IgM paraproteinaemic demyelinating neuropathy

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Condition for which IVIg has an emerging therapeutic role.

Specific Conditions	• IgM paraproteinaemic demyelinating neuropathy
Indication for IVIg Use	• IgM paraproteinaemic neuropathy with significant progressive disability where other therapies have failed or are contraindicated • Relapse of patients with IgM paraproteinaemic neuropathy within six months of commencement of a trial off Ig therapy
Level of Evidence	Conflicting evidence of benefit (Category 2c)
Description and Diagnostic Criteria	IgM paraproteinaemic neuropathy is a slowly progressive, predominantly distal sensory neuropathy that may eventually produce disabling motor symptoms. The condition is associated with IgM paraprotein, which may demonstrate antibody reactivity to myelin associated glycoprotein (MAG). IgM paraproteinaemic neuropathy is the most common subgroup of the monoclonal gammopathy of undetermined significance (MGUS) group. It is distinguishable from chronic inflammatory demyelinating polyneuropathy (CIDP) by: • the presence of tremor; • a greater severity of sensory loss, with ataxia and relatively mild or no weakness; • damage tends to be permanent and the degree of improvement in IgM paraproteinaemic neuropathy is much smaller than the improvement observed in CIDP patients. Nerve conduction studies usually show symmetrical conduction slowing with markedly prolonged distal motor latencies and reduced or absent sensory responses. Test for antibodies to neural antigens (MAG or other neural antigens) may be helpful. Due to the variable and often poor response to intravenous immunoglobulin (IVIg), a treatment trial is only indicated for significant progressive disability.
Justification for Evidence Category	Two randomised placebo-controlled crossover trials with intravenous immunoglobulin (IVIg) have been performed (Dalakas 1996; Comi 2002), encompassing 33 patients with IgM paraproteinemic demyelinating neuropathy. Neither provided 6 or 12 months assessments. The results of these trials are summarised in Cochrane reviews (2006, 2012) which concluded that the studies provide low quality evidence for very short term improvement (two to four weeks). Six other uncontrolled studies reported transient improvement in 22 of 50 participants with IVIg, whereas another did not report improvement. EFNS guidelines (2008) state that routine use of IVIg cannot be recommended in IgM paraproteinemic neuropathy. A trial of IVIg may be considered in patients with significant disability or rapid worsening, although its efficacy is not proven.
Diagnosis Requirements	A diagnosis must be made by a Neurologist.

Qualifying Criteria for IVIg Therapy

IgM paraproteinaemic neuropathy with significant progressive disability where other therapies have failed or are contraindicated

- Significant progressive disability as defined by an Overall Neuropathy Limitations Scale (ONLS) score of at least two points

AND

- Unresponsive to at least two alternative therapies

  OR

- Alternative therapies are contraindicated

IVIg should be used for a maximum of four months (induction plus three maintenance cycles) before determining whether the patient has responded. If there is no benefit after this treatment, IVIg therapy should be abandoned.

Review by a neurologist is required within four months and annually thereafter.

A trial off IVIg should be considered annually in stable patients on maintenance therapy to identify patients who are in remission. Ig therapy may be recommenced if a patient relapses within the first six months of a trial-off therapy. After a further two years of Ig therapy, a further trial off might be considered.

Documentation of clinical effectiveness is necessary for continuation of IVIg therapy.

Relapse of patients with IgM paraproteinaemic neuropathy within six months of commencement of a trial off Ig therapy

Once a patient has relapsed when trialled off Ig treatment, a second line immunomodulatory agent should be strongly considered as additional therapy.

- Previously stable adult with IgM paraproteinaemic neuropathy demonstrates a deterioration in disability as measured by the Adjusted Overall Neuropathy Limitations Scale (ONLS) by an increase of at least one point compared to the previous review score

  AND

- Relapse occurs within six months of the last Ig dose

Ig therapy should be used for a maximum of four months (induction plus three maintenance cycles) before determining whether the patient has responded. If there is no benefit after this treatment, Ig therapy should be abandoned.

Review by a neurologist is required within four months and annually thereafter.

Once a patient has relapsed when trialled off Ig treatment, a second line immunomodulatory agent should be strongly considered as additional therapy. After a further two years of therapy, a trial off Ig therapy should be considered annually in stable patients on maintenance therapy to identify patients who are in remission.

Documentation of clinical efficacy is necessary for continuation of IVIg therapy.

Review Criteria for Assessing the Effectiveness of IVIg Use	IgM paraproteinaemic neuropathy with significant progressive disability where other therapies have failed or are contraindicated

IVIg should be used for a maximum of four months (induction plus three maintenance cycles) before determining whether the patient has responded. If there is no benefit after this treatment, IVIg therapy should be abandoned.

Review by a neurologist is required within four months and annually thereafter.

A trial off IVIg should be considered annually in stable patients on maintenance therapy to identify patients who are in remission. Ig therapy may be recommenced if a patient relapses within the first six months of a trial-off therapy. After a further two years of Ig therapy, a further trial off might be considered.

Documentation of clinical effectiveness is necessary for continuation of IVIg therapy.

Clinical effectiveness of Ig therapy may be assessed by:

On review of the initial authorisation period

- Improvement in disability as measured by a decrease in the Adjusted Overall Neuropathy Limitations Scale (ONLS) score of at least one point less than qualifying

On review of a continuing authorisation period

- Stabilised or continued improvement in disease as measured by the Adjusted Overall Neuropathy Limitations Scale (ONLS)

  AND

- A trial of Ig weaning/cessation of Ig therapy is planned for patients who are clinically stable to identify those in remission, or a valid reason is provided as to why a trial is not being planned or is contraindicated at this time

A trial of Ig weaning should be considered annually in stable patients on maintenance therapy to identify patients who are in remission.

Relapse of patients with IgM paraproteinaemic neuropathy within six months of commencement of a trial off Ig therapy

Ig therapy should be used for a maximum of four months (induction plus three maintenance cycles) before determining whether the patient has responded. If there is no benefit after this treatment, Ig therapy should be abandoned.

Review by a neurologist is required within four months and annually thereafter.

Once a patient has relapsed when trialled off Ig treatment, a second line immunomodulatory agent should be strongly considered as additional therapy. After a further two years, a trial off Ig therapy should be considered annually in stable patients on maintenance therapy to identify patients who are in remission.

Documentation of clinical efficacy is necessary for continuation of IVIg therapy.

Clinical effectiveness of Ig therapy may be demonstrated by:

On review of the initial authorisation period

- Improvement in disability as measured by a decrease in the Adjusted Overall Neuropathy Limitations Scale (ONLS) score of at least one point compared to the re-qualifying assessment following relapse

On review of a continuing authorisation period

- Adult demonstrating stabilised or continued improvement in disease as measured by the Adjusted Overall Neuropathy Limitations Scale (ONLS) compared to the previous review assessment

  AND

- A trial of Ig weaning toward cessation of Ig therapy is planned for patients who are clinically stable to identify those in remission, or a valid reason is provided as to why a trial is not being planned or is contraindicated at this time

Once a patient has relapsed in the first six months of a trial off therapy, a further trial might be considered after at least two years.

Dose	IgM paraproteinaemic neuropathy with significant progressive disability where other therapies have failed or are contraindicated • **Induction Dose** - 2 g/kg in 2 to 5 divided doses. • **Maintenance Dose** - 0.4–1 g/kg, 2 to 6 weekly. The amount per dose should be titrated to the individual's response. A maximum dose of 2g/kg may be given in any 4 week period. This might be by small doses more frequently than fortnightly. 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 on dose, administration and contraindications. Relapse of patients with IgM paraproteinaemic neuropathy within six months of commencement of a trial off Ig therapy • **Induction Dose** - 2g/kg in 2 to 5 divided doses. • **Maintenance Dose** - 0.4–1 g/kg, 2–6 weekly. The amount per dose should be titrated to the individual's response. A maximum dose of 2 g/Kg may be given in any 4 week period. This might be by small doses more frequently than fortnightly. Deterioration of a patient on Ig therapy may be an indication for alternative or additional immunosuppressant agents. Once a patient has relapsed when trialled off Ig treatment, a second line immunomodulatory agent should be strongly considered as additional therapy. 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 on dose, administration and contraindications.

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