

The Long-term Treatment of Multifocal Motor Neuropathy with Intravenous Immunoglobulin

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Abstract

Multifocal motor neuropathy (MMN) is a rare, purely motor neuropathy. It is a progressive disorder, most patients eventually developing severe fatigue and weakness in the arm muscles that severely impair daily functioning and quality of life. Unlike other motor neuropathies such as motor neurone disease, MMN is treatable with regular infusions of intravenous immunoglobulin (IVIg). Four double-blind, randomised, placebo-controlled studies have shown that in the short term, IVIg significantly improves muscle strength and disability in more than 70 % of patients. The 11 observational studies reviewed in this article confirm that long-term maintenance treatment with IVIg maintains clinical improvement compared to pre-treatment baseline in most patients. Infusions are generally well tolerated, but regular monitoring and re-evaluation of the IVIg maintenance regimen is essential, as most patients need progressive increases in dosage or reduced intervals between infusions to maintain their response to treatment. In the absence of accepted predictive markers, maintenance IVIg should be individualised, based on each patient's initial response, disability and the interval between the first infusion and decline in muscle strength.

Keywords

Multifocal motor neuropathy, intravenous immunoglobulin, maintenance, treatment

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Multifocal motor neuropathy (MMN) is a rare, purely motor neuropathy with a prevalence of approximately 0.6 per 100,000 and a median age of onset of 40 years.¹ Men are more likely than women to be affected, in a ratio of 2.7:1 and are usually diagnosed at an earlier age.¹ Patients with MMN typically present with asymmetrical, predominantly distal limb weakness that follows individual nerves. There is no apparent sensory loss and weakness usually starts in the forearm or hand muscles, though the first symptoms may occur in the distal leg and upper arm. Respiratory and bulbar muscles are unaffected and patients have a normal life expectancy. However, since MMN is a progressive disorder, most patients eventually develop severe fatigue and weakness in the arm muscles, resulting in disability that can seriously impair daily functioning and quality of life.

Unlike other motor neuropathies such as motor neurone disease (MND), MMN is treatable with intravenous immunoglobulin (IVIg).² Most patients require regular infusions in order to maintain clinical response and the aim of this review is to consider the effectiveness and safety of long-term or maintenance treatment of MMN with IVIg.

Method

The terms 'multifocal motor neuropathy', 'treatment', 'long term', 'maintenance' and 'IVIg' were used to conduct a PubMed search of articles published in English language journals between 1 January 1980 and 31 December 2011 (see *Table 1*). Papers were excluded if

they were single case reports, or were superseded by subsequent publications following up the same group of patients.

Results

The manual search of the results of the PubMed literature search identified a total of 14 studies concerning the long-term or maintenance treatment of MMN with IVIg. Three papers were excluded:

- a case report in one patient;³
- a publication concerning six patients included in a subsequent, larger study;^{4,5}
- and a study of dose titration in patients on maintenance IVIg.⁶

The remaining 11 studies listed in *Table 2* were included in the analysis.^{1,5,7–15} All were retrospective, observational studies, except for one cross-sectional, descriptive study.

Patient Demographics

The 11 studies included a total of 297 patients who, except 10 of them,¹⁵ were treated at centres in Europe. One study of long-term home IVIg treatment included 26 patients with MMN, but did not provide demographic information.¹¹ Of the 271 patients included in the remaining 10 studies,^{1,5,7–10,12–15} 183 (67.53 %) were male. Five studies^{5,8,13,14} reported the age of onset of MMN: the lowest median age of onset was 36.5 (21–57) years¹⁴ and the highest was 48 (32–59) years.¹⁵

Follow-up

Nine of the 11 studies reported duration of IVIg treatment.^{1,5,7,9-15} This ranged from a median of nine (2–32) months in eight patients⁹ to a mean of 8.1 (1–17) years in 26 patients.¹¹

Intravenous Immunoglobulin Regimen

The initial IVIg dosage regimen was 2 g/kg in two to five days in all studies. Maintenance IVIg dosage and treatment intervals were individualised for each patient, based on their response to treatment and to maintain clinical improvement.^{1,5,7-15}

Response to Intravenous Immunoglobulin

In the four studies also including treatment-naïve patients,^{1,7,10,13} a minority of patients – 20 of 189 (10.58 %) – were unresponsive to IVIg. Where reported, treatment with IVIg resulted in improvement in muscle strength and disability compared with baseline.^{1,5,7-9,11-15} Most patients remained dependent on IVIg. Five studies reported cessation of IVIg therapy without relapse in 15 of 99 patients.^{7,9,10,11,15} In a sixth study, three of 10 patients were able temporarily to withdraw from IVIg treatment when clinically stabilised on cyclophosphamide.¹²

Four studies^{1,5,9,14} reported that IVIg dosage was progressively increased in order to maintain clinical response to treatment. There was significant clinical improvement in 10 patients receiving maintenance IVIG for a mean of 7.25 years in one study.¹⁵ However, in three other studies^{1,5,14} clinical parameters worsened gradually over time despite treatment with IVIg, though remaining above baseline in most patients.

Factors Predicting Response to Intravenous Immunoglobulin

Results were inconsistent in studies that examined objective factors predicting response to IVIg. Six studies reported the results of antibody testing^{1,7-9,12,13} but only one found significant changes in anti-GM1 antibodies in response to long-term IVIg therapy.⁷

There was similar inconsistency when studies investigated electrophysiological outcomes. Two found that electrophysiological changes paralleled improvements in paresis and muscle strength in most patients.^{9,11} In other studies, results were inconsistent. A study comparing patients with and without conduction block (CB) found no difference in IVIg efficacy between the two groups, with improvements in distal CMAP amplitude in three of 13 patients with CB and four of 20 without CB.⁹ In 16 of 22 evaluable treatment-naïve patients in another study, CB decreased in eight patients (this included complete disappearance of CB in two patients), remained stable in four patients and increased in two patients.¹⁰ Similarly, IVIg reduced the magnitude of CB in individual nerves in 12 out of 16 patients, but CB did not change in one patient and worsened in three patients despite their reporting less disability.¹³

Two studies compared the effects of IVIg treatment on nerves with and without CB at entry to the study.^{5,15} After a mean of 5.6 (4–8) years, proximal CMAP amplitude and area in nerves with CB at baseline significantly increased after IVIg treatment, while distal CMAP area and proximal CMAP amplitude and area decreased in nerves without CB before treatment or during follow-up.⁵ In contrast, a mean 7.25 (3.5–12) years treatment resulted in significant net improvement in CB from baseline, including a reduction in proximal CMAP amplitude and area in nerves developing CB during IVIg treatment.¹⁵

Table 1: Long-term Treatment of Multifocal Motor Neuropathy – PubMed Search Strategy

Step	Search Term	Number of Results
1	Multifocal motor neuropathy	636
2	Treatment	4,971,582
3	1 and 2	260
4	Long term	393,544
5	1 and 4	35
6	Maintenance	160,237
7	1 and 4	21
8	IVIg	9,417
9	1 and 8	180

Sections highlighted in bold were retrieved and searched for manually. IVIg = intravenous immunoglobulin.

Adverse Effects

Seven of the 11 studies provided information on adverse effects. Infusion-related side effects were generally mild, transient and as expected, with studies highlighting headache, fever, rash, nausea, itching and fatigue.^{5,7,9,10-12,15} Aseptic meningitis occurred in one patient,⁷ while a patient in another study experienced a transient ischaemic attack (TIA) without permanent deficit.¹⁵

Discussion

IVIg is currently recommended by consensus guidelines as the standard, evidence-based therapy for MMN.¹⁶ Studies of other treatments have been disappointing. Unlike patients with chronic inflammatory demyelinating polyneuropathy (CIDP) and Lewis-Sumner syndrome, patients with MMN do not respond to corticosteroids even given in high, intravenous doses; indeed, this treatment may worsen symptoms.¹⁷ Similarly, plasma exchange may result in the appearance of CB in previously unaffected motor nerves.¹⁸ Immunoabsorption and CSF filtration are also ineffective in most reported patients with MMN.¹⁹

A recent Cochrane review noted that there is some evidence that cyclophosphamide is effective in MMN when it is used in first-line treatment or when patients do not respond to IVIg. However, its use in maintenance is limited by its potentially significant adverse events, which may be delayed by a number of years.²⁰ The Cochrane reviewers found little or no robust evidence supporting other, less cytotoxic immunosuppressive agents such as azathioprine, beta interferon, ciclosporin or rituximab.²⁰ In the only randomised placebo-controlled trial of an immunosuppressive agent in MMN, mycophenolate mofetil did not significantly improve strength or motor function, or reduce the need for IVIg.²¹ In contrast, use of IVIg in MMN is supported by evidence from four double-blind, controlled clinical trials.²²⁻²⁵ A Cochrane meta-analysis of these short-term trials concluded that, when compared with placebo, treatment with IVIg results in significant improvements in muscle strength and disability in more than 70 % of patients.² The studies discussed in this review confirm that, in long-term treatment, IVIg maintains clinical improvement compared with pre-treatment baseline in the majority of patients. However, patients require progressive increases in dosage or reductions in intervals between infusions to maintain this response. As a result, regular monitoring and re-evaluation of the IVIg maintenance regimen are essential.

The mild, gradual decline in muscle strength generally reported in IVIg-treated patients^{1,5,14} is probably due to continuing axonal degeneration.²⁶ The single group reporting clinical improvement, as well as re-innervation and significant reduction in CB and axonal

Table 2: Summary Results of Maintenance Treatment with Intravenous Immunoglobulin in Multifocal Motor Neuropathy

Study	Patient Demographics	Follow-up	IVIg Dose/Regimen	Response to IVIg	Factors Predicting Response to IVIg	Adverse Effects Associated with IVIg
Azulay et al., 1997 ¹ Retrospective, observational study	18 patients (14 male, 4 female). Mean age at end follow-up: 45.8 (30–71)	Mean duration of IVIg treatment: 25.3 (9–48) months	Initial: 0.4 g/kg/day for 3–5 days. Maintenance: 0.4 g/kg/day, treatment intervals determined for each patient based on effect of first course	12/18 patients: final increase in muscle strength (MVIC) of at least 30 %. Parallel subjective improvement of at least one grade on Rankin disability scale. 2/18 patients: IVIg withdrawn without signs of relapse after 12 months. 6/18: non-responsive to IVIg after 3–7 courses	11/12 patients: correlation between long-lasting response to IVIg and initial high titres of IgM anti-GM1 antibodies	8 patients: headache, fever, rash. 1 patient: aseptic meningitis
Cats et al., 2010 ¹ Cross-sectional, descriptive	88 (64 male, 22 female) Median age at study inclusion: 52 (27–78) years	67/88 patients receiving maintenance IVIg: median duration of treatment: 6 (0–17) years	Initial: cumulative dose 2 g/kg/day. Median maintenance dose: gradually increased from 12 to 17 g/kg/week (p<0.01)	4 patients never received IVIg. 79/84 patients responded to first course of IVIg (increase of ≥ 1 MRC grade in at least 2 muscle groups). 5/84 non-responsive	Lack of response to IVIg associated with more axon loss (p<0.01) and longer disease duration before first IVIg treatment (p<0.03)	Not reported
Delmont et al., 2006 ⁸ Retrospective, observational study	33 IVIg-treated patients (24 male, 9 female). Median age at onset: 41.5 (19–66) years in 20/33 with CB; 47 (27–59) years in 13/33 without CB	Median follow-up after diagnosis: 7 (4–22) years	Initial: 0.4 g/kg/day for five days. Maintenance: dose and treatment intervals determined for each patient to maintain clinical improvement (usually 3 days IVIg every 6–8 weeks depending on response after first infusion)	14/20 patients with CB and 8/13 without CB: improvement of at least 1 point in MRC sum scores. 3/13 patients with CB and 4/20 CMAP amplitudes increased (p>0.05)	Response to IVIg not influenced by CB, IgG anti-GM1 antibodies	Not reported
Jaspert et al., 1996 ⁹ Retrospective, observational study	8 IVIg-treated patients with CB (4 male, 4 female) with MMN with CB. Mean age at diagnosis: 46 (18–64) years	Median duration of IVIg therapy: 9 months (2–32 months)	Initial: 0.4 g/kg/day for five days, repeated (usually for one day) after four weeks at same dosage. Maintenance: dosage and treatment intervals (every 2–12 weeks) determined for each patient according to clinical course. 2 of 8 patients: IVIg dosage increased or treatment intervals reduced to achieve clinical stabilisation	8/8 patients: rapid improvement in pareses and muscle strength. 5/8 patients: continuing regular treatment. Significant improvement from baseline, but deterioration in muscle strength when therapy interrupted. 3/8 patients no longer undergoing therapy: 1/3 in remission for 22 months; 2/8 in incomplete remission for 10–41 months. 7/8 patients: rapid improvement in conduction block or temporal dispersion after first IVIg course. 4/8 patients: CB or temporal dispersion reappeared as before treatment simultaneous with clinical deterioration	Not reported	One patient: headache and sickness during first two treatment cycles. No other clinical/laboratory adverse effects

Table 2 Continued: Summary Results of Maintenance Treatment with Intravenous Immunoglobulin in Multifocal Motor Neuropathy

Study	Patient Demographics	Follow-up	IVig Dose/Regimen	Response to IVig	Factors Predicting Response to IVig	Adverse Effects Associated with IVig
Léger et al., 2008 ⁹ Retrospective, observational study	40 patients (23 male, 17 female); median age at inclusion: 50.2 (27–54) years. 22 treatment-naïve (13 male, 9 female); median age at inclusion: 48.4 (31–74) years. 18 previously treated (10 male, 8 female); median age at inclusion: 52.2 (27–66) years	Mean duration of follow-up of 40 patients: 2.2 years (± 2.0 years)	Initial: 2 g/kg/day over 3–5 days monthly for at least six months. Maintenance: at same dose if needed by recurrent clinical worsening	8/40 patients: in remission (lasting stabilisation of clinical improvement [≥ 6 months]) without further treatment after initial IVig therapy during at least 6 months). 25/40 patients: stabilisation or clinical improvement and dependent on maintenance IVig. 4/40 patients: non-responders. 3/40 patients: data missing	No significant factors (best two non-significant factors: female gender [$p=0.08$], lower MRC score at inclusion [$p=0.07$])	Mild and as expected
Lucas et al., 2010 ¹¹ Retrospective, observational study	26 patients (of 45 patients with autoimmune diseases receiving home IVig). No gender or age stated	45 patients: mean 8.1 (1–17) years since start of treatment	Initial: 2 g/kg/day. Maintenance treatment (begun within 2 weeks of last full dose while patient in full remission): 0.25–1.0 g/kg/day every 1–4 weeks based on duration of clinical response	1/26 MMN patients stopped therapy and in permanent remission. 4/45 total patients returned to hospital infusion for domestic reasons. 2/46 total patients died of unrelated causes	Not reported	No significant infusion-related adverse events
Meucci et al., 1997 ² Retrospective, observational study	6 patients IVig-treated (3 male, 3 female). Mean age: 41.3 (26–60) years	Mean duration of IVig treatment: 47 (37–61) months	Initial: 0.4 g/kg/day for five days. Maintenance treatment: 0.4 g/kg/day for two days + oral cyclophosphamide 1–3 mg/kg/day for two days at time of clinical worsening	6/6 patients: clinical and electrophysiological improvement. 3/6 patients: maintenance IVig. 3/6 patients: returned to IVig after withdrawal for 17–24 months	Not reported	At end of first IVig infusion: mild, transient headache (4/6 patients) associated with nausea and moderate fever (3 patients), itching (2 patients). Cyclophosphamide: 2 patients: haemorrhagic cystitis (resolved after withdrawal); 1 patient: persistent amenorrhoea
Slee et al., 2007 ¹³ Retrospective, case cohort analysis	47 patients (31 men, 16 women). Median age at onset 42 (22–74) years	Follow-up all patients: 1–16 years; IVig-treated patients: mean 6.4 years; untreated patients: mean 4.5 years. Median IVig duration: hospital patients: 3 (1–8) years; home patients: 4.5 (2–12) years	Initial: 0.4 g/kg/day for five days. Maintenance treatment: determined by clinical response over next 6–10 weeks. Treatment intervals adjusted for each patient to prevent clinical worsening	24/47 long-term IVig (12/24 converted to home treatment). 18/47 never treated with IVig. 5/47 unresponsive to IVig. Initial response to IVig: marked reduction in disability ($p<0.0001$). Response to maintenance IVig: significant improvement ($p<0.001$) compared to pre-treatment ... (cont. next page)	Neither CB nor antibody status predicted response to IVig	Not reported

Table 2 Continued: Summary Results of Maintenance Treatment with Intravenous Immunoglobulin in Multifocal Motor Neuropathy

Study	Patient Demographics	Follow-up	IVIg Dose/Regimen	Response to IVIg	Factors Predicting Response to IVIg	Adverse Effects Associated with IVIg
Terenghi et al., 2004 ¹⁴ Retrospective, observational study	10 IVIg-treated patients (6 men, 4 women). Median age at onset: 36.5 (21–57) years	Mean duration of IVIg treatment: 8.2 (5–12) years	Initial: 2 g/kg/day over 4–5 days. Maintenance dose: 1–1.2 g/kg over 2–3 days at clinical worsening. From year 2 of therapy, IVIg dosage progressively increased to maintain or achieve improvement	(cont. from previous page) ... disability scores in both hospital and home patients. CB improved in 12/16 patients, no change in one patient, worsened in three patients despite less disability 7/10 patients maintained on IVIg during follow-up. 3/10 patients discontinued IVIg for 1–4 years because of clinical stabilisation under cyclophosphamide. MRC, limb impairment and Rankin scores at end of follow-up: 5/10 patients improved compared with baseline; 1/10 patient deteriorated to baseline; 4/10 deteriorated below baseline	Not reported	Not reported
Van den Berg-Vos et al., 2002 ⁵ Retrospective, observational study (includes 6 patients in Van den Berg 1998 ¹)	11 IVIg-treated patients (10 male, 1 female). Median age at onset 40 years (20–58)	Mean duration of IVIg treatment: 5.6 (4–8) years	Initial: 0.4 g/kg/day for five days. Maintenance dose: one IVIg infusion every week for one year, then dosage and treatment intervals tailored to each patient's reported functioning: stable or improved functioning: dose maintained; deteriorated functioning: dose titrated based on hand-held dynamometry	At last follow-up, mean MRC sum score significantly higher than mean scores before first full course of IVIg (p<0.001). Muscle strength improved significantly within 3 weeks of IVIg initiation (p<0.02), decreased slightly and significantly during follow-up, but still significantly better at end of follow-up than before treatment. Significant improvement in proximal CMAP and amplitude in nerves with CB before treatment. Reduced distal CMAP area and proximal CMAP amplitude and area in nerves without CB before treatment and during follow-up	Significant association between electrophysiological changes consistent with improvement and CB before IVIg treatment	Minor headache, rash, fatigue
Vucic et al., 2004 ¹⁵ Retrospective, observational study	10 IVIg-treated patients (4 men, 6 women). Median age at disease onset: 48 (32–59) years	Mean duration of IVIg treatment: 7.25 (3.5–12) years	Initial: three courses (0.4/kg/day for five days) every fourth week. Maintenance: every four weeks, dose adjusted to prevent functional decline before next treatment	At end of follow-up compared with baseline: significant and sustained improvement in muscle strength, functional disability, number of CB, axonal degeneration while receiving IVIg. 1/10 patients achieved clinical remission 3 years after IVIg initiation	None stated	1/10 patients: transient ischaemic attack without permanent deficits 2.8 years after treatment initiation. No other adverse effects reported

CB = conduction block; CMAP = compound muscle action potential; IVIg = intravenous immunoglobulin; MRC = Medical Research Council; MVC = maximum voluntary isometric contraction.

degeneration, suggest that their findings may be due to the larger mean IVIg maintenance doses used in their study.¹⁵ However, in the absence of comparative dosing studies or further long-term observational studies, the optimal dose and treatment interval for maintenance IVIg has yet to be established.

CB outside the usual sites of nerve compression is the hallmark of MMN¹⁶ and IgM antibodies against GM1 can be detected in about half of all patients.²⁷ Some studies have found an association between these objective markers and clinical response to IVIg^{5,7,9,12}, but other groups have not confirmed these findings.^{8,10,13} In the absence of accepted predictive markers, the IVIg maintenance regimen should be tailored to each patient based on clinical criteria. These include the patient's initial response to IVIg, their disability and the interval between the first infusion and decline in muscle strength.

It is difficult to investigate the relationship between IVIg dose and response in MMN because of the rarity of the disease and difficulties in randomising the small numbers of patients due to individual variations in affected muscles, paresis, disease duration, age and side effects.⁶ However, using the lowest effective IVIg dose and the longest tolerated interval between doses may lead to under-dosing in the long-term.⁶ Reduced response to IVIg can be restored in most patients by increasing the dose during the first few years of therapy, but not in longer-term follow-up.¹⁴ So the IVIg maintenance regimen should be adjusted based on close monitoring of each patient's muscle strength and function, using validated assessment instruments.²⁸

Few patients with MMN experience a stable disease course without maintenance treatment with IVIg, but remission does occur in a minority of patients. A thorough evaluation of the effects of the first and subsequent IVIg courses is therefore important to identify these patients before committing them to long-term treatment. Equally, since early initiation of IVIG therapy may help to postpone the development of axonal degeneration and permanent deficits,¹ patients should not be denied a trial of this treatment. This applies

especially to patients presenting with a typical MMN clinical phenotype but without evidence of CB, who may respond to IVIg.

Mild and transient side effects such as rash, chills, fever, nausea, malaise, headache and mild arthralgia are common in short-term studies of IVIg in MMN, being reported in up to 71 % of patients.² The studies in this review confirm that IVIg is also well tolerated when used as maintenance treatment. Two of the studies reported serious adverse events – one case of aseptic meningitis and one TIA – that may have been related to IVIg treatment.^{7,15} This underlines the importance of careful monitoring in patients receiving maintenance therapy, including blood pressure and renal function. Use of loop diuretics should be avoided and patients should be advised to ensure that they are adequately hydrated before IVIg administration.

Because of the importance of monitoring patients' response and of identifying any serious adverse events, initial courses of IVIg should be administered in hospital. Thereafter, infusion at home is feasible if patients are carefully monitored, and supported and trained by a specialist nurse.¹¹ Home IVIg not only maintains patients' function as effectively as hospital treatment,¹³ but can be cost saving and is preferred by patients.^{26,29} Subcutaneous immunoglobulin (SCIG) has similar advantages, especially for patients with difficult venous access,³⁰⁻³² though some patients may not tolerate subcutaneous treatment or may find self-administration too challenging.^{30,31}

Conclusion

Unlike other motor neurone diseases, MMN is treatable with IVIg. However, although most patients respond to initial and maintenance treatment, progressive axon loss means that there is usually a gradual decline in muscle strength. Randomised controlled studies are needed to determine if axon loss could be prevented by higher dose IVIg regimens or by currently available immunosuppressive therapies. For the future, the development of other effective maintenance treatments is likely to depend on basic research into the underlying pathogenesis of MMN and the subsequent identification of evidence-based targets for therapy. ■

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