WITH PREDNISOLONE AND AZATHIOPRINE FOR GENERALIZED MYASTHENIA GRAVIS**

In general, the patient should be admitted for initiation of therapy. Even with gradual introduction of prednisolone there can be rapid deterioration with risk of bulbar and respiratory problems. The introduction of immunosuppression may run concurrently with IVIg/PE (see text).

- **Prednisolone**
  - Use alternate day dosage from the outset.
  - Initial dose 10 mg.
  - Increase by 10 mg every dose until target dose reached or, rarely, symptoms and signs resolve at a lower dose.
  - Target dose = 1.5 mg/kg body weight on alternate days, or 100 mg on alternate days, whichever is the lower.

- **Azathioprine**
  - Target dose = 2.5 mg/kg body weight/day.
  - Use a bd regime because there is a lower risk of gastro-intestinal adverse effects than once daily, e.g., nausea and diarrhoea.
  - Start on 25 mg once daily.
  - Increase by 25 mg daily until on target dose.
  - Check full blood count and liver function every third day until up to target dose, then weekly for one month, then monthly for three months, and then three-monthly.
think that initial high-dose therapy is going to be the better option and there is no doubt that it often leads to initial deterioration. So introduce steroids gradually in all patients, and use IV Ig or PE to get an early response in particularly severe cases.

Patients must be given detailed counselling (including written information) about the potential adverse effects and complications of steroids. These include increased risk of infections, osteoporosis, hypertension, diabetes, cataracts, and peptic ulceration. Often underemphasized problems, which frequently complicate therapy, include mood disturbance (depression, mood swings, psychosis) and insomnia. Many patients are particularly concerned by the prospect of weight gain. In our experience, steroid-myopathy does not develop in patients on alternate day prednisolone, even when used at high dosage. Additional drug therapy to prevent osteoporosis and peptic ulceration are summarized later. Standard ‘Steroid Information Cards’ should of course be issued.

Azathioprine
It has been shown that combining azathioprine with prednisolone lowers the eventual steroid requirement and so reduces steroid-related adverse effects such as weight gain (Palace et al. 1998). However, azathioprine is slow to act and benefit may not appear for 12 months. The drug should therefore be used for at least 24 months at appropriate dose before deeming it ineffective. Our practice is to introduce azathioprine with prednisolone at the outset of treatment in patients with generalized myasthenia (Box 2).

About 10% of patients are intolerant of the drug with symptoms developing shortly after its introduction (notably nausea, vomiting or diarrhoea). Potentially more severe problems are liver and bone marrow dysfunction and, whatever other measures are taken, blood tests (full blood count and liver function) must be performed every three days or so until it is clear there are no adverse reactions. Once patients are on the full dose of azathioprine, the blood tests should be weekly for one month, then monthly for three months, then three-monthly. Macrocystosis, lymphopenia, and mild elevation of bilirubin and transaminases are normal reactions to the drug but may alarm the primary care physician organizing the blood tests unless informed.

Azathioprine is metabolized by the enzyme thiopurine methyltransferase (TPMT). Allelic polymorphisms of the TPMT gene determine enzyme activity. Those patients who lack enzyme activity (about 1 in 300) are bound to develop myelosuppression, which is potentially fatal, with conventional doses of azathioprine. If the assay is available then it is sensible to use it. However, even those with ‘normal’ enzyme activity can develop myelosuppression and hepatitis and so the golden rule must still be to regularly monitor the full blood count and liver function from the outset. Those with high levels of enzyme activity may need higher than standard doses of the drug to achieve the desired effect. One approach is to use a standard target dose (e.g. 2.5 mg/kg body weight/day) and, where there is an inadequate therapeutic response, and no significant lymphopenia or macrocystosis, to increase the dose to 3 mg/kg body weight/day.

Other immunosuppressant drugs
Numerous immunosuppressant drugs other than azathioprine have been used and there is no reason to doubt that they can be effective (Box 3). However, none has yet been subjected to an adequate randomised trial so the benefit to harm ratio is unknown. They probably work more rapidly than azathioprine. We will confine comment to those that are fairly widely used - the order is simply alphabetical. All carry the risk of myelosuppression and hepatitis and regular blood monitoring is required.

Ciclosporin
Ciclosporin is widely used in transplant medicine so there is considerable experience available. At the doses normally used for treating myasthenia, serum level estimation is not required. Hypertension, impaired renal function (watch the serum creatinine) and hypercholesterolaemia are relatively frequent complications. Hirsutes, tremor, peripheral paraesthesiae and cramps are common adverse effects. Methotrexate is probably the most widely used of all second-line immunosuppressant

**BOX 3 OTHER IMMUNOSUPPRESSANTS**

Target doses are given. Full blood count and liver function must be monitored, and in the case of ciclosporin also creatinine.

- Ciclosporin 2.5 mg/kg body weight/day in two divided doses.
- Methotrexate (in an adult) 7.5–20 mg once weekly (+ folate).
- Mycophenolate mofetil 1 g bd.
drugs (at least in rheumatological and dermatological practice), which has the advantage that primary care physicians are familiar with it and have well-established monitoring programmes. It is generally well-tolerated but the potential for pulmonary involvement must be noted (reported predominantly in patients with rheumatoid arthritis on relatively high doses), and for the interaction with aspirin and non-steroidal anti-inflammatory drugs (both of which may increase serum methotrexate levels and thus increase the risk of toxicity). Concomitant use of folic acid reduces adverse effects.

Mycophenolate mofetil has recently received a lot of publicity in the myasthenia patient literature. A randomised trial is planned to start soon. This drug has the advantage of a simple fixed dosage regime (1 g twice daily). There is some evidence, which requires confirmation, that it may act more quickly than the other drugs discussed.

**A PRACTICAL APPROACH**

**Initiation of treatment**

Figures 2 and 3, together with Boxes 1–4, outline the management of ocular and generalised myasthenia gravis, respectively. The management of myasthenia in patients with thymoma is the same, but as noted above the thymoma should be removed in most patients. In all patients having thymectomy, whether for a thymoma or as management of the myasthenia, peri- and postoperative complications will be less if the myasthenia is well-controlled at the time of surgery - IVIg or plasma exchange about a month before surgery may be appropriate (see above).

There are conflicting opinions, within and between different countries, concerning osteoporosis prophylaxis when long-term relatively high-dose steroid therapy is being used. Some advocate bone density scanning and treating only those with an abnormality, others note that steroid-induced osteoporosis can develop within months of starting treatment and therefore bisphosphonates should be introduced from the outset. Some advocate different approaches to high and low risk groups of patients. When available, it would seem most appropriate to follow existing locally agreed guidelines. Box 5 shows our approach. We continue a bisphosphonate and calcium/vitamin D throughout the duration of steroid therapy.

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**Figure 2** Management of ocular myasthenia gravis.

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**Box 4 PREDNISOLONE FOR OCULAR MYASTHENIA GRAVIS**

It can be introduced more slowly than in generalised myasthenia, as an outpatient:

- Use an alternate day dose from the outset
- Maximum dose typically 0.75 mg/kg body weight/alternate days, or 60 mg on alternate days, whichever is lower.
- Initially 5 mg on alternate day for three doses then 10 mg on alternate days for three doses.
- Continue increasing at same rate either until symptoms resolve or target dose is reached.
After remission

Ocular myasthenia often responds within 1-2 months of initiating treatment and the dosage of prednisolone required to achieve remission is usually substantially lower than in generalized myasthenia. A common error is to fail to appreciate that generalized myasthenia may take a long time to enter remission, and anxiety about the relatively high dose of prednisolone may lead to it being reduced too soon.

Once the patient is in remission (which in practice means minimal residual symptoms and signs) the pyridostigmine should be withdrawn gradually over 2-4 weeks. If symptoms and signs return, the patient is not in remission. The prednisolone should then be reduced gradually, trying to determine the minimum dose required to keep the disease under control. In generalized myasthenia gravis a reasonable approach is:

- reduce by 10 mg/month until down to 40 mg on alternate days;
- then reduce by 5 mg/month until down to 20 mg on alternate days;
- then reduce by 1 mg/month.

A slower rate of prednisolone reduction when nearing the previously noted critical dosage should be applied.
In over 90% of patients with generalized myasthenia it should be possible to get them back to normal or near-normal strength, and for them to lead a normal lifestyle. But in most patients requiring long-term immunosuppression some adverse effects are inevitable, although usually tolerable. Don’t use excessive doses of pyridostigmine (i.e. > 360 mg daily). If pyridostigmine does not give adequate control of symptoms other forms of treatment (e.g. thymectomy or immunosuppressant drugs other than azathioprine) should be considered.

Getting myasthenia under control takes time (many months in most cases) – neither the patient nor the doctor should become impatient.

Time spent in discussion with the patient early-on will pay dividends in the long term.

Myasthenia is not a disease to be managed by a different doctor every time the patient comes to clinic – continuity of care is essential.

There are still many unanswered questions to do with the optimum use of thymectomy and immunosuppressant drugs.