

HOW I TREAT MYASTHENIA GRAVIS TAILORING TREATMENT AND EXAMINING THE OPTIONS

Treatment for myasthenia gravis (MG) should be tailored to the individual patient. The following case studies explore different treatment options for MG by looking at the cases of five different patients. Due to the variable presentation of MG, it is important to individualise patient treatment plans for specific needs and symptoms.

How would you progress each patient's care?

Case study 1: Lisa

Presentation

Lisa is a 58-year-old woman, referred for ongoing management of MG. She developed diplopia in her 20s and was diagnosed with MG following a positive Tensilon test. Pyridostigmine 60 mg four times a day and a prednisone dose – currently 12 mg daily in the morning, with previous doses ranging from 9–20 mg daily – were prescribed to control the diplopia.

Examination

On examination, Lisa weighed 104 kg, had thin skin and bruised easily. A mild right medial rectus weakness was observed on alternating cover testing, mild fatigable weakness of deltoid and hip flexors, plus more generalised proximal muscle weakness. Lisa's MGC score was 4 and her MGFA score was 2A.

AChR antibodies were positive; decrement was noted in the trapezius on repetitive nerve stimulation; and CT of the chest showed no thymoma or substantial thymic tissue.



HOW WOULD YOU TREAT?

- ▶ Change prednisone to 20 mg on alternate days, decreasing the overall weekly dose. Some evidence suggests switching to alternate-day corticosteroids could minimise metabolic corticosteroid side effects.¹ However, expert opinion suggests 20 mg on alternate days may be too high a dose for long-term use.² Intolerable corticosteroid side effects are an indication to introduce immunosuppression to reduce corticosteroid maintenance dose.^{3,4}
- ▶ Add mycophenolate mofetil (MMF) 500 mg twice daily orally for an introductory week then increase to 1000 mg twice daily. MMF has not been proven with negative trials but remains a widely used steroid-sparing immunosuppressive medicine in MG. Mycophenolate sodium is an alternative – the recommended dose is 360 mg orally, twice daily (maximum 1080 mg twice daily). Disease-modifying effects may not be observed over a treatment period of less than 12 months. Some patients may experience intolerable dizziness or insomnia and will need to change therapy.^{3,5}
- ▶ Oral azathioprine at 1.5–2.5 mg/kg daily is another option. A randomised trial demonstrated efficacy after a median of 15 months.⁶ For patients in remission or with significant lymphopenia, the dose may be weaned, but relapse is common after complete cessation in patients who remain antibody positive.⁵
- ▶ Weekly oral methotrexate (MTX) may be as effective as MMF, with the same time interval to efficacy, and is much cheaper than MMF. The main side effects are nausea and vomiting. Daily folic acid supplements 1–5 mg (except on the day of MTX) may help with side effects and are recommended for patients taking MTX.^{3,5}

Practice points

- ▶ Corticosteroid dose adjustment often corrects diplopia relapse within weeks.^{3,5}
- ▶ Long-term steroid side effects can be significant, so attempt to minimise the dose used.
- ▶ The addition of a steroid-sparing agent such as mycophenolate often allows complete weaning of corticosteroids, but typically only after 6–12 months.³
- ▶ Seropositive patients on steroid-sparing therapy alone are at greater risk of relapse after ceasing these agents. This often requires the reintroduction of corticosteroids for many patients.

Case study 2: Robyn

Presentation

Robyn is a 23-year-old woman who presented with 6 weeks of fluctuating diplopia, left ptosis and more recently slurred speech, difficulty swallowing, and weakness holding her arms above her head. On examination, there was fatigable ptosis and diplopia within 10 seconds of sustained upgaze and lateral gaze, respectively. She showed intermittent slurred speech and mild shoulder abduction weakness with fatigability (MGC score = 11).

Robyn was diagnosed with generalised MG. AChR antibodies were strongly positive, and CT of the chest showed likely thymic hyperplasia but no discrete masses.

HOW WOULD YOU TREAT?

- ▶ Start regular pyridostigmine and prednisolone escalation. Pyridostigmine is first-line therapy for most patients with mild generalised MG or ocular myasthenia. In patients with MuSK-positive MG, it is less effective and more likely to cause side effects.^{3,5}

A typical pyridostigmine regimen starts with 30 mg orally, three times daily. Depending on response and tolerance, the dose can be adjusted every 4–7 days to a usual maximum of 120 mg 4-hourly through the day, aiming for the lowest effective dose. If the response is inadequate on review at 4–6 weeks, consider adding corticosteroid (see below). Pyridostigmine dose escalation is often limited by side effects, including diarrhoea or muscle cramps – these may be reduced by anticholinergic medication such as propantheline.

Once symptoms improve after introduction of prednisolone, pyridostigmine can be slowly withdrawn over a few weeks. This allows better interpretation of disease modification rather than simply symptom control.⁵

- ▶ Corticosteroid dosing. Steroids may be initiated with oral prednisolone 5 mg daily, increasing by 5 mg every 3 days until a response is seen, up to a maximum of 1 mg/kg (up to 75 mg) daily. Maintain the effective dose for 4–6 weeks, then reduce the daily dose by 5 mg every 2 weeks to 25 mg daily, then more slowly according to response and side effects.⁵

Case continued...

Robyn's symptoms gradually resolved as prednisolone was increased to 30 mg daily. She kept taking this dose for a month before slowly decreasing by 5 mg per month to 15 mg daily (MGC score = 0). Once clinically stable, a robotic thymectomy was performed 6 months after diagnosis. Following surgery, she had an ocular, bulbar and limb relapse (MGC score = 15).

HOW WOULD YOU TREAT?

- ▶ Increase prednisolone dose back to 30 mg daily and give intravenous immunoglobulin 2 g/kg over 3 days. IVIg is an effective bridging treatment while introducing medications such as pyridostigmine or effective immunosuppressants.^{5,7} A rapid response is required when bulbar weakness may limit oral intake, and/or respiratory weakness develops.
- ▶ IVIg efficacy has been studied when given as a bolus of 1–2 g/kg during severe exacerbations of MG and myasthenic crises, and preoperatively before thymectomy;⁸ however, IVIg doses of 1 g/kg are not inferior to 2 g/kg when treating myasthenic crises or severe exacerbations⁸ and pre-thymectomy.⁸ As IVIg therapy may wear off after 4 weeks,³ top-up doses of IVIg at 4 weeks may be necessary because the benefit from a steroid boost may be delayed for 6–8 weeks. Maintenance IVIg doses can range from 0.4–1 g/kg, but the amount per dose should be titrated to the patient's response.

Outcome...

Within a week, Robyn's MGC score was 4. However, over the next 12 months, she experienced bulbar relapses with choking episodes and difficulty swallowing fluids or medication.

HOW WOULD YOU TREAT?

- ▶ Add mycophenolate (MMF, see Case study 1). Side effects include anaemia, leukopenia, gastrointestinal discomfort and diarrhoea.⁵
- ▶ The Therapeutic Goods Administration advises that women of childbearing potential must use two forms of reliable contraception while taking MMF⁹ due to the risk of severe birth defects and miscarriage. If the patient wishes to become pregnant, alternative immunosuppression should be used (see Case study 5).³
- ▶ Administer further courses of IVIg over the next 12 months to treat bulbar relapses.
- ▶ IVIg should be trialled for up to 4 months (induction plus three maintenance cycles) before determining if the patient has responded. If there is no objective benefit, IVIg therapy should be stopped.⁷

Outcome...

Three years after her diagnosis of MG, Robyn was in pharmacological remission (MGC score = 0) and taking prednisolone 5 mg every second day and MMF 1 g twice daily.

Practice points

- ▶ Corticosteroid doses of up to 0.5–1 mg/kg (maximum dose 75 mg daily) may be required to induce symptom remission in patients with generalised MG.⁵
- ▶ Risk of relapse is minimised by maintaining an effective dose of corticosteroids for several weeks once MG symptoms remit, and by a slow corticosteroid taper.
- ▶ Patients undergoing thymectomy may have symptom worsening in the immediate post-operative period. This risk is reduced (but not zero) in patients with optimum disease control before surgery. IVIg can help manage MG symptoms in the post-surgical period.^{10,11}
- ▶ With appropriate education, patients can safely adjust their prednisolone doses according to fluctuations in their MG symptoms.
- ▶ IVIg is an effective bridging treatment while introducing medications such as pyridostigmine or effective immunosuppressants.⁷

Case study 3: Alex

Presentation

Alex is a 68-year-old male with multiple medical comorbidities, including coronary artery disease with previous cardiac stents, obesity (BMI 36), hypertension, glucose intolerance, depression and prostatic hypertrophy. He was referred to an outpatient clinic due to global weakness and shortness of breath on exertion (SOBOE). Extensive cardiac testing by his cardiologist was unrevealing. On examination, he had moderate fatigable upper limb weakness, mild fatigable lower limb weakness, mild neck flexion weakness, and mild facial weakness. His MGC score was 9. His AChR and MuSK antibodies were negative. SFEMG and repetitive stimulation studies of the upper limb and neck musculature results were consistent with a neuromuscular junction disorder. Respiratory function tests showed normal spirometry but reduced mean inspiratory and expiratory pressures, suggesting respiratory muscle weakness. A CT scan of the chest showed normal lung fields and no obvious thymic pathology.

? HOW WOULD YOU TREAT?

- ▶ Start pyridostigmine and low-dose prednisolone in consultation with the patient's cardiologist (see Case studies 1 and 2). Carefully escalate the prednisolone dose (see Case studies 1 and 2). Be aware that pyridostigmine can provoke bradyarrhythmia in some patients, while corticosteroids may adversely affect cardiovascular risk profile, or aggravate heart failure.

Case study continued...

Alex's symptoms remained problematic despite slowly increasing the prednisolone dose up to 50 mg daily. He required hospitalisation to manage lower limb cellulitis associated with worsening hypertension and elevated blood sugars requiring insulin therapy.

? HOW WOULD YOU TREAT?

- ▶ Initiate an induction course of IVIg (2 g/kg) over 5 days. The use of IVIg falls under indication three of the Criteria⁷: the patient has at least moderate MG (MGC score > 4) and two treatments are either ineffective, have intolerable side effects or contra-indicated.^{3,7} PLEX may also be an option if it is available locally with suitable venous access. This treatment is also effective and may have a lower risk of thrombosis given that prior ischaemic heart disease is a risk factor.
- ▶ After the acute infection resolves, start MMF as a corticosteroid-sparing agent (see Case study 1).⁵
- ▶ Reduce the prednisolone dose to 20 mg daily by weekly reductions in dose (see Case study 2).

Case study continued...

Despite the corticosteroid dose reduction, Alex required ongoing oral hypoglycaemic agents and escalating doses of antihypertensive agents. He had an excellent clinical response to IVIg, with a reduction of his MGC score to 6. However, the effect wore off after 3 weeks, and Alex required ongoing maintenance therapy of 4-weekly IVIg at 0.4 g/kg. Alex continued to experience significant corticosteroid side effects necessitating further dose reductions down to 12.5 mg daily.



HOW WOULD YOU TREAT?

- ▶ Introduce other effective immunosuppressants to minimise reliance on maintenance IVIg for patients with moderate to severe MG, when standard treatments have been ineffective or caused intolerable side effects – IVIg is usually a temporary measure.⁷
- ▶ Review effectiveness of IVIg therapy within 4 months of commencement, to determine if ongoing treatment is indicated, or should be stopped due to lack of benefit.⁷
- ▶ At least annual review of efficacy is required to ensure ongoing supply of IVIg. If a patient no longer has demonstrable features of MG, continuation of IVIg infusions is not warranted.⁷
- ▶ Consider further immunosuppressive therapies such as rituximab, cyclosporin or cyclophosphamide.^{12,13,14}

Outcome...

Almost 3 months after initiating rituximab, Alex's prednisolone dose was slowly reduced to 10 mg, alternating with 5 mg daily. Attempts to increase the interval between IVIg treatments (an approach to weaning therapy) were unsuccessful due to worsening limb weakness and SOBOE. After 18 months of combined treatment, Alex continued to take 4-weekly IVIg (0.4 g/kg), MMF 1 g twice daily, prednisolone 10 mg alternating with 5 mg, and low-dose pyridostigmine. His MGC score varied between 3 and 6.

Practice points

- ▶ Monitoring for side effects from corticosteroids and other immunomodulatory therapy is crucial when treating patients with MG. Corticosteroids remain one of the most useful treatments for MG, but side effects limit their long-term use at doses greater than 8 mg prednisolone equivalent/day. While the onset of effect is usually rapid, an initial deterioration of MG symptoms can be encountered if high doses of corticosteroids are started or stopped suddenly. Therefore, progressive dose escalation and de-escalation is preferred.^{1,3,4}
- ▶ Complications and significant side effects of corticosteroids and other immunosuppressant therapies may require the judicious use of IVIg to maintain symptom control.⁷
- ▶ Failure to achieve reasonable symptom control in patients with generalised MG despite standard immunosuppressive therapies may warrant a trial of rituximab or cyclophosphamide.^{13,14}
- ▶ Cardiac disease may be associated with MG as incidental co-morbidity, medication effects, or uncommonly with direct myocardial involvement related to striated muscle antibodies. These may present as asymptomatic ECG changes, ventricular tachycardia, myocarditis, conduction disorders or sudden death.¹⁵
- ▶ In Australia, pyridostigmine was the most prescribed medication for MG (72% of patients), followed by prednisolone (68%). Among steroid-sparing immunosuppressants, azathioprine was used by 38% and mycophenolate 18% of MG patients, with fewer receiving MTX, rituximab, cyclosporine, cyclophosphamide and tacrolimus.¹⁶
- ▶ Several medicines used to treat MG can have serious cardiac side effects. Pyridostigmine may cause heart block, or bradycardia secondary to its muscarinic effects on cardiac tissue. Corticosteroids can produce hyperglycaemia, hypertension, fluid retention or dyslipidaemia, which can worsen cardiovascular risk.^{17,18}

Case study 4: James

Presentation

James, a 40-year-old salesman, was admitted to the hospital for elective resection of a mediastinal mass detected after presenting with episodic dysarthria, ptosis and diplopia. James's AChR antibody test was positive. He was taking pyridostigmine 60 mg 8-hourly with partial benefit.

On the day of admission, James reported SOBOE, and difficulty talking and elevating his arms. He was anxious with slurred speech, ptosis and increased diplopia.



HOW WOULD YOU TREAT?

- ▶ Defer surgery, increase pyridostigmine and initiate prednisolone dose escalation (see Case study 2), aiming to stabilise condition before elective surgery.
- ▶ Given that James has bulbar and respiratory features, initiate a course of IVIg therapy before thymectomy.⁷ Ideally, IVIg therapy needs to start approximately 12 days prior to surgery and/or thymectomy. The effects peak about 15 days after the first dose.¹⁹

- ▶ A normal pre-operative protocol for patients who require disease stabilisation could be two to five doses of IVIg (0.4 g/kg/day), with the final dose at least 7 days before the procedure.¹⁹
- ▶ PLEX is an alternative and has a shorter onset time than IVIg, but in patients with MuSK-MG, it has been suggested that patients are more likely to respond to PLEX.

Case study continued...

James had a good initial response to pyridostigmine 300 mg per day and prednisolone 25 mg daily, and thymectomy was rescheduled. A course of IVIg 2 g/kg was completed 1 week prior to the planned operation date. After his surgery, James experienced increased respiratory weakness, difficulty talking and swallowing saliva. He had weakness of the neck and shoulder muscles, as well as ptosis and diplopia, with oxygen saturation of 98%, but forced vital capacity (FVC) was less than 900 mL. James was transferred to high-dependency care for monitoring and possible assisted ventilation.

HOW WOULD YOU TREAT?

- ▶ Maintain pyridostigmine but increase prednisolone to 40 mg daily until condition stabilises followed by gradual weaning (see Case study 1 and 2).
- ▶ Consider PLEX for a more rapid response. The standard schedule is three times per week for up to six exchanges. Side effects include paraesthesia during the procedure; hypotension, nausea, vomiting due to fluid shifts; and electrolyte variations. Significant complications can include infections and thrombosis related to intravenous catheter access.²⁰ Up to 75% of patients can be treated with peripheral catheters.
- ▶ Generally, IVIg or PLEX for myasthenic crisis are regarded as having the same efficacy. However, weak evidence suggests PLEX may be more effective than IVIg in the treatment of myasthenic crisis.¹¹ A retrospective review of 54 episodes of myasthenic crisis treated with PLEX or IVIg showed PLEX was associated with a superior ventilatory status at 2 weeks.²¹
- ▶ PLEX may have a faster onset of action than IVIg therapy – 2 days versus 4–5 days for IVIg.^{11,22}

Outcome...

The patient was monitored in the high-dependency unit, given increased prednisolone (40 mg daily) and underwent four plasma exchanges over 10 days, with improvement in bulbar, respiratory and proximal limb strength. Infection and electrolyte disturbance were excluded, the pyridostigmine dose was adjusted, and he was eventually discharged after 2 weeks on a slowly reducing schedule of corticosteroids.

Practice points

- ▶ IVIg can be used pre-operatively to help offset the risk of post-operative myasthenic deterioration but is not universally effective.^{19,20}
- ▶ Doses of pyridostigmine higher than 480 mg/day may contribute to increased weakness in MG although the response is quite variable.⁵ The side effects of pyridostigmine can be confused for disease symptoms. Sometimes less is more!
- ▶ The respiratory crisis is recognised by clinical signs and confirmed by reduced vital capacity on spirometry. Reduced oxygen saturation is a late sign and should not be relied on to exclude respiratory compromise.
- ▶ A myasthenic crisis may be provoked by intercurrent infection, surgery, various medications, and can sometimes be the presenting feature of MG. Removal of a thymoma does not treat the features of MG overall; it is done to remove the invasive thoracic tumour.
- ▶ Myasthenic crisis can be ameliorated by either PLEX or IVIg; the former has a more rapid onset of action and could be efficacious against MuSK-positive MG.¹¹

Case study 5: Ella

Presentation

Ella is a 24-year-old woman with known MG who presented to discuss pregnancy options. She presented 6 years ago with fatiguing proximal limb weakness, positive AChR serology, and abnormal repetitive nerve stimulation.

Her myasthenic control was variable with pyridostigmine and corticosteroid treatment, or corticosteroids alone. The corticosteroid was poorly tolerated, causing weight gain and mood changes. Her MG was subsequently maintained on azathioprine with good control, but on occasion, single courses of 1 g/kg IVIg were required to restore control when this was not achieved with standard doses of pyridostigmine and prednisolone.



HOW WOULD YOU TREAT?

- ▶ As the patient plans to fall pregnant, discuss the role of immunosuppression and the risks of continuing treatment during pregnancy. Given the risk of birth defects it may be advisable to withdraw azathioprine, though optimal immunosuppression should be decided on a case-by-case basis. Pyridostigmine can be continued to offset symptoms.
- ▶ The reintroduction of prednisolone is relatively contraindicated due to previous systemic and mental health side effects.²³ There are few alternatives because mycophenolate, MTX and cyclophosphamide are teratogenic and cannot be used by women with the potential to become pregnant.³
- ▶ Initiate PLEX or monthly IVIg infusions.²⁴
- ▶ Rituximab cannot be administered several months before conception and is contraindicated in pregnancy.²⁴
- ▶ Once pregnant, management should be shared between obstetricians and neurologists, with close follow-up and communication.

Case study continued...

The monthly IVIg infusions produced good control of Ella's ocular, bulbar and limb weakness, but symptoms recurred when the dosing interval was increased to every 6 weeks. Poor venous access precluded consideration of PLEX.

Ella subsequently became pregnant and delivered a healthy baby via normal vaginal delivery. For 3 months post-partum, Ella experienced increasing weakness and depression. It proved difficult to determine if the weakness was due to MG or depression. Several attempts were made to wean IVIg and trial alternate therapies.



HOW WOULD YOU TREAT?

- ▶ Continue IVIg for 3 months post-partum.
- ▶ Reintroduce azathioprine in the post-partum period. Side effects include idiosyncratic flu-like reaction, leukopenia, hepatotoxicity, alopecia, and possible risk of neoplasia.²⁴
- ▶ Discuss lactation with Ella. Small amounts of mercaptopurine are excreted into breast milk but no adverse effects have been noted in the breastfed child.²⁵
- ▶ Some studies indicate that azathioprine could be used after a risk versus benefits assessment. If breastfeeding is delayed for 4 hours after a dose, this would markedly decrease the concentration in breast milk. The vast majority of studies show no adverse effects on the health and growth of the child up to 3.5 years of age, but long-term follow-up for effects such as carcinogenesis has not been studied.^{24,26}

Outcome...

All symptoms settled over the next 3–4 months, and Ella remains well, taking azathioprine therapy. On review at 12 months she had no ongoing myasthenic symptoms or signs, MGC score = 0, and was considered in remission.

Practice points

- ▶ Pregnancy adds an additional layer of complexity to the management of MG due to limitations with medicines and the possibility of disease exacerbation, especially in the post-partum period. However, pregnancy proceeds without complication for most women, and fertility isn't affected by MG. Caesarean deliveries are common due to muscle weakness, exhaustion and an abundance of caution.^{3,24} but vaginal delivery is possible.
- ▶ Pyridostigmine and prednisolone can be used safely in pregnancy if required. Antimetabolites such as MTX and azathioprine are contraindicated in pregnancy²⁴ although the latter is not teratogenic.
- ▶ IVIg is safe but should only be used if other treatments are not effective or tolerated.²⁴
- ▶ Clinical assessment of MG can be challenging in patients with mental health disorders, especially depression, which may result in inadvertent over-treatment.²³
- ▶ Exacerbations can be effectively treated with either IVIg or PLEX.

Access to IVIg in Australia

In Australia, the NBA provides the framework for access to Ig products currently funded under the National Blood Agreement (the Agreement). The NBA manages contracts with suppliers to ensure a safe, secure, adequate, and affordable supply of blood and blood product derivatives such as Ig sourced from domestic and imported plasma. The NBA has contracted the Australian Red Cross LifeBlood to assess, authorise, and provide clinical advice on established or emerging therapeutic medical conditions identified in the [Criteria for the Clinical use of Immunoglobulin in Australia \(the Criteria\)](#).⁷ The Criteria also define the conditions for which Ig can be used in exceptional circumstances.

To access Ig under the Agreement, a medical officer must submit an application through the National online system BloodSTAR. The system manages the authorisation request and review process and ensures that access to Ig products is consistent with the Criteria. Ig products are funded by the government and provided to eligible patients at no direct cost.

Conclusion

These five case studies highlight the highly favourable outcome for patients with MG when treated with an optimal, patient-centred approach to care, with specialist expert clinical care tailored specifically to them. For complex cases, additional evaluation and assessment by a senior specialist should be sought to assist with management.

Abbreviations

AChR: acetylcholine receptor

BloodSTAR: Blood System for Tracking Authorisations and Reviews

BMI: body mass index

Criteria: Criteria for the Clinical use of Immunoglobulin in Australia

CT: computerised tomography

ECG: electrocardiogram

Ig: immunoglobulin

IVIg: intravenous Ig infusion

MG: myasthenia gravis

MGC: myasthenia gravis composite score

MGFA: the Myasthenia Gravis Foundation of America score

MMF: mycophenolate

MTX: methotrexate

MuSK: muscle-specific tyrosine kinase

NBA: National Blood Authority

PLEX: plasma exchange

SFEMG: single-fibre electromyography

SOBOE: shortness of breath on exertion

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