Update on the Clinical Use and Mechanisms of Action of IVIG in the Treatment of Autoimmune Neurological Disorders

By Marinos C. Dalakas, M.D.

Supported by an unrestricted educational grant from Talecris Biotherapeutics

About the Author

Marinos C. Dalakas, M.D., is currently Professor and Chair of Neuromuscular Diseases at Imperial College, London, UK; he also maintains the position of Professor of Neurology at Jefferson Medical College of Thomas Jefferson University in Pennsylvania. Prior to coming to Jefferson, Dr. Dalakas spent more than 20 years with the Neuromuscular Diseases Section at the National Institute of Neurological Disorders and Stroke (NINDS) in Bethesda, Maryland. He joined the NINDS staff in 1981 and became Chief of the Neuromuscular Diseases Section in 1989.

Dr. Dalakas’ research is focused on exploring the immune, viral, and genetic basis of various neuromuscular, demyelinating and neuronal disorders affecting muscle, nerves, or brain, and applying new therapeutic interventions via target-oriented control therapeutic clinical trials. He is the author or coauthor of more than 500 scientific papers or chapters in peer-reviewed journals. He has also edited 11 books and monographs and currently serves on the editorial board of several journals, including Brain, Neurology, BMC Neurology, and Neuromuscular Disorders. Dr. Dalakas also holds a patent on an immunotoxin for the treatment of focal movement disorders.

Board certified in neurology and psychiatry, Dr. Dalakas is a Fellow of the American Academy of Neurology, as well as a member of the American Neurological Association, the European Neurological Society and the World Muscle Society. He is also a Diplomate of the American Board of Psychiatry and Neurology. He received a doctor of medicine degree in 1972 from the Medical School of the National University of Athens, Greece. He then completed a neurology residency at the University of Medicine and Dentistry of New Jersey, followed by a fellowship in neuromuscular diseases and a staff fellowship in neurovirology and neuroimmunology at NINDS.

Dr. Dalakas is the recipient of a number of honors and awards, including the U.S. Public Health Service Special Recognition Award, NIH Director’s Award, and many others.
Introduction

During the last two decades the use of intravenous immunoglobulin (IVIg) has dramatically changed the way we approach the treatment of autoimmune neuromuscular disorders and dominated the immunotherapeutic drugs. Its relative safety for long-term therapy and undisputable efficacy based on class I evidence derived from randomized trials, have had a major impact in the quality of life of patients with a number of these disorders, some of which were previously unresponsive, or insufficiently responsive, to available immunotherapies. In some disorders, IVIg is as effective as plasma exchange or steroids but safer and easier to administer; in others, it is superior to all existing drugs; and in still others like Multifocal Motor Neuropathy, it is the only effective therapy. Based on controlled clinical trials, IVIg has been effective in various acute and chronic demyelinating neuropathies, neuromuscular transmission defects, inflammatory myopathies and stiff-person syndrome and is providing promise in treating various neuroinflammatory or even neurodegenerative disorders. The success and enthusiasm in safely and effectively treating such immunologically diverse disorders, however, has led clinicians to use the drug more liberally even in diseases where the data is weak and not evidence-based, causing logistical problems regarding supply, drug reimbursement and long-term safety. Because all indications for IVIg in neurology (except for CIDP for one IVIg product) are still “off-label,” these issues have generated considerable skepticism and scrutiny from insurance carriers, health care organizations, and government agencies.

General Issues Regarding Mechanisms of Action of IVIg as Relates to Autoimmune Neurologic Disorders

There is overwhelming evidence that IVIg has multiple actions, which often operate in concert with each other. For each neuromuscular disorder, however, there appears to be a predominant mechanism dictated by the underlying immunopathogenetic cause of the respective disorder. Among the main mechanisms of action of IVIg, those relevant to its efficacy in autoimmune neuromuscular disorders include the following:

- **Effect on autoantibodies.** The IgG molecules within the IVIg contain antibodies with a wide range of idiotypic and anti-idiotypic specificities, which may neutralize pathogenic autoantibodies and prevent their interaction with the autoantigen. This effect has been shown experimentally, when extracted F(ab)2 fragments of IVIg bound to and neutralized known autoantibodies, such as anti-DNA, anti-AChR, anti-thyroglobulin, anti-GM1, and others. The idiotypic/anti-idiotypic effect has also been seen in patients with acute Guillain-Barre’ Syndrome (GBS) whose serum contains various IgG glycolipid antibodies. In an in vitro nerve-muscle preparation, the F(ab)2 portion of IVIg neutralized the “blocking” effect exerted by the serum of acute GBS patients on the quantal release. The effects of IVIg on autoantibodies may be relevant in explaining the effect of IVIg in antibody-mediated autoimmune neuromuscular diseases, such as myasthenia gravis (MG), Lambert-Eaton myasthenic syndrome, stiff-person syndrome, and the antibody-mediated demyelinating neuropathies (GBS, chronic inflammatory polyneuropathy [CIDP], and multifocal motor neuropathy [MMN]).

- **Inhibition of complement binding and prevention of membrane attack complex (MAC) formation.** The effect of IVIg on complement binding has been demonstrated in vitro, in animal models, and in patients who received IVIg. In early studies, IVIg was shown to prevent death in guinea pigs from the complement-dependent Forssman shock by inhibiting the uptake of complement C3 and C4 fragments to the endothelial cells. In patients with dermatomyositis, which is a complement-dependent microangiopathy mediated by activation of C3 and deposition of MAC on the endomysial capillaries, IVIg is not only clinically effective as discussed later, but it also inhibits complement uptake and intercepts the formation...
and deposition of MAC on the endomysial capillaries\textsuperscript{9}. Post-IVIg, but not post-placebo serum, inhibits the uptake of C3b and C4b fragments by sensitized in vitro targets, probably due to formation of covalent or noncovalent complexes between C3 and specific receptor sites within the infused IgG molecules.\textsuperscript{10} Such an inhibition limits the available C3 molecules for further incorporation into the C5 convertase assembly, thereby preventing the formation and in situ deposition of MAC, as confirmed in the repeated muscle biopsy specimens of patients with dermatomyositis treated with IVIg\textsuperscript{2,6,18,20}. The effect of IVIg on the complement, as proven in dermatomyositis, is directly relevant to GBS, CIDP and MG, where the complement pathway is activated\textsuperscript{21} and complement fragments are fixed in the targeted tissues.\textsuperscript{1,6} Indeed, IVIg has been shown to protect the anti-ganglioside antibody-mediated cytotoxicity implicated in the pathogenesis of GBS and other autoimmune neuropathies by displacing complement C3 fragments fixed on the sciatic nerve.\textsuperscript{22}

- **Modulation or blockade of Fc receptors on Macrophages**. The IgG molecules bind through their Fc region to Fcy receptors on macrophages and via intracellular signaling mediate inflammation or immune effector functions.\textsuperscript{5,23} The ratio of expression of the inhibitory and activation FcγR receptors determines the final immune response; overexpression of FcγR I and FcγR III favors activation, whereas overexpression of FcγR II infers inhibition of phagocytosis and interception of antibody-dependent cell-mediated cytotoxicity.\textsuperscript{5,23} IVIg upregulates the inhibitory FcγRII receptors and modulates the FcγRII/FcγRII ratio on macrophages.\textsuperscript{23} In GBS and CIDP, a blockade of the Fc receptors on the macrophages could inhibit the macrophage-mediated phagocytosis of antigen-bearing target cells, and might interrupt the macrophage-mediated demyelination\textsuperscript{20, 14, 25}. An increase in the number of monocytes bearing the FcγRII inhibitory receptors and an increase in the FcγRII/FcγRII ratio on monocytes has been noted one week after IVIg in GBS and CIDP patients who started to improve, suggesting that such inhibitory signaling may be clinically relevant.\textsuperscript{26}

- **Suppression of pathogenic cytokines and other immunoregulatory molecules**. In vitro and in vivo studies have shown that IVIg causes a dose-dependent downregulation of tissue expression or reduction in the circulating levels of cytokines and adhesion molecules, such as IL\textsubscript{1}, TNF-α, IL\textsubscript{1β}, TGF-β and TGF-β mRNA, MHC-I, ICAM-I on the endothelial cells and lymphocyte function-associated antigen-1 (LFA-1) on activated T-cells.\textsuperscript{28,31} The latter has been convincingly shown in the repeated muscle biopsies of patients with dermatomyositis who improved after IVIg therapy\textsuperscript{18} and on the lymphocytes of GBS patients one week after infusion with IVIg.\textsuperscript{26} Because upregulation of cytokines and adhesion molecules is critical in almost all of the autoimmune neuromuscular diseases in which IVIg appears to be effective,\textsuperscript{6,24} its downregulatory effect on these molecules is probably pathogenetically relevant. Whether such an effect is a downstream event related to an upstream effect on the primary immune process of the disease, remains unclear.

### Status of IVIg in Autoimmune Neuromuscular Disorders: Evidence from Controlled Clinical Trials

In this section, the clinical efficacy of IVIg based on clinical trials and practical issues unique to each disorder will be discussed.

**Guillain-Barre’ Syndrome (GBS)**

GBS is an acute demyelinating polyneuropathy that peaks within two weeks of onset and causes severe weakness or paralysis of the limbs and respiratory muscles. Although the target antigen is still unknown, humoral and cellular immune mechanisms are implicated, as evidenced by activation of complement and deposition of membranolytic attack complex on the myelin sheath, the presence of circulating antiganglioside or glycolipid antibodies, an increase of T-cell activation products and cytokines, and invasion of the myelin sheath by sensitized macrophages.\textsuperscript{35,39}

Up to about a decade ago, during the first week of the illness the recommended therapy for patients with Guillain-Barré syndrome who have severe disease and require assistance to walk has been plasmapheresis. This practice has been based on controlled clinical trials which showed that plasmapheresis hastens recovery in as many as 52% of patients, compared to 38% of patients receiving sham apheresis.\textsuperscript{40,43} Since then, this practice has changed based on at least two controlled randomized trials which have shown that IVIg has comparable effects. The first randomized trial concluded that up to 52.7% of 74 patients receiving IVIg, compared to 34% of 73 patients undergoing plasmapheresis, had functional improvement of one grade or more after four weeks.\textsuperscript{42} This conclusion was strengthened with a second larger trial which compared, in parallel, the efficacy of IVIg therapy alone (5-day regimen of 0.4 gm/Kg/d), plasmapheresis alone, and plasmapheresis followed by IVIg therapy. After 4 weeks of therapy and 48 weeks of follow-up, no statistically significant difference was seen between the three treatments, in outcome measures including time to unaided walking and discontinuation of ventilation.\textsuperscript{33} The study confirmed that although each treatment is beneficial, combining IVIg with PE produces no incremental response. A pilot study of patients with the GBS, that combined IVIg and 500 mg intravenous methylprednisone showed that the combination was better than IVIg therapy alone.\textsuperscript{44} However a controlled, randomized trial showed no benefit of steroids.\textsuperscript{45} In atypical Guillain-Barré syndrome, such as Miller-Fisher variant,\textsuperscript{46} acute dysautonomia or other variants, IVIg appears to be efficacious but controlled studies have not been conducted.

**Need for a second IVIg infusion.** A common clinical dilemma in managing patients with Guillain-Barré syndrome is whether a second IVIg infusion may add more benefit when three weeks after the first infusion, improvement has either not occurred or is deemed inadequate. There is a clinical challenge to try a sec-
ond IVIg infusion, but the available data are not adequate to support such practice. The reported improvement of a few patients following a second infusion three to four weeks later, requires confirmation with a controlled study to assess whether the reported benefit is due to IVIg rather than due to the natural course of the disease. After almost 10 years of trying to conduct such a study, funding became possible only recently and a controlled study is expected to begin in 2010 in the Netherlands.

**Early relapses.** In some patients with GBS, early relapse may occur after the initial beneficial response either to plasmapheresis or to IVIg therapy. Based on the two large controlled trials, it is clear that relapses occur almost equally in patients treated first with plasmapheresis and those treated first with IVIg therapy. Another retrospective study of 54 patients also confirmed that there are no increased relapses in patients treated with IVIg as opposed to plasmapheresis. Changing from one treatment to another is not recommended; instead, staying with the chosen treatments supplemented with supportive care is most appropriate. An associated medical condition appears to correlate best with an increased risk of relapses, while earlier treatment onset is associated with a lesser chance for relapse.

**Markers of response to therapy with IVIg:** Recently, the pharmacokinetics of IVIg in relation to clinical outcome, were examined in 174 patients with GBS treated with IVIg. It was found that the increase in serum IgG (DeltaIgG) two weeks after IVIg treatment varied considerably between patients (mean, 7.8 g/L; standard deviation, 5.6 g/L). Patients with a low DeltaIgG recovered significantly more slowly, and fewer reached the ability to walk unaided at six months (log-rank p < 0.001). In multivariate analysis adjusted for other known prognostic factors, a low DeltaIgG was independently associated with poor outcome (p = 0.022). It seems that patients with a small increase in serum IgG level after IVIg may have a poor outcome; if confirmed, this is important because such patients may benefit from a higher dosage or second course of IVIg early in the disease course.

**Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)**

Chronic inflammatory demyelinating polyneuropathy (CIDP) is a distinct acquired demyelinating polyneuropathy characterized by the slow onset (over weeks to months) of weakness, areflexia, and impaired sensation. The immunopathologic alterations in CIDP, although fragmentary, are considered similar to Guillain-Barré syndrome. Molecular mimicry, antiglycolipid antibodies, T cell sensitization, myelin invasion by activated macrophages and activation of complement are the main immunopathological features of the disease. However, unlike GBS, which is a monophasic disease, CIDP requires long-term therapy to maintain improvement. Steroids have long been considered the first choice for treating CIDP, hence its designation as a “steroid-responsive neuropathy.” Evidence from controlled studies, however, has shown that plasmapheresis and IVIg are also effective and their efficacy is similar or even superior to steroids.

A randomized, controlled, crossover study compared a six-week course of oral prednisolone (tapered from 60 to 10 mg/d) with a two-day course of IVIg 1.0 g/kg/d for the treatment of CIDP. Treatment was switched after a four-week washout period. Both treatments produced significant improvements in disability after two weeks, although there was slightly more improvement with IVIg in the two treatment periods. Also observed were improvements favoring IVIg in the time to walk 10 meters after two weeks and disability grade after six weeks. Intravenous immunoglobulin was also equal to plasma exchange (PE) in a single-blind, controlled, crossover study of CIDP patients assigned to a 6-week course of PE or IVIg 0.2-0.4 g/kg given weekly. Similar improvements in neurological disability occurred with IVIg compared with placebo in a parallel controlled study.

The position of IVIg in the hierarchy of CIDP treatment was investigated in a three-year placebo-controlled study of IVIg in treatment-naïve patients. Patients received an infusion of IVIg 1.0 g/kg/d or placebo on days 1, 2, and 21. Differences in muscle strength favoring IVIg were seen as early as day 10, and this trend increased over time. At day 42, muscle strength had improved significantly more with IVIg than with placebo (P = .006), and functional performance was also significantly better (P = .019). These findings support IVIg as first-line therapy in the early inflammatory phase of CIDP, a strategy that could ameliorate the significant axonal degeneration that typically accompanies disease progression.

The IVIg-triggered improvement generally begins after a mean period of nine days and reaches maximum improvement after three to four weeks. Repeated treatments every three- to six-week intervals, usually with 1 g/kg, are needed to maintain response. It should be noted that sometimes a number of patients who initially responded to IVIg may show a less consistent response in subsequent infusions; such patients should be identified early to supplement their therapy with other agents. In general, CIDP may be more difficult to treat if axonal changes have become extensive, regardless of the regimen used.

The most important study in the use of IVIg, not only in CIDP but in neurology in general, was the ICE trial. This was the largest trial ever conducted involving 117 CIDP patients randomized to IVIg (Gammunex) or Placebo given every three weeks for 24 weeks (primary end point). Patients who showed an improvement at 24 weeks were re-randomized in a blinded 24-week extension. The study confirmed that 54% of those receiving Gammunex compared to 21% receiving placebo, improved their disability scores and maintained it up to 24 weeks (P = 0.0002). Results were similar in the extension phase for another 24 weeks. A strong and positive effect on quality of life was also noted; some electrophysiologic measurements also improved. The study not only confirmed the short-term efficacy of IVIg in CIDP but also established the long-term benefit and safety of maintenance therapy. The study led to the first FDA-
MMN responds remarkably well to IVIg therapy. The improvement was more pronounced in patients categorized as responders than in those without a response. Among patients with CIDP and opens the way to explore whether responsiveness to IVIg is dependent on genetic determinants.

Another marker recently explored in CIDP was the expression of inhibitory FcγRIIB on B cells. The FcγRIIB on B cells transduce inhibitory signals on B cells and prevent their transformation into IgG-producing plasma cells; as a result, mice lacking FcγRIIB develop autoimmune diseases. Patients with CIDP were found to have lower FcγRIIB on naïve B cells and failed to upregulate FcγRIIB develop autoimmune diseases. Mutated FcγRIIB protein expression was upregulated on monocytes in a large number of patients studied prospectively.

**Multifocal Motor Neuropathy**

Multifocal motor neuropathy (MMN) presents with a slow onset weakness and muscular atrophy, usually in the distal upper extremities, with areflexia and preserved sensation. The disease is characterized by conduction block of the motor axons and, in many patients, by the presence of antibodies to the GM1 ganglioside. Unlike CIDP, MMN does not respond to steroids or plasmapheresis. However, based on controlled trials and several open-label studies, MMN responds remarkably well to IVIg therapy. The improvement usually begins after seven to 10 days, as in CIDP, and predictably lasts for four to six weeks, at which time a new infusion is required either with 2 gm/kg or 1 gm/kg. We have noticed that even chronic cases of MMN with already significant loss of motor axons can respond to a certain degree. As symptoms diminish, the electrophysiologic conduction block may resolve.

Therapy with IVIg is currently the treatment of choice in MMN. However, some patients may not respond adequately after a period of time, probably because of further progression of the underlying disease and axonal degeneration. In these circumstances, Rituximab or intravenous cyclophosphamide, as much as 1 g/m² body surface area, may be helpful. The long-term maintenance therapy with IVIg was investigated in 11 MMN patients, followed for four to eight years. Patients initially received IVIg 0.4 g/kg/d for 5 days followed by one 0.4-g/kg infusion every week for one year and, as needed, in subsequent years with a mean dose of 7-48 g/wk. Muscle strength improved significantly within three weeks of IVIg treatment but declined slightly and significantly during the follow-up period. Interestingly, electrophysiologic changes consistent with improvement (remyelination or reinnervation) and worsening (demyelination or axon loss) occurred simultaneously in different nerves. Conduction block also disappeared in some nerve segments but appeared in others. These results contrast with those from Vucic et al who were able to maintain response when the monthly infusions of IVIg were kept high up to 2 gram/kg monthly (instead of less than 1 gram/kg as in the Dutch study). Although the optimal maintenance dose remains still empirical, the latter study suggests that IVIg, at the full maintenance dose, has the potential to arrest disease progression and prevent axonal degeneration. Patients with amyotrophic lateral sclerosis (ALS), which sometimes resembles MMN, do not respond to IVIg. In a study of nine patients with ALS, IVIg treatment failed to change the course of the disease.

**Paraproteinemic Demyelinating Polyneuropathies**

Demyelinating polyneuropathies associated with IgG or IgA monoclonal gammopathies respond to IVIg therapy like patients with CIDP. Patients with IgM monoclonal gammopathy and demyelinating polyneuropathy (IgM-DP), however, form a distinct subset. More than 50% of these patients have antibodies against myelin-associated glycoprotein (MAG) and sphingoglycolipids and comprises a more uniform group, which is clinically characterized by a predominantly sensory ataxic or a sensorimotor neuropathy. Because patients with anti-MAG neuropathies respond poorly to therapies, a double-blind controlled study with IVIg was performed. The study was prompted after the improvement observed in two patients treated with IVIg in an open-labeled fashion.

Eleven patients were randomized to IVIg or placebo, given monthly for three months in a double-blind study; after a washout period, they crossed over to the alternate therapy. The trial showed modest, but not significantly different, benefits. After IVIg, strength improved in only two of 11 patients and declined after placebo; in one other patient, only the sensory scores improved. Antibody titers to MAG/SGPG or gangliosides did not change appreciably. A second trial conducted in Europe, also showed modest benefits which were statistically significant only in the secondary end-points. Because elevated IgM may cause high serum viscosity which can be further increased with IVIg as discussed below, caution is needed when IVIg is infused in such patients to avoid triggering thromboembolic events. Because the disease responds to Rituximab, based on a controlled study, Rituximab is becoming the treatment of choice for the IgM anti-MAG neuropathy.
Myasthenia Gravis

Myasthenia gravis (MG) is characterized by fluctuating weakness or fatigability of the extraocular, bulbar, respiratory, and limb muscles. Diplopia, dysphagia, and dysarthria are common. Myasthenia is the prototypic autoimmune disease mediated by pathogenic autoantibodies against the acetylcholine receptor (AChR) and possibly against muscle specific kinase (MuSK).

Patients with MG respond fairly well to the available therapies, such as anticholinesterases, thymectomy, steroids, azathioprine, cyclosporine and plasmapheresis. The need for another effective immunomodulating therapy without long-term side effects has prompted experimentation with high-dose IVIg.

As reviewed previously, IVIg is promising for disease exacerbations, but the evidence is weak regarding the chronic management of the disease or as a steroid-sparing agent. The first randomized study compared the efficacy and tolerance of two doses of IVIg to plasma exchange in MG exacerbations. A total of 87 patients were randomized to receive either three courses of PE or IVIg 0.4 g/kg/d for three to five days. The study demonstrated similar efficacy, measured by variation in myasthenic muscular score, in both the PE and IVIg groups; the anti-AChR antibody titers fell by about two thirds in both groups among. Interestingly, the three-day IVIg regimen was slightly superior to the five-day regimen, although methodologic deficiencies limit a rigorous comparison. A second large controlled study conducted also by the same group, randomized 173 patients to 1g/kg IVIg for one day or to 2g/kg for two days. At day 15, the myasthenic scores improved equally in both groups concluding that IVIg is efficacious in MG but that there is no difference between 2 g/kg versus 1.0 g/kg.

A recent trial compared IVIg to placebo in MG patients who had “worsening weakness” defined as increasing symptoms or signs severe enough (as judged by both the patient and the physician) to warrant a change in therapy. Fifty-one AChR-positive patients were randomized to receive either IVIg 2g/kg or the equivalent volume of dextrose 5% over two days. The main endpoint was the change in Quantitative MG scores (QMGS) from baseline (day 0) to day 14. On day 14, the mean change in QMGS was -2.5 in the IVIg group and -0.9 in the placebo group (p = 0.047). On day 28, these values were -3 in the IVIg group and -1.2 in the placebo group (p = 0.055). For the mild MG cases, the mean change in QMGS on day 14 was similar in the two groups: -0.7 in the IVIg group and -1.1 in the placebo group. The only significant difference was noted for the moderate to severe MG group where these values were -4.1 in the IVIg group and -0.7 in the placebo group (p = 0.01); that treatment effect was maintained at day 28. This study, has several limitations. First, the effect was modest, as patients improved by 2.54 QMG units compared to 0.89 in the placebo; considering that individual QMG scores usually vary up to 2.6 units, this effect might not have been clinically meaningful. Second, the effect did not reach the 3.5 units cited as clinically significant and used to calculate the sample size. Third, it was statistically significant (by more than 4.1 points) only in a small number of patients with severe MG, suggesting that the study lost power because of including patients with less severe disease. Fourth, the definition of “worsening weakness” was rather subjective.

Two additional randomized controlled studies have addressed the efficacy of IVIg for the treatment of moderate to severe but stable MG, one comparing IVIg to plasma exchange and the other to placebo. None showed a significant difference.

From these data, along with other published series and our own observations, several conclusions can be drawn, as recently discussed. First, the majority of patients with MG exacerbations can respond to IVIg therapy. The improvement is seen early, beginning after a mean period of three to 10 days lasting for a mean period of 30 days. Second, IVIg appears to be as effective as plasmapheresis, but for myasthenic crises plasmapheresis is superior. Third, the role of IVIg in the chronic management of MG has not yet been established. The numbers of confounding factors involved in deciding the best therapy of MG at a given state of the disease demand carefully designed studies, clear objectives, accurate assessment of efficacy, and precise control of the concomitant immunosuppressive drugs. At present and until further controlled trials are conducted, IVIg may be justified in lieu of plasmapheresis: a) for acutely worsening disease to prevent or minimize impending bulbar or respiratory failure; b) prepare a weak patient for thymectomy and c) as adjuvant to immunosuppressive therapies and periodically (every one to three months) to minimize the long-term side effects or stabilize a patient until immunosuppressants, such as azathioprine or cyclosporin, become effective.

Lambert-Eaton Myasthenic Syndrome

Patients with LEMS have a presynaptic neuromuscular junction defect that results in proximal muscle weakness, oculomotor signs and autonomic dysfunction. The symptoms are caused by antibodies against presynaptic voltage-gated calcium channels resulting in decreased acetylcholine release. Patients respond to dexamethasone, steroids and azathioprine. Even though IVIg is rarely needed, a controlled study has been conducted comparing IVIg to placebo. The IVIg-randomized patients showed a statistically significant increase in muscle strength compared to placebo, which peaked at two to four weeks and declined by eight weeks. The effectiveness of IVIg was associated with a statistically significant reduction of antibodies against voltage-gated calcium channel. IVIg is useful in difficult cases of LEMS, especially when steroids and azathioprine are not very effective or cause significant side effects.

Inflammatory Myopathies

The main subsets in this group include: Dermatomyositis, Polymyositis and Inclusion Body Myositis.
Dermatomyositis is an acquired myopathy causing proximal muscle weakness and a violaceous rash on the face and extremities. Early deposition of membranolytic attack complex (MAC) on the endomyal capillaries leads to capillary destruction, muscle ischemia, and inflammation.\textsuperscript{16,17} The disease responds to steroids but often becomes steroid-resistant. Azathioprine, methotrexate, or cyclosporine offer modest benefit but rarely cause a remission. Administration of IVIg to patients with dermatomyositis has proven effective. In a double-blind, placebo-controlled study, 15 patients with treatment-resistant dermatomyositis received IVIg 2.0 g/kg or placebo once a month for three months, with the option of crossing over to the alternative therapy for three more months.\textsuperscript{18} At the end of the first three-month treatment phase, IVIg-treated patients experienced a significant improvement in MRC (Medical Research Council) scores (\(P < .018\)) and neuromuscular symptoms (\(P < .035\)) compared with those receiving placebo. Marked improvements were also noted in the active violaceous rash or the chronic scaly eruptions.\textsuperscript{18} In subsequent open-label infusions, the benefit of IVIg has been documented in a large number of patients treated by us or under our supervision, and by several investigators throughout the world.\textsuperscript{107,108} Repeat open muscle biopsies on patients who clinically improved have shown marked improvement in the muscle cytoarchitecture including muscle fiber diameter, revascularization with increased number of capillaries per fiber, and reduction of inflammation and connective tissue.\textsuperscript{18} Immunopathologically, it was shown that IVIg inhibits the deposition of MAC on the endomyal capillaries by intercepting the incorporation of C3 into the C5 convertase assembly, downregulates the expression of the intercellular adhesion molecule (ICAM-I) on the endomysial capillaries and the major histocompatibility complex class I (MHC-I) antigen on muscle fibers, and reduces the expression of TGF-\(\beta\)1 protein and mRNA in connective tissue.\textsuperscript{19,107,108} IVIg also modified certain immunoregulatory and structural genes in the muscles of DM patients who responded to IVIg therapy, as determined by gene array studies.\textsuperscript{109} Although a controlled study was never performed, IVIg is also effective in patients with polymyositis. Because both polymyositis and dermatomyositis initially responds to steroids, IVIg therapy is best reserved as second line add-on therapy in patients who are not adequately controlled with combination of steroids and methotrexate or azathioprine, and for patients who are immunodeficient or in whom steroids are contraindicated.\textsuperscript{110}

Inclusion-body myositis (IBM) is the most common acquired inflammatory myopathy in patients above the age of 50 years. Immunopathologically, IBM is identical to polymyositis, characterized by sensitized, antigen-driven cytotoxic T cells that invade MHC-I expressing muscle fibers.\textsuperscript{15,17} What makes IBM unique however is the presence of vacuolated fibers which contain amyloid deposits. The disease is resistant to most immunosuppressive medications. The efficacy of IVIg was tested in 19 patients with IBM in a study designed similarly to the previously mentioned dermatomyositis trial.\textsuperscript{107,111} In the IVIg-treated group, there was an increase in muscle scores compared to placebo, but the differences were not statistically significant, perhaps because the study lacked sufficient power.\textsuperscript{111} Nonetheless, significant regional differences occurred in IVIg-treated patients, especially in the swallowing function which improved significantly in patients receiving IVIg compared with those receiving placebo (\(P < .05\)). The mild benefits noted in certain muscle groups, prompted a larger study aimed to investigate the potential synergistic effect of IVIg with prednisone.\textsuperscript{112} Thirty-six patients were randomized to IVIg 2.0 g/kg or placebo once a month for three months. Before infusions, all patients received prednisone (tapered from 60 mg/d). After 3 months of treatment, there was no significant difference in muscle strength score, between the IVIg-plus-prednisone group and the placebo-plus-prednisone group. A third trial showed similar results.\textsuperscript{113} In spite of these negative trials, a few patients may show transient signs of improvement which, although minor and difficult to capture with the methods used, can be at times clinically significant for the patients’ activities and lifestyles, at least for a period of time. When life-threatening dysphagia is apparent, IVIg is a treatment option in view of the positive results noted above.\textsuperscript{114}

**Stiff Person Syndrome (SPS)**

Stiff Person Syndrome (SPS) is a disabling central nervous system disorder characterized by muscle rigidity, episodic muscle spasms, and high titers of antibodies against glutamic acid decarboxylase (GAD65), the rate-limiting enzyme for synthesis of gamma-aminobutyric acid (GABA). Various other autoantibodies (e.g., anti-amphiphysin) are also present.\textsuperscript{115}

Drugs that enhance GABA neurotransmission, such as diazepam, provide only mild to modest relief of clinical symptoms; however, treatment with IVIg confers substantial benefit. This improvement was documented in a placebo-controlled crossover study in 16 patients administered IVIg 2.0 g/kg or placebo once a month for three months.\textsuperscript{114} Efficacy was assessed with the use of an objective distribution-of-stiffness index and heightened-sensitivity scale. Among patients initially treated with IVIg, stiffness scores decreased significantly (\(P = .02\)) and heightened-sensitivity scores declined markedly, but they rebounded during placebo administration; the opposite pattern occurred among those treated with placebo first. Eleven patients who received IVIg were able to walk more easily or without assistance and to perform work-related or household tasks; their frequency of falls decreased. The study convincingly showed that IVIg is effective as supplementary therapy in patients with SPS.\textsuperscript{110}

**Treatment Considerations**

The therapeutic dose of IVIg is empirically set at 2 g/kg. Although past practice has been to divide the total dose for infusion into...
five daily doses of 400 mg/kg each, the preference now is to di-
vide the total dose into two daily doses of 1 g/kg each especially
in younger patients who have normal renal and cardiovascular
function. In our experience, the two-day infusion is not associ-
ated with more adverse reactions than the five-day infusion, and
it is preferable except for patients with major cardiovascular
risks. In children with Kawasaki syndrome, a single, large, 2 g/kg
dose of IVIg given in a 10-hour infusion was more effective than
four daily infusions of 400 mg/kg each. Similar experience was
noted in children with Guillain-Barré syndrome. The new ICE
trial in CIDP was also conducted with a two-day infusion with ex-
cellent safety and tolerance profile.

In general, adverse reactions to IVIg therapy are usually minor
and occur in no more than 10% of the patients with neurological
disorders (see the box below for a brief list). Mild to moderate
headache, which responds to nonsteroidal anti-inflammatory
medications, is common. Chills, myalgia, or chest discomfort
may develop in the first hour of the infusion and usually re-

### Adverse Reactions to IVIg Therapy

- **Serum Viscosity and Thromboembolic Events.** IVIg therapy
  causes an increase in serum viscosity, up to 0.5 centipoise, and
  in patients with high-normal or slightly elevated serum viscously,
  such as those with cryoglobulinemia, hypercholesterolemia,
  or hypergammaglobulinemia, the viscosity level increases even
  further. Serum viscosity greater than 2.5 cp (normal, 1.2-1.8
  cp) increases the risk of thromboembolic events and may be
  one of the factors responsible for rare cases of stroke, pul-
  monary embolism or myocardial infarction noted after IVIg
  treatment. Patients with recent deep vein thrombosis,
  or immobilized patients who are at higher risk of having a sub-
  clinical thrombosis, may be more prone for developing a throm-
  boembolic event after IVIg. In such patients, prudence in
  justifying the use of IVIg, screening the legs with an ultrasound
  for subclinical clots, and very slow infusion rate are recom-
  mended. Whether low-dose heparin or anti-platelet agents can
  prevent thromboembolic events in such patients is uncertain.
  A reversible cerebral vasospasm has also been noted.

- **Migraine Headache.** In patients with a history of migraine,
  IVIg therapy may trigger a migraine attack, which can be pre-
  vented by pretreatment with propranolol. The occurrence of
  aseptic meningitis, discussed below, is also high in mignain-
  ous patients. IVIg therapy has been associated with a stroke
  in a young woman with a history of migraine.

- **Aseptic Meningitis.** Aseptic meningitis develops in some pa-
  tients treated with IVIg. Its occurrence is unrelated to the pro-
  prietary product, the rate of infusion, or the underlying
disease. Prophylaxis with intravenous steroids is often in-
  effective. The symptoms respond to strong analgesia and
  subside in 24 to 48 hours. Additional diagnostic testing is
  rarely necessary.

- **Skin Reactions.** Skin reactions to IVIg therapy, although rare, can
develop two to five days after the infusions and may last up to
30 days. They include urticaria, lichenoid cutaneous lesions, pru-
ritus of the palms, and petechiae of the extremities. Skin re-
actions, associated with various lots of IVIg, have occurred in
seven of the 120 patients we had initially treated.

- **Severe Anaphylactic Reaction.** A severe anaphylactic reaction has been
reported in patients with an absence or severe defi-
cency of IgA who also have anti-IgA antibodies. Selective IgA
deficiency is common (prevalence about 1:1000), but asympto-
matic. About 29% of these individuals have anti-IgA antibodies,
which do not necessarily predict the development of adverse re-
actions. Theoretically, when these patients receive IVIg, the
small amount of IgA present with the IVIg may lead to anaphy-
laetic reaction due to formation of macromolecular complexes
between the infused IgA and circulating anti-IgA antibodies. The
reaction is rare and we have not seen it, nor has it been reported
to our knowledge, in neurological patients; it may occur in pa-
tients with common variable immunodeficiency.

- **Renal Tubular Necrosis.** Acute renal tubular necrosis, mostly
  reversible, occurs rarely with IVIg therapy in patients who have
  pre-existing kidney disease and volume depletion, especially
  the elderly and those with diabetes or poor hydration. It is
  usually reversible, but rare fatalities have been noted. Serum
  creatinine may rise one to 10 days after the infusion but
  returns to baseline within two to 60 days of discontinuation.
  This complication has often, but not exclusively, been associ-
  ated with the high concentration of sucrose in some propri-
  etary IVIg products. Osmotically induced tubular injury and
  vacuolization are the common histopathological findings on
  renal biopsy. Identical osmotic tubular nephrosis is caused
  by intravenous solutions containing a concentration of hyper-
tonic sucrose similar to that of IVIg. Diluting the IVIg prepa-
  ration, slowing the rate of infusion or selecting products with
  low osmolality minimizes the risk. In patients with pre-existing
  kidney disease, if there is no alternate therapy to IVIg treat-
  ment, close monitoring of creatinine and BUN are essential.

- **Spurious Results on Serological Tests.** After IVIg therapy, the
  erythrocyte sedimentation rate increases sixfold or more, prob-
  ably as the result of enhanced rouleaux formation and re-
duced surface area caused by the infused gamma globulin. This
  increase can persist for two to three weeks, and should
  not be considered a sign of a developing vasculitis. We have
  also observed hyponatremia, with sodium concentrations as
  low as 130 mg/l (normal, 135-145 mg/l), after IVIg therapy, but
  not after placebo use. Hyponatremia appears to be related to
  the assay method used to measure Na⁺ because additional
dilution of the sample is required owing to the high serum
protein concentration that follows IVIg infusion.
sponds to stopping the infusion for 30 minutes and resuming it at a slower rate. Post-infusion fatigue, fever, or nausea may occur and last for up to 24 hours. The cause of these reactions is unclear, but activation of complement by aggregated immunoglobulin molecules or various stabilizing agents in the IVIg preparation have been implicated. A slow rate of infusion is advisable in patients with a compromised cardiovascular system or congestive heart failure to avoid rapid fluid overload.

References
2. Dalakas MC. Intravenous immunoglobulin in autoimmune neuromuscular diseases. JAMA. 2004; 291:2367-2375


Dalakas MC. Inhibiting leucocyte recruitment to the brain by IV Ig. Is it relevant to the treatment of demyelinating CNS disorders? (Editorial) Brain 2004;127:2569-2571.


