Intravenous Immunoglobulin Use for Neurologic Diseases

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Abstract

Intravenous immunoglobulin (IVIG) has been used primarily for immune deficiency patients, and its greatest expansion is seen more and more in the treatment of autoimmune disorders, especially in neurology. The benefits of IVIG treatment include its availability in all treatment centers and its ease of administration in an outpatient setting. This article gives an overview of some autoimmune neurologic diseases and explores the clinical evidence supporting the use of IVIG.

Intravenous immunoglobulin (IVIG) is a polymeric highly purified immunoglobulin fraction derived from large pools of up to 60,000 plasma donors. It has the potential to bind many common pathogens and modulate a wide range of effectors of autoimmune disease. The action of IVIG is mediated through both the variable and the constant regions of the Fab, as well as the Fc portion of the immunoglobulin molecule. Immunomodulatory for both humoral and cellular immune mechanisms, it inhibits complement activity by binding the first component of complement, neutralizing C3a and C5a, thought specific to antibody. It also limits terminal complement complex formation on target membranes, interferes with the ability of the specific host antibody to bind to a target antigen, and modulates the ability of B cells to produce antibody. It neutralizes pathogenic cytokines such as tumor necrosis factor and interleukin-1 as well as superantigens that prevent activation of classes of T lymphocytes. Blood from patients treated with IVIG is reported to have increased suppressor CD8-positive T-cells.

The use of IVIG in neurology has increased dramatically over the past 2 decades. Its use is supported by a series of randomized and controlled trials assessing diseases
that affect the peripheral nerve, neuromuscular junction, and skeletal muscle. The use of IVIG is perhaps more controversial for demyelinating disorders of the central nervous system such as multiple sclerosis.

**INFLAMMATORY IMMUNE-MEDIATED NEUROPATHIES**

The inflammatory neuropathies affect 1 to 2 individuals per 100,000 population, resulting in major disability and impairment even with treatment. Autoimmune neuropathies encompass acute forms such as Guillain-Barré syndrome (GBS) and its variants, as well as chronic forms including chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), multifocal motor neuropathy, and polyneuropathies associated with immunoglobulin M (IgM) monoclonal gammopathy and paraneoplastic neuropathies. Other forms of chronically acquired inflammatory neuropathies include Lewis Sumner syndrome, a pure sensory disorder, and distal demyelinating neuropathy (Table 1).

**ACUTE INFLAMMATORY NEUROPATHY**

Acute inflammatory demyelinating polyneuropathy, also known as GBS, is an acute or subacute monophasic, ascending, areflexic paralysis, with loss of deep tendon reflexes developing over 1 to 4 weeks. It affects approximately 5,000 to 10,000 people annually in the United States. In more than 60% of these patients, a preceding upper respiratory tract infection or diarrheal illness can be identified. Respiratory failure and/or other autonomic instabilities develop in 40% of these patients. Peripheral nerve damage of either the myelin or axon is mediated by an immune cascade involving cytokines, monocytes, and complement-fixing antibodies. Most of the evidence supports the conclusion that the immune damage is triggered by shared reactivity to peripheral nerve components and epitopes on the surface of infectious particles.

Two treatments for GBS were shown to be beneficial in large randomized and controlled trials involving more than 700 patients. In 2 large randomized controlled trials, plasma exchange was more effective in shortening the course and decreasing the morbidity of GBS than supportive therapy. Plasma exchange, however, is not universally available and may be contraindicated for patients with autonomic instability. The effectiveness of IVIG in GBS was proved equal to that of plasma exchange in 3 clinical trials. A randomized open controlled clinical trial by van der Meché and van Doorn compared IVIG (0.25-0.4 g/kg x 4 days) with plasma exchange in 127 patients. In this trial, 53% of the patients treated with IVIG and 34% of the patients treated with plasma exchange improved at least 1 clinical grade on the Hughes Scale within 4 weeks. In another randomized open study, Bril et al compared IVIG (0.5 g/kg daily for 4 days) with plasma exchange in 50 patients. In this trial, 69% of the patients treated with IVIG improved, as compared with 61% of patients treated with plasma exchange, although more complications were seen with plasma exchange than with IVIG. In a multicenter, controlled, randomized, blinded trial involving 379 patients, no difference was seen between IVIG and plasma exchange, nor was any advantage gained by fol-

**TABLE 1**

<p>| Inflammatory Immune-mediated Neuropathies |
|-----------------------------------------|-------------------------------------------------|</p>
<table>
<thead>
<tr>
<th><strong>Diagnosis</strong></th>
<th><strong>Clinical Features</strong></th>
<th><strong>Treatment</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute</strong></td>
<td>Ascending paralysis. Loss of DTRs over 1 to 4 wk. Respiratory failure and autonomic disorder in 40% of cases</td>
<td>IVIG</td>
</tr>
<tr>
<td>GBS</td>
<td></td>
<td>PE</td>
</tr>
<tr>
<td><strong>Chronic</strong></td>
<td>Progressive weakness</td>
<td>Corticosteroids</td>
</tr>
<tr>
<td>CIDP</td>
<td>&gt;8 wk. Symmetrical sensory loss, areflexia. Little involvement of cranial nerves and respirations.</td>
<td>IVIG</td>
</tr>
<tr>
<td>MMN</td>
<td>Slowly progressive asymmetric weakness of distal extremities over a decade. Minimal or without sensory/cranial involvement.</td>
<td>PE</td>
</tr>
<tr>
<td>Lewis Sumner syndrome</td>
<td>Progressive asymmetric, multifocal sensory and motor loss over several weeks to years.</td>
<td>IVIG</td>
</tr>
<tr>
<td>IgM monoclonal gammopathy</td>
<td>Slowly progressive. Primarily sensory or sensorimotor. Symptoms include ataxia, postural tremor, loss of vibratory sense, and proprioception. High antibody titers to MAG.</td>
<td>Inconsistent response to treatment regimens.</td>
</tr>
</tbody>
</table>

GBS, Guillain-Barré syndrome; DTRs, deep tendon reflexes; PE, plasma exchange; CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; MMN, multifocal motor neuropathy; IgM, immunoglobulin M; MAG, myelin-associated glycoprotein.
lowing plasma exchange with IVIG in a third arm of the study.7

On the basis of guidelines issued by the American Academy of Neurology and recommendations from a Cochrane Review, a single course of IVIG or plasma exchange currently is considered standard therapy for the treatment of GBS in adults and children who are not able to ambulate independently.5,6,7 However, IVIG is more frequently used because of convenience, availability, and safety, particularly for patients with autonomic instability.

### Chronic Inflammatory Neuropathies

Among the chronic inflammatory neuropathies, CIDP is the most common and, despite its rarity, responsible for most of the long-term off-label use of IVIG. Other chronic acquired inflammatory neuropathies are distinct from CIDP in their clinical presentation and response to immune therapy.

#### Idiopathic CIDP

Patients with CIDP experience a progressive, relatively symmetric weakness and sensory loss in the proximal and distal extremities that are associated with areflexia. Progression must extend over more than 8 weeks. This disorder rarely can affect the cranial nerves and respiration. Nerve conduction studies are consistent with demyelination, showing various combinations of conduction block, temporal dispersion, prolonged F waves, and slowed conduction velocities. Nerve biopsy may show sparse inflammatory infiltrates, macrophage-mediated demyelination, and remyelination that contribute to the formation of “onion bulb.” Its clinical course may be monophasic over several months to years, chronically progressive, or relapsing-remitting. A primarily sensory form can occur, although motor signs develop in most of these patients within 3 years. Because of its response to a variety of immunomodulatory therapies, CIDP is thought to be immune mediated.

Findings proved IVIG to be effective in 6 controlled trials involving 170 patients with either chronic progressive or relapsing CIDP.8 Each trial used different administration regimens for IVIG. Dyck et al8 used a weekly dose of 0.4 g/kg for 3 weeks, followed by a weekly dose of 0.2 g/kg for an additional 3 weeks. Hahn et al10 used 0.4 g/kg over 5 days, whereas Mendell et al11 used 1 g/kg per day over 2 days, followed by a single infusion of 1 g/kg after 3 weeks. In the Mendell trial, IVIG was given as the initial treatment. A favorable response occurred in 56% to 79% of the patients with chronic progressive disease and in 71% of the patients with relapsing disease. In the relapsing patients, treatment was associated with remission of symptoms for an average of 6 weeks, and the remissions were maintained with IVIG doses of 1 g/kg or less.

A limited number of other immunotherapies have been tested in controlled trials, including plasma exchange and corticosteroids. In 3 randomized controlled trials, plasma exchange (twice weekly over 3 to 6 weeks) improved the neurologic disability score, nerve conduction velocity, and grip strength within 2 to 6 weeks in 80% of the patients, with a return to baseline 7 to 14 days after discontinuation.2 Plasma exchange requires an experienced team because complications may include electrolyte imbalance, cardiac arrhythmia, citrate-induced hypocalemia, hemolytic anemia, infection and thrombosis at the site of venous access, activation of coagulation, complement, fibrinolytic cascades, aggregation of platelets, anticoagulation attributable to removal of platelets, and clotting factors from plasma and hypotension. The requirement for venous access contributes to venous sclerosis and thrombosis and limits the use of plasma exchange as long-term therapy.

Oral prednisone (1 mg/kg daily, tapered over 9 months) produced small but significant improvements in graded muscle strength, neurologic disability, and nerve conduction, but a Cochrane Review rated this as weak evidence for clinical efficacy.12 Corticosteroids are used, partly because with long-term use they have serious side effects such as irritability, depression, psychosis, diabetes, osteoporosis, ischemic necrosis of the femoral head, hypertension, gastric ulcers, and weight gain. The incidence of these side effects worsens as the dosage and duration of treatment increases. Alternate-day therapy or high-dose intravenous methylprednisolone (1 g/day over 5 days monthly) may reduce side effects, but have not been studied systematically. Other oral immunosuppressive drugs such as cyclophosphamide, mycophenolate mofetil, interferon (IFN-1), and cyclosporin or tacrolimus may be of variable benefit, but require further study.

In summary, IVIG induces a clinical response in 56% to 79% of patients as early as 7 days after administration and is effective when treatment starts within 1 year of clinical disease onset. Some series report complete remission in 17% to 30% of patients after a single infusion. However, 40% or more continued to need smaller IVIG treatments every 2 to 8 weeks to maintain the response. The efficacy of IVIG is similar to that of plasma exchange and, in the short term, to that of prednisone.13 Because of administration ease and good patient tolerance, IVIG frequently is considered as the initial treatment of choice.

#### Multifocal Motor Neuropathy

In patients with multifocal motor neuropathy, a distal asymmetric weakness of the extremities usually develops, often affecting the upper limbs first, then usually progressing slowly over decades, with minimal or no sensory or cranial nerve involvement. The involved nerves show diagnostically persistent partial conduction blocks...
Involving motor fibers that somewhat spare sensory nerves. Antibodies to GM1 gangliosides are found in 30% to 60% of patients. Less frequently, patients have antibodies to asialo GM1, GM2, and GD1a antigens, most of which are preferentially expressed on motor neurons and axons. The role of these antigens in the neuropathy, except as a marker of disease, remains to be established.

In contrast to the response of patients with CIDP, those with multifocal motor neuropathy do not benefit from steroids or plasma exchange, but worsen in up to 20% of cases. However, in 4 randomized, placebo-controlled trials with limited numbers of patients, IVIG was demonstrated to be effective. Of the 49 patients treated with IVIG, 80% responded within 1 to 2 weeks, showing improved motor function and reduced conduction block. Responses were maintained with infusions each 2 to 4 weeks. In many patients, treatment must be maintained indefinitely. Over years, the effect of IVIG does not completely eliminate underlying axonal loss, but does slow it.

Lewis Sumner Syndrome

Lewis Sumner syndrome is characterized by a persistently asymmetric, multifocal pattern of sensory and motor loss, designated as multifocal acquired demyelinating sensory and motor neuropathy (MADSAM). Nerve conduction studies show a conduction block, and the disorder can progress over several weeks to years in a stuttering fashion. This condition can involve cranial nerves innervating oculomotor and bulbar muscles. Different studies have reported underlying demyelination or distal axon loss. Many propose this disorder to be a variant of CIDP. Clinically, however, this disease overlaps with brachial and lumbar plexitis. Focal involvement of discrete portions of nerves in both of these disorders can be demonstrated with magnetic resonance imaging (MRI). In the patients with plexitis, histology shows perivascular lymphocytic cuffs in the perineurium consisting, in some patients, primarily of CD8 cells (unpublished data, C. L. Koski).

Although no randomized controlled trials have investigated Lewis Sumner syndrome, the results of several case reports have documented that treatment with either corticosteroids or IVIG led to improvements in patients with widespread asymmetric involvement of cranial and peripheral nerves. For most of these patients, treatment with IVIG had to be repeated every 4 to 8 weeks.

Neuropathy Associated With a Monoclonal Immunoglobulin M Gammopathy Specific for the Myelin-associated Glycoprotein

Patients with an immunoglobulin M (IgM) monoclonal gammopathy involving high titers of antibody to myelin-associated glycoprotein (MAG) have a slowly progressive neuritis that is primarily sensory or sensorimotor. This condition can result in ataxia, postural tremor, areflexia, and a profound loss of vibratory sense and proprioception. The patients are predominantly men in the 6th and 7th decades of life, with 10% becoming severely disabled and wheelchair-bound. Electrophysiologic findings indicate a demyelinating neuropathy, with a disproportionate prolongation of distal latencies. Sural nerve biopsies show loss of myelinated fibers, segmental demyelination, and remyelination. Electron microscopy shows a typical widening of the peripheral myelin lamellae, whereas the periodicity of the inner lamellae is normal. These changes appear to reflect the deposition of anti-MAG IgM in the myelin sheath.

Patients may experience transient improvements when treated initially with plasma exchange, IVIG, corticosteroids, cyclophosphamide, chlorambucil, interferon (INF)-2α, fludarabine, rituximab, or combinations of these drugs. In 24 consecutively diagnosed patients, none of these treatments appeared to be superior. The median IgM levels of responding patients decreased by 25%, but could not be maintained at the lowered levels. A randomized, placebo-controlled, crossover trial of IVIG showed that only 18% of patients had improvements, and that these were primarily in their motor function. Chimeric anti-CD 20 antibodies are now used anecdotally, with increased muscle strength in 5 to 6 months, although patients were not uniformly responsive.

Of these patients, 30% have only mild symptoms and can be stable for extended periods. Treatment of this neuropathy, particularly with cytotoxic drugs, should be reserved for patients with significant disability and a progressive course.

NEUROMUSCULAR JUNCTION

Myasthenia Gravis

One of the best-characterized antibody-mediated autoimmune disorders is myasthenia gravis (MG). In MG, complement fixing antibodies to the α1 muscle nicotinic acetylcholine receptor or associated molecules results in altered function of the neuromuscular junction through loss of acetylcholine receptors. This alteration contributes to the characteristic symptoms of fatigue and weakness in the ocular, bulbar, and skeletal muscle groups, including those of respiration. This disorder affects 5 to 14 individuals per 100,000 population. The disease frequency within the population is bimodal. A higher number of women younger than 40 years experience MG and have associated germinal center hyperplasia in the thymus. Men with MG are predominantly 50 years of age or older and frequently have an atrophied thymus. A proportion of patients between the ages of 40 and 60 years present with a paraneoplastic disorder in association with thymoma. The range of effective treatments used for this disorder include anticholinesterase agents, prednisone and other immu-
nosuppressive medications, thymectomy, plasma exchange, and IVIG (Table 2).

Anticholinesterases are used as primary therapy for patients with only mild disease and as supplementary therapy for patients with more severe disease. For patients with more severe disease resulting in dysphagia or reduced pulmonary vital capacity, treatment is directed toward limiting the antibody load or reducing the ability of antibody to mediate membrane damage. Historically, large doses of corticosteroids (up to 1 mg/kg/day) were used, which were maximal only within 6 to 8 weeks. Such doses can be associated with transient worsening in 30% of patients and, as discussed earlier, can be associated with debilitating side effects that accumulate with time. Steroid-sparing agents such as azathioprine and mycophenylate mofetil are effective in reducing maintenance doses of corticosteroids, and are associated with fewer treatment failures, longer remissions, and fewer adverse effects than treatment with corticosteroids alone. However, clinical improvement may require up to 6 months.

Other immunosuppressive drugs used to treat MG include methotrexate, cyclophosphamide, and cyclosporine. Of these, only cyclosporine has been tested in a randomized controlled trial. A retrospective analysis of 57 patients receiving cyclosporine for an average of 3.5 years showed that clinical improvement occurred in 96% of the patients. This improvement peaked after 7 months’ usage of the drug. Major side effects included hypertension and renal damage, with elevated serum creatinine in 28% and malignancy in 11% of the patients.

In a series of open-label trials, IVIG was reported to be beneficial in the management of MG. The principal portion of these patients had recently experienced exacerbation of their disease, whereas the condition of the others was stable or progressive. More than half were receiving corticosteroids. With immunoglobulin treatment, 48% to 92% (mean, 87%) of the patients were reported to improve at least 1 grade on the global myasthenic severity scale, as assessed in a review by van der Meché and van Doorn. Benefit was noted within 4 days to 2 weeks and persisted for 2 to 6 weeks. The results of these studies provided support for 4 subsequent controlled trials that tried to determine the role of IVIG in the management of acute and chronic MG manifestations.

**Acute Exacerbations**

Both plasma exchange and IVIG are used in the management of myasthenic crisis because of their rapid clinical benefit. A randomized controlled trial has suggested that these 2 treatments are equivalent, confirming the prior results of Cosi, who compared IVIG-treated patients with a retrospective plasma exchange group. The controlled trial of 87 patients compared plasma exchange 3 times on alternate days with IVIG 0.4 g/kg daily for 3 or 5 days. Plasma exchange and IVIG exhibited similar efficacy within 2 weeks, 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 plasma exchange group. There was no significant statistical difference in the outcome measures between the 2 treatment groups at 0 and 15 days or between the 2 doses of IVIG. Acetylcholine receptor antibody titers fell in 65% of the IVIG group and 63% of the plasma exchange group. The complication rate was lower in the IVIG-treated group, but the study was not blinded, and there was greater severity in the 5-day versus the 3-day IVIG group. A major multicenter trial in Europe has been completed recently, but results are not yet available.

**Stable Disease**

In 2 patient trials, IVIG has been used in an attempt to improve the clinical function of patients who, despite immunosuppressive therapy, continued to have moderate to severe deficits in the stable phase of their disease, including respiratory deficiency, dysphagia, and systemic

<table>
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<td><strong>Neuromuscular Junction</strong></td>
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<tr>
<th>Diagnosis</th>
<th>Clinical Features</th>
<th>Treatment</th>
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<tbody>
<tr>
<td>MG</td>
<td>AChR antibody titers in 90% of systemic MG cases. Fatigue, ocular, bulbar, skeletal muscle weakness. Respiratory involvement in acute exacerbations. Relapses and remissions. A proportion are paraneoplastic in association with thymoma.</td>
<td>Anticholinesterase agents, Corticosteroids, Immunosuppressive agents, PE, IVIG, Combination PE/IVIG, Thymectomy for thymoma</td>
</tr>
<tr>
<td>LEMS</td>
<td>Lower limb muscle weakness, extraocular muscle involvement. Serum Ca++ channel antibody titers.</td>
<td>Corticosteroids, PE, IVIG</td>
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</table>

AChR, acetylcholine receptor; MG, myasthenia gravis; PE, plasma exchange; LEMS, Lambert Eaton myasthenic syndrome.
weakness. Ronager et al studied 12 moderately severe patients with MG in a crossover study comparing plasma exchange with IVIG over a 4-week period. All the patients had been receiving corticosteroids, azathioprine, or both for at least 1 year. At 4 weeks after both plasma exchange and IVIG treatments, a small but significant improvement in the quantitative MG scale was observed, as compared with baseline in both groups. Although there was no statistically significant difference between the 2 therapies 1 and 4 weeks after treatment, a more rapid improvement was demonstrated 2 weeks after treatment with plasma exchange.

Wolf et al attempted a randomized, double-blinded controlled trial comparing IVIG with 5% albumin in the treatment of mild to moderately involved MG patients. A total of 15 patients were enrolled (n = 6 IVIG; n = 9 placebo) and treated with IVIG 2 g/kg, then 3 weeks later with 1 g/kg. Within 42 days, there was no statistical difference between the two groups. The trial was stopped for a lack of IVIG from the supporting pharmaceutical company. In a subsequent 6-week open trial, positive trends for IVIG were reported. Both brevity and the small number of subjects limited both of these trials.

Ronager et al showed temporal but significant responses from the more severe patients in whom plasma exchange and IVIG results were largely equivalent. The ability to repeat this improvement was demonstrated in the crossover portion of the trial, which showed similar but short-term improvement with the alternate therapy using plasma exchange or IVIG. Monthly use of IVIG may contribute to enhanced independence in activities of daily living among responding patients.

Anecdotal reports have successfully shown IVIG as both a steroid-sparing agent and a monotherapy much like that used in CIDP. These measures, although attractive particularly for younger patients, need to be tested in controlled trials.

### Inflammatory Myopathies

Inflammatory myopathies are a diverse group of disorders that involve skeletal muscle in either a focal or diffuse fashion. The prevalence of autoimmune myositis varies between 10 and 63 cases per 1 million population. The more diffuse acquired disorders include dermatomyositis (DM), polymyositis (PM), and inclusion body myositis (IBM). Diagnosis requires a confirming muscle biopsy unless the typical changes in skin characteristic of DM are present. Up to 40% of patients with DM and PM may have associated connective tissue disorders such as scleroderma and missed connective tissue disease. An increased risk of malignancy is reported for both DM (up to 6-fold) and PM (up to 2-fold) patients, as reviewed by Mastaglia et al.

Corticosteroids remain the first line of treatment for DM and PM, despite only limited data from controlled clinical trials. Corticosteroids are supplemented with chemotherapeutic/immunomodulatory agents in resistant cases or to reduce dependence of corticosteroids. These supplementary agents include methotrexate, azathioprine, cyclophosphamide, cyclosporine, and IVIG.

### Dermatomyositis

Dermatomyositis, an inflammatory disease of skin and muscle, can occur in children or adults. More common in females, it is manifested by an acute, progressive weakness predominantly in the pelvic and shoulder girdle and by a skin rash over the eyelids, face, knuckles, elbows, upper chest, and shoulders. Autoantibody-mediated complement-dependent damage to the vascular-endothelial component of skeletal muscle is the primary pathogenic mechanism that results in marked reduction of capillaries in muscle. Dalakas et al studied 15 patients with therapy-resistant dermatomyositis in a double-blind, placebo-controlled, randomized crossover study using IVIG at a dose of 1 g/kg for 2 days and monthly for 3 months. In the IVIG-treated group, 9 of 12 patients had major improvement, as compared with none of the 11 patients in the placebo group. In the latter group, 3 had mild improvement, 3 had no change, and 5 had worsening of their condition. Because of the potential consequences from corticosteroid use, IVIG is proposed as a first-line therapy for children.

### Lambert Eaton Myasthenic Syndrome

Lambert Eaton myasthenic syndrome is another autoimmune disease that affects the neuromuscular junction. Antibodies to the presynaptic calcium channels at the motor end plates occur primarily in male patients, and frequently are associated with an underlying, most commonly small cell, carcinoma of the lung. Patients present with muscle weakness, predominantly in the lower limbs, and extraocular muscle involvement. Treatment includes high-dose corticosteroids, plasmapheresis, or chemotherapy.

In 1996, a single randomized, double-blind, placebo-controlled crossover trial by Bain et al involved 9 patients using IVIG at a dose of 1 g/kg daily for 2 days. Of the 9 patients treated with IVIG, 8 showed significant improvement in all functional measures, with a significant decline in serum calcium-channel autoantibody titers (Table 2).
Polymyositis

Polymyositis occurs more commonly in women after the second decade. It is associated with infiltration of muscle with CD8 in addition to cytotoxic T lymphocytes, causing individual destruction of fibers engulfed by macrophages. Clinically, PM causes weakness of the proximal muscles. The presence of anti-Jo-1 antibodies can contribute to interstitial lung disease. As with DM, treatment consists of corticosteroids and chemotherapy in resistant cases. More than 50 cases have been reported in which IVIG was used to treat refractory PM managed with IVIG as a supplementary treatment, with a positive response rate of approximately 70%. However, IVIG used as a first-line therapy without corticosteroids did not suppress disease activity.29

Inclusion Body Myositis

Inclusion body myositis occurs primarily in men older than 50 years. The prevalence of this disorder in a recent Australian study was 35.5 per 1 million individuals older than 50 years. The onset is frequently insidious, and weakness may asymmetrically involve the quadriceps and forearm flexors. Activated CD8 DR positive T-cells that express perforin and granzyme can be shown in the muscle biopsy. Muscle fibers contain rimmed vacuoles and deposition of the Aβ fragment of the amyloid precursor protein.

Unlike DM and PM, this disorder is resistant to treatment with conventional forms of immunotherapy. Early reports describe responses to corticosteroids and other immunosuppressives, although these usually are incomplete and not long-lasting.

The results of trials assessing the efficacy of IVIG for inclusion body myositis are variable. Two short-term placebo-controlled trials that compared IVIG with placebo in 19 patients as well as IVIG with or without prednisone in 36 patients showed no significant improvement in the overall muscle strength of the patient.30,31 In a third placebo-controlled crossover study, 22 patients received IVIG monthly for 6 months, and 90% of the patients reportedly stabilized. Mild improvement was supported only by the neuromuscular symptom score, but not by other measures.32 The use of IVIG may temporarily have more significant effects in a limited number of patients, including those with severe life-threatening dysphagia.33,34 The long-term use of an agent, particularly with only mild benefit, may not be warranted without additional long-term trials.

In most patients, IVIG is well tolerated. Side effects can include headache, myalgias, tachycardia, renal tubule necrosis, and hyperviscosity, with the potential for stroke or myocardial infarction, anaphylaxis, and hemolysis. A macular-papular rash of the forehead, forearms, and chest may occur in the first 2 weeks after administration. Occasionally, the rash may be leukocytoclastic. A series of hepatitis C cases were linked to the administration of a particular IVIG preparation, but such cases have not been seen subsequently because of changes in the manufacturing process. The association of thromboembolic events with IVIG treatment may be multifactorial, reflecting the infusion rate, IVIG concentration, hyperosmolarity, and inclusion of activated factor XI, as well as a history of atherosclerotic or cardiovascular disease in individual recipients. Rarely, in 8 per 10,000 patients, acute renal failure can occur. It is known that 90% of renal failure associated with IVIG occurs with preparations containing a high concentration of sucrose.

Factors such as efficacy of the agent, age of the patient, reproductive status, and the presence of comorbid diseases must be considered in the selection of a therapeutic regimen for patients with autoimmune disease. Corticosteroids may be contraindicated for patients with diabetes mellitus or osteoporosis. Antimetabolites, alkylating agents, and immunophilins have teratogenic effects that

**CONCLUSION**

In most patients, IVIG is well tolerated. Side effects can include headache, myalgias, tachycardia, renal tubule necrosis, and hyperviscosity, with the potential for stroke or myocardial infarction, anaphylaxis, and hemolysis. A macular-papular rash of the forehead, forearms, and chest may occur in the first 2 weeks after administration. Occasionally, the rash may be leukocytoclastic. A series of hepatitis C cases were linked to the administration of a particular IVIG preparation, but such cases have not been seen subsequently because of changes in the manufacturing process. The association of thromboembolic events with IVIG treatment may be multifactorial, reflecting the infusion rate, IVIG concentration, hyperosmolarity, and inclusion of activated factor XI, as well as a history of atherosclerotic or cardiovascular disease in individual recipients. Rarely, in 8 per 10,000 patients, acute renal failure can occur. It is known that 90% of renal failure associated with IVIG occurs with preparations containing a high concentration of sucrose.

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**TABLE 3**

Inflammatory Myopathy

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Clinical Features</th>
<th>Treatment</th>
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<tbody>
<tr>
<td>Dermatomyositis</td>
<td>Skin rash in face, elbows, chest, shoulders. Weakness of pelvic and shoulder muscles.</td>
<td>IVIG Corticosteroids</td>
</tr>
<tr>
<td>Polymyositis</td>
<td>Weakness of proximal muscles.</td>
<td>Corticosteroids Cytotoxic agents IVIG</td>
</tr>
<tr>
<td>IBM</td>
<td>Insidious onset in older (most frequently) men. Onset may be asymmetrical weakness of quadriceps and forearm flexors.</td>
<td>Corticosteroids Immunosuppressive agents IVIG (variable result)</td>
</tr>
</tbody>
</table>

IBM, inclusion body myositis.
may be cumulative over time and thus are contraindicated for younger patients with childhood potential. Patients with preexisting hepatic, hematopoietic, or renal disease do not tolerate individual drugs. Poor venous access, cardiovascular instability, and unavailable technology limit the use of plasma exchange. A history of allergy, IgE antibody to IgA in a patient with IgA deficiency, or renal disease may prevent the use of IVIG. The benefits of IVIG treatment include its availability in all treatment centers, the ability to administer it through peripheral intravenous access, and its ease of administration in the outpatient setting.

REFERENCES