Myasthenia gravis (MG)

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Condition for which IVIg has an established therapeutic role.

Specific Conditions	• Myasthenia gravis
Indication for IVIg Use	• As an alternative to plasma exchange in acute exacerbation of MG (myasthenic crisis). • As an alternative treatment to plasma exchange prior to surgery and/or thymectomy. • As maintenance therapy for moderate to severe MG when other treatments have been ineffective or caused intolerable side effects.
Level of Evidence	Clear evidence of benefit (Category 1)
Description and Diagnostic Criteria	MG is an autoimmune disease associated with the presence of antibodies to acetylcholine receptors (AChR) or to muscle-specific tyrosine kinase (MuSK) at the neuromuscular junction. Some patients with myasthenia gravis are antibody negative. Clinical features are characterised by fluctuating weakness and fatigability of voluntary muscles, namely levator palpebrae, extraocular, bulbar, limb and respiratory muscles. Patients usually present with unilateral or bilateral drooping of eyelid (ptosis), double vision (diplopia), difficulty in swallowing (dysphagia) and proximal muscle weakness. Weakness of respiratory muscles can result in respiratory failure in severe cases or in acute severe exacerbations (myasthenic crisis). Diagnosis is suspected based on the clinical picture described above, without loss of reflexes or impairment of sensation. Repetitive nerve stimulation typically shows a decreasing response at 2–3 Hz, which repairs after brief exercise (exercise facilitation). Edrophonium can be used for confirmation. Other useful investigations include serum anti-AChR or MuSK antibody titre, or SFEMG (single-fibre electromyography).
Justification for Evidence Category	A Cochrane review of four randomised controlled trials (RCTs) (a total of 147 children and adult patients) found benefit but no significant difference between IVIg and plasma exchange, and no significant difference between intravenous immunoglobulin (IVIg) and methylprednisolone. One of the four studies found no benefit of IVIg (i.e. no significant difference between IVIg and placebo). The individual trials were of poor design and some had small numbers of participants, so more research is needed (Biotext 2004). Anecdotal evidence of efficacy has come from clinicians. There is insufficient placebo-controlled evidence for IVIg use as a steroid-sparing agent or before thymectomy in stable MG, although multiple case reports suggest benefit in this context. The Asia–Pacific Advisory Group (Kornberg 2004) supports the use of IVIg over a single day for the treatment of myasthenia gravis exacerbations, in myasthenic crisis, or in patients with severe weakness poorly controlled with other agents. It does not support the use of IVIg for maintenance in stable moderate or severe MG, unless other therapies have failed and IVIg has shown benefit. Effectiveness of IVIg is equivalent to steroids and plasma exchange, but IVIg may be easier to administer than plasma exchange and avoids the side effects of steroids.

Diagnosis Requirements	A diagnosis must be made by a Neurologist.

Qualifying Criteria for IVIg Therapy	As an alternative to plasma exchange in acute exacerbation of MG (myasthenic crisis).
	• Symptoms of myasthenic crisis.
	
	As an alternative treatment to plasma exchange prior to surgery and/or thymectomy.
	• Surgery is planned.
	
	As maintenance therapy for moderate to severe MG when other treatments have been ineffective or caused intolerable side effects.
	• Moderate to severe MG as assessed by one of the following measures:
	  ○ Myasthenia gravis composite score
	  ○ Forward arm abduction time (up to full five minutes)
	  ○ Quantitative myasthenia gravis score (Duke)
	  ○ Respiratory function (Forced Vital Capacity)
	  ○ Quantitative dynamometry of proximal limb muscles
	  ○ Myasthenic muscular score (MSS).
	AND
	• Alternative treatments have been ineffective.
	OR
	• Alternative treatments have caused intolerable side effects.

Review Criteria for Assessing the Effectiveness of IVIg Use	As an alternative to plasma exchange in acute exacerbation of MG (myasthenic crisis). Review is not mandated for this indication however the following criteria may be useful in assessing the effectiveness of therapy. • Improvement in fatigability and weakness. As an alternative treatment to plasma exchange prior to surgery and/or thymectomy. Review is not mandated for this indication however the following criteria may be useful in assessing the effectiveness of therapy. • Improvement in fatigability and weakness.

As maintenance therapy for moderate to severe MG when other treatments have been ineffective or caused intolerable side effects.

IVIg should be used for three to six months (three to six courses) before determining whether the patient has responded. If there is no benefit after three to six courses, IVIg therapy should be abandoned.

Review by a Neurologist is required within six months and annually thereafter. A trial off period should be conisdered at each review.

Documentation of clinical efficacy is necessary for continuation of IVIg therapy. For stable patients on maintenance treatment, review by a Neurologist is required at least annually.

On review of the initial authorisation period

Clinical effectiveness of Ig therapy can be demonstrated by:

- Improvement in fatigability and weakness compared to qualifying, as assessed by improvement in at least one of:
    - Forward arm abduction time (up to full five minutes)
    - Quantitative myasthenia gravis score (Duke)
    - Respiratory function (e.g. forced vital capacity)
    - Quantitative dynamometry of proximal limb muscles
    - Myasthenic muscular score (MSS).

On review of a continuing authorisation period

Clinical effectiveness of Ig therapy can be demonstrated by:

- Improvement in, or stabilisation of fatigability and weakness compared to the previous review, as assessed by at least one of:
    - Forward arm abduction time (up to five minutes)
    - Quantitative myasthenia gravis score (Duke)
    - Respiratory function (e.g. forced vital capacity)
    - Quantitative dynamometry of proximal limb muscles
    - Myasthenic muscular score (MSS).

Dose	As an alternative to plasma exchange in acute exacerbation of MG (myasthenic crisis). • **Induction or during myasthenic crisis** - 1–2 g/kg in 2 to 5 divided doses. **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.** **Refer to the current product information sheet for further information.** As an alternative treatment to plasma exchange prior to surgery and/or thymectomy. • **Prior to surgery and/or thymectomy** - 1–2 g/kg in 2 to 5 divided doses. **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.** **Refer to the current product information sheet for further information.** As maintenance therapy for moderate to severe MG when other treatments have been ineffective or caused intolerable side effects. • **Induction Dose** - 1–2 g/kg in 2 to 5 divided doses. • **Maintenance Dose** - 0.4–1 g/kg, 4–6 weekly. Aim for minimum dose to maintain optimal functional status. **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.** **Refer to the current product information sheet for further information.**

Bibliography

Biotext 2004, 'Summary data on conditions and papers', in *A systematic literature review and report on the efficacy of intravenous immunoglobulin therapy and its risks*, commissioned by the National Blood Authority on behalf of all Australian Governments, pp. 188–9. Available from: http://www.nba.gov.au/pubs/pdf/report-lit-rev.pdf

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