AANEM PRACTICE TOPIC

ABSTRACT: Intravenous immunoglobulin (IVIG) is a therapeutic biologic agent that has been prescribed for over two decades to treat various neuromuscular conditions. Most of the treatments are given off-label, as little evidence from large randomized trials exists to support its use. Recently, IGIV-C has received an indication for the treatment of chronic inflammatory demyelinating polyneuropathy (CIDP). Because of the lack of evidence, an ad hoc committee of the AANEM was convened to draft a consensus statement on the rational use of IVIG for neuromuscular disorders. Recommendations were categorized as Class I–IV based on the strength of the medical literature. Class I evidence exists to support the prescription of IVIG to treat patients with Guillain–Barré syndrome (GBS), CIDP, multifocal motor neuropathy, refractory exacerbations of myasthenia gravis, Lambert–Eaton syndrome, dermatomyositis, and stiff person syndrome. Treatment of Fisher syndrome, polymyositis, and certain presumed autoimmune neuromuscular disorders is supported only by Class IV studies, whereas there is no convincing data to substantiate the treatment of inclusion body myopathy (IBM), idiopathic neuropathies, brachial plexopathy, or diabetic amyotrophy using IVIG. Treatment with IVIG must be administered in the context of its known adverse effects. There is little evidence to advise the clinician on the proper dosing of IVIG and duration of therapy.

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CONSENSUS STATEMENT: THE USE OF INTRAVENOUS IMMUNOGLOBULIN IN THE TREATMENT OF NEUROMUSCULAR CONDITIONS REPORT OF THE AANEM AD HOC COMMITTEE

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Consensus statements are important for developing treatment recommendations when evidence-based medicine (EBM) and treatment based on controlled trials is sparse or nonexistent. In this setting, it is clinically helpful to assemble a group of experts to review the medical literature with the purpose of creating recommendations for disease management, based on the best available evidence, until data from controlled studies are available to make recommendations. Such is the case for prescription of intravenous immunoglobulin (IVIG) for neuromuscular conditions. A team of neurologists was organized to create a consensus statement on the use of IVIG for patients with neuromuscular disorders. A four-round modified Delphi process was used to develop the consensus criteria.[1] Each member was assigned clinical disorders to review that were collected using MEDLINE from 1966 through the present and Cochrane databases. The keywords searched were IVIG, IGIV (IVIG and IGIV are synonymous), and intravenous immunoglobulin. After reading the articles, each member classified the data using criteria from the American Academy of Neurology Quality Standards Subcommittee

Abbreviations: CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; DLSRP, diabetic lumbosacral radiculoplexopathy; EBM, evidence-based medicine; GBS, Guillain-Barré syndrome; IBM, inclusion body myositis; IVIG, intravenous immunoglobulin; MAC, MG, myasthenia gravis; membrane attack complex; MMN, multifocal motor neuropathy; QMG quantitative myasthenia gravis

Key words: IVIG; IGIV; Guillain-Barre syndrome; Fisher syndrome; chronic inflammatory demyelinating polyneuropathy; autoimmune neuropathy; cryoglobulinemia; myasthenia gravis; Lambert-Eaton myasthenic syndrome; polymyositis; dermatomyositis; stiff person syndrome

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Table 1. Definitions for classification of evidence.[53]

Class I: Prospective, randomized, controlled clinical trial with masked outcome assessment, in a representative population.* The following are required:
- a) primary outcome(s) clearly defined
- b) exclusion/inclusion criteria clearly defined
- c) adequate accounting for drop-outs and crossovers with numbers sufficiently low to have minimal potential for bias
- d) relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

Class II: Prospective matched group cohort study in a representative population with masked outcome assessment that meets a-d above OR a randomized, controlled clinical trial in a representative population that lacks one criterion from a-d.

Class III: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurement.†

Class IV: Evidence from uncontrolled studies, case series, case reports, or expert opinion.

In exceptional cases, one convincing Class I study may suffice for an "A" recommendation if 1) all criteria are met, and 2) the magnitude of effect is large (relative rate improved outcome > 5 and the lower limit of the confidence interval is > 2).

†Objective outcome measurement: an outcome measure that is unlikely to be affected by an observer's (patient, treating physician, investigator) expectation or bias (e.g., blood tests, administrative outcome data).

report (Table 1) as Class I, II, III, or Class IV.[2] Reports were compiled into a single document that was circulated to every member for comments. Issues were discussed and reconciled, and the revised document was recirculated and rediscussed until consensus was reached.

IVIG is a therapeutic biologic agent manufactured through the fractionation of blood obtained from multiple donors. The plasma sources of a single infusion for a patient may vary from 2,000 to 16,000 patients. The immunoglobulin of highest concentration in IVIG is immunoglobulin G, which consists of four subclasses of IgG1, IgG2, IgG3, and IgG4. The purity of the product is 97%–100%, and the half-life ranges from 21–33 days. The products differ in pH, IgA content, half life, osmolarity, type of sugar, form (liquid or lyophilized), shelf life, sodium content, and viral reduction inactivation.

The mechanism whereby IVIG improves neurologic autoimmune disorders is complex, as immunoglobulins act at multiple sites in the immune regulatory network. IVIG interferes with costimulatory molecules, has anti-idiotype activity, suppresses antibody production, interferes with the activation of complement, and intercepts the formation of membrane attack complex (MAC).[3,4] Immunoglobulins also modulate the expression and function of Fc receptors on macrophages, suppress cytokines, chemokines, and adhesion molecules, and alter the activation, differentiation, and effector functions of T cells.[3]

IVIG has been established as a mainstay treatment for immunodeficiency conditions and bullous skin disorders. It has been prescribed to treat numerous autoimmune and inflammatory neurologic conditions for ≈20 years or more. Recently, based on the results of the recent ICE trial (IGIV-C CIDP Efficacy), the Food and Drug Administration has approved the use of IGIV-C for the treatment of CIDP. This is the first approved indication of an intravenous immunoglobulin product for a neurologic condition.[5]

GUILLAIN–BARRÉ SYNDROME

No trials exist that compare IVIG to placebo or supportive treatment in adult patients with Guillain–Barré syndrome (GBS). Since plasma exchange was the accepted treatment for GBS before trials of IVIG were published, four Class I randomized trials were reviewed that directly compared IVIG to plasma exchange.[6–9] Each trial used an ordinal disability grading system identical or similar to that described by Hughes in 1978.[10]

A trial from the Netherlands tracked 150 patients who were unable to ambulate 10 m independently and who entered the study within 2 weeks of onset of the neuropathy.[9] Subjects were randomized to receive either plasma exchange, 200–250 ml/kg in five sessions over 7–14 days, or IVIG in a dose of 0.4 g/kg daily for 5 days. In the plasma exchange group, 34% improved by one or more functional grades after 4 weeks compared to 53% in the IVIG group. This difference of 19% carried a 95% confidence interval (95% CI) −2 to 39% and was statistically significant ($P = 0.024$). As a secondary outcome measure, the median time for improvement by one functional grade was significantly shorter in the IVIG group (27 days for IVIG and 41 days for plasma exchange, $P = 0.05$). Another secondary outcome, the median time to recovery of independent ambulation, was also

shorter in the IVIG than in the plasma exchange group (55 days vs. 69 days, $P = 0.07$).[9] A major criticism of this publication was the considerably lower response rate of the plasma exchange group compared to the response rate reported in the Guillain–Barré Syndrome Study Group of Plasmapheresis.[11] Other randomized trials of patients with GBS were found: one from Canada, another the international trial of 383 patients who received either IVIG, plasma exchange, or both treatments, and a third trial of 55 patients from Germany.[6–8] These studies showed that IVIG and plasma exchange are of equal benefit for the treatment of GBS. On the basis of these trials, we conclude that IVIG is at least as effective as plasma exchange for the treatment of GBS. IVIG is recommended for adult patients with GBS, particularly those who require an aid to walk (disability grade ≥ 2) within 2 weeks of the onset of symptoms.

The question of the relative efficacy of IVIG versus plasma exchange in adult GBS was analyzed in a recent Cochrane systematic review. The authors performed a meta-analysis on the combined data from five randomized and quasi-randomized trials.[12] Collectively, 273 patients were treated with IVIG and 263 received plasma exchange. The outcome measure of improvement in disability grade at 4 weeks after randomization was discernable for all trials. The meta-analysis showed a -0.02 grade greater improvement after treatment with IVIG than with plasma exchange (95% CI, -0.25 more improvement to 0.20 less improvement). The review concluded that no significant difference existed in the degree of recovery at 4 weeks between IVIG and plasma exchange in adult patients with GBS.[12]

Another question addressed by the authors is whether combination treatment with plasma exchange followed by IVIG in adult GBS is superior to single modality therapy. In a single randomized international trial of Sandoglobulin,[8] the mean improvement in disability grade after 4 weeks was 0.8 in the IVIG group and 1.1 in the combination therapy group. The difference of 0.29 grade improvement between the groups showed a 95% CI of -0.04 to 0.63 and was not significantly different. Based on this study result, combined treatment with plasma exchange followed by IVIG is not superior to treatment with IVIG alone.[8]

The effectiveness of IVIG in the treatment of childhood GBS has also been studied.[13–15] One trial from Turkey compared the outcome after IVIG at 1 g/kg daily for 2 days compared with supportive treatment. The intervals from onset to maximal symptoms (9.3 vs. 12.5 days), from maximum weakness to time of first improvement (7.5 vs. 11.8 days) and duration of hospitalization (16.5 vs. 23.8 days) all significantly favored the IVIG group ($P < 0.05$).[14] A second study from Germany compared the treatment of IVIG at 1 g/kg given over 2 days to supportive treatment in children who were able to walk. Fourteen patients were randomly allocated to the IVIG group and 7 to the supportive treatment group. The primary outcome measure of maximal disease severity at nadir was not significantly different between the treatment groups; however, secondary outcome measures favored the group that received IVIG treatment for time to improvement from onset (4.5 vs. 30 days, $P = 0.001$) and median disability score at 4 weeks (1 vs. 2, $P = 0.025$). In the same article the authors reported a second study in which 51 children with GBS received either IVIG 1 g/kg daily over 2 days or 0.4 g/kg daily over 5 days. To enter the second study, patients must have been unable to walk 5 m unaided. Recovery did not differ significantly between the children treated for 2 days versus 5 days (median time to unaided walking: 19 days vs. 13 days). Secondary transient deterioration in the disability score occurred more frequently in the group undergoing 2 days of IVIG infusion than in the group treated for 5 days (5 of 23 patients vs. 0 of 23 patients).[16]

A number of case series have demonstrated a benefit of IVIG in childhood GBS in various outcome measures compared to control patients from other trials or historic cases from natural history studies.[15,17–20] From these studies, Class II and Class III evidence exists to support IVIG as beneficial in hastening recovery in pediatric patients with GBS compared with supportive treatment alone.

Relapses are not uncommon in adult GBS patients treated with IVIG and plasma exchange. A meta-analysis addressing this issue was performed as part of a Cochrane review of patients from the Dutch[12] and international Sandoglobulin[8] trials for which these data are available. A total of 12 of 204 patients in the IVIG group and 13 of 194 patients in the plasma exchange group experienced clinically significant treatment-related fluctuations or relapses, for a relative risk of 0.89 (95% CI 0.42–1.98) for IVIG versus plasma exchange.[12] Results from this meta-analysis suggest that GBS relapses in adult patients are no more common after IVIG than plasma exchange treatment. There is no evidence-based literature on the indication for, or efficacy of, repeat infusions of IVIG for relapses of GBS.

Insufficient data exist to recommend an optimal IVIG treatment dose or duration for GBS

patients, although 0.4 mg/kg daily for 5 days is reasonable based on the available data. The efficacy of IVIG has not been examined in patients who had GBS for more than 2 weeks before the infusion is started.

FISHER SYNDROME

A Cochrane Neuromuscular Review of Fisher syndrome in 2007 identified no randomized prospective controlled trials of immunotherapy in the condition.[21]

In a retrospective analysis of 92 Japanese patients admitted to a single center between 1979 and 2005, 28 were treated with IVIG (0.4 g/kg/day on 5 consecutive days), and 23 patients underwent plasma exchange (2–6 treatments every other day).[22] Forty-one patients received no immunemodulating treatment and served as a control group. The time from onset of ataxia and/or ophthalmoplegia to the start of clinical improvement was shorter in the IVIG group than in the control group (ophthalmoplegia 12.0 vs. 13.5 days, $P = 0.04$, and ataxia 8.0 vs. 10.0 days, $P = 0.027$). There was no difference in the improvement times between the IVIG and plasma exchange groups or the plasma exchange and control groups.[22] Several case reports and case series have been published on the treatment of Fisher syndrome with IVIG. In these reports, patients who received IVIG experienced clinical recovery in a slightly shorter time frame than would be expected based on the natural history of the illness.[23–29]

On the basis of the single retrospective analysis and the case reports listed above, it is difficult to clearly define the role of IVIG in treating Fisher syndrome. The literature suggests that best medical management may suffice for many patients.[21]

CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY

The efficacy of IVIG in CIDP has been demonstrated in six of seven double-blind, controlled trials[5,30–34] (Class I). In three of four trials, treatment with IVIG was significantly superior to placebo, and in two other trials it was equivalent to treatment with plasma exchange or prednisone.[5,30–34] A Cochrane Review meta-analysis showed a significant improvement in strength and disability compared to placebo.[35]

Since CIDP is a chronic illness prone to relapses and remissions, continued treatment is often necessary for years. Although no controlled trials exist that address issues of dosing or frequency of treatments, many clinicians begin treatment with a loading dose of 2 g/kg, over 2 to 5 days, and often repeat infusions of either 0.5 g/kg every 2 weeks, 1 g/kg every 3 weeks, or 2 g/kg every month, over a total of 2 or 3 months. If a patient improves, treatments are continued until maximal improvement is achieved. Thereafter, IVIG can be tapered or discontinued to determine whether continued use is needed. If the patient relapses, maintenance therapy will be required at doses and frequencies that are determined empirically for each patient.[36]

Over time CIDP can produce permanent neurologic deficits attributed to secondary axon loss,[37] thus prompt treatment is needed to prevent permanent deficits.

MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE-ASSOCIATED NEUROPATHIES

Two double blind, placebo-controlled trials of IVIG for the neuropathy associated with IgM monoclonal proteins were negative for attaining primary endpoints. In one placebo-controlled crossover study of 11 patients, 20% improved, two in motor and one in sensory function.[38] A second study of 22 patients did not report a benefit in the primary endpoint, i.e., disability at 2 weeks.[39] However, improvement was noted in one of the secondary outcomes, disability at 4 weeks, favoring the IVIG treatment group ($P = 0.001$). At the conclusion of the study, 10 patients improved, 11 were stable during the IVIG period, and only one worsened. During the placebo period, four patients improved, four deteriorated, and 14 remained stable.[39] From these Class I studies we can conclude that IVIG benefits only a minority of patients with the neuropathy associated with IgM paraproteinemia. Gorson et al.[40] reported more encouraging results describing improvement in 40% of patients with the neuropathy associated with an IgG monoclonal protein after receiving IVIG.

CHRONIC AUTOIMMUNE NEUROPATHIES

No double-blind, placebo-controlled trials of IVIG have been published for the neuropathy associated with Sjogren's syndrome,[41–47] Churg-Strauss angiitis,[48,49] systemic sclerosis,[50] anti-sulfatide neuropathy,[51,52] postinfection sensory neuropathy,[53] sarcoidosis,[54] systemic lupus erythematosus,[55] CANOMAD (chronic ataxic neuropathy, ophthalmoplegia, monoclonal protein, agglutination, and disialosyl antibodies),[56] and inflammatory bowel disease.[57] The best available Class IV evidence

suggests that some of these patients improve after receiving IVIG.

IVIG for the treatment of cryoglobulinemic neuropathy remains uncertain. Kuhl et al.[58] and Caporale et al.[59] reported improvement in patients with cryoglobulinemic neuropathy (one with hepatitis C) after treatment with IVIG. However, several studies (all Class IV) have reported serious side effects when IVIG is used to treat cryoglobulinemic neuropathy, including acute renal failure[60] and cutaneous vasculitis.[61] The latter complication has been attributed to increased immune complex formation precipitated by the IVIG infusion.[61] In one observational study, IVIG was ineffective in treating a patient with neuropathy and hepatitis C and type II mixed cryoglobulinemia.[48]

IDIOPATHIC NEUROPATHIES

Twenty percent of neuropathies remain undiagnosed despite extensive evaluation. It is likely that some of these patients have immune-mediated neuropathies, despite the lack of a definitive diagnosis. Some patients with chronic progressive idiopathic neuropathies have been reported to respond to IVIG,[62–64] and other patients with idiopathic painful sensory neuropathies may also respond to IVIG.[65,66] At the present time, there is insufficient evidence to advise the use of IVIG for the treatment of idiopathic neuropathy.

MULTIFOCAL MOTOR NEUROPATHY

Three Class I randomized clinical trials have been conducted in multifocal motor neuropathy (MMN). The largest two were published by Leger et al. and Federico et al.[67–69] All three studies incorporated crossover trial designs in which patients received IVIG or placebo, either before or after the crossover phase. In the Leger et al.[69] study, 12 of 18 patients improved after receiving IVIG, four patients did not improve, and two benefited from the placebo infusion. Similar results were published by Frederico et al.[68] Azulay et al.[67] studied 12 patients with MMN also implementing a placebo-controlled, crossover design. In their patients, IVIG produced significant increases in muscle strength only in patients with conduction block on nerve conduction studies. Oral prednisone and plasma exchange are not effective in MMN despite the frequent consideration of this disorder as a variant of chronic inflammatory demyelinating neuropathy.[70]

A Cochrane Review published in 2005 concluded that limited evidence existed from randomized controlled trials to demonstrate benefits in strength and disability in patients with MMN who receive IVIG.[71] Guidelines of the European Federation of Neurological Societies and Peripheral Nerve Society on the same subject made the following recommendations for using IVIG in MMN: "dosing at 2 gm/kg given over 2-5 days should be considered as the first line treatment."[72] Repeated treatment with IVIG should be considered if the initial infusion of IVIG is effective, and the frequency of maintenance therapy should be guided by the individual response.[73] The guidelines recommended 1 g/kg every 2–4 weeks or 2 g/kg every 4–8 weeks for repeated treatments.[72]

MYASTHENIA GRAVIS

A randomized, placebo-controlled masked study reported the effectiveness of IVIG compared to placebo (5% dextrose in water) in patients with myasthenia gravis (MG) who were experiencing worsening of weakness[74] (Class I). The Quantitative Myasthenia Gravis (QMG) Score for Disease Severity was chosen as the primary outcome measure and was graded by a masked observer at baseline and at days 14 and 28.[75] In the IVIG-treated patients a statistically significant improvement in the QMG score was recorded at 14 days ($P = 0.047$), and the clinical improvement was maintained at 28 days. The QMG score at 28 days just failed to reach statistical significance ($P = 0.055$). Patients who underwent IVIG treatment were 3 times more likely to achieve improvement compared to the placebo group. The greatest improvement was observed in patients with the most severe disease.[74] Responsiveness was independent of age, sex, disease duration, and antibody status.[74]

Placebo-controlled clinical trials of exacerbations of MG treated with IVIG have shown approximately the same benefit as plasma exchange or methylprednisolone[76,77] (Class I). The largest trial reported the results from 87 patients who experienced acute worsening of myasthenia who were treated with IVIG and compared to a population of patients receiving therapeutic plasma exchange[76] (Class I). No significant difference was observed among the three arms of the study: three plasma (1.5 plasma volumes) exchanges, or IVIG given as 0.4 g/kg/day daily for 3 days (1.2 g/kg) or 5 days (2 g/kg). Criticisms of the study include the lack of a control arm, the nonblinding of the plasma exchange group, and the lack of stratification between seropositive and seronegative patients. The study concluded that IVIG is as effective as

therapeutic plasma exchange, and might be preferable because of its lower complication rate[76] (Class I). Stricker et al.[78] reported that plasma exchange was superior to IVIG in their small uncontrolled series of patients with an acute exacerbation of weakness (Class IV).

Another controlled trial that compared two doses of IVIG for the treatment of MG exacerbation demonstrated high methodological quality, large numbers, and good compliance[77] (Class I). It demonstrated no significant superiority of IVIG 2 g/kg infused over 2 days compared to IVIG 1 g/kg administered on a single day, although a trend was apparent toward a slight superiority of IVIG 2 g/kg. Thus, 1 g/kg IVIG on a single day may be a sufficient dose for the treatment of MG exacerbations.

Insufficient data exist on the role of IVIG in the chronic management of patients with MG.

LAMBERT–EATON SYNDROME

One controlled trial has been conducted using IVIG to treat patients with Lambert–Eaton syndrome. Bain et al.[79] studied nine patients using a double-blind, randomized crossover design. Improvement was observed in limb strength, respiratory function, and bulbar strength in all patients after IVIG treatment. Paralleling the improvement was a decline in the serum level of voltage-gated calcium channel antibodies directed against the presynaptic junction of the neuromuscular junction (Class III).

INFLAMMATORY MYOPATHIES

One Class I (double blind, randomized, crossover) trial has been published in which high-dose IVIG was shown to be effective in treating steroid-resistant dermatomyositis.[80] A number of Class IV studies have confirmed the effectiveness of IVIG as adjunctive therapy to steroids in treating dermatomyositis.[81–86] However, the results from at least one study imply that IVIG may not be effective as a sole therapy for either polymyositis or dermatomyositis.[87] Since dermatomyositis tends to be steroid-responsive, IVIG therapy is generally recommended as add-on treatment in refractory cases.

No controlled, double-blind studies of IVIG have been reported for the treatment of polymyositis, due to the difficulty of acquiring a sufficient number of suitable subjects with biopsy-proven polymyositis. Two uncontrolled studies demonstrated conflicting results. In a small study, Cherin et al.[88] described treating five polymyositis patients with IVIG, none of whom improved in muscle strength. An open label study of 35 patients with refractory polymyositis by the same authors reported a beneficial effect in more than 70% of patients who were not responsive to immunosuppressant medications administered earlier in their disease.[89] In an earlier study published by Cherin et al.,[81] significant improvement was recorded in 10 of 14 patients with polymyositis after infusions of IVIG. In patients who responded to IVIG, doses of corticosteroids were reduced in 9 of 14 patients, and serum CK levels dropped in all patients who initially had elevated levels.[81] IVIG appears to be more effective as an adjuvant treatment than as first-line therapy in polymyositis.[87]

At present, there are no definitive guidelines regarding the initial dose, total days of administration, and timing or dosing of subsequent administration of IVIG for dermatomyositis or polymyositis. Several studies have administered IVIG at a dose of 2 g/kg body weight over a 5-day period as the initial course, followed by monthly booster doses over 1–3 days for a period of 3–6 months. Dalakas[3] believes that improvement tends to occur by the end of the first or second IVIG course, and, if there is no improvement by the end of the second infusion, additional IVIG is not likely to be effective. In some patients, sustained improvement may be achieved using lower maintenance doses,[90] while other patients may require more frequent IVIG infusions (e.g., every 2–3 weeks) to maintain function.

INCLUSION BODY MYOSITIS

Three randomized, double-blind, controlled studies have been conducted to study the efficacy of IVIG for the treatment of inclusion body myositis (IBM)[91–93] (Class I). Dalakas et al.[92] performed a placebo-controlled, crossover study of 19 patients and demonstrated mild regional improvement of swallowing and lower extremity strength in a third of cases. However, there was no statistically significant improvement in overall muscle strength. Walter et al.[93] performed a placebo-controlled study of IVIG therapy in 22 patients with IBM. There was variable improvement in muscle strength, although stabilization of the condition occurred in 90% of patients and mild improvement in the others.[93] Dalakas et al.[91] performed a subsequent 3-month study in which IVIG combined with prednisone was compared to prednisone treatment alone. In 36 patients no significant clinical improvement was recorded in muscle strength when IVIG and

prednisone were combined, although muscle biopsies obtained at the end of the study showed a posttherapy reduction in endomysial inflammation and number of necrotic muscle fibers.[91] At present, IVIG is not recommended as routine therapy for IBM due to the variability of response and treatment expense. However, even though some studies suggest a mild to moderate degree of improvement in swallowing and leg strength after IVIG infusion, at present IVIG is not recommended as a treatment for IBM.[94]

IDIOPATHIC BRACHIAL NEURITIS

No controlled trials of IVIG have been reported in brachial neuritis. A few observational studies in patients with brachial neuritis have reported improvement after IVIG treatment[95–97] (Class IV).

DIABETIC LUMBOSACRAL RADICULOPLEXOPATHY

Diabetic lumbosacral radiculoplexopathy (DLSRP) may in part be immune-mediated and potentially responsive to immunomodulatory therapy.[98] No controlled studies of IVIG therapy have been reported in this condition. Pascoe et al.[99] compared the response of 12 patients with DLSRP, some of whom received IVIG, to untreated patients. The authors noted that, despite eventual improvement in all patients, the group treated with IVIG improved more quickly and to a greater degree. Krendel et al.[100] reported that all 15 patients with DLSRP who were treated with IVIG, prednisone, or cyclophosphamide showed improvement, including a marked improvement in five. There have been several uncontrolled reports that detail clinical improvement in patients with DLSRP after treatment with IVIG.[101–106] However, not all studies have shown improvement when IVIG is prescribed. Zochodne et al.[107] documented lack of clinical improvement in three patients with DLSRP who were treated with immunotherapy.

STIFF PERSON SYNDROME

Dalakas et al.[108] have published the only Class I trial using IVIG to treat patients with stiff person syndrome. Using a crossover design and 3-month treatment periods of IVIG or placebo, followed by a wash-out period, and subsequent treatment with the alternate therapy, the authors showed IVIG to be statistically superior to placebo in reducing stiffness ($P = 0.01$).[108] Eleven of 16 patients experienced improved gait, fewer falls, and improved activities of daily living. The duration of benefit ranged from 6 weeks to 1 year.

ADVERSE EFFECTS OF IVIG

Numerous adverse effects have been reported after infusions of IVIG. Headaches, myalgia, fever, chills, and nausea are common, whereas less frequently occurring side effects include backache, lightheadedness, stroke, transient leukopenia or neutropenia, aseptic meningitis, acute renal failure, proteinuria, dyspnea, hypotension, rash, urticaria, and immune complex-mediated arthritis.[109,110] Brannagan et al.[109] reported major complications in 4.5% of patients who received infusions of IVIG. Those included congestive heart failure in a patient with polymyositis, deep venous thrombosis in a bedbound patient, acute renal failure in a patient with diabetic nephropathy, and hypotension after a recent myocardial infarction.[109] In this series of 88 patients, 59% developed at least one adverse effect. Headache, fever, shortness of breath, and vasomotor changes constituted the most common complications. Six percent of patients experienced an asymptomatic laboratory abnormality. Most common were elevated liver function studies and neutropenia. The adverse events led to discontinuation of the therapy in 16% of the patients.

Other authors have reported a lower incidence of adverse effects. In the large study reported by the Sandoglobulin GBS Trial Group, 14 patients (5.6%) who received IVIG alone or IVIG and plasma exchange experienced symptoms that could be attributed to the infusion.[8] Those included nausea and vomiting, meningismus, exacerbation of chronic renal failure, a possible myocardial infarction, and painful erythema at the infusion site. In the study reported by van der Meche and Schmitz,[9] only five incidents were noted in 76 patients during 380 infusions of immunoglobulin. In children, the incidence of adverse effects may be higher. Four of 11 children experienced side effects from IVIG infusions in a Japanese study of high-dose immunoglobulin therapy for GBS.[111] Surprisingly, the adverse effects were more likely to be hematologic (granulocytopenia, anemia, reticulocytosis, eosinophilia) than systemic symptoms.

The publication of a recent large study of IGIV-C for the treatment of CIDP reported detailed information on adverse events after an initial and crossover phase of 24 weeks and an extension phase of 24 weeks.[5] Because of the study design, the exposure rate to IGIV-C was twice that

Table 2. Class of evidence supporting use of IVIG in the treatment of specific neuromuscular disorders.

Neuromuscular disorder	Class of evidence
Gullain-Barre syndrome in adults	I
Guillain-Barre syndrome in children	II
Fisher syndrome	IV
Chronic inflammatory demyelinating polyneuropathy	I
Neuropathies associated with monoclonal proteins	IV
Chronic auto-immune neuropathies	IV
Neuropathies associated with cryoglobulinemia	IV
Idiopathic neuropathies	IV
Multifocal motor neuropathy	I
Myasthenia gravis	I
Lambert-Eaton myasthenic syndrome	I
Dermatomyositis	I
Polymyositis	IV
Inclusion body myositis	None
Idiopathic brachial plexopathy	IV
Diabetic lumbosacral radiculoplexopathy	IV
Stiff person syndrome	I

of placebo. Approximately 80% of patients were able to tolerate the full loading dose of 2 g/kg over 2 days and the maintenance infusions of 1 g over 1 day. The most common adverse events, using the calculation of events per infusion, were headache (5.2%), pyrexia (2.5%), and hypertension (1.8%).[5] Less common events were asthenia, chills, back pain, rash, arthralgia, nausea, dizziness, and influenza. Most of the adverse events were mild and self-limited. Serious adverse events were more common in the placebo group (eight compared to six in the IGIV-C group). All of the serious adverse events resolved by the end of the study except for one case each of bronchopneumonia and a relapse of CIDP symptoms.

CONCLUSIONS

Class I evidence exists to support the use of IVIG to treat patients with GBS, CIDP, multifocal motor neuropathy, exacerbations of myasthenia gravis, Lambert–Eaton syndrome, dermatomyositis, and stiff person syndrome (Table 2). If untreated, CIDP can result in permanent disability which has been attributed to irreversible axon loss. For this reason, the Committee advises timely treatment of CIDP to prevent progression or relapses that can lead to disability. IVIG, prednisone, and plasma exchange have been shown to be equally efficacious as first-line therapy for CIDP.[30,32] Although their efficacy and toxicity are similar in the short term,[32] use of steroids long term can result in many adverse effects.[112] Long-term toxicity has not been shown to occur after periodic use of IVIG or plasma exchange.

There is Class IV evidence for the use of IVIG in Fisher syndrome. There is only Class IV evidence for a role of IVIG to treat chronic neuropathies associated with IgM and IgG monoclonal proteins, polymyositis, and neuropathies associated with cryoglobulins. At the present time, there are no objective data to support the prescription of IVIG to treat IBM, idiopathic neuropathies, idiopathic brachial neuritis, or diabetic lumbosacral radiculoplexopathy. Even in conditions where Class I evidence is robust, there is little evidence to guide the clinician in the proper dosing of IVIG and the duration of therapy.

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