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Intravenous Immunoglobulin in Autoimmune Neuromuscular Diseases

Marinos C. Dalakas, MD

AUTOIMMUNE DISEASES AFFECT more than 8.5 million Americans and cause significant morbidity and disability.¹ Neurologic disorders represent about half of the diseases for which there is evidence of autoimmune pathogenesis. Although immunopathologically distinct, most autoimmune neurologic diseases fall into 4 general categories: the autoimmune neuropathies, which include Guillain-Barré syndrome and its variants, chronic inflammatory demyelinating polyneuropathy (CIDP) and its variants, multifocal motor neuropathy, and paraproteinemic demyelinating neuropathies; the autoimmune neuromuscular junction defects, which include myasthenia gravis and Lambert-Eaton myasthenic syndrome; the inflammatory myopathies, which include dermatomyositis, polymyositis, and inclusion body myositis^{2,3}; and a number of central nervous system disorders, of which multiple sclerosis (MS) and stiff-person syndrome are most representative.

Substantial progress has been made recently in elucidating the immunopathogenesis of these diseases and introducing evidence-based treatment. Among the new immunotherapies, intravenous immunoglobulin (IVIG) has emerged as a major force, providing safe and effective long-term therapy and relieving previously untreatable conditions. This article reviews the immunology of autoimmune neuromuscular

Context Intravenous immunoglobulin (IVIG) enhances immune homeostasis by modulating expression and function of Fc receptors, interfering with activation of complement and production of cytokines, providing anti-idiotypic antibodies, and affecting the activation and effector functions of T and B cells. These mechanisms may explain the effectiveness of IVIG in autoimmune neuromuscular disorders.

Objective To systematically review the current status of the treatment of autoimmune neuromuscular diseases with IVIG, with emphasis on controlled trials.

Data Sources Peer-reviewed publications identified through MEDLINE (1966-2003), EMBASE (1974-2003), and references from bibliographies of pertinent articles. Each autoimmune neuromuscular disease term was searched in combination with the term *intravenous immunoglobulin*.

Study Selection and Data Extraction Criteria for selection of studies included controlled study design, English language, and clinical pertinence. Data quality was based on venue of publication and relevance to clinical care.

Data Synthesis Outcomes of controlled trials indicate that IVIG at a total dose of 2 g/kg is effective as first-line therapy in Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, and multifocal motor neuropathy and as second-line therapy in stiff-person syndrome, dermatomyositis, myasthenia gravis, and Lambert-Eaton myasthenic syndrome. In other controlled studies, IVIG produced a modest, variable, and transient but not statistically significant benefit in patients with inclusion body myositis and paraproteinemic anti-myelin-associated glycoprotein antibody demyelinating polyneuropathy. Intravenous immunoglobulin is not effective in patients with multiple sclerosis who have established weakness or optic neuritis. In myasthenia gravis, it should be reserved for difficult cases or before thymectomy in lieu of plasma exchange.

Conclusion Intravenous immunoglobulin is effective in many autoimmune neurologic diseases, but its spectrum of efficacy, especially as first-line therapy, and the appropriate dose for long-term maintenance therapy are not fully established. Further controlled studies of IVIG, combined with a dose-finding effect, pharmacoeconomics, and quality-of-life assessments, are warranted to improve the evidence base for clinical practice.

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diseases and summarizes the use of IVIG based on controlled clinical trials.

METHODS

Peer-reviewed publications identified through searches of MEDLINE (1966-2003), EMBASE (1974-2003), and references from bibliographies of pertinent articles for IVIG-related data were systematically reviewed. Each autoimmune neuromuscular disease term was searched in combination with the

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term *intravenous immunoglobulin*. Criteria used for study selection included controlled study design, English language, pertinence for clinicians, and validity based on power analysis and venue of publication.

DATA SYNTHESIS

Immunopathogenesis of Autoimmune Neuromuscular Diseases

Autoimmune neurologic diseases result from loss of immune tolerance to self-antigens through various mechanisms, such as defective clonal deletion and “molecular mimicry.” In the latter, epitopes on microbial agents are presented by antigen-presenting cells to the T-cell receptor and thereby lead, via the effect of costimulatory molecules, to clonal expansion of T cells. These expanded T cells transmigrate across the vascular endothelium of the blood-nerve or blood-brain barrier to target tissues, where they exert a cytotoxic action.²⁻⁵ Additionally, autoantibodies, produced by B-cell clones from the interactions of T cells, interleukin 4, and interleukin 6, recognize targeted neural or muscle tissues via either macrophages or complement fixation. Cytokines secreted by the T cells upregulate intercellular adhesion molecule 1, vascular cell adhesion molecule 1, or matrix metalloproteinases in endothelial cells, allowing the transmigration of activated lymphocytes; cytokines also stimulate resident macrophages to bind via the Fc receptors to the targeted tissues.

In Guillain-Barré syndrome, the immunopathogenesis likely involves antibody responses against bacterial structures, especially those of *Campylobacter jejuni*, that mimic neural glycolipids and gangliosides, thereby breaking tolerance.^{2,3,6-11} In particular, patients with severe Guillain-Barré syndrome and marked axonal degeneration often have IgG antibodies against GM1, GD1b, or GD1a gangliosides expressed in peripheral nerves.⁶⁻¹¹ Antibodies to GQ1b ganglioside are very closely associated with Miller-Fisher syndrome, a related disorder.^{9,11} Data on the immunopathol-

ogy of CIDP are more fragmentary; however, molecular mimicry, antiglycolipid antibodies, and T-cell involvement are also the main immunopathologic features of CIDP.^{12,13} Antibodies against myelin-associated glycoprotein may mediate demyelination in patients with neuropathy and IgM-monoclonal gammopathy; in multifocal motor neuropathy, anti-GM1 antibody titers may be elevated, but their pathogenetic role remains unclear.^{2,14} Some of the effector mechanisms that underlie myelin destruction have been described.^{2,13} In Guillain-Barré syndrome and CIDP, for example, activated macrophages invade myelin or release injurious molecules (eg, cytokines),^{2,13} while circulating antibodies may cause myelin damage by activating the complement system, generating chemotactically active split products, and assembling the membrane attack complex (MAC).^{15,16} Such antibodies may also target the myelin sheath by binding to the Fc receptors of activated macrophages that invade the myelinated nerve fibers.

Similar immune-mediated mechanisms also play a primary role in the immunopathogenesis of inflammatory muscle diseases.¹⁷⁻²⁰ The serum of patients with active dermatomyositis has high levels of complement fragments and MAC, which are deposited on capillaries within the muscle parenchyma, leading to capillary loss and muscle fiber necrosis.²⁰ In polymyositis and inclusion body myositis, but not dermatomyositis, autoinvasive CD8⁺ cytotoxic T cells are clonally expanded, presumably by muscle-specific autoantigens, in the context of class I major histocompatibility complex expression.²⁰

Myasthenia gravis is the prototypical autoimmune disorder of the neuromuscular junction because 2 antigens, the acetylcholine receptor and the muscle-specific receptor tyrosine kinase,^{21,22} have been well characterized; anti-acetylcholine receptor or anti-muscle-specific receptor tyrosine kinase antibodies are detected and measured.^{21,22} Likewise, Lambert-Eaton myasthenic syndrome is a disease of neuromuscular transmission in which IgG

autoantibodies directed against voltage-gated calcium channels in motor nerve terminals play a crucial role in the deficient release of acetylcholine.²³ Molecular mimicry, with similar antigens in motor nerve terminals and in tumors, may explain the frequent association of Lambert-Eaton myasthenic syndrome with malignancies, especially small-cell lung cancer.²⁴

The therapeutic function of IVIG in autoimmune neuromuscular diseases is complex (FIGURE 1). Intravenous immunoglobulin affects all the components the immune regulatory network. Its effects include interference with costimulatory molecules; provision of anti-idiotypic antibodies or suppression of antibody production; interference with the activation of complement and interception of MAC formation; modulation of the expression and function of Fc receptors on macrophages; suppression of cytokines, chemokines, and adhesion molecules; and alteration of the activation, differentiation, and effector functions of T cells.²⁵⁻³⁴

The supply of idiotypic antibodies or suppression of antibody production are relevant to the activity of IVIG in Guillain-Barré syndrome, myasthenia gravis, stiff-person syndrome, and Lambert-Eaton myasthenic syndrome.³⁴ The inhibition of complement binding and prevention of MAC formation are relevant in dermatomyositis, Guillain-Barré syndrome, CIDP, and myasthenia gravis,³⁵ whereas modulation of Fc receptors on macrophages is relevant in CIDP, Guillain-Barré syndrome, and inflammatory myopathies.³⁴ Suppression of pathogenic cytokines, chemokines, and adhesion molecules on endothelial cells has putative relevance in inflammatory myopathies and demyelinating neuropathies. These combined effects of IVIG translate into clinical efficacy, as documented in controlled clinical trials (TABLE).

Autoimmune Neuropathies

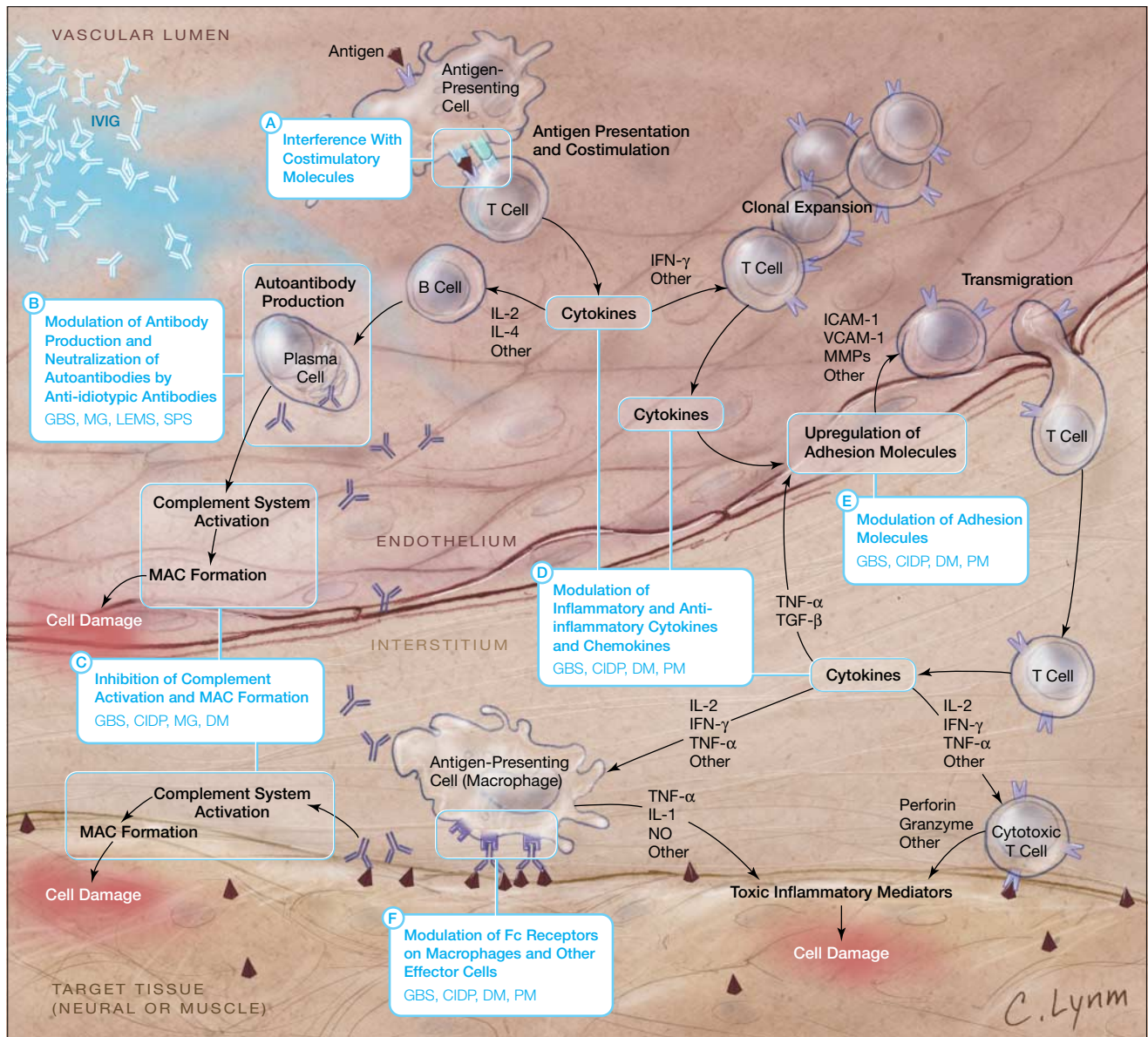
Guillain-Barré syndrome is the most common cause of acute muscle weakness in the developed world. Patients

often present with a rapidly ascending paralysis together with variable autonomic involvement and sensory symptoms.⁶ Plasma exchange hastens recovery

ery from Guillain-Barré syndrome, but IVIG is comparable with plasma exchange in improving symptoms and reducing time to recovery.

An early controlled trial found that IVIG, 0.4 g/kg per day for 5 days, improved motor function and facilitated recovery in significantly more patients

Figure 1. Immunomodulatory Actions of IVIG in Autoimmune Neuromuscular Diseases



Intravenous immunoglobulin (IVIG) modulates multiple immunologic events (blue boxes) involved in the pathogenesis of autoimmune neuromuscular diseases. Diseases for which specific therapeutic actions of IVIG are supported by experimental evidence are listed in each box. In autoimmune neuromuscular diseases, an antigen, through molecular mimicry, defective clonal deletion, or other mechanisms, triggers an immune response that results in loss of immune tolerance to self-antigens. Infused IVIG interferes with costimulatory molecules involved in antigen presentation and modulates subsequent immunologic events. These events, mediated by activation of B cells with production of autoantibodies and by T cells, lead to tissue damage via complement activation, macrophage-Fc receptor interaction, and cytotoxic T cells. Other possible therapeutic actions of IVIG not shown in this illustration include increased catabolism of IgG, alteration of effector functions of T cells, and modulation of apoptosis. CIDP indicates chronic inflammatory demyelinating polyneuropathy; DM, dermatomyositis; GBS, Guillain-Barré syndrome; ICAM-1, intercellular adhesion molecule 1; IFN- γ , interferon γ ; IL, interleukin; LEMS, Lambert-Eaton myasthenic syndrome; MAC, membrane attack complex; MG, myasthenia gravis; MMP, matrix metalloproteinase; NO, nitric oxide; PM, polymyositis; SPS, stiff-person syndrome; TGF- β , transforming growth factor β ; TNF- α , tumor necrosis factor α ; VCAM-1, vascular cell adhesion molecule 1.

Table. Controlled Clinical Trials of IVIG in Autoimmune Neuromuscular Diseases

Study	Treatment	No. of Participants	Outcomes
Guillain-Barré Syndrome			
Van der Meche and Schmitz, ³⁶ 1992	IVIG (0.4 g/kg per day for 5 days) vs plasma exchange	150	Improved strength in significantly more IVIG-treated than plasma exchange-treated patients ($P = .024$)
Plasma Exchange/Sandoglobulin Guillain-Barré Syndrome Trial Group, ³⁷ 1997	IVIG (0.4 g/kg per day for 5 days) vs plasma exchange vs IVIG + plasma exchange	383	No significant difference in change in disability, time to unaided walking, or discontinuation of ventilation
Raphael et al, ³⁹ 2001	IVIG (0.4 g/kg per day for 3 or 6 days)	39	Nonsignificantly shorter time to assisted walking in 6-day group than in 3-day group ($P = .08$) but significant superiority for 6-day group in patients with ventilation ($P = .04$)
Chronic Inflammatory Demyelinating Polyneuropathy			
Hughes et al, ⁴¹ 2001	IVIG (1.0 g/kg per day for 2 consecutive days) vs prednisolone	32	Slightly more improvement in disability with IVIG than with prednisolone; increased quality of life in IVIG group
Dyck et al, ⁴² 1994	IVIG (0.2-0.4 g/kg per week for 6 weeks) vs plasma exchange	20	Similar improvements in neurological disability score with IVIG and plasma exchange
Mendell et al, ⁴⁴ 2001	IVIG (1.0 g/kg per day on days 1, 2, and 21) vs placebo	33	Significantly improved muscle strength with IVIG compared with placebo at day 42 ($P = .006$); differences favoring IVIG seen at day 10; data support IVIG as initial treatment
Multifocal Motor Neuropathy			
Federico et al, ⁵¹ 2000	IVIG (0.4 g/kg per day for 5 days) vs placebo	16	Significantly improved neurologic disability with IVIG ($P = .038$) but worse with placebo; significantly improved grip strength with IVIG ($P = .0021$) but worse with placebo
Van den Berg-Vos et al, ⁵² 2002	IVIG (0.4 g/kg per day for 5 days followed by 0.4 g/kg per week for 1 year)	11	Muscle strength improved with IVIG but declined from peak during long-term follow-up; long-term benefit of IVIG but disease continues to progress
IgM Paraproteinemic Demyelinating Neuropathy			
Dalakas et al, ⁵⁵ 1996	IVIG vs placebo	11	Modest improvement in strength in 2 of 11 patients with IVIG
Comi et al, ⁵⁶ 2002	IVIG (2 g/kg over 24-48 hours) vs placebo	22	Significant decrease in overall disability ($P = .001$) with IVIG on secondary outcomes (ie, Rankin scale scores, time to walk 10 m, grip strength, sensory symptoms score)
Myasthenia Gravis			
Gajdos et al, ⁵⁷ 1997	IVIG (0.4 g/kg per day for 3 or 5 days) vs plasma exchange	87	Variation in myasthenic muscular score similar with IVIG and plasma exchange
Gajdos, ⁵⁸ 2004	IVIG (1 g/kg per day for 1 day vs 2 g/kg per day for 2 days)	173	Scores improved equally in both groups at day 15
Lambert-Eaton Myasthenic Syndrome			
Bain et al, ⁵⁹ 1996	IVIG (1.0 g/kg per day for 2 days) vs placebo		Significant improvement in 3 strength measures ($P = .017-.038$) with IVIG compared with placebo; significant decline in serum calcium channel antibody titers ($P = .028$) with IVIG compared with placebo
Dermatomyositis			
Dalakas et al, ⁶³ 1993	IVIG (2 g/kg per month for 3 months) vs placebo	15	Significant improvement in muscle strength ($P < .018$) and neuromuscular symptom scores ($P < .035$) with IVIG compared with placebo; improved muscle cytoarchitecture; downregulation of class I major histocompatibility complex, transforming growth factor β , and intercellular adhesion molecule 1 expression by muscle
Inclusion Body Myositis			
Dalakas et al, ⁶⁶ 1997	IVIG (2 g/kg per month for 3 months) vs placebo	19	Nonsignificantly better strength scores overall with IVIG than with placebo, but significantly improved duration of swallowing functions ($P < .05$)
Dalakas et al, ⁶⁸ 2001	IVIG (2 g/kg per day for 3 months) + prednisone vs placebo + prednisone	36	No significant difference in strength scores between IVIG + prednisone and placebo + prednisone
Stiff-Person Syndrome			
Dalakas et al, ⁷¹ 2001	IVIG (2 g/kg per month for 3 months) vs placebo	16	Significant decrease in stiffness scores ($P = .02$) and substantial decrease in heightened-sensitivity scores with IVIG compared with placebo; rebound during placebo treatment; some long-term benefit

Abbreviation: IVIG, intravenous immunoglobulin.

with Guillain-Barré syndrome than did plasma exchange.³⁶ Although both treatments are beneficial, combining plasma exchange with IVIG produces no incremental benefit. In a large controlled study (N=383) comparing a 5-day regimen of IVIG, 0.4 g/kg per day alone, plasma exchange alone, and IVIG plus plasma exchange, there were no significant differences among treatment groups in mean change in disability 4 weeks after randomization.³⁷ There were also no significant differences in secondary outcome measures, including time to unaided walking and discontinuation of ventilation. Results from another controlled study suggest that IVIG plus methylprednisolone might not be superior to IVIG alone in patients with Guillain-Barré syndrome.³⁸

Insight into optimal IVIG dosing in Guillain-Barré syndrome was provided in a French multicenter controlled trial comparing IVIG, 1.2 g/kg given in a 3-day regimen, and 2.4 g/kg given in a 6-day regimen.³⁹ Time to walking with assistance was shorter in the 6-day treatment group (84 vs 131 days) and significantly shorter in those who received ventilation. The proportion of patients who recovered full muscular strength at 1 year was also greater in the 6-day treatment group. Thus, IVIG may be more beneficial when given in a full dose of at least 2 g/kg, especially in patients who need ventilatory assistance. Whether a second IVIG infusion is needed in patients with incomplete recovery, as suggested,⁴⁰ remains unclear because the natural course of the disease confounds assessment. The usefulness of IVIG in mild, ambulatory cases has not been established.

Since plasma exchange is not readily available, IVIG has now become the treatment of choice for Guillain-Barré syndrome. Combining plasma exchange or steroids with IVIG does not confer a significant advantage. Although IVIG works in Guillain-Barré syndrome via a combination of factors illustrated in Figure 1, its effect on neutralizing neuromuscular blocking antibodies, probably via the effect of anti-idiotypes, has been demonstrated *in vitro*.^{31,32}

Chronic Inflammatory Demyelinating Polyneuropathy. Clinically, CIDP is characterized by progressive symmetric proximal and distal weakness, sensory loss, and areflexia.^{2,13} Unlike Guillain-Barré syndrome, which is a monophasic disease, CIDP is a slowly progressive or relapsing disease that requires long-term therapy to maintain improvement.^{2,13,33} Controlled studies have confirmed the value of steroids and plasma exchange in CIDP. Traditionally, the former has been considered the criterion standard of treatment, but evidence from controlled trials indicates that the efficacy of IVIG is similar to that of steroids or plasma exchange, at least for the short term.

A randomized, controlled crossover trial compared a 6-week course of oral prednisolone (tapered from 60 mg/d to 10 mg/d) with a 2-day course of IVIG, 1.0 g/kg per day, for treatment of CIDP.⁴¹ Treatment was switched after a 4-week washout period. Both treatments produced significant improvements in disability after 2 weeks, although quality of life was superior in the IVIG group owing to lesser adverse effects.⁴¹ Intravenous immunoglobulin was also equal to plasma exchange in a single-blind, controlled crossover trial of CIDP patients assigned to a 6-week course of plasma exchange or IVIG, 0.2-0.4 g/kg administered weekly.⁴² Similar improvements in neurologic disability occurred with IVIG compared with placebo in a parallel controlled trial.⁴³

The position of IVIG in the hierarchy of CIDP treatment was investigated in a 3-year placebo-controlled study of IVIG in treatment-naïve patients.⁴⁴ Patients received IVIG, 1.0 g/kg per day, or placebo on days 1, 2, and 21. Differences in muscle strength favoring IVIG were observed as early as day 10; by day 42, strength and functional performance had improved significantly more with IVIG than with placebo. These findings support the use of IVIG as first-line therapy, especially in the early inflammatory phase of CIDP.

A number of disease-associated variants of CIDP have been identified.^{45,46} Although IVIG seems to be effective in

these forms, formal controlled trials have not been conducted. Some reports indicate that 12% to 18% of patients with diabetes meet the electrophysiologic criteria for CIDP, and the risk of CIDP is 11 times greater in those with type 2 diabetes than in those without diabetes.⁴⁷ Patients with demyelinating polyneuropathy in the setting of diabetes respond to IVIG,⁴⁷ but the response depends on how the disease is defined. Clearly, a controlled trial is needed to establish the safety and efficacy of IVIG in diabetes-associated CIDP.

Because of its similar efficacy to plasma exchange and steroids, IVIG has emerged as a major treatment of CIDP, either as first-line therapy to mitigate the long-term axonal degeneration that typically accompanies disease progression or as supplementary therapy. Although the long-term efficacy of IVIG and the appropriate dose have not been established, IVIG is an attractive long-term treatment mode, given the serious adverse effects of prolonged therapy with steroids or immunosuppressants. The added value of combination therapy has not been studied.

Multifocal Motor Neuropathy. Clinically, multifocal motor neuropathy is characterized by slowly progressive asymmetric, predominantly distal weakness, usually prominent in the forearms.¹⁴ The diagnostic hallmark of multifocal motor neuropathy is persistent localized motor conduction blocks with normal function of sensory nerves. A number of patients have anti-GM1 antibodies, which may recognize epitopes at the node of Ranvier,⁴⁸ but their role in disease pathogenesis is unclear.

Unlike CIDP, multifocal motor neuropathy does not respond to steroids; in fact, steroids may worsen the disease. In contrast, several placebo-controlled trials have shown that IVIG improves muscle strength and neurologic disability scores as well as conduction block.⁴⁹⁻⁵¹ Long-term maintenance therapy with IVIG was also investigated in 11 multifocal motor neuropathy patients followed up for 4 to 8 years.⁵² After an initial dose of 0.4 g/kg per day for 5 days, patients received one

0.4-g/kg infusion every week for 1 year and as needed thereafter. Muscle strength improved significantly within 3 weeks of initiation of IVIG treatment but declined slightly yet 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, while conduction block disappeared in some nerves but appeared in others. These results suggest that IVIG maintenance treatment is beneficial in multifocal motor neuropathy but that the disease continues to progress slowly over many years.

Because multifocal motor neuropathy resembles a motor neuron disease, the strict criteria of conduction block may need to be redefined to capture subsets of patients without apparent block who have the potential to improve. In contrast with multifocal motor neuropathy, patients with amyotrophic lateral sclerosis, which sometimes resembles multifocal motor neuropathy, do not respond to IVIG. In a study of 9 patients with amyotrophic lateral sclerosis, IVIG treatment failed to change the course of the disease.⁵³

Paraproteinemic Demyelinating Neuropathies. While the IgG and IgA paraproteinemic demyelinating neuropathies behave like CIDP, the IgM paraproteinemic demyelinating neuropathies, which are most often associated with anti-myelin-associated glycoprotein antibodies, comprise a distinct subset.^{54,55} Anti-myelin-associated glycoprotein IgM antibodies are probably pathogenic because they are deposited on myelinated fibers, where they split the myelin lamella, causing demyelination.⁵⁴ The efficacy of IVIG in IgM anti-myelin-associated glycoprotein paraproteinemic demyelinating neuropathies was tested in a randomized, placebo-controlled crossover trial that showed modest benefit in 2 of 11 patients.⁵⁵ A second trial showed a statistically significant but very modest benefit in secondary end points.⁵⁶

Autoimmune Neuromuscular Junction Defects

Myasthenia Gravis. Myasthenia gravis is characterized by fluctuating weakness or fatigability of the extraocular, bulbar, respiratory, and limb muscles.²¹ Ptosis, diplopia, dysarthria, and dysphagia are common. Current treatment includes anticholinesterase drugs, thymectomy, steroids, immunosuppressants, and plasma exchange.²¹

To date, only 1 randomized controlled trial of IVIG in patients with myasthenia gravis has been published.⁵⁷ In that study, 87 patients with myasthenia gravis exacerbation received 3 courses of plasma exchange or IVIG, 0.4 g/kg per day, for either 3 or 5 days. Efficacy, as measured by change in myasthenic muscular score, was similar in the plasma exchange and IVIG groups; anti-acetylcholine receptor antibody titers decreased by about two thirds in all groups. Interestingly, the 3-day IVIG regimen (1.2 g/kg) was slightly superior to the 5-day IVIG regimen (2 g/kg). Another controlled trial randomly assigned 173 patients to receive IVIG, 1 g/kg for 1 day, vs 2 g/kg for 2 days. At day 15, the myasthenia scores were increased equally in both groups.⁵⁸ At present, and until more controlled trials are conducted, IVIG is recommended for crisis, in patients with severe weakness poorly controlled with other agents, or in lieu of plasma exchange.

Lambert-Eaton Myasthenic Syndrome. Patients with Lambert-Eaton myasthenic syndrome often present with proximal muscle weakness, autonomic dysfunction, and ocular-bulbar symptoms.^{23,24} The disorder is paraneoplastic in about 60% of patients, most of whom have small-cell lung carcinoma.²⁴ The majority of patients with Lambert-Eaton myasthenic syndrome respond to immunosuppressive agents (eg, steroids, azathioprine) as well as to IVIG. In a placebo-controlled crossover trial, IVIG, 1 g/kg per day for 2 days, produced significant improvements in muscle strength and reduction in serum calcium channel antibody titers.⁵⁹ Improvement peaked at 2 to 4 weeks but declined by 8 weeks.

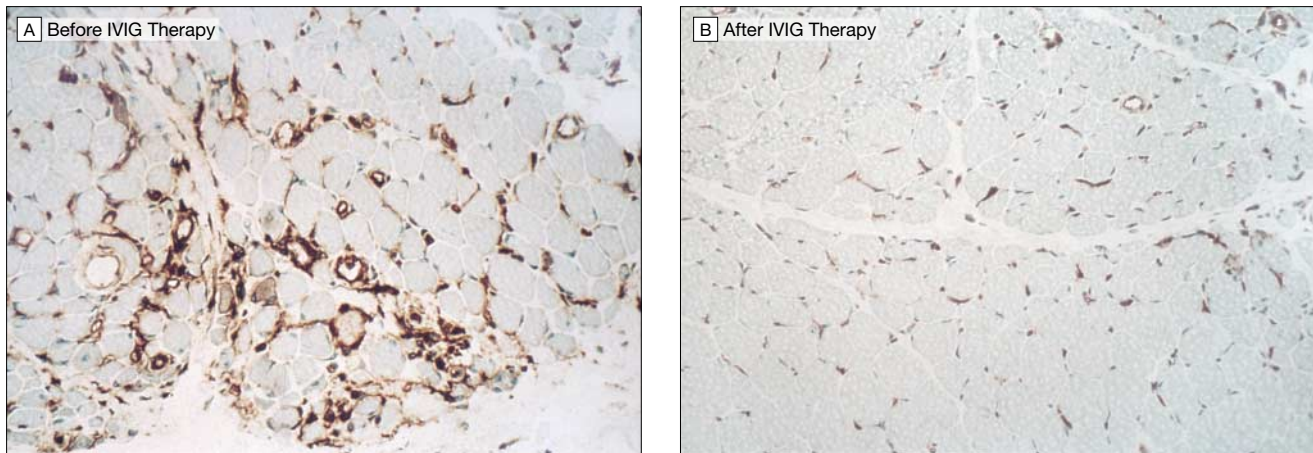
Immunoglobulin is useful as adjuvant therapy in difficult Lambert-Eaton myasthenic syndrome cases.

Inflammatory Myopathies

All 3 forms of inflammatory myopathy are characterized by proximal and often symmetric muscle weakness that develops subacutely or, occasionally, as in inclusion body myositis, insidiously.^{20,60} High-dose IVIG has been tested in controlled trials of patients with dermatomyositis or inclusion body myositis but not with polymyositis, although in uncontrolled series, IVIG has been shown to be effective in patients with polymyositis.^{61,62}

Dermatomyositis. Administration of IVIG to patients with dermatomyositis produces striking clinical benefits in parallel with histopathologic improvements (FIGURE 2). In a double-blind, placebo-controlled crossover trial, patients with treatment-resistant dermatomyositis received IVIG, 2.0 g/kg, or placebo once a month for 3 months.⁶³ At the end of the first 3-month treatment phase, IVIG-treated patients experienced significant improvement in muscle strength and neuromuscular symptoms compared with those receiving placebo. A dramatic improvement in rash, which often preceded or coincided with improved muscle strength, was also observed.

Histological examination of repeated muscle biopsies detected markedly improved muscle cytoarchitecture, with resolution of aberrant immunopathologic parameters, including downregulation of class I major histocompatibility complex, intercellular adhesion molecule 1 (Figure 2),⁶³ and transforming growth factor β ⁶⁴ confirming the in vivo effect of IVIG in suppressing cytokines and adhesion molecules. Consistent with its proposed mode of action, it also was shown in vivo that IVIG inhibited complement C3 in the circulation and intercepted the formation and intramuscular deposition of MAC, the lytic component of the complement pathway.⁶⁵ Thus, IVIG is an important mode of therapy in patients with dermatomyositis resistant to

Figure 2. ICAM-1 Expression in Muscle Biopsy Specimens From a Patient With Dermatomyositis Before and After IVIG Therapy

Muscle biopsy specimens from a patient with dermatomyositis who had substantial clinical improvement after 3 infusions of intravenous immunoglobulin (IVIG) were stained with monoclonal antibodies to intercellular adhesion molecule 1 (ICAM-1) using an immunoperoxidase technique. A, Before IVIG therapy, ICAM-1 is strongly expressed on endothelial cells, infiltrating lymphocytes, and occasional muscle fibers (brown chromogen). B, After therapy, ICAM-1 expression is markedly suppressed, and the size of the muscle fibers is increased. Nuclei appear blue in both panels. (Counterstain: hematoxylin; original magnification $\times 125$).⁶³ Photo source: National Institutes of Health.

conventional therapies; it interrupts immunopathologic mechanisms of the disease and restores normal histology.

Inclusion Body Myositis. Inclusion body myositis is the most common acquired inflammatory myopathy in patients older than 50 years.^{20,60} Patients present with distal and proximal muscle weakness, frequent falls, and dysphagia. Immunopathologically, inclusion body myositis is identical to polymyositis, but histologically, it is differentiated by the presence of vacuolated fibers and amyloid deposits.^{20,60}

Inclusion body myositis is notoriously resistant to treatment with immunosuppressive medications. Therefore, the efficacy of IVIG was tested in 19 patients in a placebo-controlled crossover trial similar to that of the dermatomyositis trial.⁶⁶ Although muscle strength scores improved more in IVIG-randomized patients, the differences were not statistically significant,⁶⁶ except for regional differences, most notable in the muscles used for swallowing. A second study showed similar results.⁶⁷ A third study, carried out to investigate the potential synergistic effect of IVIG and prednisone, randomly assigned 36 patients to IVIG, 2 g/kg, or placebo once a month for 3

months.⁶⁸ All patients received prednisone concurrently (tapered from 60 mg/d). After 3 months of treatment, there was no significant difference in muscle strength between the IVIG-plus-prednisone group and the placebo-plus-prednisone group. Despite these negative findings, some inclusion body myositis patients may derive modest, transient benefit from IVIG therapy, sufficient to justify a 2- to 3-month trial, especially in those with severe dysphagia, as recently noted.⁶⁹

Autoimmune Central Nervous System Disorders

Intravenous immunoglobulin has also been used in the treatment of other autoimmune neurologic disorders, such as stiff-person syndrome and MS. Stiff-person syndrome is characterized by fluctuating muscle rigidity, episodic muscle spasms induced by unexpected external stimuli, and high titers of antibodies against glutamic acid decarboxylase, the rate-limiting enzyme for synthesis of γ -aminobutyric acid.⁷⁰ Drugs that enhance γ -aminobutyric acid neurotransmission, such as diazepam, provide only mild to modest relief of clinical symptoms⁷⁰; however, treatment with IVIG confers substantial benefit. This im-

provement was documented in a placebo-controlled crossover trial in 16 patients administered IVIG, 2 g/kg, or placebo once a month for 3 months.⁷¹ Efficacy was based on distribution-of-stiffness and heightened-sensitivity scales. Among patients initially treated with IVIG, stiffness scores decreased significantly and heightened-sensitivity scores declined markedly, but they rebounded during placebo administration; the opposite pattern occurred among those treated with placebo first.⁷¹ Patients were able to walk without assistance and perform work-related or household tasks; their frequency of falls decreased.

The efficacy of IVIG in MS is less clear. In controlled trials, IVIG treatment was beneficial to patients with relapsing-remitting MS,^{72,73} but additional studies must be conducted to substantiate this benefit. A placebo-controlled trial in MS patients with chronic optic neuritis demonstrated no significant improvement in visual acuity among patients randomized to receive IVIG compared with placebo, although some improvement in visual function occurred in patients with clinically stable disease.⁷⁴ In a separate placebo-controlled trial, IVIG did not

reverse established weakness in MS patients.⁷⁵

Immunoglobulin has been used to treat some forms of intractable childhood epilepsy, mainly in those with West syndrome and Lennox-Gastaut syndrome, with promising results, although studies are heterogeneous and controls are lacking.^{76,77} Controlled trials are also needed to confirm the benefits of IVIG therapy reported in other autoimmune systemic inflammatory conditions, such as Rasmussen encephalitis, Isaacs syndrome, vasculitis, and recurrent acute disseminated encephalomyelitis.⁷⁸⁻⁸⁰

Risks and Complications

Adverse reactions associated with use of IVIG include (1) minor, self-limited reactions, such as headache, chills, myalgia, low back pain, or chest discomfort, that occur early in the infusion but dissipate after the infusion rate is slowed³⁴; (2) moderate but rare and inconsequential incidences of aseptic meningitis, especially in patients with a history of migraine,⁸¹ and dermatologic reactions, including urticaria, lichenoid lesions, palmar pruritus, or petechiae, that develop up to 5 days after infusion^{28,34}; and (3) more serious but rare reactions, including anaphylaxis in patients with a severe deficiency of IgA when they have anti-IgA antibodies, acute but often reversible renal tubular necrosis in patients with preexisting kidney disease and volume depletion, and thromboembolic events, such as stroke, myocardial infarction, or pulmonary embolism due to IVIG-associated increased plasma viscosity in patients at increased risk for thrombosis, such as elderly, diabetic, thrombocytotic, or hypergammaglobulinemic patients.^{82,83}

COMMENT AND CONCLUSION

Intravenous immunoglobulin is used in the treatment of a wide range of immunologic diseases that affect the entire neuraxis, including brain, spinal cord, peripheral nerves, neuromuscular junction, and muscles. Based on controlled clinical trials, IVIG is the treatment of choice for Guillain-Barré

syndrome, multifocal motor neuropathy, and CIDP and is useful instead of plasma exchange in myasthenia gravis management; IVIG is also effective in aggressive or treatment-resistant dermatomyositis and improves function in patients with stiff-person syndrome. Occasionally, patients with inclusion body myositis may derive modest but transient benefit, especially in dysphagia, but most do not respond. However, IVIG cannot reverse established weakness or chronic optic neuritis in patients with MS. The efficacy of IVIG in relapsing-remitting MS is unsettled and currently under investigation in a large controlled trial.

In sum, therapy with IVIG is effective for an array of autoimmune neurologic diseases, but its spectrum of efficacy, especially as first-line therapy, has not been fully established. Further controlled trials are needed to improve the evidence base for clinical practice and to evaluate the use of IVIG in conditions for which its efficacy is theorized but not proved. The dose needed for maintenance therapy, the frequency of administration, and the effect of IVIG when combined with other therapies remain to be established.

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