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Immunoglobulin (Ig) in multifocal motor neuropathy (MMN): update on evidence for Ig treatment in MMN

J.-M. Léger
National Referral Centre for Neuromuscular Diseases, University Hospital Pitié-Salpêtrière and University Paris VI, Paris, France
Correspondence: J.-M. Léger.
E-mail: jean-marc.leger@psl.aphp.fr

Multifocal motor neuropathy (MMN), which was first described in 1986, is a purely motor neuropathy, characterized by progressive distal asymmetric limb weakness that usually starts and predominates in the upper limbs, with minimal or no sensory impairment. Nerve conduction studies show persistent multifocal conduction blocks (CB) on the motor nerves, with normal sensory potentials, which are the hallmark of MMN [1,2]. It is a rare disease as its prevalence is estimated to be less than one per 100 000 [1], with males more frequently affected than females, at a ratio of 2·7:1, in a recently reported series [3]. According to retrospective studies, high titres of serum immunoglobulin (Ig) M antibodies to the ganglioside GM1 have been reported in 43–64% of patients with MMN [3,4]. Several methods to increase the detection of autoantibodies in MMN have been published recently in a series of original studies [2].

MMN mainly has a chronic slowly or stepwise progressive course. The aim of treatment is to reduce the motor deficit, reverse or improve the motor CB and limit ongoing axonal degeneration, which leads to irreversible functional impairment. However, current therapeutic options for MMN are limited, as patients do not respond to corticosteroids or plasma exchange and may eventually worsen under these treatments.

Four randomized, double-blind, placebo-controlled trials (RCTs) investigated the use of intravenous immunoglobulin (IVIg) in a total of 34 MMN patients [5–8]. Across these four RCTs, 78% of included patients had a significant improvement in muscle strength, selected as primary outcome measure, following IVIg therapy, when compared with 4% following placebo [9], indicating that IVIg is an efficacious, short-term treatment for MMN. The meta-analysis, however, did not show a significant improvement in disability and identified a need for further studies.

In a first step, the beneficial response to immune modulation shown in these RCTs have led the joint European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) taskforce to recommend that IVIg be used as a first-line treatment for MMN [10]. Currently it is recommended that 2 g/kg IVIg be administered for 2–5 days when disability is sufficiently severe to warrant treatment. If initial treatment is effective, repeated IVIg should be considered in selected patients and the frequency of maintenance therapy should be guided by the response. Typically, maintenance doses are 1 g/kg every 2–4 weeks, or 2 g/kg every 1–2 months [10].

Since the EFNS/PNS guidelines were published, a controlled trial aiming to critically assess the efficacy, safety and tolerability of 10% liquid IVIg was reported in 44 MMN patients [11]. Patients were randomized 1:1 to receive either double-blind treatment with IVIg followed by placebo for 12 weeks each, or the reverse receiving placebo followed by IVIg [11]. A significant difference ($P = 0{\cdot}005$) in mean maximal grip strength was observed during IVIg treatment (increased 3·75%) compared to placebo treatment (decline 31·4%). In addition, in 35·7% of participants, Guy's Neurological Disability scores for upper limbs worsened during placebo and not during IVIg, whereas the converse was true in 11·9% of subjects ($P = 0{\cdot}021$). Treatment with 10% liquid IVIg was well tolerated, with most adverse events (AEs) being mild and transient, the most common reported of which was headaches. Overall, 69% of patients switched prematurely from placebo to open-label IVIg and 2·4% switched from blinded IVIg to open-label IVIg ($P < 0{\cdot}001$), suggesting that patient perceptions greatly favoured IVIg to placebo. This RCT therefore concluded that IVIg is an effective treatment in improving both muscle strength and disability in MMN patients.

IVIg, at a cumulative dose of 2 g/kg, was efficacious also in 70% of 22 treatment-naive MMN patients in our retrospective study [4], and in 94% of 84 MMN patients in another retrospective study [3], both based on an increase of at least one Medical Research Council (MRC) grade in at least two muscle groups, without a decrease in other muscle groups. Analysis of predictive criteria in our study revealed that the only best predictive factors for response to IVIg

(although not significant) were female gender ($P = 0{\cdot}08$) and lower MRC score at inclusion ($P = 0{\cdot}07$) [4]. In addition, among the 22 treatment-naive patients, the number of CBs decreased for eight patients, with complete disappearance of CB for two patients, remained stable for four patients and increased for two patients [4].

To date, studies investigating Ig therapy in the treatment of MMN have only looked at short-term therapy, and options for the long-term treatment for MMN remain unclear. No long-term, placebo-controlled trials investigating the use of IVIg in MMN have been carried out. However, four retrospective studies described groups of MMN patients who have received periodic IVIg infusions over several years and may be used to assess the long-term options for treatment of MMN [4,12–14]. Studies by Van den Berg-Vos *et al.* [12] and Terenghi *et al.* [13] observed their patients for 4–8 years and 5–12 years, respectively, and have examined the beneficial long-term effects of IVIg treatment in MMN patients. Van den Berg-Vos *et al.* showed that compared to pretreatment results, muscle strength in 11 MMN patients, treated initially with one full course of 2 g/kg of IVIg, followed by 0·4 g/kg every week, improved significantly ($P < 0{\cdot}001$) within 3 weeks of IVIg initiation and remained significantly better at the last patient follow-up. However, this improvement in muscle strength declined significantly during the follow-up period ($P < 0{\cdot}01$). Additionally, although CB was no longer evident in six nerve segments, new CB occurred in eight motor nerves and a decline in motor function was observed [12]. Terenghi *et al.* observed the long-term effects of IVIg treatment in 10 MMN patients. All patients had improved muscle strength following initial IVIg treatment; however, at the last patient follow-up, only two patients had maintained the maximal improvement achieved during therapy. Motor decline began after an average of 4·8 years of therapy and correlated with a reduction of distal compound muscle action potential (CMAP) amplitudes ($P < 0{\cdot}019$) [13]. Conversely, a third long-term follow-up study by Vucic *et al.* reported an overall improvement in 10 patients receiving IVIg over a mean follow-up of 7·25 years [14]. Muscle strength improved significantly ($P = 0{\cdot}02$) following initiation of treatment compared to assessment prior to treatment, an improvement which was maintained at last patient follow-up. Patients in this study additionally had an improvement in CB with a net reduction of 45%, a significant decrease in axonal degeneration ($P = 0{\cdot}03$) and evidence of re-innervation by the end of the study period. The difference from the findings of the two previous studies may be explained by the different regimens in giving IVIg, the patients in the third study being treated with significantly higher IVIg maintenance doses.

In the fourth long-term follow-up study by Léger *et al.* the population comprised 22 treatment-naive patients and 18 previously treated patients [4]. For long-term evaluation, patients were divided into three groups according to IVIg dependency; at the end of the follow-up period group 1 (responders) patients were stabilized by initial treatment with IVIg for at least 6 months. Group 2 patients were stabilized but dependent upon maintenance IVIg with (2a) or without (2b) additional immunosuppression and group 3 patients were non-responders. At the end of the follow-up period (mean $2{\cdot}2 \pm 2{\cdot}0$ years), eight of the 40 patients were in group 1, 17 were in group 2a and 8 were in group 2b. Group 3 comprised four patients and data were not available for the remaining three patients. No statistical analysis was carried out on these groups; however, there was a clear trend towards improvement on IVIg. In all, 25 patients followed for an average of 4 years were dependent upon maintenance treatment at the time of the study.

Although there are no RCTs investigating the long-term effects of IVIg in the treatment of MMN, there are data from these retrospective trials showing that IVIg could be an effective long-term therapy in MMN.

Although IVIg therapy is the mainstay of treatment in MMN patients, alternative treatment options, including subcutaneous immunoglobulin (SCIg), have been investigated in recent years. Many primary immunodeficiency (PID) patients prefer to receive SCIg due to the greater convenience offered by this method of administration in addition to the lack of end of dose weakening. In order to show bioequivalence of IVIg and SCIg in the treatment of MMN, studies have investigated weekly doses of SCIg equivalent to current monthly doses of IVIg. Harbo *et al.* conducted a randomized, single-blinded, cross-over trial of nine IVIg responsive patients receiving IVIg or SCIg to compare their efficacy in the treatment of MMN patients [15]. The changes in mean muscle strength and the SF-36 quality of life questionnaire were not significantly different between patient groups, indicating that SCIg was a suitable treatment alternative to IVIg. One patient presented with sustained erythema and oedema at the injection sites for a few weeks, but all other adverse events with SCIg were mild and transient. After the study, five of nine patients preferred to continue with SCIg. In a single-centre, open-label pilot study in 10 patients, Eftimov *et al.* investigated whether SCIg in the treatment of MMN was feasible and safe in maintaining muscle strength. When dosing SCIg at 100% of the monthly IVIg dose, four patients maintained muscle strength compared to baseline as assessed by MRC sum score, three of which opted to continue SCIg as future treatment [16]. Finally, a 2-year follow-up study was reported by Harbo *et al.* in six IVIg-responsive MMN patients [17]. The dosage of SCIg varied between 13 and 51 g per week, corresponding to a volume of 80–320 ml, infused twice or thrice weekly. No major side events were reported, including local skin reactions being mild and transient. The impairment and disability scores remained stable.

In conclusion, several data have shown Ig therapy should be administered to MMN patients as a first-line treatment. Conversely, some patients with MMN do not respond to

IVIg, while others require progressively more frequent doses to maintain remission, and some scarce patients have an involvement of new motor nerves despite periodic IVIg/SCIg infusions. Consequently, RCTs are needed (i) to clarify the circumstances in which IVIg should be recommended in the long-term and (ii) to determine if there is a role for alternative or adjunctive immunomodulatory therapies.

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