

Use of intravenous gamma globulins in neuroimmunologic diseases

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Intravenous gamma globulin (IVIg) is used in the treatment of immunologic diseases that affect the entire neuroaxis, including the brain, spinal cord, peripheral nerves, muscles, and neuromuscular junction. The panel reviewed the available literature on the use of IVIg in order to evaluate the efficacy of this therapy in neuroimmunologic diseases. In prospective, rigorously controlled, double-blinded clinical trials, IVIg was found to have proven efficacy in the Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy, dermatomyositis, and Lambert-Eaton myasthenic syndrome. It was found to be probably effective in myasthenia gravis and polymyositis, and possibly effective in several other neuroimmunologic diseases. Further studies are needed to evaluate the use of IVIg for neuroimmunologic diseases in which its efficacy is suspected but not proven and to elucidate its mechanisms of action. (*J Allergy Clin Immunol* 2001;108:S126-32.)

Key words: Intravenous gamma globulin, peripheral neuropathy, neuropathy, chronic inflammatory demyelinating polyneuropathy, Guillain-Barré syndrome, inflammatory neuropathy, neuroimmunology

Immune mechanisms have been implicated in the pathogenesis of more than 20 neurologic syndromes or diseases, involving every aspect of the neuroaxis (Table I). Therapy with intravenous gamma globulin (IVIg) has been used in most of these conditions, with varying degrees of success. IVIg has proven efficacy and is standard therapy in several of these diseases, is probably or possibly effective in a few others, and has been shown to be without benefit in some.¹⁻³

The advisory panel reviewed the available literature on the use of IVIg in clinical practice in order to evaluate its efficacy in immune-mediated neurologic diseases. The following classification was used: (1) diseases in which the efficacy of IVIg has been proven in rigorous, double-

Abbreviations used

CIDP: Chronic inflammatory demyelinating polyneuropathy
CNS: Central nervous system
DM: Dermatomyositis
GBS: Guillain-Barré syndrome
IVIg: Intravenous gamma globulin
MG: Myasthenia gravis
MMN: Multifocal motor neuropathy
MS: Multiple sclerosis
PE: Plasma exchange

blind, controlled clinical trials; (2) diseases for which IVIg probably is useful based on published case reports and studies, but lacks confirmation in rigorously controlled clinical trials; (3) diseases in which IVIg may be useful, but data are insufficient to decide efficacy; and (4) diseases in which IVIg was reported to be without benefit (Table II).

DISEASES IN WHICH IVIg HAS PROVEN EFFICACY

Guillain-Barré syndrome

Guillain-Barré syndrome (GBS) is an acute, remitting paralytic illness that results from an immunologic attack on the peripheral nerves. It affects approximately 4000 people in the United States each year. Plasmapheresis or plasma exchange (PE) has been shown to be effective in shortening the course and decreasing the morbidity of GBS. It is not always available, however, and should be used with caution in patients with autonomic involvement.

The efficacy of IVIg in GBS has been demonstrated in 3 clinical trials. Van der Meche et al⁴ studied 147 patients with GBS in a randomized, open, controlled clinical trial comparing IVIg (0.25 to 0.4 g/kg $\times$ 4 days) with PE. Clinical response was seen in 53% of patients treated with IVIg and 34% of patients treated with PE. Bril et al⁵ studied 50 patients in a randomized, open study of IVIg (0.5 g/kg daily for 4 days) versus PE. At 1 month, clinical response was seen in 69% of patients treated with IVIg as compared with 61% of patients with PE. In addition, more complications were seen in the PE group. In a multicenter, controlled, randomized, and blinded trial of 379 patients, the Plasma Exchange/Sandoglobulin Guillain-Barré Syndrome Trial Group⁶ compared the effectiveness

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Presented at the IVIg Advisory Meeting 2000, Bayer Biologicals, October 26-29, 2000, Santa Barbara, Calif.

The authors have no significant financial relationship or interest in Bayer Corporation. They have prepared this report to present factual, unbiased information and attest that no commercial association has influenced this report, nor does this publication constitute a commercial or personal conflict of interest.

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0091-6749/2001 \$35.00 + 0 1/0/118300

doi:10.1067/mai.2001.118300

TABLE I. Neurological diseases in which immunological mechanics have been implicated

Central nervous system (CNS) disease
Multiple sclerosis
Acute disseminated encephalomyelitis
Optic neuritis
Transverse myelitis
CNS vasculitis: systemic and non-systemic
Cerebral infarctions with antiphospholipid antibodies
Rasmussen's syndrome (chronic encephalitis and epilepsy)
Intractable childhood epilepsy (Lennox-Gastaut or West syndromes)
Paraneoplastic syndromes: opsoclonus myoclonus, cerebellar degeneration, limbic encephalitis
Sydenham's chorea
Pediatric autoimmune neuropsychiatric disorders associated with streptococcus (PANDA), including post-infectious tics and obsessive compulsive disorder
Stiff-man syndrome
Vogt-Koyanagi-Harada syndrome
Human T-lymphotropic virus-1 associated myelopathy
Amyotrophic lateral sclerosis
Peripheral nerve diseases
Guillain-Barré syndrome and variants
Chronic inflammatory demyelinating polyneuropathy
Multifocal motor neuropathy
Ganglioneuritis, with or without Sjögren's syndrome
Peripheral nerve vasculitis: systemic and non-systemic
Antiglyconjugate antibody-associated neuropathies with or without IgM monoclonal gammopathy (anti-MAG, sulfatide, GD1b and disialosyl gangliosides and GM2 ganglioside antibodies)
Lumbosacral or brachial plexitis
Paraneoplastic sensory neuropathy
Subacute autonomic neuropathy
Neuromyotonia (Isaacs' syndrome)
Diseases of the neuromuscular junction
Myasthenia gravis
Lambert-Eaton myasthenic syndrome
Inflammatory myopathies
Dermatomyositis
Polymyositis
Inclusion body myositis

of PE, IVIg, and PE followed by IVIg. At 4 weeks, they found no difference in the mean improvement among the 3 groups. IVIg therefore is considered equivalent to PE in the treatment of GBS and is used more frequently because of convenience and safety, particularly in children or patients with autonomic instability.

Chronic inflammatory demyelinating polyneuropathy

Chronic inflammatory demyelinating polyneuropathy (CIDP) is a chronic inflammatory disease that targets the myelin sheaths of peripheral nerves. Its true incidence is unknown. It has been traditionally treated with cortico-

TABLE II. Efficacy of IVIg in neuroimmunological diseases

Proven effective; demonstrated in prospective, rigorously controlled, double-blinded clinical trials
Guillain-Barré syndrome
Chronic inflammatory demyelinating polyneuropathy
Multifocal motor neuropathy
Dermatomyositis
Lambert-Eaton myasthenic syndrome
Probably effective; generally agreed to be effective in patient studies, but lacking confirmation in rigorously controlled clinical trials
Myasthenia gravis
Polymyositis
Possibly effective; benefit reported in occasional patients or inadequate clinical trials
Multiple sclerosis
Acute disseminated encephalomyelitis
Cerebral infarctions associated with antiphospholipid antibodies
Rasmussen's syndrome
Intractable childhood epilepsy
Human T-lymphotropic virus-1 associated myelopathy
Demyelinating neuropathy associated with IgM
Monoclonal gammopathy or anti-MAG antibodies
Lumbosacral or brachial plexitis
Stiff-man syndrome
Pediatric autoimmune neuropsychiatric disorders associated with streptococcus (PANDA)
Not effective
Inclusion body myositis
Amyotrophic lateral sclerosis
POEMS syndrome
Paraneoplastic cerebellar degeneration, sensory neuropathy, or encephalopathy

steroids or PE. In more resistant cases, CIDP may be treated with chemotherapy using immunosuppressive drugs.

The efficacy of IVIg in CIDP has been demonstrated in 3 controlled clinical trials. Dyck et al⁷ studied 20 patients in a double-blind, randomized, crossover study, comparing PE with IVIg (0.4 g/kg once a week for 3 weeks, then 0.2 g/kg once a week for another 3 weeks). Because response to either treatment was equally favorable, they were considered equivalent. Hahn et al⁸ studied 30 patients in a double-blind, randomized, placebo-controlled crossover trial using IVIg at a dose of 0.4 g/kg daily for 5 days. A total of 63% of patients in the IVIg-treated group improved within 4 weeks, whereas 5 patients (17%) improved only transiently with placebo infusions. Three of the 5 patients subsequently exhibited a large and sustained response when given IVIg. Mendell et al⁹ treated 30 patients with CIDP using IVIg and 23 received placebo. Eleven of the subjects in the IVIg group improved, compared with 2 in the placebo group. IVIg therefore is considered the preferred treatment, particularly in children, patients whose poor venous access precludes the use of

PE, and those susceptible to the complications of long-term corticosteroid therapy.

Multifocal motor neuropathy

Multifocal motor neuropathy (MMN) is a chronic inflammatory condition that selectively affects the motor nerves. It is characterized by progressive motor weakness and muscle atrophy, which usually is asymmetric, and often is associated with increased titers of IgM anti-GM1 antibodies. It is not responsive to PE and can be severely exacerbated by corticosteroids. Chemotherapy often is effective, but requires maintenance or repeated treatments.¹⁰

The efficacy of IVIg in MMN has been demonstrated in several controlled clinical trials. Azulay et al¹¹ studied 5 patients in a double-blind, placebo-controlled, crossover trial using IVIg (0.4 g/kg daily for 5 days). All patients experienced a beneficial response to IVIg. Van den Berg et al¹² studied 6 patients in a randomized, double-blind, placebo-controlled crossover trial. Five of the 6 patients treated with IVIg improved. In a randomized, double-blind, crossover trial of 16 patients with MMN, Federico et al¹³ reported that 11 of 16 patients in the IVIg group and none of the patients in the placebo group showed either subjective or objective improvement. Improvement was noted by the Neurological Disability Score, grip strength, or reversal of conduction block. MMN also may present as a lower motor neuron syndrome without conduction abnormalities that also responds to IVIg.¹⁴ Currently, IVIg is the therapy of choice, alone or in combination with chemotherapy, for MMN.¹⁵

Dermatomyositis

Dermatomyositis (DM) is an inflammatory disease of the muscles and skin manifested by progressive weakness and skin rash. An autoantibody-mediated, complement-dependent attack against vascular endothelial cells is responsible for marked loss of muscle capillaries. The prevalence is less than 1 per 100,000. It traditionally is treated with corticosteroids or, in resistant cases, with chemotherapeutic agents. Dalakas et al¹⁶ studied 15 patients with therapy-resistant DM, in a double-blind, placebo-controlled, randomized crossover study, using IVIg (1 g/kg for 2 days, then monthly for 3 months). In the IVIg-treated group, 9 of 12 patients had major improvement. None of the 11 patients in the placebo group had major improvement: 3 had mild improvement, 3 had no change, and 5 had worsening of their condition.

Lambert-Eaton myasthenic syndrome

Lambert-Eaton myasthenic syndrome is an autoimmune disease with antibodies to the presynaptic, voltage-gated, calcium channels at the motor end plates of the neuromuscular junction. It occasionally is associated with an underlying malignancy, most commonly small cell carcinoma of the lung. Patients present with muscle weakness, predominantly in the lower limbs, hyporeflexia, autonomic dysfunction, and extraocular muscle involvement. Treat-

ment usually includes high-dose corticosteroids, plasmapheresis, or chemotherapy.

Bain et al¹⁷ studied 9 patients in a randomized, double-blind, placebo-controlled crossover trial using IVIg (1 g/kg daily for 2 days). Eight of the 9 patients treated with IVIg had significant improvement in all functional measures and there was a significant decline in serum calcium-channel autoantibody titers.

DISEASES IN WHICH IVIg PROBABLY IS EFFECTIVE

Myasthenia gravis

Myasthenia gravis (MG) is an autoimmune disease with antibodies to the acetylcholine receptor at the neuromuscular junction. It manifests with fluctuating weakness or fatigability of the extraocular, bulbar, respiratory, and/or limb muscles. The estimated prevalence ranges from 43 to 84 per million, affecting approximately 15,000 patients in the United States. Current therapies include thymectomy, cholinesterase inhibitors, and immunotherapies such as PE, corticosteroids, or chemotherapy.

More than 150 patients with MG have been given IVIg, as reported in case reports and open uncontrolled trials. Overall, about 65% achieved clinical benefit within 4 days to 2 weeks following therapy. In several reports, IVIg permitted patients to decrease or discontinue the use of steroids. In the only randomized, open, comparative trial of 87 patients, Gajdos et al¹⁸ compared PE with IVIg (0.4 g/kg daily for 3 or 5 days). IVIg and PE exhibited equal efficacy, with improvement noted in 14 of 23 patients in the 3-day IVIg group, 9 of 23 patients in the 5-day IVIg group, and 27 of 41 patients in the PE group. Acetylcholine receptor antibody titers fell in 65% of the IVIg-treated group and in 63% of the PE-treated group. The complication rate was lower in the IVIg-treated group, but the study was not blinded and the groups were not necessarily equivalent. There was a consensus among the panel members that IVIg is probably an effective therapy for MG, but a more rigorous clinical trial is needed to prove efficacy.

Polymyositis

Polymyositis is an inflammatory muscle disease that causes weakness of the proximal muscles. It is mediated by cytotoxic T-lymphocytes. Treatment includes corticosteroids and chemotherapy in resistant cases. There are reports of more than 20 patients treated with IVIg, with a positive response rate of about 65%.^{19,20}

DISEASES IN WHICH IVIg MIGHT BE EFFECTIVE

Multiple sclerosis

Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system (CNS), with a progressive course marked by remissions and exacerbations. There are about 350,000 patients with MS in the United States. Current therapies include corticosteroids

for acute exacerbations, and IFN- β or copolymer I to reduce exacerbations and delay progression to disability.

Fazekas et al²¹ studied 148 patients in a randomized, double-blind, placebo-controlled trial using low-dose IVIg (0.15 to 0.20 g/kg monthly for 2 years). The IVIg-treated patients had improved clinical disability status and reduced number of relapses compared with controls. Sorensen et al²² studied 25 patients in a randomized, double-blind, placebo-controlled crossover study of IVIg (1 g/kg daily for 2 days at 4-week intervals for 6 months). In the IVIg-treated group, 65% had no exacerbations during the treatment period versus 35% in the control group. There was, however, only an insignificant change in the clinical disability scores, although serial MRIs demonstrated a 60% reduction in the number and volume of gadolinium-enhanced lesions.²³ Achiron et al²⁴ studied 40 patients in a randomized, double-blind, placebo-controlled trial of IVIg (0.4 g/kg $\times$ 5 days, followed by 0.4 g/kg once every 2 months for 2 years). In the IVIg-treated group, 30% had no exacerbations during the entire study, while all 20 patients in the placebo group had exacerbations. Noseworthy et al,²⁵ in a double-blind, placebo-controlled study, reported that IVIg does not reverse established weakness in MS. The panel determined that although IVIg might be beneficial in MS, more rigorously controlled trials are needed to prove its efficacy. A large, double-blinded, controlled clinical trial of IVIg in MS is ongoing in Europe.

Rasmussen's syndrome

In a retrospective case series, 7 of 9 patients with Rasmussen's syndrome (chronic encephalitis and epilepsy) had improvement in seizure control following IVIg therapy. Improvement was maintained in 4 of the cases.²⁶

Intractable pediatric epilepsy

Two randomized trials of IVIg in pediatric epilepsy have been reported. Illum et al,²⁷ in a single-blind, placebo-controlled, crossover study, reported improvement in 2 of 10 patients with drug-refractory Lennox-Gastaut syndrome following IVIg therapy. Van Rijckevorsel-Harmant et al,²⁸ in a randomized, double-blind, placebo-controlled trial of 61 patients with intractable epilepsy (Lennox-Gastaut syndrome, West syndrome, or early myoclonic encephalopathy), reported that IVIg therapy reduced seizures by 50% in 52% of patients. Only 28% of the placebo-treated group had a similar clinical response.

Demyelinating neuropathy with IgM monoclonal gammopathy or anti-myelin-associated glycoprotein antibodies

Following therapy with IVIg, Cook et al²⁹ reported improvement in 2 patients with demyelinating neuropathy associated with IgM monoclonal gammopathy resistant to other treatments. Leger et al³⁰ reported improvement in 4 of 7 patients with IgM monoclonal gammopathy and anti-myelin-associated glycoprotein (MAG) antibodies treated with IVIg. Dalakas et al,³¹ in

a randomized, double-blind, placebo-controlled crossover trial, noted improvement in strength in only 2 of 11 patients with the same disease. Mariette et al³² noted improvement in only 1 of 10 patients. Treatment with IVIg is ineffective in most patients with anti-MAG neuropathy, but a few patients exhibit motor function improvement. Additional studies are needed to identify patients who might benefit from IVIg.

Other diseases

Improvement following therapy with IVIg also was reported in isolated or few cases of patients with the following syndromes: chronic sensory ataxic neuropathy,³³ small fiber neuropathy,³⁴ chronic relapsing axonal neuropathy,^{35,36} neuropathy associated with Sjögren's syndrome,³⁷ progressive lumbosacral plexopathy,³⁸ brachial plexopathy,³⁹ lower motor neuron disease that may be a presentation of MMN,^{14,40} acute idiopathic dysautonomia that may be a variant of GBS,⁴¹⁻⁴³ adrenal leukodystrophy,⁴⁴ acute disseminated encephalomyelitis,⁴⁵ opsoclonus myoclonus,⁴⁶ Vogt-Koyanagi-Harada syndrome (uveitis, skin changes, and CNS inflammatory lesion),⁴⁷ chronic progressive central and peripheral demyelination syndrome,⁴⁸ postinfectious cerebellar ataxia,⁴⁹ postinfectious tics and obsessive compulsive disorder,⁵⁰ human T-lymphotropic virus-1 associated myelopathy,⁵¹ stiff-man syndrome,⁵² recurrent cerebral infarctions associated with antiphospholipid antibodies,⁵³ and CNS vasculitis associated with Wegener's granulomatosis⁵⁴ or systemic vasculitis.⁵⁵

DISEASES IN WHICH IVIg HAS BEEN REPORTED TO BE INEFFECTIVE

Treatment with IVIg was reported to be ineffective in patients with inclusion body myositis,²⁰ amyotrophic lateral sclerosis,^{56,57} POEMS syndrome,⁵⁸ paraneoplastic cerebellar degeneration, sensory neuropathy, or encephalopathy.^{59,60}

IVIg DOSE AND DOSING INTERVALS

The initial loading dose is 2 g/kg, which can be given over 2 to 5 days in succession or within a 2-week time period. Kubori et al,⁶¹ in comparing 3 doses of IVIg in patients with CIDP or MMN, reported that a dose of 400 mg/kg/day for 5 days was superior to 200 mg or 50 mg/kg/day for 5 days. In GBS, a 5-day initial course is recommended for patients with autonomic instability. The treatment is repeated if there is a relapse. In patients with a chronic progressive disease, a trial period of 3 months, with repeated treatments at 2- to 4-week intervals, may be required to determine whether there is a response.

In patients for whom repeated therapy is required, a repeat infusion of 2 g/kg may be given at the earliest sign of a relapse. Alternatively, the patient may be maintained with repeated infusions at 2- to 4-week intervals, depending on the individual response. In general, maximal responses can be achieved with a total monthly dose of 0.5

to 2 g/kg. The specific dose and dosing intervals should be determined empirically depending on the individual.

MECHANISMS OF ACTION

IVIg has the potential to modulate many different effectors of autoimmune disease. Action mechanisms that have been implicated in neurologic disorders reflect the ability of IVIg to interfere with the activity of humoral components such as antibody and complement and to limit cytokine production. Sturfelt et al⁵³ saw a correlation between immunoglobulin infusion and a rising platelet count in a patient with antiphospholipid antibodies and recurrent cerebral infarctions. There was no drop in antibody titer, suggesting that IVIg did not limit antibody production but instead inhibited the antibody-mediated effector mechanisms, such as complement activation or Fc receptor binding. In their studies of muscle biopsies in DM, Basta and Dalakas⁶² reported that IVIg resulted in restoration of the intramuscular capillaries in DM by blocking the antibody-dependent formation of C5b-9, the terminal membrane attack complexes of complement that mediate endothelial cell damage. The response of CIDP patients to IVIg also did not reflect Fc receptor blockade, as shown by Vermeulen et al,⁶³ who reported no response to anti-D immunoglobulins in a patient with CIDP who routinely responded to IVIg.

Other studies also have investigated the potential ability of IVIg to modulate disease by limiting antibody production. The clinical response to IVIg did not correspond with a drop in anti-GM1 and antiacetylcholine receptor antibody titers in patients with MMN¹¹ or MG,¹⁷ but was associated with a fall in anticalcium channel antibody titers in Lambert-Eaton myasthenic syndrome.¹⁷ Malik et al⁶⁴ in 1996 reported that Fab fragments of IVIg inhibited antibody binding to GM1-coated microplates, suggesting an anti-idiotypic effect. The report failed to take into account potential binding of the Fab fragments to GM1, however. In GBS, Sharief et al⁶⁵ reported that IVIg modulated the levels of proinflammatory cytokines, selectively reducing TNF- α and IL-1, the levels of which can be correlated with disease activity. Other suggested action mechanisms include saturation of FcRn receptors resulting in increased degradation of IgG,⁶⁶ or co-ligation of FcR2 with the B-cell receptor,⁶⁷ resulting in inhibition of B-cell activation.

In animal studies, IVIg reduced the severity of experimental allergic encephalomyelitis, a model for acute disseminated encephalomyelitis and multiple sclerosis.^{68,69} In experimental allergic neuritis, a model for GBS, Miyagi et al⁷⁰ and Gabriel⁷¹ reported that IVIg suppressed the disease, whereas Pashov et al⁷² and Enders et al⁷³ found no benefit. Immunoglobulins also have been reported to promote CNS remyelination.⁷⁴ These studies are difficult to interpret, however, due to the potential induction of immune reactivity to human IgG and the aberrant interactions of human IgG with immune receptors in the experimental animal species.

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