Subcutaneous IgG in neurologic diseases

Subcutaneous administration of IgG (SCIG) has become widely used in primary immune deficiency diseases but it has only recently been studied for maintenance therapy in autoimmune peripheral neuropathies, such as chronic idiopathic demyelinating polyneuropathy and multifocal motor neuropathy. Weekly self-administration of SCIG is safe and well-tolerated, and results in steady-state serum IgG levels, as contrasted with the peaks and troughs of monthly immune globulin (human) for intravenous use. Freedom from the need for venous access or medical personnel for infusions, flexibility in scheduling, convenience of home therapy, and improved clinical stability due to the steady-state IgG levels, lead many patients to prefer SCIG to immune globulin (human) for intravenous use. Long-term studies are needed to determine if the constant IgG levels and clinical stability translate into better long-term outcomes.

KEYWORDS: adverse events ▪ chronic idiopathic demyelinating polyneuropathy ▪ IgG ▪ intravenous IgG ▪ mechanism of action ▪ multifocal motor neuropathy ▪ myositis ▪ neuropathy ▪ pharmacokinetics ▪ subcutaneous IgG

Melvin Berger

Immunology Research & Development, CSL Behring, LLC, 1020 First Avenue, King of Prussia, PA 19406, USA
and
Pediatrics & Pathology, Case Western Reserve University, Cleveland, OH, USA
Tel.: +1 610 505 4256
mel.berger@cslbehring.com

Intravenous IgG (IVIG) is now widely used in neuropathies and other neuromuscular diseases. Although subcutaneous IgG (SCIG) has become well established as a treatment for primary immune deficiency diseases (PIDD), its use in neurological diseases is in its infancy. In neurologic diseases, SCIG has been studied solely as a maintenance therapy in patients already on IVIG. SCIG has not been studied in acute monophasic diseases such as Guillain–Barré Syndrome (GBS), nor as initial therapy in chronic conditions such as chronic idiopathic demyelinating polyneuropathy (CIDP) or multifocal motor neuropathy (MMN).

There are two fundamental differences between SCIG and IVIG that lead to most of the practical differences between the two routes [1,2]. The first of these is the lack of a requirement for venous access with SCIG, the second is the relatively slow absorption of SCIG into the intravascular compartment. A trained professional is usually required to establish venous access and administer IVIG. Administration of large doses of IgG (1–2 g/kg) at one time by the intravenous (IV) route, especially if rapid infusion rates are used, may contribute to systemic adverse effects (AEs); while the slow absorption of SCIG minimizes systemic AEs. These two underlying differences set the stage for several other effects that may lead to a preference for one route versus the other in different individual situations.

IVIG is infused directly into the intravascular compartment, so its concentration peaks as soon as an infusion is completed. By contrast, with SCIG, IgG must first diffuse into lymphatics, before it reaches the bloodstream indirectly, via the thoracic duct. Thus, with SCIG, the intravascular IgG concentration increases more gradually, peaking at 36–72 h after the end of an infusion [3,4,101]. Most other features of SCIG are consequences of this difference in kinetics. For example, many of the systemic AEs of IVIG are related to the rate of the infusion and resolve when the infusion is slowed [5–7]. Other AEs may be due to the extremely high serum IgG concentrations, which occur immediately after high IVIG doses [6–8]. The incidence of severe, and indeed all systemic AEs is extremely low with SCIG – in most series, below 1% of all infusions [1,2,4]. By contrast, systemic tolerability is often a limiting factor in IVIG therapy. This freedom from systemic AEs and the lack of the need for venous access allows most patients (or parents/partners) to infuse SCIG at home. This, in turn, frees the patient and family from costs and constraints involved in having nurses come to the home or from the need to schedule visits to hospitals or other facilities where IVIG is usually administered and eliminates the time necessary for travel. Home infusion regimens are associated with improved health-related quality of life (QoL) in PIDD patients, mainly because they increase the patient's autonomy and the family's flexibility [9,10]. Many of the advantages of SCIG are also likely to apply to patients with autoimmune neuromuscular diseases.

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Another major difference in SCIG versus IVIG regimens derives from limitations in the volume of subcutaneous (SC) infusion that most patients can tolerate. Few patients infuse more than 1 ml/kg per infusion, with a maximum of approximately 30 ml into a single site, so most patients use multiple sites for each individual infusion. Even with the most highly concentrated SCIG solutions, such as 16 or 20% IgG, this translates into a maximum of 16–20 g of IgG per day. By contrast, with IVIG, patients can receive as much as 1 g/kg or 80–100 g total in a single day. Thus, even for 'high-dose' indications (1–2 g/kg/month), the total monthly dose of IgG can be given on one or two consecutive days if the IV route is used. To achieve the same total monthly dose with SCIG, multiple doses must be used, so it is common for the monthly dose to be divided into four doses, given at weekly intervals. The use of weekly or more frequent fractional doses of SCIG leads to steady-state IgG levels, however, which creates another set of advantages preferred by many patients (Figure 1). An online supplement entitled: 'The Nuts and Bolts of SCIG Therapy' is available at www.futuremedicine.com/doi/suppl/imt.13.146.

Pharmacokinetics of IgG administered by the SC & IV routes

With IVIG, the peak serum IgG concentration (C_{max}) is achieved as soon as the infusion is completed [3,11]. With a dose of 2 g/kg, frequently used in neuropathies and other autoimmune diseases, this peak concentration is likely to be fivefold higher than the pretreatment 'baseline', or greater than 5000 mg/dl [8]. The serum IgG level then falls rapidly as the IgG diffuses out of the intravascular compartment and equilibrates into a volume of distribution approximately equal to the total extracellular fluid, over 24–48 h [3,11]. Early studies with radioactively labeled IgG showed that after equilibration, 45% of the IgG remained intravascular [11]. Because the ratio of total extracellular fluid volume:body weight is fairly constant in individuals with different BMIs [12], there seems little justification for limiting the dose of IVIG according to the 'ideal body weight' in obese individuals, and a recent paper documents that dose adjustments for BMI are not necessary for SCIG therapy [13].

IgG is maintained at relatively high circulating concentrations compared with IgA, IgM and most other serum proteins by the action of a specific, saturable receptor on endothelial cells,

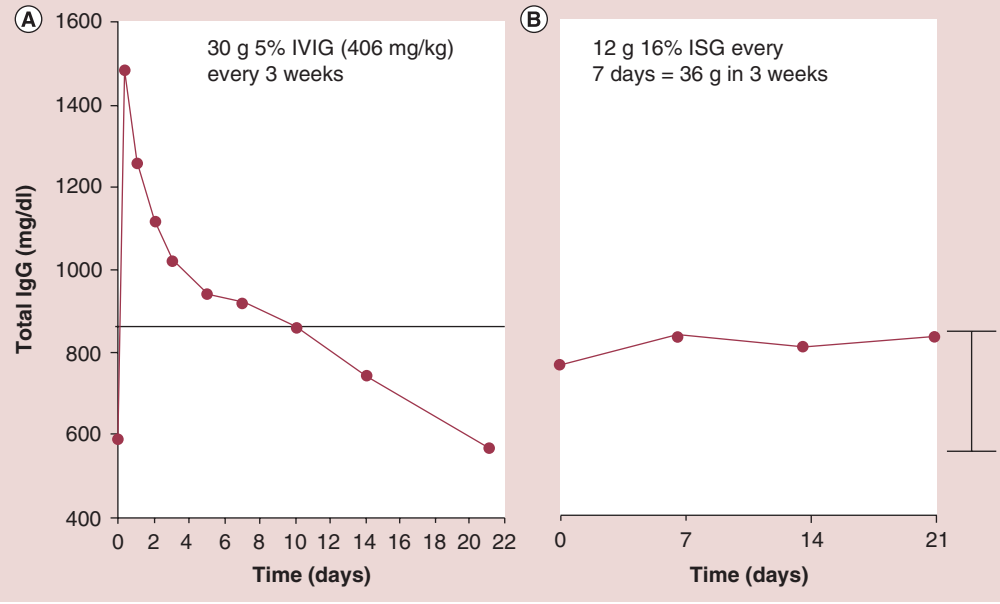

Figure 1. Serum IgG levels in a 34-year-old man with X-linked agammaglobulinemia, who makes little IgG of his own. (A) Patient on 406 mg/kg of IVIG every 3 weeks, the C_{max} reaches 1500 mg/dl and the C_{min} (trough) 3 weeks later is only 600 mg/dl. The solid black line indicates the mean serum IgG level over the entire interval. **(B)** Patient on subcutaneous IgG, with a 20% increment in dose (12 g/week), the IgG remains at a steady state equal to 850 ± 43 mg/dl. The bracket at the right shows the increment in trough level (C_{min}) on subcutaneous IgG.
ISG: Immune serum globin (human, 16% for intramuscular use), given subcutaneously every 7 days); IVIG: Intravenous IgG.
Reproduced with permission from [1].

termed FcRn [14,15]. This receptor binds only albumin and IgG, and recycles these proteins through an endosomal pathway which avoids intracellular degradation [14,15]. The catabolism of IgG proceeds with first-order kinetics, with a fractional catabolic rate of about 6.7% of the intravascular pool per day (as noted, only 45% of the IgG is intravascular, so this is roughly the equivalent of 3% of the total body IgG per day), resulting in half-lives which are usually reported to be in the range of 20–40 days [3,11]. For this reason, IVIG is usually given at approximately monthly intervals. In treating PIDD, most physicians aim for a 'target' IgG trough level (C_{min}) ≥500 mg/dl, and adjust the dose and/or infusion interval to keep above this threshold, which is believed to be the minimum serum IgG concentration necessary to prevent acute severe infections [3]. However, in neurologic and other autoimmune diseases, such a target level has not been defined.

With regard to SCIG, the initial direction of the movement of IgG is the opposite of IVIG; SCIG is first absorbed into and is transported through lymphatic vessels, then enters the bloodstream via the thoracic duct [101]. Equilibration of the IgG from SCIG into the total intravascular and extracellular fluid space requires about the same amount of time as equilibration of IVIG out of the intravascular compartment. Thus, with SCIG, the C_{max} is reached at 36–72 h [1,3,16,101]. The C_{max} achieved with SCIG is, on average, only 61% of the peak achieved with IV infusions (reviewed in [16,17]). In three recent studies comparing IVIG and SCIG in PIDD patients, the mean peak serum C_{max} immediately after IV infusions was 2303 mg/dl. By contrast, the mean peak with SCIG was 1410 mg/dl and the interval (T_{max}) between beginning an SCIG infusion and the peak IgG concentration was 62.6 h (2.61 days) [17]. The slower rate of ascent towards the peak and the truncation of its height are believed to be responsible for the much lower incidence of systemic AEs with SCIG [1–3,7]. This is consistent with numerous reports that many IVIG AEs are rate-related [5–7]. No differences have been reported in the half-life ($t_{1/2}$) of IgG given by the SC versus IV routes [3,16]. With modern preparations of IgG, $t_{1/2}$s having generally been reported to be about 30–35 days [3]. With weekly SCIG, only about 4.5 days elapse between achieving the the C_{max} of one dose and the administration of the next dose, suggesting that only about 10–20% of the administered IgG is metabolized before the serum level starts to rise again. By contrast, with IVIG dosing intervals of 3–4 weeks, approximately 36–48% of the IgG may be metabolized by the time the next dose is due. These differences in the dosing intervals used in most SCIG versus IVIG regimens result in increased C_{min} serum IgG levels with SCIG. Pooled data from seven 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 10–20% (mean: 12.7%) higher with weekly SCIG [16,17].

After 6–12 weekly infusions, SCIG results in near-steady-state IgG levels, with differences between C_{min} and C_{max} only 5–10% of the overall mean. This steady state can also be achieved by 'loading' the patient with five or six consecutive daily infusions of what will then be the weekly SCIG dose [18]. By contrast, with IVIG the trough-to-peak difference is often greater than 50% of the overall mean [1,3]. In general, 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 [19].

The area under the curve (AUC) of serum concentration versus time of a drug after a single IV infusion is defined as 100% bioavailability. The bioavailability of the drug when given by any other route is generally lower. This concept is most commonly applied to the 'oral bioavailability' of small molecule drugs, which is usually less than 100% due to incomplete absorption from the GI tract. On the basis of arguments that intramuscular administration of IgG resulted in significant local degradation, animal studies showing decreased bioavailability of SCIG versus IVIG, and human studies of SC versus IV infusions of therapeutic monoclonal antibodies and fusion proteins containing the Fc portion of IgG [20], it was expected that polyclonal SCIG would also have lower bioavailability than IVIG. Therefore, in licensing studies of SCIG, the US FDA mandated adjustment of the dose of SCIG so that its AUC would equal that previously measured with IVIG in the same patients. Dose-adjustment coefficients were 1.37–1.53-times the IV doses, but closer examination of the data show that the bioavailability of SCIG is about two-thirds (i.e., dose adjustment would be 1.5) of that of IVIG, regardless of the preparations being compared [20]. The decreased bioavailability may involve degradation in the tissues and/or local binding in the intercellular matrix, but seems to be a general property of IgG. The EMA does not require this type of dose adjustment, and there is no evidence that switching from IVIG to SCIG at the same monthly dose increases the risk of infection.

At first glance, it seems easy to understand how IgG therapy in PIDD should be targeted: when

the serum IgG reaches its lowest level there should be sufficient antibody to prevent the patient from being infected with common pathogens. Determining how to target IgG therapy in autoimmune neurologic diseases is more difficult. The immunopathogenesis of most of these diseases is not well understood, and the mechanisms of action of IgG that may be most important have not been defined in any of them. Dosing of IVIG in neurological diseases has mostly been empirical-based on the serendipitous observation that 2 g/kg led to rapid improvement in immune-mediated thrombocytopenic purpura. Few dose–response studies have been performed. Therefore, it is not clear which pharmacokinetic parameters are important determinants of the efficacy of IgG therapy – the C_{max} IgG level achieved, the mean IgG level over time (integrated AUC), or the C_{min}.

Mechanisms of action of IgG

Many anti-inflammatory and immunomodulatory effects of IVIG have been reported *in vitro* and in animal models, as summarized in Box 1 [21–23]. However, few studies actually distinguish which mechanism(s) are most important in which disease. Several of the putative mechanisms of action appear to be concentration-dependent and may involve direct competition between therapeutic IgG and pathologic autoantibodies. These include direct neutralization of autoantibodies by anti-idiotypic antibodies, increasing catabolism of endogenous IgG by saturating FcRn, and inhibiting complement activation and deposition. Of these three mechanisms likely involving competition between 'good and bad' antibodies, only the third has actually been demonstrated *in vivo* in humans – high dose IVIG has been reported to decrease complement membrane attack complexes on endomysial capillaries in dermatomyositis (DM) [23,24]. Competitive mechanisms might be expected to induce rapid responses when the serum IgG concentration is sharply raised by a high-dose of IVIG, and may be analogous to rapid effects of plasmapheresis in removing autoantibodies. Conversely, mechanisms involving competition might be expected to diminish or 'wear-off' as the serum concentration of therapeutic IgG and the ratio of 'good versus bad' antibodies falls. Careful studies of the kinetics of the clinical response to different doses and blood levels of IgG are necessary to determine the importance of the high C_{max}, which is reached after a large bolus of IVIG versus other pharmacokinetic parameters, but there have only been a few studies relating efficacy to serum IgG levels [19,25,26]. Some reports of the kinetics of IgG effects are discussed in the specific disease sections below, and may be useful in informing hypotheses to be investigated in future comparisons of SCIG with IVIG. Other putative mechanisms of action of IgG involve inhibiting the maturation and function of antigen-presenting dendritic cells. This may account for the decrease in dendritic cells in the cerebrospinal fluid in patients with GBS and CIDP [27], but the role of those cells in the pathophysiology of the diseases is far from clear. IgG can alter the balance between proinflammatory and anti-inflammatory cytokines, and has been reported to decrease the activity of receptors involved in phagocytosis and tissue inflammation. However, the roles of cytokines in neurologic diseases and the pathophysiologic contribution of the antibodies and complement, versus phagocytes and other inflammatory cells have yet to be clearly delineated. Furthermore, the compartments which IgG must reach to affect its target(s): lymphatics, spinal fluid, Schwann cell versus axon membrane, node of Ranvier versus internode, and so on; and the effects of inflammation on permeability and access to these target sites is similarly undefined in most situations. Thus, many further studies are needed before the mechanism(s) of action of therapeutic IgG in any given condition can be confidently identified. Therefore, it is also difficult to predict whether the steady-state IgG levels achieved with SCIG versus the high peaks of IgG achieved with IVIG should be equally effective in any given disease, or whether one should be preferred over the other from a mechanistic perspective.

Box 1. Putative mechanisms of action of high-dose IgG.

- Anti-idiotypic neutralization of autoantibodies (or T-cell receptors)
- Enhanced catabolism of autoantibodies due to saturation of FcRn
- Inhibition of complement uptake on target tissues
- Blockade of macrophage Fc receptors (inhibition of RES phagocytosis)
- Inhibition of proinflammatory cytokines, increased regulatory cytokines
- Blockage of leukocyte adhesion molecules expression or binding
- Neutralization of microbial toxins
- Alterations in apoptosis
- Induction of inhibitory FcγRIIb receptors on effector macrophages (by sialylated IgG)
- Neutralization of B-cell growth factors for B cells (such as BAFF)
- Inhibition of T-cell proliferative responses
- Expansion and/or activation of Tregs
- Inhibition of differentiation and maturation of dendritic cells

RES: Reticuloendothelial system.

Wear-off effects

In 2003, before SCIG was licensed in the USA, 68% of respondents in an Immune Deficiency Foundation survey answered that they could

'usually' or 'sometimes' feel the effects of their IVIG 'wearing off' before the next dose was due [102]. By making frequent (i.e., weekly or even more often) administration of IgG convenient, SCIG regimens can eliminate the low troughs associated with monthly IVIG regimens. Maintenance of relatively high steady-state IgG levels with SCIG seems to eliminate or minimize these 'wear-off' or 'end-of-dose' effects in PIDD. Freedom from symptoms of subclinical/chronic infection with SCIG therapy may contribute to an increased sense of well-being and improved health-related QoL reported by PIDD patients who switched from IVIG to SCIG [9,10].

Among neurologic diseases, IVIG is most widely used for peripheral motor neuropathies. Many neurologists report anecdotally that a considerable proportion of patients experience increased strength and/or ability to perform daily tasks just after they receive IVIG infusions, with diminishing strength towards the end of their dosing interval. This has been illustrated very graphically in a patient with CIDP reviewed by Pollard and Armati, and has been attributed to changes in axonal excitability due to autoantibodies which block or disrupt sodium channels at nodes of Ranvier [28]. It has been suggested that these effects of the autoantibodies, rather than demyelination *per se*, are counteracted by the high serum concentrations of normal IgG achieved just after IVIG infusions [29,30]. Electrophysiologic studies which show cyclic improvement and worsening corresponding to monthly cycles of IVIG treatment in CIDP patients [28–30] are consistent with hypotheses which suggest that therapeutic effects predominate when the serum concentration is high just after the IV infusion, while the effects of the pathologic IgG predominate when the serum IgG level falls as the next dose is due. Rajabally *et al.* recently reported that 47% of CIDP patients required dosing intervals less than once a month to maintain optimal control of their symptoms [26]. Similarly, a review of specialty pharmacy/home nursing service records in the USA showed that 28% of patients with CIDP or myasthenia gravis were receiving IVIG at intervals of 15 days or less [31]; and Kuitwaard *et al.* recently reported that when the dose and frequency of IVIG treatments in CIDP patients were individually optimized, 14 out of 25 (56%) patients were rescheduled to receive their IVIG at intervals equal to or shorter than once every 2 weeks because of 'end-of-dose symptoms and signs' [19]. It seems likely that the use of weekly SCIG to maintain steady-state serum IgG levels higher than the residual trough levels 3–4 weeks after an IV bolus could ameliorate 'end-of-dose' symptoms. A few case reports, such as in FIGURE 2, support this hypothesis, but further studies will be needed to determine how commonly this occurs and its impact on long-term outcomes.

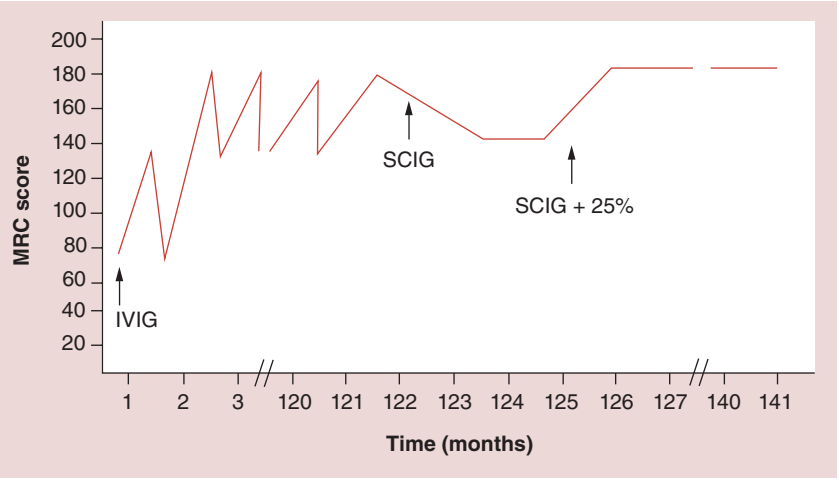

Figure 2. Medical Research Council score showing response to IgG therapy in a 63-year-old man with multifocal motor neuropathy. Sharp fluctuations in therapeutic response as assessed by MRC sum score are apparent during monthly IVIG treatment. Switching to SCIG resulted in stabilization of strength, but an increase in dose was necessary to achieve optimal results.
IVIG: Intravenous IgG; MRC: Medical Research Council; SCIG: Subcutaneous IgG.
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Experience with SCIG in specific neurologic conditions

Chronic idiopathic demyelinating polyneuropathy

CIDP is characterized by symmetric weakness affecting distal and proximal muscle groups, usually accompanied by sensory disturbances and areflexia [32,33]. Pain is not a prominent symptom, and the course is often chronically progressive, although there may be intermittent relapses. CIDP is considered to be the most common autoimmune peripheral neuropathy, with an estimated prevalence of eight to nine cases per 100,000 individuals [32,33]. Numerous immunologic abnormalities have been described in CIDP [32,33]. Because many patients respond to plasma exchange, and antibodies to nerve cell glycolipids and/or proteins have been often identified, autoantibodies are believed to be important mediators [32,33]. The efficacy of IVIG in CIDP has been demonstrated in a randomized clinical trial which enrolled 117 patients [34], and confirmed in two smaller trials [35,36]. Several reports have shown that the response to IVIG in CIDP is rapid, with documented increases in strength within days to 2 weeks after IVIG is started, although several doses may be needed to reach

maximal therapeutic effects [37–39]. Together with electrophysiologic studies showing that IVIG causes transient improvement in axonal excitability [28–30], these results seem to suggest that the response to IVIG in CIDP may be better explained by blocking autoantibody-induced functional impairments than by repair of myelin or degenerating axons [28–30]. In turn, this view of IgG therapy may suggest that CIDP offers a good opportunity to evaluate the efficacy of maintaining high steady-state IgG levels by the use of SCIG.

Markvardsen *et al.* have recently completed a randomized, placebo-controlled trial of 12 weeks of SCIG in 29 CIDP patients on stable IVIG therapy [40]. A total of 2 weeks after their last IVIG treatment, patients randomized to receive SCIG began receiving weekly doses of SCIG equal to a quarter of their previous monthly IVIG dose on a mg/kg basis, while placebo patients received a weekly volume of saline equal to a quarter of the volume of their previous IVIG treatment. After training, infusions were given at home, using multiple sites with a maximal volume of 20 ml/site, two to three times per week, over 0.5–2 h each, via small pumps. Although both patient groups had similar mean serum IgG levels 2 weeks before the study, at the end of the study period, the mean IgG level in the SCIG patients went up by 34%, while the mean IgG level in placebo patients decreased by 19.8% ($p = 0.0001$ for IgG levels at study-end). Patients on SCIG showed improvements in isokinetic muscle strength, Medical Research Council (MRC) disability score, grip strength, and 40-m walk test, while two-thirds of the placebo patients deteriorated. At the end of the 12-week study period, differences between the means of the scores for the two groups in all of the above end points were significant ($p < 0.05$). Only the results with the nine-hole peg test failed to show a significant difference between the SCIG and placebo groups. Side effects were limited to mild local site reactions, and 20 of the 29 subjects indicated a preference for SCIG [40].

Prior to that study, only case reports and/or small series of the use of SCIG in CIDP had been reported. A large clinical has been started by CSL Behring, but results are not yet available [103]. In 2008, Lee *et al.* described two CIDP patients who had been maintained on SCIG after difficulties with other forms of therapy [41]. The first patient was a 73 year old with biopsy confirmed CIDP. IVIG, at 0.8 g/kg/month (total monthly dose of 60 g), resulted in "temporary, fluctuating stabilization and worsening paresis", and required central venous access. SCIG was substituted using 16 g/week (total monthly dose of 64 g). Each weekly dose was broken up into five doses of 20 ml each (3.2 g of 16% IgG solution), given on consecutive days. SC swelling limited the maximum daily dose to 40 ml, but the 20 ml/dose regimen was well tolerated. On this regimen, the patient maintained stable grip strength and could walk with assistance. Measurements of compound muscle action potential, nerve conduction velocity and distal motor latency remained stable [41]. For this patient, several advantages of SCIG are apparent: lack of a requirement for indwelling venous access and hospitalization, easily tolerated AEs limited to local swelling only, stabilization of clinical status and increased independence. A second patient, who progressed on IVIG and azathioprine was switched to SCIG and mycophenolate mofetil and remained stable for more than 2 years on a dose of 6.4 g/week [41].

In a subsequent study by Cocito *et al.*, five CIDP patients who had been stabilized on IVIG for at least 3 months were switched to SCIG at the same total monthly dose, which was divided into 3–6 doses/week, each consisting of 3.2 g (20 ml) of 16% IgG infused over 90 min [42]. After 6 months on this regimen, there were no significant differences in life quality index, MRC score, overall neuropathy limitations scale, grip strength or Inflammatory Neuropathy Cause and Treatment Group (INCAT) sensory sum score. At the end of the study, four out of the five patients preferred SCIG, while only one returned to IVIG treatment. There were no AEs during SCIG therapy, and three patients reported the absence of the frequent headaches they had experienced on IVIG [43]. A follow-up study compared QoL measurements (using the SF-36 health survey) after 6 months of SCIG to measurements when the patients were on IVIG. In a group of five CIDP and five MMN patients, SCIG resulted in significant improvements in all three life quality index scores, and in several scales on the SF-36 [43].

A recent report on two cases of Lewis-Sumner syndrome (multifocal acquired demyelinating sensory and motor neuropathy), which is considered a variant of CIDP, illustrates some advantages of SCIG which might be more widely applicable [44]. One patient responded well to 2 g/kg of IVIG initially, but the interval between doses had to be shortened to every 2 weeks, and the patient twice suffered transient ischemic attacks on the days of IVIG infusions. He was switched to weekly SCIG at a dose of 9.6 g (42 g/month) and had no systemic AEs. His dose was tapered to 28 g/month,

but fluctuations in disease activity sometimes required increases to as much as 62 g/month. He subsequently continued on SCIG for nearly 4 years at the time of the publication, with no recurrence of thromboembolic events [44]. A second patient who failed to respond to steroids did respond to IVIG, but 90 g/dose was required and the patient still complained of recurrent weakness every 3 weeks. He was switched to SCIG, at 75.5–90 g/month, taking as much as 40 ml of 16% IgG solution (6.4 g) every other day. This was accompanied by flu-like symptoms, which stopped after he was switched to a different SC product on which he remained stable for more than 3 years with only mild infusion site reactions [44].

The above results show how the advantages of SCIG may be particularly important for some patients with CIDP who have had problems with IVIG. However, the observations of Kuitwaard, *et al.* [19], Rajabally [26] and Broyles *et al.* [31] suggest that many, perhaps even a majority of patients, require or prefer IgG at intervals much shorter than once a month. SCIG is ideal for use at intervals as short as 1 week or even just a few days between doses. The ability of SCIG to obviate 'end-of-dose' weakness may well yield important insights into the pathogenesis of CIDP and may lead to improved long-term outcomes, but those possibilities remain as subjects for future studies.

Multifocal motor neuropathy

MMN is a slowly progressive asymmetric neuropathy that is more pronounced distally and affects the upper extremities more than the lower, with an incidence of 1–2 cases per 100,000 per year [45,46]. Sensory involvement is rare. Although relatively high proportions of patients have been reported to have circulating antibodies to the ganglioside GM1, the role of these antibodies and the overall pathogenesis of MMN remains obscure. One of the most interesting features of MMN, which makes it different from other immune-mediated peripheral neuropathies, is that it responds poorly to plasma exchange and/or corticosteroids [45,46]. By contrast, a number of studies have shown efficacy of IVIG, which is now the accepted first-line treatment [47], although end-of-dose weakness is frequently observed [48]. A brief paper by Koller *et al.* in 2006 reported that SCIG was effective in two patients with MMN who had previously been managed with IVIG [49]. Subsequently, Harbo *et al.* in Denmark performed a randomized, single-blinded crossover study of SCIG in nine MMN patients whose continuing dependence on IVIG was tested by a treatment-free interval during which there was a mean loss of strength at the elbow, wrist and hand of 15.6 ± 8.4%. Patients were randomized to receive three IVIG treatments at a mean interval of 28 days, or weekly SCIG at the equivalent total monthly IVIG dose in grams for the same duration. There were no significant differences in muscle strength, motor performance or nerve conduction studies at the end of either regimen, so the authors concluded that both regimens were equally effective. Six patients experienced transient side effects at SC injection sites, one of whom had to have a reduction in volume per site; three patients had more severe AEs on IVIG, including phlebitis and Port-a-Cath infections. There were no significant differences in health related QoL as assessed with SF-36. Four patients preferred SCIG, two preferred IVIG and three expressed no preference. In actuality, five patients continued on SCIG [50]. A follow-up report after 2 years on SCIG also included one other patient with MMN [51]. All six patients were initially given the same total monthly dose of IgG they had previously received by the IVIG route, divided into 2–3 SCIG infusions per week. During the 24 months of follow-up, four of the six patients had their dose of SCIG increased by a mean of 21% "to stabilize motor performance." All patients had mild local reactions at the injection sites, but there were no systemic AEs. There were no significant changes in neurologic impairment score, overall disability sum score or isokinetic muscle strength. These patients had been on IVIG for a mean of 6 years before switching to SCIG, and remained stable for a further 2 years on SCIG, so the investigators concluded that SCIG was as effective as IVIG for long-term maintenance of strength in MMN [51].

The effect of SCIG in smoothing out end-of-dose weakness effects of IVIG is illustrated graphically in a case report by Dacci *et al.* [52]. **Figure 2** shows MRC scores recorded while the patient received 2 g/kg of IVIG monthly for several months, then 0.8 g/kg every 3–4 weeks. His Rankin disability scale improved 1–2 weeks after each dose, but then progressive weakness recurred in the third week of each cycle, resulting in inability to walk without support (Rankin scale 3–4). After 10 years of IVIG, the patient was switched to SCIG at a total monthly dose of 1 g/kg (equivalent to his monthly IVIG dose at that time)

divided into four doses, given at weekly intervals. Although the fluctuations in his strength disappeared, overall he became weaker, so his SCIG dose was increased by 25% at month 125. This resulted in continuous maintenance of the peak strength he had previously achieved only transiently after each IVIG dose. This improvement in strength was accompanied by an increase in the trough serum IgG level from 1500 mg/dl to a steady state of 2100 mg/dl, and he remained stable. The increase in SCIG dose required to optimize the patient's strength may be due to the decreased bioavailability of SCIG, as discussed earlier. Conversely, the response to the higher dose, which resulted in a higher steady-state IgG level, may suggest that this patient's strength at any point in time is directly related to the concentration of normal IgG in his circulation. It is tempting to speculate that this kind of dose response is due to need for a certain level normal IgG to compete with the putative autoantibody (the patient was positive for IgM anti-GM1).

Dose-dependency with SCIG was also demonstrated in a study from Eftimov *et al.* in The Netherlands. In this prospective, open-label, noncontrolled trial five patients with MMN on stable IVIG for at least 6 months were switched to weekly SCIG at mean monthly dose equal to 50% of their previous IVIG dose [53]. One patient withdrew because of infusion site AEs. In the four patients who continued, a decrease in the MRC sum score became apparent within 4 weeks. The patients were given a 'booster' of 1 g/kg IVIG and improved transiently, but then deteriorated again on SCIG at the previous dose. A different group of five patients were 'loaded' with two doses of IVIG, then given SCIG at 100% of the previous monthly IVIG dose. On this regimen, four out of the five patients maintained stable MRC sum scores for at least 6 months, with steady-state serum IgG levels in the range of 1380–1740 mg/dl [46]. There were no serious AEs, but all subjects reported tolerable local AEs at the infusion sites, which decreased in frequency as the study progressed [53].

The patient reported by Dacci *et al.* was actually part of a larger prospective, open-label study subsequently reported by Misbah *et al.*, in which eight MMN patients on stable IVIG regimens were transitioned to weekly SCIG at the same total monthly dose. One patient was considered a nonresponder to SCIG and was withdrawn, and one other patient required a 25% increase in SCIG dose to maintain strength. The seven patients continuing for the full 24-week study period maintained stable muscle strength, motor function and disability score, and all chose to continue with SCIG [54].

Taken together, these results all suggest that SCIG can be a useful alternative to IVIG in MMN, which may be particularly attractive for some patients. Besides those who prefer the home treatment options and flexibility of SCIG, patients with pronounced 'wear-off' or end-of-dose weakness effects on IVIG may especially benefit from the clinical stability afforded by the steady-state IgG levels achieved with SCIG. 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 to promote long term recovery and prevention of axonal loss [55], while others find that in the long run, a majority of patients gradually worsen despite this type of approach [39]. It may be that recurrent damage to Schwann cells and/or axons *per se* increases at the end of each dosing interval, when the IgG level is relatively low and the patient is experiencing increased weakness. If that is the case, using SCIG to maintain high steady-state IgG levels without cyclic troughs may decrease long-term deterioration in MMN, but that hypothesis remains to be tested.

Other neurologic conditions in which SCIG may be applicable

Although CIDP and MMN account for the greatest use of IVIG in neuropathies, chronic IVIG therapy has also been used for certain patients with myasthenia gravis [56], stiff-person syndrome and other neuromuscular disorders [57], chronic regional pain syndrome [58], and some CNS disorders including neuromyelitis optica [59]. The use of SCIG in those disorders has not yet been reported, but trials in CIDP, MMN and myasthenia gravis are listed on the Clinicaltrials website [104]. Although not neuropathies *per se*, polymyositis and DM are often treated by neurologists because weakness is a major component of these clinical syndromes. Corticosteroids are first-line treatment for these disorders but immunosuppressives are frequently added, and IVIG has an important place as an adjunctive therapy [60]. In 2008, Schleinitz *et al.* reported on a patient with DM who failed corticosteroids and other immunosuppressives, and was put on IVIG, prednisone and cyclophosphamide. She initially responded well, so

the interval between IVIG infusions was lengthened to once every 2 months. She then relapsed, but responded well to resumption of monthly IVIG, corticosteroid pulses and mycophenolate mofetil. However, she suffered two episodes of infection of central IV catheters, necessitating their removal, and leaving the patient without venous access. Home treatment with SCIG was initiated at 1.7 g/kg/month divided into doses given 2 days each week. This was well tolerated, with no local or systemic AEs. The rash of her DM cleared within a month, and she continued to improve over the course of a year, with decreased CPK levels despite tapering of her prednisone, and there were no further infectious complications [61]. Another report, of a young boy with ocular myositis also described a good response within 1 month of starting SCIG, which was well tolerated and allowed tapering and discontinuation of prednisone (over a course of 2 years), as well as the withdrawal of other immunosuppressives [62]. The same group reported a prospective study of SCIG in seven patients with severe myositis (three DM and four polymyositis). Six of these patients were already on IVIG, in addition to prednisone and other immunosuppressives, and two also had plasma exchange. SCIG was given at a total dose of 2 g/kg/month divided into weekly infusions. All patients tolerated the SCIG well, with only two complaining of mild infusion site reactions lasting less than 48 h, and no systemic AEs. All patients experienced improved muscle power, four had large drops in their CPK levels, and all patients were able to taper and/or discontinue presdnisone and other immunosuppressives. One patient had a transient flare after 6 months, which was controlled by 3 months of IVIG treatments. That patient subsequently continued on SCIG without further problems. All patients reported improvements in the 'global physical' and/or 'global mental' indexes on the SF-36. At the time of publication, the mean follow-up period was 12 months [63]. A recent report describes a 70-year-old man with inclusion body myositis who, besides weakness, had dysphagia controlled by IVIG (1.25 g/kg every 4–5 weeks). He requested to try SCIG to enable increased autonomy, and responded quite well to a regimen of 0.77 g/kg/month, given as 20 ml of 16.5% IgG (3.3 g) four times a week. He has continued on this regimen for 4 years as of the time of the publication, with no further complaints of difficulty swallowing and stable weight, although there was slow progression of weakness in the legs [64].

Adverse reactions with SCIG: local & systemic

Systemic AEs due to SCIG are infrequent. In a 2004 review of data on more than 40,000 SCIG infusions in 232 PIDD patients, the overall incidence of systemic AEs was 0.43% [1]. By contrast, a recent comprehensive review reported that 20–40% of patients receiving IVIG experience systemic AEs at one time or another, accompanying or following 5–15% of all infusions [7]. Infusing 20–30 ml of IgG solution into a single SC site in less than 2 h causes some swelling, due to the infused volume itself. Additional fluid may be drawn into the site osmotically and/or by local production of mediators which increase vascular permeability. Locally produced mediators may also cause erythema, warmth and an itching or burning sensation which usually resolves over 12–24 h. These symptoms are generally considered 'mild' or 'moderate' and do not require any treatment. In most studies discussed in this review, only a few patients reported AEs other than mild injection site reactions, and many of them have been on SCIG for many months and even years. Probably because they resolve quickly and are not very troublesome, detailed histo- or immuno-pathologic studies of biopsies of SCIG infusion sites have not been reported. Several studies in PIDD patients have reported initially high rates of local reactions, which decreased over time (e.g., see [65]). The decreases over time, and the large differences in reported frequency of infusion site reactions in different studies are more likely due to the eventual recognition by the patients that some swelling and redness is routine, and should have been expected, rather than to actual physiologic changes in the SC tissues or in IgG metabolism [66]. Long-term changes at injection sites such as lipodystrophy, fibrosis, atrophy or long-lasting SC nodules have not been reported. Nevertheless, rotating the sites used for consecutive infusions seems prudent. If patients are instructed to recognize and expect these injection site phenomena, and if they are shown photographs of infusion sites or can talk to patients already on SCIG, they rarely complain [66]. More severe local reactions and infected sites are extremely rare and may be due to poor technique and/or contamination of the infused drug. As evidenced by the series described in this review, most patients who have been on SCIG in trials prefer to remain on SCIG. This observation likely includes some bias, however, since patients who might have pre-existing reasons for preferring SCIG may self-select by volunteering for trials.

The predominance of patients with autoimmune neuropathies are in the 6–8th decades of life. Therefore, it may be useful to review the experience with SCIG in PIDD patients above the age of 65, as reported in detail by Stein *et al.* [67]. Of 47 patients using SCIG, 39 (83%) self-infused at home; 98% received one infusion per week, with a mean volume of approximately 40 ml distributed into two or three sites, requiring a mean duration of 65 min per infusion and delivering a mean of 103 mg/kg/week. It is thus easy to imagine that doubling the volume per site or doubling or tripling the number of infusions per week would result in doses of 0.2–0.3 g/kg per week, or 0.8–1.2 g/kg/month, which is in the range most often used by patients with neurological diseases. Despite multiple comobidities and the use of anticoagulants and/or antiplatelet drugs, there was no bleeding or bruising at the infusion sites and there were no significant systemic AEs in this elderly cohort.

Pharmacoeconomics

In the current era, the main cost of IgG therapy, by whatever route, is likely to be that for the IgG itself. In a large 1995 study, Gardulf *et al.* reported that the overall costs of treating PIDD patients with SCIG were only approximately 25–33% of the cost of IVIG treatment [68]. However, that was based on the availability of a large inventory of intramuscular immune serum globulin which was inexpensive. At present in the USA, two of the three products labeled for SC use are also labelled for IV use. The third, a 20% solution, is the same as its 10% IV counterpart, except for a final concentration step. Thus, there should be little or no difference in the cost of the products themselves regardless of the route.

IVIG, particularly at the high doses used for neurologic and other autoimmune diseases, is usually given by a nurse or other trained professional. Either the nurse must travel to the patients' home, or more commonly, the patient (and often an accompanying family member) must travel to an infusion center or hospital. In many cases, patients receiving high-dose IVIG are admitted to the hospital as inpatients 2 or more days per month. Obviously, these situations add to the overall cost of the therapeutic regimen, both in the direct charges for the personnel and facilities, and the indirect costs of transportation, time off from work, among others. Supplies for the more frequent SCIG infusions may add to the cost of this modality. However, an analysis of the economic impact of switching CIDP patients in Germany was quite dramatic, dropping from €60,000 for IVIG to €30,000 for the same dose of SCIG [41]. In contrast, a recent cost-minimization analysis by Cocito *et al.* in Italy estimated the difference in total direct costs for treating a 70 kg patient for 12 months with SCIG versus IVIG only at approximately 1.5% [43]. Obviously, the differences in costs between SCIG and IVIG may vary depending on the local situations. Besides direct costs, differences in indirect costs and perhaps most importantly, effects on the clinical stability of the patient and the QoL of the patient and family should also be considered in evaluating the relative merits of SCIG versus IVIG in any given case.

Conclusion

The results reviewed here certainly suggest that SCIG is a reasonable alternative to IVIG, which may be preferred by many patients for a variety of reasons. To date, experience with SCIG in chronic peripheral neuropathies is limited, but some larger studies have been initiated. Because giving SCIG weekly or more often results in steady-state serum IgG levels, it may be particularly valuable in chronic diseases like CIDP and MMN, in which IVIG treatment is associated with clinically significant fluctuations in symptoms. Conversely, because SCIG takes longer to reach maximal serum concentrations and individual doses may be limited, SCIG is less likely to be applicable in acute situations like GBS or encephalopathies, which probably require rapid increases in the serum IgG level.

Future perspective

Future studies identifying the targets and mechanisms by which therapeutic IgG acts in specific neurologic conditions will hopefully provide new tools for optimizing therapy in individual cases, and may yield insights into whether the different routes of IgG therapy result in different long-term outcomes. The availability of 20% or even more concentrated IgG products should further facilitate the use of SCIG, since the same dose of IgG can be administered in half the volume, or half the number of doses. Recent reports on the use of small injections of recombinant human hyaluronidase into the site(s) just before starting SCIG infusions may be a useful way to promote more rapid uptake of SCIG into the systemic circulation and increase its bioavailability [69], but more clinical experience and data on its long-term safety are required. Overall, results to date with SCIG in neurologic disease can be regarded as promising, and its use seems likely to increase as more neurologists and patients gain experience

with this route of therapy and results of larger clinical trials become available.

Financial & competing interests disclosure

M Berger is a salaried employee of CSL Behring and holder of equity interests. M Berger has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Executive summary

- Differences in pharmacokinetics of subcutaneous IgG (SCIG) versus intravenous IgG result in decreased systemic adverse effects and near steady-state serum IgG levels.
- The ease of subcutaneous versus intravenous access facilitates home SCIG treatment, and the availability of high-concentration IgG products for subcutaneous administration make even high-dose therapy (1–2 g/kg/month) practical for most patients.
- Although there is decreased bioavailability when IgG is given by the subcutaneous route, increasing the frequency of dosing results in steady-state serum IgG levels which are higher than the troughs achieved with monthly intravenous bolus therapy.
- More studies of the short- and long-term efficacy of SCIG in neurologic diseases are necessary, but those which have been published suggest that SCIG may be preferable in many autoimmune neuromuscular diseases.
- An online supplement entitled: 'The Nuts and Bolts of SCIG Therapy' is available at www.futuremedicine.com/doi/suppl/imt.13.146.

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