

# Autoimmune neuropathies and treatment with intravenous immunoglobulins

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Intravenous immunoglobulins are an effective treatment for a variety of immune-mediated neuropathies. The benefits have been recognized from the controlled studies for Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy and multifocal motor neuropathy. In monoclonal gammopathy of undetermined significance and neuropathy, the effectiveness is variable. Tolerability of intravenous immunoglobulins is very good and adverse reactions are usually minor. Further controlled trials are needed to assess the efficacy of secondary intravenous immunoglobulin infusion in nonresponders in Guillain-Barré syndrome, maintenance intravenous immunoglobulin dose and frequency in chronic inflammatory demyelinating polyneuropathy and multifocal motor neuropathy, efficacy of intravenous immunoglobulins in diabetes-associated chronic inflammatory demyelinating polyneuropathy and the benefits of combination therapy with other immunomodulating medications.

The exact prevalence of neuropathies in the general population is unknown. The Neuropathy Association (NY, USA) estimates that, in the USA alone, up to 20 million patients suffer from peripheral neuropathies. Polyneuropathies have a variety of causes including a subset mediated by immune mechanisms. The treatment of autoimmune neuropathies with intravenous immunoglobulin (IVIg) has been clinically evaluated for almost 20 years and research continues today. The outcomes of the studies significantly influenced the treatment strategies of immune-mediated neuropathies.

IVIg is a solution of a highly purified immunoglobulin, derived from a large pool of human plasma. The commercially available IVIg contains more than 95% of IgG and less than 2.5% of IgA. The half-life of IVIg is approximately 30 days and may vary among individuals. The mechanism of action of IVIg as an immunomodulating agent is unknown, but several mechanisms of action have been advocated. One mechanism is the IVIg effect on autoantibodies by supplying idiotypic antibodies that neutralize pathogenic autoantibodies [1-3]. The second mechanism is an Fc receptor blockade on macrophages, which may render them inactive [4,5]. The third action is a complement deactivation and preclusion of deposition of membranolytic attack complex [6,7]. The fourth mechanism is via suppression of pathogenic cytokines [8]. Furthermore, modulation of T-cell function may have a role in certain immune-mediated neuropathies [9].

The therapeutic dose of IVIg is 400 mg/kg/day, repeated over 5 days, for a total of 2 g/kg. Some researchers advocate dividing the total dose into two daily doses, especially in younger adults. They found no increase in adverse reactions with that approach [10]. The recommended rate of infusion should not exceed 200 ml/h. Tolerability of IVIg is very good, and adverse reactions are usually minor. The most common side effects are headache, nausea, chills, flushing, myalgia, hypotension, hypertension, chest discomfort and fatigue [10,11]. Infrequent adverse reactions include thromboembolic events, skin reactions, aseptic meningitis, renal tubular necrosis and severe anaphylactic reaction [12-14].

The costs of IVIg therapy are high, especially in the USA, with lower costs in Europe. The actual cost of IVIg therapy must be assessed comprehensively, taking into consideration its effectiveness and tolerability. The interventions that are more expensive may, in fact, be favorable when compared with less expensive treatments. Alternative therapies, such as steroids, are less costly yet have limited effectiveness and frequent long-term side effects.

## Guillain-Barré syndrome & variants

Guillain-Barré syndrome (GBS) is the most common immune-mediated neuropathy, with an annual incidence of one to two cases per 100,000 in the general population. Its variants include two subgroups. The first, consisting of syndromes with predominant weakness, includes acute inflammatory demyelinating

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polyradiculoneuropathy (AIDP), acute motor axonal neuropathy (AMAN) and acute motor sensory axonal neuropathy (AMSAN). The second subgroup, where weakness is not predominant, includes Miller Fisher syndrome, acute panautonomic neuropathy and pure sensory neuropathy [15].

In GBS syndromes with predominant weakness, the clinical syndrome usually follows a viral illness (60–70%) or *Campylobacter jejuni* enteritis (30–40%) [16,17]. Clinical presentation usually begins with paresthesias and lower back pain. Ascending muscle weakness follows. The disease can progress for days up to 4 weeks. Autonomic manifestation, partial or complete ophthalmoplegia and facial weakness may be seen. Ventilator support may be needed in a third of patients. In addition to muscle weakness, physical examination shows distal sensory loss, except in AMAN form, and absent or depressed muscle stretch reflexes. Patients may develop ataxia, tremor and dysautonomia. The mortality rate is approximately 5% and the rate of disabling consequences is approximately 15%. Examination of cerebrospinal fluid (CSF) shows elevated protein without leukocytosis in 90% of patients.

Electrophysiologic features are characterized by prolonged distal and F-wave latencies, demyelinating ranges of conduction velocities, and partial motor conduction blocks. Several sets of electrodiagnostic criteria have been published and the guidelines for demyelination vary [18–20]. Although sensory studies are normal in AMAN, in both AMSAN and AMAN a marked reduction of compound muscle action potential amplitude is prominent. Electromyographic features depend on the severity and subtype of GBS, with abnormal spontaneous activity being more prominent and present earlier in the disease in AMSAN and AMAN. An important observation in AMAN is the definite evidence of immunopathogenesis on cytochemical studies which may show positive GM1 or GD1a antibodies of an IgG subclass, especially with *C. jejuni* infection [21]. Magnetic resonance imaging with gadolinium in GBS may show spinal root enhancement [22].

Miller Fisher syndrome accounts for approximately 5% of all GBS patients. It is clinically characterized with ophthalmoplegia, ataxia and areflexia. Sensory loss in the distal part of the limbs is mild and a small degree of muscle weakness may be present. Electrophysiologic studies show decreased sensory amplitudes

with a normal motor conduction studies. As in other GBS syndromes, the albuminocytologic dissociation in CSF is present.

Patients with an acute panautonomic neuropathy frequently show clinical manifestations such as dizziness, orthostatic hypotension, diarrhea, blurred vision, heat intolerance, nausea, vomiting and voiding problems. Electrophysiologic studies are usually normal and the CSF shows elevated proteins in most patients. In a pure sensory GBS variant, patients present with an ataxic, sensory neuropathy without motor impairment, frequently associated with tremor and autonomic disturbance. As indicated by its name, the electrophysiologic abnormalities are limited to the sensory nerves.

Controlled clinical trials evaluating plasma exchange (PE) in the early course of GBS showed hastened recovery of treated patients [23,24]. A study assessing the optimal number of PEs showed that, in mild cases, two are more effective than none, yet in moderate cases, four PEs were more beneficial than two. In severe cases, six PEs were no more beneficial than four [25]. The role of IVIg in GBS was first evaluated in a controlled, randomized trial by comparing it with plasmapheresis [26]. In this study, 52.7% of 74 patients in the IVIg-treated group showed functional improvement after 4 weeks and, in the plasmapheresis group, 34% of 73 patients improved. Another trial demonstrated that combining the IVIg with plasmapheresis treatment did not show additional benefits to each treatment alone [27]. Another study compared an IVIg dose of 1.2 g/kg over 3 days versus a dose of 2.4 g/kg over 6 days, concluding that a higher dose is superior [28]. The two large trials demonstrated no difference in the frequency of an early relapse following an initial favorable therapeutic response to either IVIg or plasmapheresis [26,27]. The analysis of the multicenter trial showed no differences in exposure to IVIg therapy outcomes, regardless of the axonal or demyelinating GBS subtype or *C. jejuni* infection [27]. A recent controlled trial using methylprednisolone in combination with IVIg showed no significant difference in improvement of GBS disability scores between IVIg alone and the IVIg and methylprednisolone group [29].

### Chronic inflammatory demyelinating polyneuropathy

Chronic inflammatory demyelinating polyneuropathy (CIDP) is an acquired immune-mediated neuropathy with a peak incidence in

the 40- to 60-year age group. The prevalence is estimated from 1 to 7.7 per 100,000 population and rises with age [30–32]. It is clinically characterized by a slowly progressive symmetric weakness and a panmodal sensory loss. Weakness usually affects the legs first and is not associated with atrophy or fasciculations. A large fiber sensory loss is present with absent or depressed stretch reflexes. By definition, symptoms develop over at least 2 months [15]. Elevated CSF proteins are seen in 95% of CIDP patients [33].

The electrophysiologic criteria have been defined, requiring three out of the following four parameters [34]:

- Reduction in conduction velocity in two or more nerves
- Partial conduction block or abnormal temporal dispersion in one or more motor nerves
- Prolonged distal latencies in two or more motor nerves
- Absent F-waves or prolonged minimum F-wave latencies in two or more motor nerves

The above criteria, published by the American Academy of Neurology, have been the subject of many comments and revisions. A comparative review of ten published sets of electrophysiologic criteria for primary demyelination, which were studied on 53 patients with GBS and 28 with CIDP, showed sensitivity ranging from 24 to 83% in GBS and 39 to 89% in CIDP. This review proposed a set of electrodiagnostic criteria to achieve 72 to 75% sensitivity and 100% specificity in regards to amyotrophic lateral sclerosis and diabetic polyneuropathy [35].

Several variants of CIDP have been described. The main variant with asymmetric findings is referred to as a multifocal acquired demyelinating sensory and motor (MADSAM) neuropathy. It often begins in one limb, followed by a spread to other limbs in an asymmetric fashion. Multifocal pattern of weakness and sensory loss is present and the electrophysiologic abnormalities show conduction blocks and other features of demyelination [36]. Further variants include distal-acquired demyelinating sensory neuropathy and multifocal-acquired sensory and motor (MASAM). These patients may not satisfy criteria for clinical trials of CIDP, but they may still benefit from treatments [37].

The initial treatment option for CIDP included steroids, but a controlled trial comparing the efficacy of oral prednisolone with IVIg demonstrated improvement in disability after 2 weeks with both treatments, with

slightly more improvement with IVIg [38]. A recent retrospective study of 39 patients with CIDP compared the effect of high-dose intermittent intravenous methylprednisolone, IVIg and oral prednisolone. It demonstrated equal improvement in strength in all groups [39]. Other treatment options include plasma exchange, which has been shown to be an effective treatment for CIDP [40–42]. Four randomized trials demonstrated that IVIg was more effective than placebo [43–46]. Repeated treatments are required at 4- to 6-week intervals in order to maintain the initial therapeutic effect.

### Multifocal motor neuropathy

Multifocal motor neuropathy (MMN) is a rare disorder, with a prevalence of one to 2/100,000. Clinical and electrophysiologic diagnostic criteria have been proposed by several groups and have been summarized in a recent review [47]. This unique neuropathy is characterized by a progressive, asymmetric, distal weakness that frequently presents as a wrist drop, a bicep weakness or a foot drop with minimal or absent sensory symptoms. Weakness progresses insidiously or in a stepwise manner. Muscle cramps and fasciculations are frequently seen coupled with asymmetric stretch reflexes. Electrophysiologic findings show a persistent, focal, motor conduction block outside the common compression sites. Frequently, proximal stimulation sites at the Erb's point or root stimulation are needed to localize the conduction block. Prolonged F-wave latencies and reduced motor conduction velocities are also seen, with normal sensory responses. Laboratory investigations may be helpful in establishing diagnosis as antibodies to GM-1 are elevated in 40 to 50% of patients. Antibodies to other glycolipids, including asialo-GM1, GD1a and GM2, may be seen in a small percentage of patients [47]. Examination of CSF in patients with MMN is usually normal.

Patients with MMN respond well to IVIg, as seen in several controlled trials [48–51]. The trials support the view that IVIg is effective in two thirds of patients with MMN. The improvement usually begins after a week and lasts for 4 to 6 weeks. Repeated infusions are needed as maintenance therapy. A 4- to 8-year follow-up in these studies suggested that maintenance therapy with IVIg is beneficial, although the disease tends to progress and the improvement is not sustained [52,53]. Others found that long-term, high-dose maintenance therapy lead to a decrease in conduction

blocks, reinnervation and a more sustained benefit [54]. For some patients with poor response or further progression of MMN, the addition of alternative treatments is needed. The initial drug described as beneficial was cyclophosphamide [55]. With prolonged use, it has significant side effects, thus it may not be suitable for young and less severely affected individuals. Small uncontrolled studies showed positive effects with the use of interferon- $\beta$ 1A, rituximab, azathioprine and mycophenolate mofetil. These therapies lack controlled trials and their use should be limited to patients with a poor response to IVIg [56–60].

### Monoclonal gammopathy of undetermined significance & neuropathy

Paraprotein-associated neuropathies are a clinically heterogeneous group, depending on the type of a monoclonal paraprotein. Most affected patients do not have an underlying plasma cell disorder, thus the term monoclonal gammopathy of undetermined significance (MGUS) was coined. Commonly, patients are over the age of 50 years, with men being more affected than women. The course is slowly progressive for most patients, although rapid progression may be seen in a small number of cases. Approximately 55% of MGUS neuropathy patients have IgM monoclonal proteins, while 35% have IgG and 10% have IgA. Patients with IgG and IgA present with a progressive, sensory–motor, distal polyneuropathy. Electrodiagnostic studies typically show mixed axonal and demyelinating features. In a subset of patients with IgM gammopathy and neuropathy, approximately 50% have antibodies to a myelin-associated glycoprotein (MAG). The initial presentation of patients with anti-MAG antibodies is characterized by a mild, distal, lower extremity sensory disturbance. While approximately a third of these patients have only sensory symptoms, most patients have some degree of distal weakness and in 20% the weakness is severe. Electrophysiologic studies of patients with an anti-MAG neuropathy are characterized by predominantly demyelinating features, with a marked prolongation of distal and F-wave latencies and a demyelinating range of conduction velocities. Examination of CSF in patients with MGUS neuropathy may show normal or elevated proteins [15].

Patients with IgG and IgA monoclonal gammopathies and neuropathy tend to respond to IVIg in a similar manner to CIDP

patients [61]. In a controlled trial, three out of 11 patients showed improvement [62]. Another trial showed a modest efficacy of IVIg, with improvement seen in ten out of 22 patients with IgM associated neuropathy [63]. In treatment of anti-MAG-associated MGUS neuropathies, various uncontrolled trials described a favorable response to IVIg, plasma exchange, cyclophosphamide, azathioprine, chlorambucil and rituximab, while other case series showed less effectiveness to the same agents [15,64,65].

### Expert commentary & outlook

IVIg is a safe, costly but effective treatment option for a variety of immune-mediated neuropathies. The exact mechanism of action is unknown, although several mechanisms have been proposed to play a role in immunomodulation. A therapeutic dose of 400 mg/kg/day over 5 days has been widely accepted as the initial treatment, with some variations among researchers regarding the daily division of a total dose of 2 g/kg.

More research must be performed in order to evaluate the most beneficial aspects of IVIg therapy in a variety of neuropathies. It is effective in all subsets of GBS, but the issue of a second infusion of IVIg in GBS patients that did not respond to the initial dose needs further investigation with a controlled trial

In patients with CIDP, formal controlled trials are needed to establish the adequate dose and frequency of maintenance therapy. The effectiveness of IVIg in disease-associated CIDP must be further researched, especially in diabetes-associated CIDP since uncontrolled studies of diabetes patients and CIDP detected beneficial effects of IVIg [66–68]. Furthermore, there is a need for further investigation of combination therapy for CIDP in nonresponders to IVIg.

In MMN, IVIg is currently the treatment of choice, with further studies needed to better establish the adequate dose and frequency of maintenance therapy. In patients with MGUS and neuropathy, IVIg can be utilized as a treatment, although future studies need to establish the best treatment options, potentially with a combination immunomodulating therapy, as the IVIg benefit is variable, especially in paraproteinemic IgM anti-MAG polyneuropathies. Overall, controlled trials established effectiveness of IVIg in GBS, CIDP and MMN, with further studies needed to clarify the open questions in treatment of autoimmune neuropathies.

## Highlights

- Autoimmune polyneuropathies are a subset of neuropathies mediated by immune mechanisms.
- The therapeutic dose of IVIg, a highly purified immunoglobulin derived from human plasma, is 400 mg/kg/day repeated over 5 days. Tolerability of IVIg is very good and adverse reactions are usually minor.
- The benefits of IVIg therapy have been recognized through controlled studies for Guillain–Barré syndrome (GBS), chronic inflammatory demyelinating polyneuropathy (CIDP) and multifocal motor neuropathy (MMN). In monoclonal gammopathy of undetermined significance (MGUS) and neuropathy, the effectiveness of IVIg is variable.
- Further controlled trials are needed to clarify the open questions in the treatment of autoimmune neuropathies, including the efficacy of a second IVIg infusion in non responders in GBS, maintenance IVIg dose and frequency in CIDP and MMN, efficacy of IVIg in diabetes associated CIDP and the benefit of combination therapy with other immunomodulating medications.

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