INVITED REVIEW

OPTIMIZING IGG THERAPY IN CHRONIC AUTOIMMUNE NEUROPATHIES: A HYPOTHESIS DRIVEN APPROACH

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Accepted 17 November 2014

ABSTRACT: Prolonged intravenous immunoglobulin (IVIG) therapy is used for the chronic autoimmune neuropathies chronic idiopathic demyelinating polyneuropathy and multifocal motor neuropathy, but the doses and treatment intervals are usually chosen empirically due to a paucity of data from dose–response studies. Recent studies of the electrophysiology and immunology of these diseases suggest that antibody-induced reversible dysfunction of nodes of Ranvier may play a role in conduction block and disability which responds to immunotherapy more rapidly than would be expected for demyelination or axonal damage *per se*. Clinical reports suggest that in some cases, the effects of each dose of IVIG may be transient, wearing-off before the next dose is due. These observations lead us to hypothesize that that therapeutic IgG acts by competing with pathologic autoantibodies and that individual patients may require different IgG levels for optimal therapeutic effects. Frequent IVIG dosing and weekly subcutaneous IgG have been tried as ways of continuously maintaining high serum IgG levels, resulting in stabilization of neuromuscular function in small case series. Frequent grip strength and disability measurements, performed by the patient at home and reported electronically, can be used to assess the extent and duration of responses to IgG doses. Individualization of IgG treatment regimens may optimize efficacy, minimize disability, and identify nonresponders.

Muscle Nerve **51**: 315–326, 2015

Intravenous immunoglobulin (IVIG) is used widely for neuromuscular diseases, including Guillain-Barre Syndrome (GBS), chronic idiopathic demyelinating polyneuropathy (CIDP), multifocal motor neuropathy (MMN), idiopathic inflammatory myopathies, and myasthenia gravis (MG).[1–5] Particularly in CIDP and MMN, and in some cases of MG, IVIG doses are repeated at regular intervals for long periods of time.[3,6–9] The dose and treatment interval are often chosen empirically, or are based on observations in other diseases, with little input from dose–response studies or guidance in how to optimize usage of this expensive therapy for individual patients.

In recent years, studies in patients and in animal models have highlighted the importance of autoantibodies against gangliosides and/or membrane proteins in the acute motor axonal neuropathy (AMAN) form of GBS,[10,11] MMN,[12] and possibly acute inflammatory demyelinatiang polyradiculopathy[11] and CIDP.[13,14] These results have led to the hypothesis that antibody-induced alterations in the distribution of ion channels and/or structural proteins in the nodes of Ranvier may interfere with conduction or cause outright block by reversibly interfering with axon function.[15–21] These functional alterations may be more rapidly responsive to therapy than classically described pathologic changes such as demyelination or destruction of axons.[14] Recent studies of the kinetics of electrophysiologic and clinical effects of IVIG in CIDP and MMN suggest that remyelination or axonal regeneration may not fully explain the therapeutic effects of IVIG, and that correction of nodal dysfunction may be important in the rapid functional improvement which has been reported.[16–18,21,22] Appreciating how reversible effects of autoantibodies impact nerve conduction, weakness, and disability suggests a need for new paradigms for monitoring and optimizing IgG treatment for patients with chronic autoimmune neuropathies. This review focuses on studies which might inform new paradigms and illustrates the utility of frequent objective strength and performance assessments in optimizing patients' clinical responses and minimizing disability.

IMMUNOPATHOLOGY OF CIDP AND MMN

In many ways, CIDP resembles a chronic form of GBS.[10,14] CIDP differs from GBS in that few patients recall preceding infections or other triggering events. Also, unlike the putative role of antiganglioside antibodies in some GBS variants (e.g., AMAN), no single major target antigen(s) has been identified in CIDP.[14,23] Nevertheless, plasma exchange (PLEx), which presumably removes autoantibodies, complement, and cytokines/other soluble factors, is

Abbreviations: AChR, acetylcholine receptor; AE, adverse event; AMAN, acute motor axonal neuropathy; CIDP, chronic idiopathic demyelinating polyneuropathy; GBS, Guillain-Barre syndrome; ICE, intravenous immune globulin (10% caprylate-chromatography purified) for the treatment of chronic inflammatory demyelinating polyradiculoneuropathy (study); IgG, immunoglobulin G; IgM, immunoglobulin M; IVIG, intravenous immunoglobulin; MG, myasthenia gravis; MMN, multifocal motor neuropathy; PeriNomS, peripheral neuropathy outcome measures standardization study; PIDD, primary immunodeficiency diseases; PLEx, plasma exchange; R-ODS, Rasch-built Overall Disability Scale; SCIG, subcutaneous IgG.

Key words: CIDP; IVIG; MMN; monitoring; SCIG

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Published online 22 November 2014 in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/mus.24526

very effective in CIDP as well as in GBS, with many patients responding within a few days.[10,23–26] Reports of clinical improvement after the use of immunoadsorbents to selectively remove immunoglobulins in small series of CIDP and GBS also suggest a direct role of autoantibodies in these conditions.[27,28] The importance of autoantibodies may also be supported by reports that some MMN and CIDP patients improve with the anti-B cell antibody, rituximab,[8,29] although this effect was not observed in all studies.[30] Antibodies against peripheral myelin proteins including neurofascin and contactin-1, PMP 22, and P0; nodal proteins including gliomedin; and/or gangliosides have been reported in sera of CIDP patients.[31–41] Antibodies against any individual defined antigen are relatively infrequent in any particular series, however, and in the majority of CIDP patients the antigenic target is unknown.[14,23] Animal studies, including induction of CIDP-like experimental 'allergic' neuritis by immunization with myelin or myelin proteins, and passive transfer studies also support a role for antibodies in the pathogenesis of CIDP.[13,26,33] Shifts in the balance of helper, effector, and regulatory T-cell subsets in the blood of CIDP patients and elevations of T-cell derived cytokines all support a role for T-cells in inducing or maintaining the autoantibody response.[41–49] However, the T-cells and macrophages in biopsies appear predominately in perivascular areas, rather than along the nerve fiber itself.[50–52] The relative paucity of T-cell infiltrates in nerve biopsies from CIDP patients and the lack of cerebrospinal fluid pleocytosis[51] cast doubt on the role T-cells as major effectors of nerve damage/dysfunction *per se*. Together with the range of recognizable clinical variants of CIDP,[12,53] these observations suggest heterogeneity of the autoimmune pathology and chronic neural dysfunction.[12]

Characteristic findings on microscopic pathology of CIDP include segmental demyelination/ remyelination.[50,54] "Onion bulbs," thought to represent a response of Schwann cells and macrophages to repeated cycles of injury and repair, may also be seen. The presence of segmental demyelination and onion bulbs certainly suggest that myelin disruption plays a role in CIDP pathogenesis and the disability experienced by patients.[51,52,55–58] Myelin disruption, however, may only be a partial explanation and may occur later than the initial stages of the disease. Electrophysiologic studies are beginning to highlight the importance of nodal dysfunction, and they suggest that rapid reversal of disability may be tied to improvement in nodal function.[15–21,55,59–61] Classical electrophysiologic findings considered important for the diagnosis of CIDP include multifocal conduction velocity slowing, distal latency prolongation, conduction block, and temporal dispersion, which have generally been considered indicative of demyelination.[14,61,62] Studies of axonal excitability using the responses to multiple stimuli, strength-duration relationships, and excitability-recovery protocols offer a complementary mechanism that may be particularly relevant to the clinical experience of some CIDP patients. In a study of CIDP patients, measurements of axonal excitability in response to subthreshold polarizing currents (threshold electrotonus) were interpreted as showing hyperpolarizing changes.[60] In another study of CIDP patients, stimulus-response curves suggested increased threshold requirements.[59] Nerve excitability has also been studied before and after IVIG administration. Reduction in the strength–duration time constant was observed shortly after IVIG infusions in patients with both MMN and CIDP, perhaps reflecting a reduction in the persistent Na^+ current.[16] These membrane changes may be mediated by autoantibodies capable of disrupting Na+ channel clusters and functions of Na+/K+ ATPases in nodes of Ranvier, resulting in hyperpolarization and decreased excitability.[15–18,20,21] Similar electrophysiologic changes can be replicated in laboratory animals with antiganglioside antibodies and complement[63] or by immunizing animals against gliomedin.[13] Although focal demyelination is often considered the cause of conduction block, nodal excitability changes resulting in increased thresholds for nerve stimulation may be an alternative explanation for this classic electrophysiologic finding in CIDP.[59]

Clinical response to IVIG or PLEx may occur rapidly, often within just a few days. Remyelination or axonal regeneration, while likely important in eventual recovery, are implausible as explanations for this rapid clinical improvement.[16,55] Small studies of recordings obtained just before and at various time points after individual IVIG doses have been interpreted to suggest that improvements in motor performance correspond to rapid but reversible changes in nodal function.[16–18,20] The duration of improvements in axonal excitability and muscle strength may be limited, with a return to the preinfusion baseline before the next dose of IVIG is due.[15,18,21] An interesting analogy may be found in a recent report of MG patients who responded to IVIG. Thirty-two of the 37 patients reported improvement within a few days after each IVIG infusion but worsening of myasthenic symptoms a few days before their next scheduled IVIG infusion.[9] No change in AChR antibody titers were observed, even with prolonged IVIG therapy. Therefore, the authors concluded that the major effect of IVIG was to neutralize the autoantibody, rather than to suppress its production, and that IVIG was, therefore, not a "disease modifying treatment" in MG.[9]

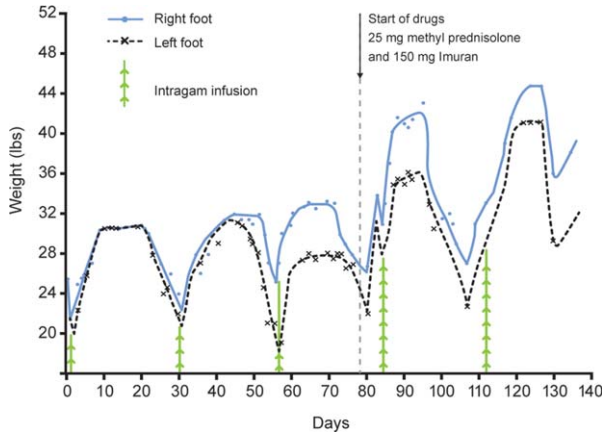

FIGURE 1. CIDP: Cyclic gain in strength of ankle dorsiflexion in response to monthly IVIG with return to baeline before next dose is due (days 0–78). After the addition of prednisolone and Imuran on day 79, cyclic response to monthly IVIG continues, but each month, peak and nadir are higher than on IVIG alone. From Pollard and Armati[18] with permission of publisher.

A dramatic example of this phenomenon in CIDP is shown in Figure 1 In cases in which the therapeutic effects of IVIG do not persist throughout the usual 28 to 30 day dosing interval, improved management of rapidly reversible responses may offer an important opportunity for optimizing short-term treatment effects. Further studies are needed to determine if optimizing short-term responses affects the long term prognosis of CIDP.

MMN is distinguished by demonstrating multiple conduction blocks limited to motor nerves, with sparing of sensory nerves.[64–67] The electrophysiologically demonstrated conduction blocks have been considered a consequence of segmental demyelination, but recent studies suggest immunologic target(s) actually on axons rather than/or in addition to Schwann cells or myelin *per se*.[67] A major puzzle in understanding MMN is the observation that corticosteroids and PLEx are usually not effective,[64,65,67] while IVIG has become the standard of care.[68] Approximately half of MMN patients have IgM antibodies against the ganglioside GM1, and these seropositive patients tend to have more severe weakness, disability, and eventual axon loss than seronegative patients.[69] MMN patients' sera containing IgM anti-GM1 have been shown to activate complement *in vitro*,[70,71] so it is possible that IVIG is acting mainly by inhibiting C3 (third component of serum complement system) activation and/or deposition on ganglioside-rich domains of axonal membranes.[21,71] Although the complement membrane attack complex is often considered a lytic lesion which kills cells, sublytic attack can also occur, because nucleated cells can remove membrane attack complex pores by shedding or internalizing microscopic membrane vesicles.[72] When this occurs, functionally important membrane proteins can be lost. This type of membrane loss is believed to explain the "simplification" of postsynaptic membrane folds and loss of AChR in MG[22] and might be hypothesized to occur at nodes of Ranvier in MMN.[21] Yuki et al. have shown that in MMN, IgM-induced complement-mediated injury occurs at the nodes of Ranvier, which in turn leads to conduction block and muscle weakness.[71] They further showed that IVIG can block antiganglioside antibody binding in a dose-dependent manner.[71] Using stimulus strength–duration measurements to assess motor axon excitability, Priori et al. showed that axonal hyperpolarization occurs in MMN, suggesting that antibody-mediated inactivation of the Na+ channels at the nodal membrane contributes to the apparent conduction block.[73] Boerio et al. performed nerve excitability studies before and just after IVIG treatment in MMN (and CIDP) patients. They reported that IVIG improved axonal excitability, which they attributed to restoration of Na+ channel expression and/or activity.[16] These electrophysiological observations could potentially explain why effects of IVIG may improve muscle strength shortly after each infusion but wane in subsequent weeks.[73–75]

Thus, taken together, the results of these recent studies of axonal excitability in CIDP and MMN, the absence of clearly identifiable effector cells attacking the involved nerves, and the rapid responses to IVIG reported in both disorders suggest that autoantibodies (± complement) may disrupt axon function in addition to inducing structural damage. In turn, the reports of rapidity and reversibility of the responses to IgG infusions in some cases may suggest competition between infused therapeutic IgG and endogenous pathologic antibodies.[21] A corollary of this hypothesis is that the specificities, titer, and affinities of the autoantibodies being produced by any given patient at any point in time, together with the susceptibility of the target axons, may be important determinants of the treatment regimen required to optimally manage that particular patient at that time.

PHARMACOKINETICS OF INTRAVENOUS (IVIG) AND SUBCUTANEOUS (SCIG) IMMUNOGLOBULIN G

The initial dose of IVIG used for most autoimmune/inflammatory diseases follows a regimen serendipitously found effective shortly after IVIG was introduced in 1981. Four CLL patients with thrombocytopenia and concomitant immune deficiency had increased platelet counts after receiving what was then the standard monthly dose of IVIG for antibody replacement, 0.4 gm/kg. Because of the rise in the platelet count, the IVIG dose was repeated the next day, then also on the remaining working days (but not the weekend days) of the

same week, leading to a cumulative dose of 2 gm/kg given over 4–5 days.[76] A subsequent randomized, multicenter trial comparing the 0.4 gm/kg per day × 5 regimen with a single infusion of 2 gm/kg over 10 h in children with Kawasaki syndrome found that the latter was more effective in preventing aneurysms and led to faster resolution of fever and biochemical markers of inflammation.[77] This suggests that the peak IgG level is the most important determinant of the success of therapy in some situations. However, Kawasaki syndrome, like GBS, is considered an acute monophasic disease; while CIDP, MMN, and MG are chronic disorders. Thus, different pharmacokinetic parameters may be more important. In current neurologic practice, a "loading dose" of 2 gm/kg divided over 2–5 days is usually followed by maintenance doses of 1–2 gm/kg every 3–6 weeks.[68,78] Infusion of 2 gm/kg of IVIG increases the serum IgG level >4-fold, from pretreatment means of 700–1,060 mg/dL to peaks well over 3,000 mg/dL.[78] The levels then drop by approximately 50% over 48–72 h, as IgG is distributed into the total extracellular fluid volume, which is approximately double the intravascular volume.[78,79] After this rapid equilibration, the IgG is catabolized with first-order kinetics and a half-life of 21–30 days, so infusions are usually repeated monthly.[78–81] The relatively slow catabolism of IgG as compared to other plasma proteins is due to a saturable endothelial cell receptor which protects endocytosed IgG from lysosomal degradation and returns it to the plasma.[80,82] Saturation of this receptor with high concentrations of normal IgG from exogenous IVIG keeps endogenous pathologic IgG from the recycling pathway and increases its degradation.[83] This is likely an important concentration-dependent mechanism by which IVIG can compete with autoantibodies without affecting their production.[21,83] Reports of patients responsive but chronically dependent upon IVIG support the notion that the effects of each dose are transient, without any cumulative effect.[9,21] Certainly, not all patients are chronically dependent on IVIG; up to 30% might achieve long-term drug free remission. Whether these observations can be explained by spontaneous remission with neuronal integrity supported by IVIG while the disease is in the active state, or if IVIG fundamentally alters the immune process remains to be clarified. In either case, accumulating evidence supports the hypothesis that the infused antibodies in IVIG compete with putative pathologic antibodies and/or complement, and that the effect diminishes as the relative concentrations of normal versus pathologic antibodies decrease with time after each dose.[21,83]

In contrast to intravenously administered IgG, with subcutaneously administered IgG (SCIG), the initial direction of the movement of IgG is opposite that of IVIG. SCIG is first absorbed into and transported through lymphatics, then enters the bloodstream by means of the thoracic duct.[84] Equilibration of the IgG from SCIG into the intravascular space requires approximately the same amount of time as equilibration of IVIG out of the intravascular compartment, 36–72 h.[84–86] The peak serum concentration achieved with SCIG is, on average, only 61% of the peak achieved with IV infusions of the same dose.[86] The slower rate of rise toward the peak and the truncation of its height are believed to be responsible for the much lower incidence of systemic adverse effects (AEs) with SCIG.[84,85,87] This is consistent with numerous reports that many of the AEs of IVIG infusions are rate-related and can be obviated by giving the IgG by the SC route.[87,88] No differences have been reported in the half-lives ($t_{1/2}$) of IgG given by the SC versus IV routes, generally reported to be approximately 30–35 days with currently marketed IgG products.[81,85,86] Because of the low incidence of systemic AEs and lack of a requirement for venous access, SCIG is commonly self-administered at home, usually weekly.[89] With weekly SCIG, only a few days elapse between the peak serum level from 1 dose and administration of the next dose. This frequent dosing obviates the low "trough" serum IgG levels experienced 3–4 weeks after a large bolus of IVIG.[85] Pooled data from 7 studies in which equivalent monthly IgG doses were given as weekly SCIG infusions versus IVIG boluses every 21–28 days showed that trough serum IgG levels were higher by 10–20% (mean = 12.7%) with weekly SCIG.[81,85,86] After 6–12 weekly infusions, SCIG results in near-steady-state IgG levels, with peak-trough differences only approximately 5% of the overall mean.[85,86] In contrast, with IVIG the trough-to-peak difference is often greater than 100% of the overall mean.[81,89] As with any other therapy, the shorter the interval between doses, the higher the trough level and the smaller the difference between peak and trough levels are likely to be, regardless of the route of administration.[81,89,90] The overall bioavailability of SCIG is approximately 30% lower than that of IVIG, presumably because of binding to extracellular matrix and/or degradation in the tissues.[91] For this reason, to achieve the same total systemic exposure to IgG, defined by the area under the curve (AUC) of serum IgG versus time, it is necessary to increase the monthly dose of SCIG by 30 to 50% compared with the monthly dose of IVIG.[86,91] However, there is little evidence which supports basing doses on the AUC, as opposed to the trough serum IgG level.

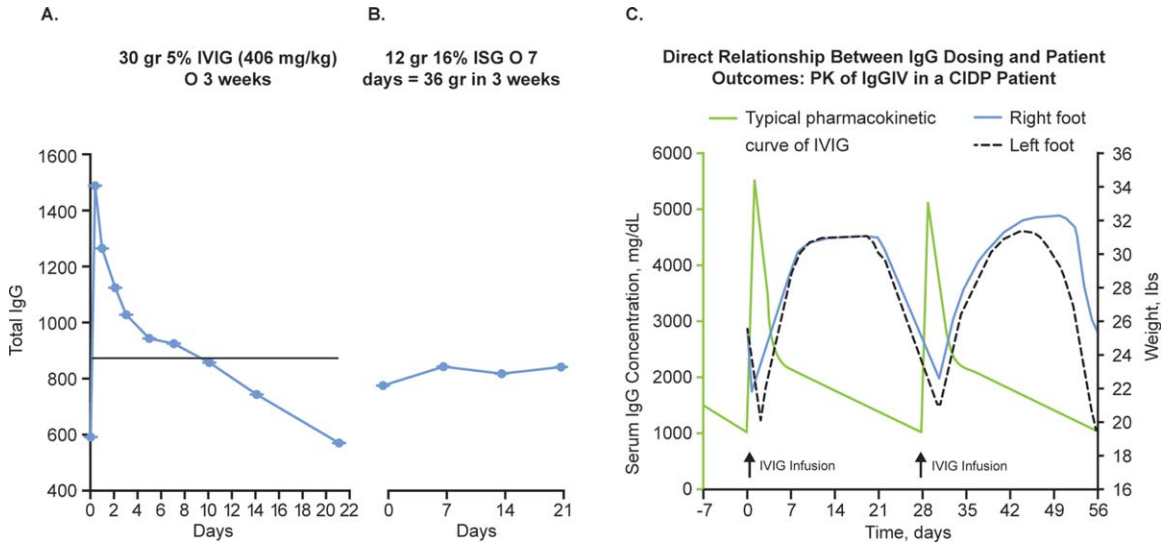

FIGURE 2. A,B: Serum IgG levels in a patient with X-linked (Bruton's) aggamaglobulinemia. **A:** IVIG at 406 mg/kg (30 grams total) every 22 days. The solid line represents the calculated mean IgG level over the entire interval. **B:** SCIG at 12 grams/week (36 grams total), a 20% increment in dose. The IgG remains at a near steady state with a mean of 850 mg/dL. Reproduced from Berger[85] with permission of the publisher. **C:** Cyclic response to IVIG from CIDP patient in Figure 1 superimposed on typical pharmacokinetic curve of IVIG (on a logarithmic scale) - from Bonilla[81] with permission of the publisher. Note the increase in muscle strength accompanying the rapid rise in serum IgG level following each monthly dose, but then the decrease in strength shortly after the IgG level falls.

Typical PK curves from IVIG and SCIG in a patient with primary immunodeficiency (PIDD) who makes only minimal endogenous IgG are shown in Figure 2A and B. The large differences in peak and trough on IVIG versus the near steady-state serum IgG levels with SCIG are readily apparent. If the effect of therapeutic IgG is proportional to its serum concentration at any point in time (for example, in PIDD, the moment when exposure to an infectious agent occurs), it is easy to see how the effect of IVIG would wane as it is metabolized and its concentration decreases. Figure 2C shows a prototypic PK curve for monthly IVIG superimposed on the muscle-strength curve from Figure 1, while the patient was on monthly IVIG but no other anti-inflammatory or immunosuppressive treatment. Seen in this way, it is quite easy to understand why there would be a rapid response to the markedly increased serum IgG level in the few days just after an intravenous dose, but also why that effect begins to "wear off" 7–10 days later, as the IgG level drops.

PREVIOUS OBSERVATIONS IN CIDP

The diagnosis of CIDP requires integration of clinical, electrophysiological, and laboratory data as well as collection of appropriate exclusionary information. Often the diagnosis is not straightforward. A recent editorial by Cornblath et al. suggests that as many as one-third of CIDP patients in the US have been incorrectly diagnosed and may be receiving inappropriate treatment.[62] Therefore, strict adherence to scientifically derived and consensus clinical diagnostic criteria is critical.[62] After the CIDP diagnosis is confirmed, ensuring that treatment is effective, tolerable, and minimizes the patient's disability become the major goals. Based upon results of the largest controlled trial of IVIG in CIDP, the "Study of IVIG, 10% caprylate-chromatography purified for the treatment of CIDP" (ICE trial), the Food and Drug Administration (US) approved IVIG for CIDP using a loading a dose of 2 gm/kg followed by maintenance dosing of 1 gm/kg every 3 weeks.[92] However, optimal IVIG doses and infusion intervals across a broader range of patients have yet to be clearly established, and prescribing regimens other than those used in the ICE trial are common.[93–95] Wide inter-patient variations in the pharmacokinetics of IVIG[94–97] further highlight the need to individualize dosing to achieve an optimal treatment response.

Nonetheless, relatively little emphasis has been placed on determining *how* to maximize treatment efficacy. There are anecdotal reports of patients asking for "booster" doses of IVIG before their next monthly dose is due, but few reports of objective measurements which correlate with these "end of dose" effects. In the absence of a validated laboratory biomarker or any other way to establish a "target" IgG level,[98] frequent measurements of muscle strength and functional capabilities may provide the best basis for individualizing and optimizing therapy (see the Unanswered Questions/Research Issues section). Studies in patients with primary antibody deficiency have demonstrated

that different individuals require different serum IgG levels to remain free from infection,[97,99] and that there is very wide variability in IgG dose and treatment interval necessary to achieve and maintain clinically determined "target" IgG levels in different patients.[86,97] GBS may have a similar dose–response relationship. Kuitwaard et al. reported that serum IgG levels obtained 2 weeks after IVIG 2 gm/kg showed a large degree of pharmacokinetic variation and that those patients with greater increments in their serum IgG levels had better clinical outcomes at 6 months posttreatment.[96] In a prospective study in CIDP, the same group showed that different patients required different IVIG dosing intervals and serum IgG levels to achieve and maintain optimal clinical responses.[90] The mean trough serum IgG level (just before each dose was given) required by the subset of these patients on a single IVIG product ($n = 17$) was 1,500 mg/dL, but the range was 1,100 to 1,900 mg/dL.[90] Besides the suggestion that different patients require different IgG levels to achieve maximum muscle strength, the doses and treatment intervals required to achieve and maintain any given IgG level are also likely to vary greatly between individuals.[90,93–95,98] Many immunodeficient patients report feeling better and remain free from recurrent symptoms of chronic low-grade infection when their serum IgG level is maintained at a steady-state with the use of weekly SCIG.[100] A few reports suggest that maintaining high steady state levels of normal IgG by the use of SCIG may also be beneficial in CIDP and MMN (see below), but additional studies are needed.

As with PLEx, the initial response to IVIG in many patients with CIDP is rapid, with symptomatic improvement beginning within days.[101–103] The beneficial effect generally wanes within weeks, and IVIG infusions are repeated at regular intervals, often for years.[104] Harbo et al. reported that 6 of 11 CIDP patients on individualized IVIG regimens began to lose strength within a few days when their IVIG was delayed beyond the usual interval.[105] Conversely, they began to regain strength in $\leq$5 days after an IVIG dose, although a plateau was not achieved for 15 days.[106] In the "ICE" trial, improvements in grip strength and INCAT score in responding subjects were seen at the first post-IVIG determination 16 days after the infusion.[101–103] Further improvement was recorded at 3 and 6 weeks, but repeated measurements were not taken before and after subsequent doses of IVIG.[101] "Wearing off" of the effect of each dose of IVIG may be a reason that as many as 30% of CIDP patients had dosing intervals of $\leq$15 days in a US survey[93] and $\leq$21 days in a UK study[94] (Fig. 3). Kuitwaard et al. recently reported results of a study in which they confirmed IVIG dependency by determining whether reducing the dose increased the patient's disability. They then used assessments of grip strength (Vigorometer), MRC sum score, INCAT sensory score, and disability assessments as part of a protocol for optimizing the IVIG regimen in which the dose was increased until the "maximal clinical response" was achieved. They then shortened the interval between infusions to eliminate "end of dose symptoms and signs".[90] Although the frequency of the efficacy measurements was not described, the use of this protocol resulted in 52% of the patients receiving IVIG at intervals of 10–14 days and an additional 8% receiving IVIG at intervals <10 days[90] (bottom bar, Fig. 3). The utility of hand grip strength measurements is also supported by a cross-sectional analysis of 31 CIDP patients using dynamometry, electrophysiology, and conventional clinical assessments, from which Rajabally and Narashimhan reported highly significant correlations between Jamar dynamometer measurements and results of global and upper extremity motor and sensory scores.[107] Ultimately, frequent measurements with hand grip dynamometers or other devices the patient can be instructed to use at home should help determine the proportion of patients who might benefit by weekly or even more frequent IgG dosing, and help to identify the treatment regimens which yield the best long-term results. Larger and longer studies using tools like grip strength monitoring that specifically address the short and long term consequences of treatment-related clinical fluctuations are needed.

If weekly or more frequent IgG dosing seems desirable on clinical grounds, self-administration of SCIG at home offers a practical route to maintain high steady-state IgG levels. The safety, efficacy and practicality of this route of therapy in CIDP has been described in case reports and a small randomized, placebo controlled study,[109–111] and is now being evaluated in a large multicenter trial.[112] Some of the patients in these studies reported improved tolerability, increased independence, and stabilization of clinical status.[109–111] While these factors may not be applicable to all patients, the possibility of maximizing treatment by maintaining a high steady-state IgG level by means of a potentially more tolerable route of IgG administration (i.e., SC) is attractive. If CIDP patients have a better response to higher IgG levels, as reported in a recent study in GBS,[96] and different patients require different IgG doses and treatment intervals to achieve optimal clinical responses,[90,93–95,98] then frequent clinical monitoring and correlation with frequent serum IgG levels may identify those patients who benefit most from frequent IV

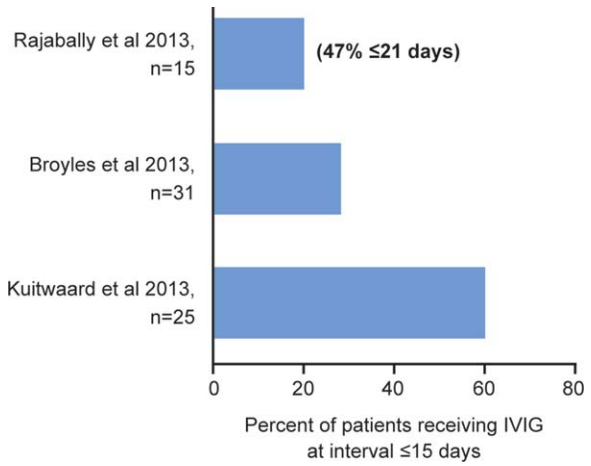

FIGURE 3. Actual IVIG dosing intervals used for CIDP patients in practice: Horizontal bars indicate % of CIDP patients receiving IVIG at intervals ≤ 14 days in each study. Sources are cited at the bottom, below the graph. Rajabally in the UK and Kuitwaard in Holland performed prospective studies designed to optimize responses, $n = 15$ and 25, respectively. Broyles et al. reported on a cross-sectional analysis of prescriptions for IVIG therapy for 46 unique patients from a home care/specialty pharmacy by 30 different doctors in the US.

infusions or the use of SCIG. The possibility that minimizing treatment-related clinical fluctuations may result in better long-term outcomes remains to be determined in long-term studies.

PREVIOUS OBSERVATIONS IN MMN

Responsiveness of the majority of MMN patients to IVIG despite the lack of response to PLEx[113] or corticosteroids[114] was demonstrated in the mid-90s by multiple anecdotal and case-series reports.[114–116] Small controlled studies soon followed,[117–120] and the results of a 44-subject randomized, double-blinded placebo-controlled, crossover trial were reported by Hahn et al. in 2013.[120] Mean maximal grip strength declined 31% during placebo treatment and increased 3.75% during IVIG treatment ($P = 0.005$),[120] IVIG was recommended as first-line treatment by a European Federation of Neurologic Societies/Peripheral Nerve Society task force in 2006[121] and 2010.[68] Of interest, even early reports noted that improvement associated with reduction in the degree of conduction block began within a few days, but lasted only 1–2 months, at best.[114,115] Others observed that the beneficial effects of IVIG generally decrease over time.[74,75,122] Although increasing the dose or shortening the interval generally restores short-term efficacy, gradual worsening with progressive reduction of MRC sum scores and/or distal CMAP amplitudes still occurs commonly.[74,75] Baumann et al., reported that the use of a protocol designed to determine the lowest effective IVIG dose and longest tolerable interval resulted in slowly progressive muscle weakness over a 4-year period while the patients received a mean of 0.5 gm/kg/month of IVIG given at 4- to 12-week intervals.[123] The investigators subsequently performed a prospective dose escalation study and observed that 6 of 9 subjects improved when their dose was increased to 1.2 gm/kg/month. The authors concluded that their initial strategy of trying to find the lowest dose at the longest tolerated interval resulted in significant underdosing.[123] Others have also reported that MMN patients gradually decline despite therapy and need slowly escalating IVIG doses to maintain their strength.[74,75,122] Notably, these reports initially used mean cumulative IVIG doses equal to or less than 1.2 gr/kg/mo.[74,75,122] In contrast, Vucic et al. reported the results over a 7.25 year mean follow-up period of 10 patients initially treated with 3 courses of 2 gm/kg IVIG at 4 week intervals then maintained on a mean IVIG dose of 1.63 gm/kg/4 weeks. Muscle strength in these patients was stable, the number of nerve segments showing conduction block decreased by 45%, and distal compound muscle action potential amplitudes were stable or improved.[124] Thus, we have much to learn about optimizing the use of IgG in MMN. Early diagnosis and institution of therapy, followed by close monitoring and frequent adjustment of dose and interval to assure that the patients are achieving maximal short-term responses may offer the best chances for favorable long-term outcomes.

Monthly IVIG is now the accepted first-line treatment for MMN.[68,121] Even so, treatment-related fluctuations in strength and "end-of-dose" weakness are also reported in this condition.[125] Several case reports and small case series have suggested that SCIG may be as effective as IVIG for long-term maintenance of strength in MMN,[126–130] but large clinical trials have not compared the efficacy of SCIG versus IVIG. SCIG may have advantages over IVIG, including the ability to maintain IgG levels at a higher steady-state[81,85,86] and perhaps smooth out "end-of-dose weakness". An MMN patient who had cyclic fluctuations in disability while receiving IVIG every 3–4 weeks for 10 years provides a provocative example. Switching to weekly SCIG and increasing the total monthly dose by 25% resulted in increased strength, which was stable at the peak he had previously achieved only transiently after each IVIG dose.[128] This improvement was accompanied by an increase in the trough serum IgG level from 1,500 mg/dL to a steady state of 2,100 mg/dL, consistent with the hypothesis that the patient's strength at any point in time is directly related to the total IgG concentration of in his circulation.[128] Similar dose-dependency observations were reported in small prospective, open-label, noncontrolled trials in which 4 of 5 patients maintained stable MRC sum scores for at least 6 months

with steady-state serum IgG levels of 1,380 to 1,740 mg/dL.[129,130]

Taken together, these results suggest that SCIG may be a useful alternative to IVIG for some MMN patients, particularly those that experience treatment-related "wear-off" or "end-of-dose" weakness. There remains a controversy as to whether prolonged IVIG treatment totally controls the progression of MMN, or whether axonal degeneration and long term deterioration are inevitable. Some studies suggest that careful optimization of therapy with frequent adjustments to avoid end-of-dose weakening may help promote long-term recovery and prevent axonal loss,[124] although other reports suggest gradual worsening despite this approach.[75] It may be that axon damage increases toward the end of each dosing interval, when the ratio of the putative autoantibodies to normal IgG is relatively high and the patient is experiencing increased weakness. If that is the case, using SCIG to maintain higher steady-state IgG levels without cyclic troughs may decrease long-term deterioration in MMN, but that hypothesis remains to be tested.

EXPERIENCE WITH USE OF FREQUENT DYNAMOMETRY AND FUNCTIONAL ASSESSMENTS (SUCH AS R-ODS) TO INDIVIDUALLY OPTIMIZE IGG THERAPY

In 2007, the Peripheral Neuropathy Outcome Measures Standardization (PeriNomS) study began.[131] A major aim of this international collaboration is to better define the metrics used to follow patients with inflammatory neuropathies. In 2013, the group analyzed outcome measure data collected from cross-sectional validity and reliability studies as well as longitudinal studies of responses.[132] The results emphasized the importance of measuring disability (i.e., activities and participation), strength and sensory impairment, and quality of life. Disability measured by the Rasch-built Overall Disability Scale (R-ODS),[133] impairment measured by grip strength (Martin Vigorimeter),[103] and quality of life measured by the Short Form-36 item health survey[134] emerged as useful metrics by which CIDP patients can be assessed and treatment responses can be better defined. Although the use of these kinds of assessments has typically been limited to clinical trials, these measures (especially R-ODS and grip strength) can be performed very quickly and reliably and, if validated, may greatly facilitate routine clinical care.

We propose that frequent collection of validated and reliable disease-specific measures between physician visits can be used to optimize clinical care and improve outcomes. Of course, continued assessment of symptoms and signs by interviewing and examining the patient during office visits is invaluable and irreplaceable. However, even these traditional observations are often subjective and open to variable interpretation. Defining the treatment response during relatively brief, intermittent office visits may be difficult and not representative of the patient's function in his/her home environment. How should we interpret patients' reports that they "feel better" but have no change on examination? What about pain, fatigue, and/or other subjective symptoms in the absence of clear indicators of disease activity? Which factors should drive the treatment plan? For the patient who demonstrates some improvement, how do we know that therapy has been maximized? Is wear-off occurring? Is there a lost opportunity for sustained benefit or prevention of axonal degeneration? These treatment challenges are further magnified by the limited frequency with which a comprehensive examination and interview can be achieved, especially with current economic pressures.

One approach to treatment optimization is frequent collection of disease-specific outcome measures like grip strength and R-ODS as discussed within PeriNomS. IVIG regimens offer a unique opportunity to perform such assessments at the time of the infusions. Efficacy can be quickly confirmed, and nonresponders can be identified quickly. If a patient achieves only a partial peak response and/or reports wear-off, the IVIG dose and frequency can be optimized with rapid confirmation of the desired effect. On the other hand, this type of monitoring can also be useful to identify patients who fail to respond or who no longer need IVIG. The dose can then be tapered or the interval between infusions lengthened with the security of frequently obtained reliable measures in case of relapse.

Use of these metrics can help establish drug efficacy in individual cases, provide a rationale for patient-specific treatment tailoring, and allow rapid detection of nonresponders. The importance of these metrics in clinical trials is obvious, but their long-term utility has yet to be studied. Extending their application to routine clinical care may offer a unique opportunity to optimize inflammatory neuropathy treatment paradigms and hopefully long term outcomes.

UNANSWERED QUESTIONS/ RESEARCH ISSUES

Many investigators are actively seeking an immunologic biomarker or soluble indicator of neuronal damage which could be used to identify those patients who are most likely to respond to IgG therapy and to monitor its effects in MMN, CIDP and other neuropathies.[33,62,64,90,95,96,122] In the absence of such biomarkers, frequent

measurements of grip strength and of disability using R-ODS may be used to better characterize treatment responses. Current treatment strategies rely heavily on data obtained through unstructured and often unsolicited communication from patients as well as from infrequent face-to-face office visits. Adherence to rigorous diagnostic standards[3,53,62,68,122,123] and collection of focused disease-specific outcome measures at more frequent intervals may assist with development of better paradigms for optimizing treatment. Prompt recognition of those patients for whom IgG or other expensive biologicals are unnecessary or ineffective is another likely benefit of frequent measurements, which may aid in the development of criteria for identifying nonresponders and selecting appropriate alternatives,.

Although several recent reports suggest that dosing IVIG as frequently as every 7–14 days, or the use of SCIG to maintain high steady-state IgG levels may be preferable in terms of maintaining consistent function and minimizing disability, several questions remain unanswered. Importantly, analyses of larger and more diverse populations are needed to determine which patients are characterized by a predominance of functional immunologic effects that are rapidly and reversibly responsive to IgG and/or other immunotherapies as opposed to those who have mainly structural and/or permanent damage. Similarly, longer term follow-up is necessary to determine whether the kinetics of responsiveness vary at different stages of disease, and whether minimizing short-term fluctuations in strength and/or disability correlates with long term outcomes.

Immunologic as well as clinical studies suggest that CIDP is a heterogeneous group of conditions with a multiplicity of immunologic targets and mediators. The kinetics and pattern of response to IgG and other therapies may be a useful criterion according to which subsets of these diseases are classified and split-out for further studies. Because IgG can act by many different mechanisms, it seems quite likely that better definition of the immunopathogenesis of particular disease subtypes might lead to preferential use of different therapies, such as steroids and anti-inflammatories, complement inhibitors, or monoclonal antibodies and other narrowly targeted biologicals.

In conclusion, recent studies of the immunology and electrophysiology of CIDP and MMN suggest that much of the morbidity and disability in these conditions is caused by readily reversible functional effects of autoantibodies rather than more slowly repairable structural damage.[18,21] These results serve as a foundation for understanding clinical observations of rapid responses and "wear-off" effects with intermittent IVIG bolus therapy. Together, these observations suggest the hypothesis that infused antibodies in IgG actually compete with pathologic autoantibodies. Observations that dosing of IVIG as often as every 7–10 days or the use of SCIG to continuously maintain high steady-state IgG levels may be preferable to the periodic extremely high peaks and low troughs of IVIG boluses given every 4–6 weeks. Giving smaller doses of IVIG more frequently or routine weekly self-administration of SCIG in the home may be associated with fewer, less severe adverse effects and significant cost savings as compared to intermittent high dose IVIG, which requires administration and monitoring by a trained nurse, even if given at home. Additional research is needed to determine how widely applicable frequent dosing of IVIG or SCIG might be, and whether continuous maintenance of optimal strength/minimal disability is associated with better long-term outcomes. This can only be achieved with the use of frequent monitoring of patients' responses and periodic re-assessments of therapeutic efficacy.

The authors thank David Schaefer and Tim Walton of AxelaCare, Lenexa, Kansas, for helpful discussions.

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