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Review Article

Immunoglobulin therapy in the treatment of multifocal motor neuropathy

Aditya Kumar, Huned S. Patwa, Richard J. Nowak *

Department of Neurology, Yale University School of Medicine, USA

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ABSTRACT

Multifocal motor neuropathy (MMN) is a chronic immune-mediated disorder leading to slowly progressive muscle weakness and wasting. Current treatments are aimed at modulating the immune system in order to avoid further decline and to maintain functional status. Intravenous immunoglobulin (IVIg) is widely used in the treatment of immune-mediated disorders and is the only treatment approved for MMN. While patients do remain stable with maintenance IVIg treatment, most patients will slowly deteriorate over many years. The use of subcutaneous immunoglobulin (ScIg) is also gaining acceptance in this disease. The amount of axonal loss and the number of years without immunoglobulin (Ig) treatment appear to be associated with the permanence of weakness. We summarize the key literature to date that supports Ig use in the treatment of MMN.

Contents

1. Introduction

Multifocal motor neuropathy (MMN) is a rare, immune-mediated disorder characterized by slowly progressive, asymmetric, primarily

* Corresponding author at: Yale University School of Medicine, Department of Neurology, Division of Neuromuscular Medicine, PO Box 208018, New Haven, CT 06520, USA.
E-mail address: richard.nowak@yale.edu (R.J. Nowak).

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distal limb muscle weakness and atrophy [1–3]. Wrist drop, reduced grip strength and foot drop are frequently the presenting symptoms [1,4]. Nerve involvement is irregular as evidenced by a difference in severity of weakness in individual muscles innervated by a single terminal nerve [5]. Proximal limb muscles are typically spared, as are the respiratory muscles and cranial nerves. Sensory symptoms are not a prominent feature and are seldom reported, however, mild impairment of vibration sense has been seen in up to 22% of MMN cases [6].

MMN was first described in the mid-1980s [7–10] and is estimated to have a prevalence ranging between 0.6 and 2 per 100,000 [1,2]. The male to female ratio is approximately 2.6:1, with a mean age of onset of 40 years with a wide range (25–80 years) [1].

Motor conduction block is the electrophysiological hallmark that distinguishes MMN from motor neuron disease. Axon loss is prominent and is the most important prognostic factor for permanent disability. Early diagnosis and treatment can reduce axonal degeneration, while also promoting remyelination [2,6]. Peripheral nerve biopsies at the site of conduction block of MMN patients show multifocal axonal degeneration, and regenerating nerve clusters, but segmental demyelination of the nerve axon or onion bulb formation reflecting recurrent episode of demyelination and remyelination, is not seen [11].

1.1. Pathophysiology

High serum levels of IgM antibodies directed against the ganglioside GM1, as well as to a lesser extent against asialo-GM1, GM1-galactocerebroside, GD1a and GM2 have been reported [10] and can be detected in about half of patients with MMN, with some recent studies reporting a range between 43 and 64% [12,13]. GM1 ganglioside is a glycolipid found abundantly in the paranodal region of the peripheral motor nerves as well as in the axolemma at the nodes of Ranvier (Fig. 1) [14]. It is thought to play a role in axonal repair and in the maintenance of tight junctions through paranodal stabilization, providing an anchor for potassium channels and concentrating sodium channels [15]. These functions are necessary for rapid action potential propagation and maintenance of conduction velocity. Antibodies to GM1, when present, have been linked to more weakness and axonal loss and thus to a greater severity of disease. On binding GM1, these antibodies activate the classical complement pathway leading to the formation of the membrane attack complex (MAC) which disrupts ion channels in the axonal membrane, thus impairing signal propagation [16–18].

Antibodies against gangliosides can also cause redistribution of lipids and other important proteins [19], thereby disrupting the function of some areas of the membrane, such as nodes of Ranvier. Sensory nerves are less vulnerable to damage following anti-GM1 IgM antibody

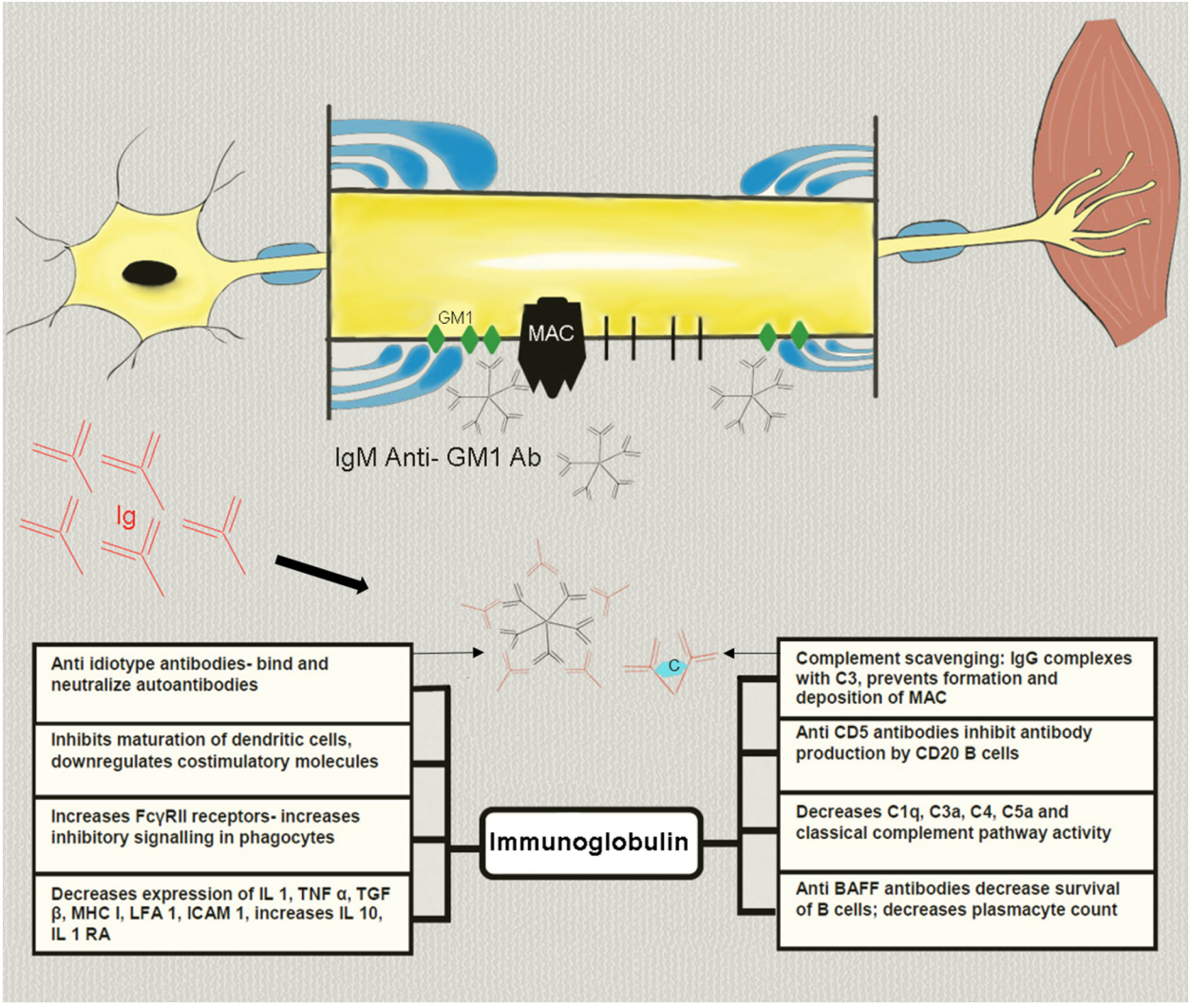

Fig. 1. IgM antibodies to paranodal GM-1 lead to complement fixation and disruption of the neural membrane at the nodes of Ranvier. Figure shows possible mechanisms by which IVIg may have benefit in the treatment of MMN.

binding [20]. Higher titers of anti-GM1 antibodies are rare in other neurological disorders such as amyotrophic lateral sclerosis (ALS) and chronic inflammatory demyelinating polyneuropathy (CIDP), and may help diagnostically when the diagnosis of MMN is uncertain [12]. However, the patients in whom this antibody is detected, have not been reported to have a different response to treatment.

1.2. Diagnosis

Several groups have proposed specific diagnostic criteria for MMN [21,3,22]. There is considerable overlap between them, with the diagnosis being based primarily on clinical and electrophysiologic characteristics, and supported by additional ancillary findings. Guidelines continue to evolve, however, these diagnostic criteria may have challenges when applying them to differentiate between other acquired demyelinating polyneuropathies, such as CIDP, in clinical practice (Table 1) [23,24].

Motor conduction block, at sites other than those attributable to entrapment, along with a reduction in the compound muscle action potential (CMAP) amplitude and area, after proximal as compared to distal stimulation, remains the defining electrophysiology of MMN. Conduction block may not be found in some patients, probably because these blocks are activity-dependent or are located in segments not routinely assessed by electrophysiological examination [25]. In a retrospective study [6] of 88 patients with definite, probable, or possible MMN, 81% were reported to have at least one definite conduction block, while 18% did not have a definite but had at least one probable conduction block. Conduction block was most often detected in the ulnar (80%) and median (77%) nerves.

Sensory nerve action potential amplitudes and conduction velocities are typically normal, but a reduction in action potential amplitude may occur years later. Other supportive findings include normal or slightly increased CSF protein (>45 mg/dl, but <100 mg/dl; CSF protein in CIDP typically >100 mg/dl) in about one-third of patients [1], GM1 specific IgM antibodies and an abnormal MRI signal in the brachial plexus.

1.3. Management overview

High doses of immunoglobulin (intravenous or subcutaneous) remain the mainstay of treatment but responses are ill sustained and a steadily progressive course is often seen despite continuation of therapy. IVIg has been recommended as the first-line treatment for MMN by the joint European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) taskforce following four randomized, double-blind, placebo-controlled trials investigating the use of IVIg in a total of 34 MMN patients. Meta-analysis of these four RCTs concluded that IVIg was an efficacious, short-term treatment for MMN as 78% of included patients had a significant improvement in muscle strength, selected as the primary outcome measure, 2–6 weeks following IVIg therapy, when compared with 4% following placebo [26,27].

Other immunomodulatory therapies like corticosteroids, plasma exchange, rituximab, cyclophosphamide and mycophenolate mofetil have shown inconsistent effects and evidence is scarce to support their use in MMN given their worrisome toxicity profiles. It has been suggested that plasma exchange and corticosteroids may even worsen the disease course [28–32].

This review focuses on the use of Ig in the effective management of MMN as well as on the possible mechanisms of its therapeutic efficacy in this disease.

Table 1
Key features.

Features	MMN	CIDP
Weakness	• Asymmetric • Distal > proximal • Upper limbs > lower limbs	• Typically symmetric • Proximal + distal • ≥8 weeks from onset to nadir
Sensory deficits	• No	• Yes • Typically symmetric
Reflexes	• Reduced or absent (multifocal or diffuse)	• Reduced or absent symmetrically
Abnormal CMAPs: demyelinating features	• Asymmetric (multifocal)	• Usually symmetric
Conduction block	• Frequent	• Frequent
Abnormal SNAPs	• SNAPs are normal	• Usually abnormal
CSF protein	• Usually normal	• Usually elevated
Monoclonal protein	• Rarely present	• Occasionally present • Usually IgG or IgA
Anti-GM1 antibodies	• Present in up to ~50% patients	• Rarely present
Sensory nerve biopsy: demyelination/remyelination	• Uncommon	• Frequent

CMAP, compound muscle action potential; SNAP, sensory nerve action potential; CIDP, chronic inflammatory demyelinating polyneuropathy; MMN, multifocal motor neuropathy.

2. Immunoglobulin therapy

2.1. Background

The immunomodulatory use of immunoglobulin was a serendipitous discovery, first demonstrated in patients with immune thrombocytopenic purpura [33]. Since then it has gained widespread acceptance in various autoimmune diseases, including several autoimmune neuromuscular disorders like myasthenia gravis, CIDP and MMN.

There are multiple effects of IVIg that have been demonstrated in vitro but very few studies have firmly identified the exact mechanism(s) in vivo. IVIg in many ways can be considered a “dirty biologic” with multiple mechanisms likely contributing to its overall therapeutic effect in autoimmune disorders.

2.2. Preparation

Each batch of Ig is made by cold ethanol fractionation of human plasma derived from pools of about 3000–10,000 donors [34,35]. It is then purified by enzymatic treatment, fractionation and chromatography. The marketed IVIg contains >95% IgG, <2.5% IgA, and a negligible amount of IgM [34,36]. IVIg preparations are derived from a large pool of human donors and so the product contains antibodies with a wide range of idiotypic specificities. IVIg products also vary based on sugar and sodium content as well as osmolality and volume load. These product characteristics should be considered based on patient risk factors and co-morbidities (i.e., renal dysfunction, cardiac issues, diabetes, thromboembolic risk, age, etc.).

2.3. Pharmacokinetics

Infusion of 2 g/kg of IVIg increases the serum IgG level > 4-fold, from pretreatment means of 700–1060 mg/dl to peaks over 3000 mg/dl [37]. Its levels drop by about 50% over 48–72 h as IgG is distributed into the total extracellular fluid volume [38,39]. The IgG is catabolized by first-order kinetics and has a half-life of approximately 21–30 days, and is as such usually repeated every 3–4 weeks in the treatment of autoimmune neurologic disease [40–42]. The change in serum IgG concentration after infusion (ΔIgG) has been reported to be higher in IVIg responders in one study [43], suggesting its use as a potential biomarker for response to treatment, however, this did not correlate with disease activity.

When administered subcutaneously, Ig is absorbed and distributed more slowly, over time. Subcutaneous doses need to be given at a higher frequency, as a limited amount can be accommodated in a single administration. Consequently, the fluctuations in Ig levels are much smaller. Trough levels of Ig are also higher with SCIg, as it maintains a better balance between the intravascular and extravascular compartments [40]. The half-life of Ig does not seem to differ between the two routes of

administration [44]. Further studies are needed to elucidate the precise pharmacokinetics of SCIg, when given in the context of autoimmune disorders.

2.4. Putative mechanisms of action

The effects of IVIg, which have been demonstrated in vitro, include neutralization of autoantibodies, inhibition of lymphocyte proliferation, down-regulation of cell adhesion molecules, inhibition of pro-inflammatory cytokines, F(c) receptor blockade, and modulation of the FcγRII/FcγRIII ratio on macrophages [45–47] (Fig. 1).

IVIg contains anti-idiotypic antibodies that may form idiotype–anti-idiotype IgG dimers [48,49]. Several groups have reported that in vitro IVIg is able to prevent the binding of anti-ganglioside antibodies to their target antigen, which is probably mediated by the F(ab) portion of the IgG molecule [50–52]. Ig can also have anti-idiotype effects on specific T-cell receptors [53]. It has been reported that both human and mouse anti-GD1a antibodies can lyse neuronal cells expressing gangliosides on their surface in the presence of complement [52]. Co-incubation with human Ig in this assay blocked the binding of antiganglioside antibodies and led to a downregulation of activated complement, resulting in reduced cytotoxicity [52]. IVIg treatment decreases classical complement pathway activity [17] and can attenuate the deposition of complement in vitro [17,54]. Complement inhibition may be the prominent mechanism of the efficacy of IVIg in MMN since IgM is a very potent activator of that system. Inhibition of C3b and C4b binding also decreases amplification of the complement cascade, decreasing C5 activation and deposition of the membrane attack complex (MAC). Inhibition of formation of the amplification convertases also reduces the generation of the potent chemoattractant C5a and thus decreases infiltration of inflammatory leukocytes [54]. In an open label study of patients with MMN [55], the complement inhibitor drug eculizumab was given in conjunction with IVIg. No difference in the requirement for IVIg was noted in this group, indicating a possible complement independent mechanism of its benefit. However, whether eculizumab is able to cross the blood-nerve barrier has not been demonstrated and no definitive conclusions could be drawn from this study.

The number of blood lymphocytes expressing adhesion molecule ICAM-1 has been shown to decrease immediately after IVIg infusion which may represent a decrease in the ability of T cells to recruit bystander leukocytes through LFA-1/ICAM-dependent cell–cell interactions [56]. A decrease of ICAM-1 expression might also occur on endothelial cells [57]. This reduction would decrease leukocyte migration into the nerves.

The balance of inhibitory FcγIIR and stimulatory FcγIIIR receptors determines cellular immune responses including degranulation, phagocytosis, antibody-dependent cell-mediated cytotoxicity, transcription of cytokine genes, and inflammatory mediator release. Changes favoring inhibitory signaling have been observed 1 week after infusion of IVIg [58].

Catabolism of IgG is controlled by an Fc receptor, FcRn [59]. FcRn on endothelial cells binds and internalizes circulating IgG, protecting it from lysosomal degradation. The IgG is recycled back to the cell surface and is again released into the plasma. This explains the relatively long half-life and the concentration dependent pharmacokinetics of IgG in the circulation [59,60].

IVIg can decrease and neutralize several pro-inflammatory cytokines like IL-1, IL-12, and IFN-γ; and increase production of regulatory molecules including IL-10 and IL-1 RA [61–63]. Altering these cytokines can affect the balance between regulatory (CD25+) and effector (CD8+) T-cells [62], and decrease the inflammatory activity of macrophages. It also neutralizes B cell activating factor (BAFF), thus limiting B cell proliferation.

The precise mechanism of benefit of IVIg in MMN cannot be clear until more light is shed on the pathogenesis of this yet incompletely understood disease.

3. Intravenous immunoglobulin

Response to IVIg treatment in patients with MMN was first reported in the early 1990s by several groups [64–68]. Since then there have been five randomized clinical trials demonstrating the efficacy of IVIg for MMN. A small study of five patients treated with IVIg at a dose of 0.4 g/kg for five days versus placebo demonstrated improved strength at 28 days [28]. Six patients were treated and responded in a double-blind, placebo controlled trial; treatment demonstrating significant improvement in MRC score assessed in 16 affected muscles, in 5 of 6 patients [30]. In a double-blind, placebo-controlled trial, nineteen patients were randomized to receive 0.5 g/kg/day IVIg for five days monthly for three consecutive months [32]. Patients in the treatment group demonstrated improvement in the MRC sum score at month 9, however, there was no statistically significant difference compared to placebo. In a crossover clinical trial, 16 patients with MMN were randomized to receive 0.4 g/kg/day IVIG for five days versus placebo. Eleven patients reported improvement in the Neuropathy disability scale in the IVIg group with no reports of improvement for those receiving placebo [31] (Table 2).

The results of these four trials showed that 78% of included patients had a significant improvement in muscle strength, selected as the primary outcome measure, following IVIg therapy, when compared with 4% following placebo. The meta-analysis of these trials, however, did not show a statistically significant improvement in disability and identified a need for further studies [27].

The most recent, and largest trial of IVIg for MMN, involved 44 patients randomized in a crossover design to 12 weeks of treatment with IVIg followed by placebo or the reverse [69]. The primary outcome measure was grip strength which demonstrated a decline of 31.38% in placebo and an increase of 3.75% in the treatment group ($p = 0.005$). A co-primary endpoint was Guys' Neurologic Disability Score (GDNS) for upper limb which showed worsening in the majority of patients on placebo ($p = 0.021$). Patient perception strongly favored IVIg as 69% of patients switched prematurely from placebo to open-label IVIg and 2.4% switched from blinded IVIg to open-label IVIg ($p < 0.001$). This trial concluded that IVIg is an effective treatment in improving both muscle strength and disability in MMN patients.

Despite the convincing evidence of the efficacy of IVIg for treatment of MMN, optimal dosage and treatment intervals remain unknown. Symptomatic improvement achieved following IVIg is transient, and repeated administration at intervals of ≤3–4 weeks is necessary to maintain clinical effect [70–73]. Long term strength may continue to decline despite ongoing treatment as a result of ongoing axonal loss [74]. As occurs in CIDP, a decrease in strength-duration time-constant for CMAP follows IVIg infusions in MMN, suggesting that decreased axonal excitability contributes to the pathology [75]. Axonal excitability improves shortly after IVIg infusions, but these effects wane in subsequent weeks, before the next infusion is due [76,74,77].

One study suggests that earlier treatment may be of benefit, and increasing dosages may be required during long term treatment over years [6]. The European Federation of Neurological Societies (EFNS) guidelines recommend 2 g/kg of IVIG as the first-line treatment given in divided doses over 2–5 days. The guidelines also indicate that maintenance therapy should be administered following initial response and recommend a dose of IVIg ranging from 1 to 2 g/kg every 2–4 weeks [26].

3.1. Long-term use of IVIg

The long-term use of IVIg has been assessed in several studies. In a longitudinal study on maintenance IVIg, 11 MMN patients underwent assessment of muscle strength by MRC sum score, disability using the GNDS, and electrophysiology over a 4–8 year follow up period [74]. This study determined that IVIg favorably influenced reinnervation or remyelination on the basis of both clinical and electrophysiologic

Table 2
Key treatment trials of IVIg in MMN.

Author year	No of patients	Trial design	Ig dose	Primary outcome measure	Outcome
Hahn et al., 2013	44	Crossover RCT	0.4–2.0 g/kg every 2–4 weeks	Grip strength GNDS-upper limb	Decline 31.38% in placebo, increase 3.75% IVIg 35.7% GNDS worsened during placebo, 11.9% worsened IVIg
Leger et al., 2001	19	RCT	2.5 g/kg every month × 3 months	MRC score	No significant change in MRC score
Federico et al., 2000	16	Crossover RCT	2.0 g/kg	NDS Grip strength	Significant increase in NDS, grip strength with IVIg
Van Den Berg et al., 1995	6	RCT	2.0 g/kg	MRC score Dynamometric strength Modified Rankin Scale	5/6 improved muscle strength with IVIg vs placebo
Azulay et al., 1994	5	Crossover RCT	2.0 g/kg	Quantitative strength	Significant increase in muscle strength; NS difference in % change in strength at 2 month follow-up

GNDS, Guy's Neurological Disability Score; NDS, Neurologic Disability Score; MRC, Medical Research Council; RCT, randomized controlled trial.

improvement. However, there was a statistically significant decrease in strength during the maintenance period associated with decreased CMAP leading the authors to conclude that axon loss cannot be prevented at a mean maintenance dose of 0.54 g/kg/month ± 0.44. Another study described 10 patients with MMN followed over a mean of 8.2 years. Eight patients worsened over the observation period despite ongoing IVIg treatment, the decline beginning at a mean of 4.8 years [77]. The correlation with reduction of distal CMAP suggested that clinical worsening was a result of axonal degeneration. In contrast, a review of 10 patients with MMN and conduction block who were followed for a mean of 7.25 years and all of whom received IVIg monthly maintenance therapy, had sustained improvement in muscle strength and functional disability, albeit at a higher mean maintenance dose of 1.6 g/kg/month ± 0.84 [78]. In addition, EMG studies demonstrated significant improvement in conduction block, decrease in axonal degeneration and evidence of re-innervation. A retrospective study of 40 patients with MMN showed that the MRC score improved in 70% of the 20 treatment-naïve patients with MMN over a 6-month period [79]. The data concerning the long-term response to IVIg showed marked variations in terms of MRC score, disease duration and IVIg infusion regimens. To evaluate the long-term efficacy (>6 months), all 40 patients were divided into three groups at the end of clinical follow-up: group 1 = remission defined as lasting clinical improvement (>6 months), without further treatment, after initial IVIg therapy for at least 6 months; group 2 = stabilization of clinical improvement dependent on maintenance IVIg infusions (2a = without additional immunosuppressive agent; 2b = with immunosuppressive agent); group 3 = non-responders. At the end of follow-up (mean of 2.2 ±2.0 years) and among the entire population (40 patients), 8 patients (22%) were in group 1 and 25 patients (68%) were in group 2, requiring periodic IVIg infusions to maintain good clinical condition. Among these 25 patients, 8 (46%) were given additional immunosuppressive agents during various periods. Four patients (11%) were in group 3. Data were missing for 3 patients.

Another cross-sectional study with 88 MMN patients showed IVIg was efficacious in 94% of those that received therapy and that the dose had to be increased gradually in those who received maintenance IVIg treatment, indicating a diminishing response over time [6]. This validated previous findings showing that IVIg has a beneficial long-term effect on muscle strength and disability but does not prevent axon loss and a slight overall decrease in muscle strength. They also demonstrated that it is the years untreated and not duration of IVIg treatment that determines severity of weakness and disability. Axon loss appears to be more extensive in patients with long disease duration without treatment. Optimization of therapy with adjustments in dose and treatment intervals to avoid end-of-dose worsening may help promote stabilization of disease and long term recovery [78].

In our practice, we treat patients with IVIg long term and typically offer a maintenance regimen of 2 g/kg every 3–4 weeks, and optimize frequency and dose further based on clinical course. We also recommend utilizing objective markers of clinical stability such as grip strength (Jamar® Hand Dynamometer) and MRC sum score.

3.2. Safety of IVIg

Intravenous immunoglobulin in general is safe and well tolerated. Serious adverse events following treatment with IVIg are rare. Some of the known serious events include aseptic meningitis, renal failure, heart failure, myocardial infarction, non-cardiogenic pulmonary edema, severe hypersensitivity reactions, hemolytic anemia, and thrombotic events [41].

In the ICE study, up to 50% of patients in the treatment arm experienced transient symptoms of headache, fever, mild hypotension or hypertension, chills, arthralgia and nausea, as compared to 17% in the placebo arm [80]. Many of these can be controlled by slowing the rate of infusion, and hydration [81].

Additionally, in a large randomized clinical trial of IVIg in MMN [69], AEs per infusion ranged from 2.9%–15.2% in the IVIg group, and from 5.9%–18% in the placebo group. A single severe adverse reaction of a 71-year-old subject with pulmonary embolism who was successfully treated, was reported. Most AEs were mild and, severe, non-serious AEs were episodes of headache in 3 subjects.

Thromboembolic events are a known rare complication of IVIg therapy with an estimated incidence of 1.7%, being more frequently reported in subjects with multiple cardiovascular risk factors. In patients with increased risk, antithrombotic measures, a lower infusion rate, as well as dividing the dose over several days can be considered [82–85].

4. Subcutaneous immunoglobulin

Subcutaneous formulations of immunoglobulins have demonstrated equal efficacy as intravenous therapy in MMN [71]. The convenience of self-administered home therapy may be of interest to MMN patients, who often require long term treatment. Additionally, ScIg results in a more uniform serum level of IgG which can limit the variability in levels between treatment cycles seen with IVIg, and potentially mitigate nerve damage.

Weekly subcutaneous IgG has shown efficacy in MMN, comparable to the IV formulation [86–88]. In a randomized, single-blinded, crossover trial of nine IVIg responsive patients receiving IVIg or ScIg [71], 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 edema at the injection sites for a few weeks, but all other adverse events with ScIg were mild and transient. A prospective observational study of 21 MMN and 45 CIDP patients with a prior sustained clinical response to IVIg, showed clinical equivalence when patients were shifted to ScIg along with an

improvement in the patient's perception of the therapeutic setting [89]. However, the CIDP and MMN groups showed a different rate of clinical worsening during follow-up, with 13.3% of CIDP (6/45) and 42.9% of MMN (9/21) patients reporting a ScIg dose increase, ScIg + IVIg combination therapy, or a return to IVIg therapy, in order to obtain stabilization of disease. In another proof-of-concept study [88], a "smooth transition protocol" was employed to switch eight patients from intravenous to subcutaneous Ig. For the first infusion, 25% of the total weekly ScIg dose was given on the day of the last IV infusion, followed by 50% of the total weekly dose in the second week and the full weekly dose (maintenance dose) in the third week. The patients were maintained on full dose ScIg for 21 weeks. There was no change in muscle strength, disability or motor function with an overall increase in the health related quality of life in the seven patients who completed the study. A recent open label trial [90] demonstrated equal efficacy of the subcutaneous preparation in 11 of 15 patients treated for 6 months using the smooth transition protocol. They also advocated an ScIg:IVIg dosing ratio of 1.53:1, based on dosage in other neuromuscular diseases, as all patients on this dose maintained strength over the 6 month period of follow up and adverse effects were minimal. Three patients on a 1:1 dose ratio of ScIg:IVIg had intolerable deterioration of strength following a precipitous drop in IgG levels. These observations show that the subcutaneous form of Ig may be an equally efficacious alternative to IVIg, being more cost effective and having the potential to improve patient compliance with this long term treatment. Local injection-site AEs were reported in 0.4–19.8% of all drug administrations ($n = 439$), and included swelling, induration, and pruritus. Systemic AEs were less common, with malaise most frequently reported, in 10.2% drug administrations.

5. Expert opinion and conclusion

MMN is a treatable immune-mediated disease and it is critically important to recognize early in its course. Both IVIg and ScIg have proven efficacy for the treatment of MMN. Multiple randomized trials have demonstrated improvement in strength and function. Although optimal dosing remains unknown, maintenance therapy is required for patients with ongoing disability. While maintenance IVIg treatment is effective in disease stabilization, a slow progressive decline in strength and function continues in many patients. The amount of axonal loss and number of years without Ig treatment appear to be associated with the permanence of weakness. This underscores the need to diagnosis MMN and initiate treatment as early as possible. There is a growing need to identify improved diagnostic markers as well as markers of disease activity in order for clinicians to establish the diagnosis of MMN as well as tailor a patient's treatment regimen (Ig dose and frequency). While Ig is a "dirty biologic" possessing multiple mechanisms of action, understanding how it benefits patients with MMN may allow further enhancement of these attributes, and development of targeted strategies.

Contributorship statement

RJN, HP and AK: article concept, drafting and revision of manuscript.

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AK reports no disclosures. HP reports serving as a speaker/advisor for Baxter and CSL Behring. RJN reports serving as a speaker, advisor/consultant for Grifols and Shire.

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