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INVITED REVIEW

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Subcutaneous immunoglobulin treatment for chronic inflammatory demyelinating polyneuropathy

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Abstract

Immunoglobulin G (IgG) therapy is an established long-term treatment in chronic inflammatory demyelinating polyneuropathy (CIDP) that is commonly administered intravenously (IVIg). The subcutaneous immunoglobulin (SCIg) administration route is a safe and effective alternative option, approved by the United States Food and Drug Administration (FDA) in 2018, for maintenance treatment of adults with CIDP. Physicians and patients alike need to be aware of all their treatment options in order to make informed decisions and plan long-term treatment strategies. In this review, we collate the evidence for SCIg in CIDP from all published studies and discuss their implications and translation to clinical practice. We also provide guidance on the practicalities of how and when to transition patients from IVIg to SCIg and ongoing patient support. Evidence suggests that IVIg and SCIg have comparable long-term efficacy in CIDP. However, SCIg can provide additional benefits for some patients, including no requirement for venous access or premedication, and reduced frequency of systemic adverse events. Local-site reactions are more common with SCIg than IVIg, but these are mostly well-tolerated and abate with subsequent infusions. Data suggest that many patients prefer SCIg following transition from IVIg. SCIg preference may be a result of the independence and flexibility associated with self-infusion, whereas IVIg preference may be a result of familiarity and reliance on a healthcare professional for infusions. In practice, individualizing maintenance dosing based on disease behavior and determining the minimally effective IgG dose for individuals are key considerations irrespective of the administration route chosen.

KEYWORDS
CIDP, immunoglobulin therapy, IVIg, SCIg, transition

Abbreviations: AE, adverse event; CIDP, chronic inflammatory demyelinating polyneuropathy; COVID-19, coronavirus disease 2019; EFNS, European Federation of Neurological Societies; EQ-5D, EuroQoL 5 Dimension; EU, European Union; FDA, United States Food and Drug Administration; fSCIG, facilitated SCIg; HCP, healthcare professional; ICE, Immunoglobulin Intravenous CIDP Efficacy (trial); IgG, immunoglobulin G; INCAT, Inflammatory Neuropathy Cause and Treatment; I-RODS, Inflammatory Neuropathy-Rasch-Built Overall Disability Scale; ITT, intention-to-treat; IVIg, intravenous immunoglobulin; LQI, Life Quality Index; MG, myasthenia gravis; MMN, multifocal motor neuropathy; MRC, Medical Research Council; ODSS, Overall Disability Sum Score; OLE, open-label extension; PATH, Polyneuropathy and Treatment with Hizentra; PFS, pre-filled syringe; PID, primary immunodeficiency; PNS, Peripheral Nerve Society; QoL, quality of life; SC, subcutaneous; SCIg, subcutaneous immunoglobulin; SmPC, Summary of Product Characteristics; TEE, thromboembolic event; TRF, treatment-related fluctuation; US, United States; USPI, United States Prescribing Information; VAS, Visual Analog Scale.

The objectives of this activity are to: 1) Choose patients appropriately for treatment with subcutaneous immunoglobulin; 2) Calculate and order induction and maintenance therapy dosing correctly; 3) Make informed choices of subcutaneous vs. intravenous immunoglobulin therapy.
I have no conflicts of interest

1 | INTRODUCTION

Chronic inflammatory demyelinating polyneuropathy (CIDP) is an immune-mediated neurological disorder causing demyelination of the peripheral nerves.[1] There are several variants and disease courses (progressive, relapsing–remitting or monophasic), but typically CIDP is characterized by symmetrical muscle weakness and impaired sensory function in distal and proximal limbs.[1,2] Unlike most other neuropathies, CIDP is treatable and reversible.[3] The aim of treatment is to reduce symptoms and improve muscle and sensory function.[4] Approximately 30% of CIDP patients can be cured (stable and off treatment for 5 or more years) or enter remission (stable and off any treatment for less than 5 y).[5] It remains a challenge to balance maintaining long-term remission without overtreating the patient, versus the risk of relapse if treatment is stopped or reduced prematurely.[4,6]

Established first-line induction therapy options include intravenous immunoglobulin (IVIg), corticosteroids, and plasma exchange.[7] Studies have shown that corticosteroids and plasma exchange can effectively treat CIDP on a short-term basis.[7] Short-term corticosteroid use has in some cases led to periods of drug-free remission (up to 12 mo).[8] Evidence suggests corticosteroids may be effective longer term,[8,9] however, intolerance and side effects often prevent their long-term use.[7] IVIg has demonstrated long-term efficacy in CIDP maintenance therapy, but IV administration can pose challenges for some patients.[10] Subcutaneous immunoglobulin (SCIg) has been used for decades in other areas, but it is a relatively recent mode of immunoglobulin G (IgG) therapy in CIDP and requires a certain level of familiarity with dosing and administration unique to the subcutaneous (SC) route of administration. Particularly in the coronavirus disease 2019 (COVID-19) environment, SCIg self-administration at home can provide more patient autonomy and potentially less inadvertent risk of exposure compared with nurse-administered IVIg and/or attendance at an infusion center. Factors dictating the choice of maintenance treatment are varied and will ultimately impact patient decision. Therefore, it is crucial to outline all the treatment options as early as possible to allow informed decisions.

In this review, we consolidate the findings of SCIg studies in CIDP with a focus on the practical application of the data. We aim to provide an overview for clinicians including when to consider SCIg, initiating the transition from IVIg to SCIg, dose adjustments, and long-term patient support and retention.

2 | COMPARISON OF IVIg AND SCIg THERAPY

IVIg has been approved for CIDP treatment in the United States (US) since 2008 following the randomized, double-blind, placebo-controlled Immunoglobulin Intravenous CIDP Efficacy (ICE) study.[11,12] Results showed a clinically meaningful improvement in disability (assessed by the Inflammatory Neuropathy Cause and Treatment [INCAT]) at 24 wk in 54% of patients who received IVIg versus 21% of patients who received placebo.[11] Efficacy of IVIg for up to 52 wk was also seen in a single-arm, open trial, although a higher frequency of adverse events (AEs; 94%) was observed in this trial compared with the 75% seen in the ICE study (75%).[11,13] In a recent online survey of 100 US community neurologists, nearly half reported using IVIg alone as their first treatment of choice for CIDP.[4] The 2010 European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) guidelines recommend that IVIg should be individualized to achieve the lowest effective maintenance dose and periodically reduce the dose, or stop IVIg, to determine the need for ongoing therapy.[14] Guidelines from the EFNS/PNS, currently under development, should provide more clarity on clinical definitions, electrophysiologic criteria, implications of nodal and paranodal antibodies, individualizing treatment, and inclusion of SCIg as an alternative option to maintain patients and optimize treatment.[15]

SCIg was first approved by the FDA in 2018 for maintenance therapy in adult patients with CIDP based on the Polyneuropathy and Treatment with Hizentra (PATH) study findings,[16] but has been used successfully in other conditions such as primary immunodeficiency (PID) for over two decades.[17] Collective experience with over 300 patients with CIDP, treated with various SCIg products over the past 15 y, supports the use of SCIg as a maintenance therapy for CIDP (Table 1). Additionally, long-term SCIg data are now available supporting continued stabilization and, in some cases, improvements in function and quality of life (QoL), for up to 7 y post initiation of SCIg therapy (N = 17, SCIg mean duration was 4.8 y [2–7 y] and an average dose of 18.5 g/wk).[18]

Currently, there are no data available from head-to-head trials comparing relapse rates in maintenance therapy with IVIg and SCIg.[19] Findings from the studies outlined in Table 1 suggest similar efficacy. A 2017 meta-analysis of eight studies concluded that the efficacy (measured by muscle strength) of SCIg is comparable with IVIg in the treatment of CIDP (n = 88) and multifocal motor neuropathy (MMN) (n = 50).[20] IVIg and SCIg therapy have distinguishing attributes that will appeal to patients differently depending on their circumstances and lifestyle (Table 2). SCIg can offer important safety and QoL advantages compared with IVIg, such as avoidance of regular venous access and reduced systemic AEs. However, disadvantages of SCIg for some patients can be the need for weekly infusions and the potential for local-site reaction.

3 | KEY FINDINGS FROM THE PATH AND OPEN-LABEL EXTENSION STUDIES

The study demonstrated that SCIg was efficacious and well tolerated in patients with CIDP previously stabilized on IVIg and treated for 24 wk.[16] Patients were randomized to receive 24 wk of weekly SCIg doses at 0.2 g/kg (n = 57), 0.4 g/kg (n = 58), or placebo (n = 57).[16] Fewer patients treated with SCIg relapsed compared with placebo. Most patients showed improvements in their INCAT total score, grip strength, and Medical Research Council (MRC) sum scores compared with the placebo group, with no statistically significant difference observed between the two SCIg doses. However, the 0.4 g/kg dose

TABLE 1 Summary of main findings from SCIg studies in CIDP

Study	Study design	No. patients	Follow-up (mo)	Main findings
Köller, et al. 2006[21]	Case report	1 CIDP; 2 MMN	6	SCIg was well tolerated with high patient satisfaction. CIDP patient improved by INCAT disability score and MRC sum score.
Lee, et al. 2008[22]	Case report	2 CIDP	8–24	SCIg was well tolerated, easy to manage and stabilization disease course. No systemic or serious side effects were reported, only mild swelling at the infusion site.
Cocito, et al. 2011[23]	Prospective, open-label, longitudinal	5 CIDP	6	SCIg efficacy, QoL, and patient satisfaction were comparable with previous IVIg—4/5 patients preferred SCIg to IVIg. A reduction in side effects was observed with SCIg and no need for pre-medication.
Markvardsen, et al. 2013[24]	Randomized, double-blind, placebo-controlled	29 CIDP *(14 SCIg vs 15 placebo)*	3	Muscle strength and disability were improved with SCIg—70% of patients preferred SCIg to IVIg. Side effects were limited to mild infusion site reactions.
Cocito, et al. 2013[25]	Open label (SCIG 16% vs SCIG 20%)	10 CIDP	3 + 3	LQI score was higher with SCIg 20% versus SCIg 16% (most likely due to less frequent infusions versus SCIg 16%)
Markvardsen, et al. 2014[26]	Prospective, open-label extension study	17 CIDP *(from previous 2013 study)*	12	Muscle strength and disability were preserved after 1 y receiving SCIg.
Cocito, et al. 2014[27]	Prospective, multicenter case series	66 CIDP; 21 MMN	4	ONLS was significantly improved with SCIg; MRC score was minimally improved
Hadden, et al. 2015[28]	Partially prospective case series	4 CIDP; 4 MMN	33 (mean)	Tolerability and patient satisfaction were improved with SCIg; patients also remained clinically stable (based on MRC and ONLS scores)
Yoon, et al. 2015[29]	Retrospective case series	3 CIDP; 1 MMN; 1 MG	39 (mean)	Patients remained stable with no serious side effects; SCIg was well-tolerated and preferred to IVIg by all patients
Cocito, et al. 2016[30]	Prospective, multicenter case-series	45 CIDP; 21 MMN *(from previous 2014 study)*	24	Adherence to SCIg was 76% at 2 y and patient satisfaction was significantly increased
Markvardsen, et al. 2017[31]	Randomized, single blind, cross-over	19 CIDP *(treatment-naïve)*	5	Similar efficacy, but maximal improvement in muscle strength was by 5 wk with SCIg versus 2 wk with IVIg
Van Schaik, et al. 2018[16]	Randomized, double-blind, placebo-controlled	172 CIDP *(115 SCIg vs 57 placebo)*	6	Two doses of SCIg (0.2 and 0.4 g/kg) were efficacious and well-tolerated. Over half preferred SCIg to their previous IVIg.
Cirillo, et al. 2018[32]	Prospective, open-label cohort	16 CIDP	24	Primary demyelinating features of nerve conduction, and clinical variables (MRC sum, INCAT, ODSS) were significantly improved with SCIg
Van Schaik, et al. 2019[33]	Prospective, open-label extension study	82 CIDP *(from previous 2018 study)*	12	SCIg demonstrated long-term efficacy and safety at both doses, although lower relapse rates were reported on the 0.4 g/kg dose
Gentile, et al. 2020[18]	Retrospective, case series	17 CIDP	84	Strength and motor functions remained stable or improved with long-term SCIg

Abbreviation: ONLS, Overall Neuropathy Limitation Scale.

TABLE 2 Comparison of IVIg and SCIg

	IVIg (10%)	SCIg (20%)
Infusion regimen		
Dose[33–35]	**Induction:** 2 g/kg body weight (20 mL/kg) in divided doses over 2–5 consecutive days **Maintenance:** 1 g/kg (10 mL/kg) administered In 1 or 2 infusions on consecutive days	**Induction:** Not approved for induction therapy **Maintenance:** 0.2 g/kg (1 mL/kg) in 1 or 2 sessions. Higher doses up to 0.4 g/kg (2 mL/kg) may be considered
Infusion rate and volume[33–35]	**Initial:** 0.5–5 mg/kg/min **Maintenance:** 8 mg/kg/min	**Initial volume:** ≤20 mL/site **Max. Volume:** ≤50 mL/site **Initial rate:** ≤20 mL/hr/site **Max. rate:** ≤50 mL/hr/site **Maximum infusion sites:** ≤8
Frequency of infusions[33–35]	Every 3-4 wk (can be administered more frequently)	Weekly
No. of infusion sites[34]	1	1–8
Overall infusion time[18a]	3–5 h/mo	1–1.5 h/wk
Onset of action[11,16,30]	1–2 wk	Relatively slow—4 wk (if not started 1 wk after last IVIg dose)
IgG level profile[36]	Cyclical, troughs and peaks	Near steady-state
Other factors		
Setting[18]	Hospital, infusion clinic, or at home with an infusion nurse	Home, work, school etc.
HCP required[37]	Yes	No
Systemic AEs[2]	Yes	Reduced
Local AEs	Rarely	Common
Need for premedication[16]	Common	Rarely
Venous access required	Yes	No
TRFs[36]	Wear-off effects can occur between doses	Potentially improved due to more regular/more frequent infusions compared with IV
Bioavailability[2]	Higher than SCIg	Estimated to be ≈ 85% compared with IVIg
High-dose requirement[b]	High doses relatively unaffected by BMI or tissue volume as delivered intravenously	High doses can be limited by available subcutaneous tissue volume in low BMI patients; may require a higher number of infusion sites
Patient satisfaction[38]	Mixed	Mixed, but generally improved versus IVIg
Cost[2]	High acquisition cost	High acquisition cost, but may be associated with reduced overall costs in the long term due to less hospital visits and HCP resource

Abbreviation: BMI, body mass index.

[a]Estimated range; actual infusion times will vary depending on infusion regimen and patient tolerability. Infusion regimens here are based on US prescribing information and may vary by country. For more information, please refer to your local prescribing information.

[b]Obese patients (BMI > 30 kg/m^2) are more likely to have cardiovascular risk factors and have a higher risk of AEs as a result of higher IgG doses; therefore, caution is recommended.[39]

(but not the 0.2 g/kg dose) was significantly more effective than placebo in preventing deterioration in overall disability, assessed by I-RODS. The most common AEs recorded were local-site reactions which were predominantly mild or moderate in intensity.

The open-label extension (OLE) provided Class IV evidence supporting maintenance treatment with SCIg in patients with CIDP for up to an additional 48 wk.[33] A summary of the key findings is provided below, but further details of the study designs and outcomes have been published previously.[16,33,40] Eligible patients could continue on SCIg for up to an additional 48 wk.[33] Eighty-two patients were enrolled (n = 62 starting on 0.4 g/kg; n = 20 starting on 0.2 g/kg). The study highlighted that relapse rates differed depending on treatment allocation in the original study with the highest probability of clinical stability seen with the 0.4 g/kg dose, although some

patients could be maintained on 0.2 g/kg without relapse (Figure SS1).[41] This disparity portrays the inter-patient heterogeneity in terms of IgG threshold and the importance of determining the minimum effective dose on a case-by-case basis.

4 | PRACTICALITIES OF USING SCIg IN CIDP

4.1 | Induction and maintenance therapy

SCIg is currently not approved for induction therapy in CIDP, where typically a higher dose is used to stabilize patients starting IgG therapy.[35] IVIg is delivered directly into the bloodstream resulting in a rapid rise in IgG levels which has been shown to lead to a faster onset of action, quicker improvements in disability, and (in many patients) "an energy boost".[42] In comparison, SCIg had a slower onset of action due to slower absorption into the bloodstream. SCIg has previously been investigated as a first-line treatment option in patients with CIDP.[31] Markvardsen et al. demonstrated that SCIg (0.4 g/kg/wk) for 5 weeks had similar efficacy to IVIg (0.4 g/kg/day) for 5 days as a first-line treatment in treatment-naïve CIDP patients.[31] However, the maximal improvement was reached sooner with IVIg (IVIg, 2 wk vs SCIg, 5 wk).[31] Newly diagnosed patients will often benefit from a quicker stabilization of their disease. An IVIg induction dose followed by IVIg maintenance doses to stabilize the patient should take place before considering transition to SCIg for longer term maintenance therapy.[35] However, we recommend introducing patients early on, and simultaneously, to the concepts of IVIg and SCIg, the same treatment administered via two different routes.

4.2 | Transitioning from IVIg maintenance to SCIg maintenance

Differences in symptom control and systemic side effects may be attributed to differences in pharmacokinetics between IVIg and SCIg.[33,42] IVIg is administered as a large intermittent bolus, typically every 3–4 wk, whereas SCIg is administered in more frequent (typically weekly) smaller doses.[37] Low IgG trough levels toward the end of IVIg dosing intervals may lead to cyclic fluctuations in disability and a return of symptoms in some patients referred to as "wear-off" effects[37] (Figure 1). Weekly SCIg dosing results in a steadier IgG concentration that is consistent between infusions, but with a peak serum IgG concentration that is lower than that achieved with IVIg.[19,37]

While country-specific labels have varying recommendations for the SCIg starting dose in CIDP, the evidence supports doses between 0.2–0.4 g/kg body weight (bw) weekly. The best approach to transition patients from IVIg to SCIg remains unclear and will vary between patients.[19] A variety of successful transition protocols have been reported in CIDP and MMN.[43,44] However, SCIg should be initiated 1 wk after the last IVIg infusion[35,45,46] so that the serum IgG concentration remains high enough to smoothly transition to a stable steady state.[19] In the Unites States (US), the recommended starting dose for SCIg is 0.2 g/kg bw/wk (with up to eight simultaneous infusion sites); the dose can be increased up to 0.4 g/kg if necessary. In Europe and Canada 0.2–0.4 g/kg bw/wk (no limit of infusion sites) is recommended.[34,35,46] The starting dose range of 0.2–0.4 g/kg/wk in the European Union (EU) and Canadian labels provides more flexibility to start patients on a dose based on a 1:1 conversion from their previous IVIg treatment (typically this would be 0.33 g/kg based on a 1 g/kg IVIg maintenance dose every 3 wk) and reduces the risk of underdosing in patients with higher IVIg requirements. It also provides the option of treating at 0.4 g/kg and down-titrating to determine the minimum requirement. Patients fearful of relapse may prefer this approach as opposed to transitioning to 0.2 g/kg, which may lead to lower IgG concentrations than their current IVIg dose and contribute to a greater risk of treatment failure. Moreover, lower IgG concentrations can arise due to the decreased bioavailability of SCIg, which may be up to 30% lower relative to IVIG.[42,47] Most reports adopt an initial SCIg dose calculated using a 1:1 conversion from the previous IVIg dose divided per week.[28,30,48]

4.3 | Dose adjustments—Stabilized patients

Physicians may want to reduce a patient's dose after a period of clinical stability.[33] Once patients treated with IgG products improve to a good baseline and do not fluctuate with therapy, tapering or discontinuation of IgG therapy should be considered to assess whether the patient is in remission. This approach may be considered in responders as early as 6–12 mo after IgG therapy initiation. There are a variety of approaches to discontinue IgG therapy once the physician deems the patient is a candidate. For IVIg, the most common approach is to progressively taper the dose by approximately 20%–25% or to extend the interval between infusions. However, some have suggested an alternate individualized approach of abrupt interruption of IVIg after two loading doses to determine response.[49] Once a responder deteriorates, the IVIg dosing interval is determined and then dosage is tapered.[49] Clinically stable patients with CIDP may have low variability in their IgG levels, however, it is not clear if using IgG levels to guide dosing can be widely adopted with IVIg therapy since IgG levels in unstable patients have not been yet evaluated.[50] For stable SCIg responders, weekly dosage tapering every month or so by 20%–25% is a sensible strategy. Alternatively, although data are lacking, abrupt discontinuation may be considered in select patients based on CIDP disease status and physician-patient discussion. The flexibility of SCIg allows minor dosing adjustments without the need for complicated scheduling challenges of clinic (or HCP)-based infusions to maximize the clinical dose–response relationship. CIDP dose adjustments are often made on the basis of the neurological examination and close monitoring of the clinical response using functional and disability assessments (INCAT, I-RODs, and grip strength etc.), with the aim of titrating to the lowest effective dose.[51] Patients may require lower or higher doses depending on factors such as IgG threshold, disease severity/course and previous treatment.[16,33,52]

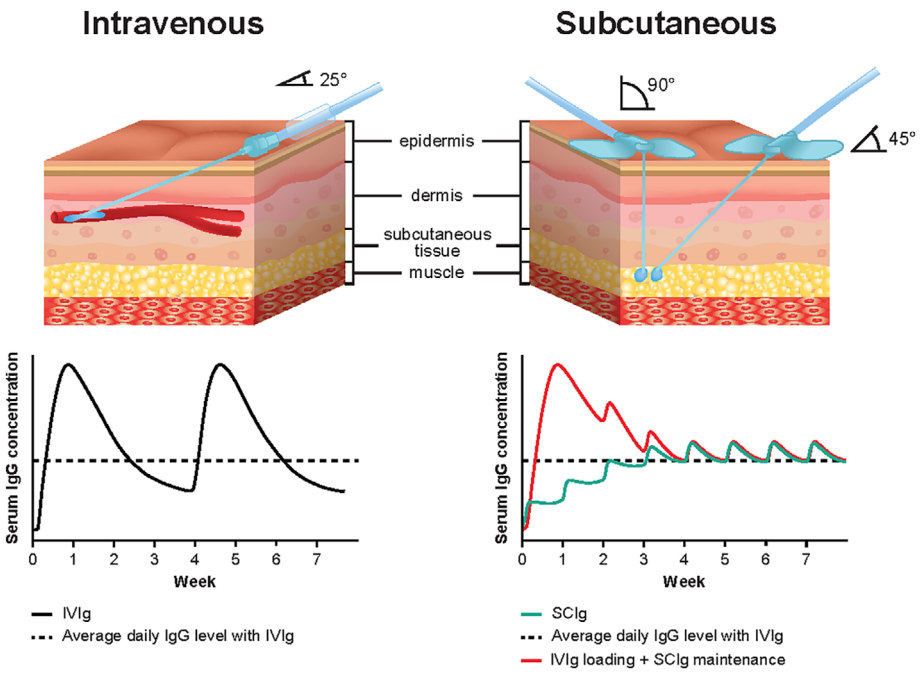

FIGURE 1 Schematic of intravenous vs subcutaneous infusions and the impact on IgG concentration. Dependent on infusion site location and patient preference, subcutaneous infusions can be conducted at a 90- or 45° angle. Red line indicates where IVIg dose is followed 1 wk later by SCIg maintenance doses

There are anecdotal reports of IVIg combination therapy with steroids during IgG dose tapering.[53,54] While there are no data to support the effectiveness of SCIg combination therapy with steroids, this approach might be a practical consideration for CIDP patients experiencing worsening or partial response while on SCIg monotherapy. Additional controlled studies are required to determine the optimal maintenance and dose-tapering strategies for IVIg and SCIg.

4.4 | Dose adjustments—Following clinical deterioration

In the case of clinical deterioration following transition to SCIg, the EU label (Summary of Product Characteristics [SmPC]) and US Prescribing Information (USPI) recommend increasing the dose to 0.4 g/kg bw/wk.[35,46] Following a relapse, patients may be more reluctant to remain on SCIg. Data suggest a good probability of recovery following up-titration with SCIg and can be cited to reassure patients.[33] For example, van Schaik et al. reported over 90% of patients who relapsed on 0.2 g/kg SCIg recovered to previous clinical levels when switched to 0.4 g/kg SCIg.[33] Up-titration of the SCIg dose can be a successful method to re-stabilize a patient following relapse as an alternative to using IVIg as rescue therapy.[33,46] As patients tend to show a preference for SCIg, they may prefer to remain on SCIg during a period of dose adjustment following a relapse rather than changing IgG treatment route. The USPI recommends reinitiating IVIg, while discontinuing SCIg, if CIDP symptoms worsen on 0.4 g/kg/wk.[35] Based on author experience, if a patient mildly worsens while on SCIg 0.4 g/kg/wk, dosage escalation to 0.5–0.6 g/kg/wk, although not rigorously studied, may be a practical approach with careful monitoring. Patients should always be assessed on a case-by-case basis to determine the best approach, and long-term maintenance therapy beyond 12–18 mo should be individualized based upon the patient's response and need for continued therapy.[35,46]

4.5 | Supporting patients with self-administration

To self-administer SCIg, patients should be adequately trained and monitored by a healthcare professional (HCP). Patients often report that learning self-administration is easy.[16] Discomfort with the technique can be an issue for some patients. SCIg (IgPro20) is available in either a vial (5, 10, 20, 50 mL) or more recently single-use pre-filled syringes (PFS) (5, 10, 20 mL [USA, EU, and Canada]).[35,45,46] As patients with CIDP are often elderly and/or can have muscle weakness in distal limbs, using PFS may be beneficial for patients with decreased dexterity, vision, or coordination.[1,55] Studies in other disease settings show that PFS can reduce preparation time, medication errors, and drug wastage and are often preferred by patients as a simplified self-administration method.[55]

SCIg infusion time is typically around 1 h.[16] It has been reported that patients tolerated volumes up to 50 mL per site and infusion rates up to 50 mL/h/site.[16] This is consistent with recommendations in the USPI, but the SmPC recommends an initial infusion rate of 20 mL/h/site and two further tolerated infusions up to 35 mL/h/site for device-assisted infusions. An increase in the infusion rate for successive infusions may be considered at the discretion of the patient and based on the HCP's judgement. The SmPC recommends infusion rates up to 120 mL/h/site for manual infusion.[35,46] SCIg infuson via an infusion pump has been the traditional method for IgG delivery. However, manual infusion (≤60 mL per injection site and flow rates of >60 mL/h per injection site for SCIg) is a simpler method that has been growing in popularity and is used successfully in patients with PID[56–59] and the benefits may be translatable to the CIDP population.

Setting patient expectations prior to initiation of SCIg therapy is important. Patients should be informed that mild to moderate local infusion-site reactions are a common side effect that improves over time.[35,46] Local infusion-site reactions can be alleviated by massage and the use of mild analgesics.[10] Watkins et al., provides a comprehensive list of strategies that patients and nurses can employ to mitigate local reactions.[60] Patients should consider rotating their infusion-site location, adjusting volume per site, needle gauge, and/or rate of infusion based on how they are tolerating infusions.[35,46] Changes to the infusion regimen or ancillary supplies should be done one at a time to allow assessment of each change. Once volume per site is optimized, the rate of infusion can be increased. Optimizing infusions will require adjustments over a period of time and with support from an HCP. Educating patients is extremely important during SCIg initiation and self-administration training and enables patients to better manage their treatment. Nursing support and good communication are essential for helping patients to successfully transition from IVIg to SCIg, along with patient factors such as motivation, ability to learn, dexterity, compliance, and caregiver availability.[60]

4.6 | Patient preference and QoL

SCIg may be a preferred route of IgG administration for many patients with CIDP due to its ease of use, safety profile, and patient independence.[61] Often, newly diagnosed patients with CIDP and those experiencing issues with their current treatment may be more receptive to SCIg, but all patients, whether new or established, should be made aware of their options with IgG therapy and the potential pros and cons associated with both IVIg and SCIg use. Table 3 provides examples of potential candidates who may prefer to remain on IVIg, and Table 4 provides example potential candidates for SCIg. These tables are intended to provide discussion points to consider with the patient.

Results from a systematic review indicate that SCIg may improve QoL over IVIg in patients with inflammatory neuropathies.[62] Many patients with CIDP have shown a preference for SCIg compared with their previous IVIg.[24,28,30,33,39] Patient preference for SCIg may be related to the convenience of self-administering at home, lower infusion volumes, fewer systemic AEs, and reduced treatment-related fluctuations (TRFs).[37,63] For example, in the recent van Schaik et al.

TABLE 3 Example CIDP candidates for IVIg

Potential IVIg candidate examples[a]	Considerations to discuss with patient
Patient lacking organizational skill or drive to self-administer	Some patients may be unwilling, or lack the skills, necessary to take on an element of their own disease management. Setting appropriate patient expectations when discussing SCIg is important to outline the responsibilities of self-administration and to help assess whether the patient would derive more benefit from an HCP-assisted mode of administration
Patient unable to self-administer due to poor dexterity, fear of needles or no reliable support network	Patients with poor manual dexterity or fear of needles may struggle with aspects of the self-administration technique (drawing solution from vial into syringe, etc.). A reliable caregiver (eg, spouse, family member, or friend) nearby to provide support or assist with the infusion can be considered if available. The use of a SCIg pre-filled syringe to simplify the process can also be an option. In the absence of the above options, remaining on IVIg may be a more appropriate plan
Patient preferring treatment in a clinic setting or administered by an HCP	Some patients may prefer a clinic setting for their infusions due to the confidence and relationships built with staff. IVIg has the advantage of access to laboratory testing at the time of initiating the IV line. There is also potentially less risk of dosing errors in treatment administered by an HCP and the reliance on an HCP to monitor for side effects
Patient familiarity and extensive history with IVIg	For established patients with CIDP, they may have received IVIg for a long time and feel comfortable with a therapy they know and trust. Patients may not get as much subjective benefit from SCIg compared with IVIg due to the route of administration and slower absorption. Physicians should periodically reassess the patient's perception of SCIg as the attributes which did not initially appeal may be viewed more favorably with changing patient circumstances
Patient preferring more infrequent infusions	Some patients may find the infrequent infusion schedule (and potentially fewer disease reminders) associated with IVIg every 3 or more weeks fits in better with their lifestyle. As above, periodic discussions on the most suitable mode of administration should take place to reflect changing circumstances
Low BMI patients requiring large IgG doses	Self-administration of large volumes of SCIg may be unappealing or challenging for low BMI patients who have less available subcutaneous tissue for infusions. Often a SCIg infusion regimen can be designed to accommodate these patients, but this may require a higher number of infusion sites

Abbreviation: BMI, body mass index.

[a]Table does not provide an exhaustive list of potential candidates, but rather highlights some of the considerations to factor in during discussions with patients.

TABLE 4 Example CIDP candidates for SCIg

Potential SCIg candidate examples[a]	Considerations to discuss with patient
Patient with venous access concerns	In patients requiring a port there is an added safety risk with infections and device maintenance. In most cases SCIg should be recommended rather than fitting a port
Patient experiencing wear-off effects between IVIg infusions	Reducing the interval between IVIg infusions can be attempted to minimize wear-off effects. However, weekly SCIg can be a practical solution to provide improved steady-state IgG levels and reduce TRFs
Patient experiencing intolerable side effects with IVIg	Some IVIg-related AEs can be managed with premedication. However, for most patients the frequency of systemic AEs is reduced with SCIg and premedication requirements are rare
Patient with scheduling and/or logistical issues attending infusion clinics	Those who live far away from their infusion facility or with demanding work/home life schedules may have options to try IVIg at home, although this still requires an HCP visit to conduct infusions. SCIg can be a practical alternative to ease logistical challenges
Patient desiring more independence and autonomy due to lifestyle	Once properly trained a patient can infuse SCIg in many locations including work, school, and while on vacation or travelling etc. The importance of good sterile technique and keeping detailed infusion records should be emphasized
Patient with comorbidities	IVIg is associated with some serious, but rare, side effects. SCIg may be considered as a preferred treatment to IVIg in patients with any existing conditions increasing their risk of renal dysfunction, TEEs, hemolysis, or aseptic meningitis. These conditions are warnings in the SCIg USPI, although their occurrence is rarer than in IVIg
Patient preferring to avoid risk of infection exposure during pandemics	In light of recent events with the COVID-19 pandemic, many patients may feel more comfortable conducting their infusions independently and at home to reduce their exposure risk and limit reliance on HCP resource—Although nurse follow-up is still required, this can be conducted via video calls or over the phone if necessary

[a]Table does not provide an exhaustive list of potential candidates, but rather highlights some of the considerations to factor in during discussions with patients.

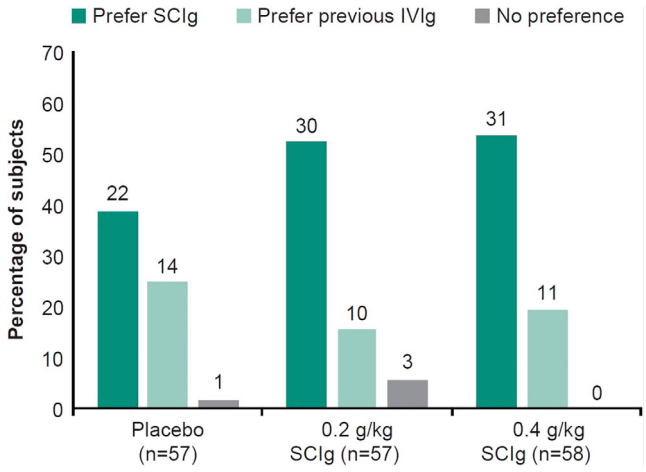

FIGURE 2 Subject preference for SCIg and IVIg. Not all subjects in the clinical trial responded to the preference questionnaire. Numbers above bars are actual numbers of subjects who responded

extension study, 82% of patients preferred SCIg to their previous IVIg citing greater independence, reduced administration time, and fewer side effects as the main reasons.[33] It can be noted that patients opting to transition to SCIg in published reports may have more reason to be unsatisfied with IVIg and, therefore, will experience a greater improvement in QoL after transitioning. In a treatment preference questionnaire, 53% of responders receiving SCIg preferred it over their previous IVIg treatment compared with 18% who preferred IVIg[16] (Figure 2). Consequently, physicians should thoroughly evaluate and discuss with patients before transitioning them between IgG therapies as some may need additional support with self-administration or have other reasons for preferring to remain on IVIg.[17]

4.7 | Long-term adherence

Although patients often prefer the convenience of home-based IgG administration, Ness et al. highlights that there is some variation in patient preference with regard to clinic versus home-based therapy.[38] Some patients may feel overwhelmed by the number of injections associated with SCIg, the idea of managing their own treatment or the loss of a regular HCP touchpoint; these patients may prefer treatment to be administered by a HCP.[37] A support program for patients opting to transition to SCIg is important to build confidence with self-administration for successful long-term adherence.[64] In one study, a nurse-led individualized program that included teaching sessions, written materials, and a clear care plan helped to successfully transition patients with neurological disorders from IVIg to SCIg. In this study, SCIg retention rates were 90% (n = 17/19) at 6 mo and 79% (n = 15/19) at 12 mo.[64] It is important to highlight to patients the importance of treatment adherence to maintain therapeutic IgG concentrations and to keep accurate records of each infusion. Nurses and pharmacists are also important in providing a continued touchpoint for patient support. Additional support can encompass areas such as patient education, refresher self-administration training, assessing treatment response in between clinic appointments, identifying treatment barriers, helping patients understand and manage local reactions,

monitoring adherence, and reporting back to the treating physician any issues.[60]

5 | SAFETY PROFILE

5.1 | Systemic adverse events

Similar to other plasma-derived IgG products marketed in the United States, SCIg carries a US FDA-mandated "black box" class warning for thrombosis.[35,37] IVIg is associated with rare but potentially serious AEs, such as thromboembolic events (TEEs), aseptic meningitis, hemolysis, and renal dysfunction.[65] Although less common, these serious AEs can also still occur with SCIg. IVIg is also associated with systemic AEs such as headache, nausea, and flu-like symptoms, which may be due to the high infusion volumes required and rapid rise in IgG concentration following infusion.[42,65] Many patients require premedication to tolerate IVIg infusions. In contrast, SCIg administration is associated with a lower rate of systemic AEs and less need for premedication.[33] The Racosta et al. meta-analysis demonstrated a 28% reduction in relative risk of moderate and / or systemic AEs with SCIg versus IVIg.[20] Van Schaik et al. reported that the rate of headaches was low for SCIg (7%) and this was maintained during the OLE study (5%).[16,33] In comparison, headaches associated with IVIg have been reported in other studies as ranging between 32% and 62% of patients.[11,66] Performing an early assessment of patient risk factors for IVIg-associated AEs can help determine if switching to SCIg would be beneficial.

5.2 | Local-site reactions

Local-site reactions tend to be the most common AE reported by patients receiving SCIg.[16,24,33,67] Local-site reactions are usually mild to moderate in intensity and have been reported to significantly decrease with subsequent infusions.[16] The decline in local-site reactions is potentially a result of improving patient self-administration technique and habituation to subcutaneous infusions. Local site reactions are rarely reported with IVIg infusions, although bruising can occur at the site of infusion.

5.3 | Venous access

Another important difference of SCIg is that it does not require venous access. The majority of patients with CIDP are over 60 y of age and may need treatment for many years.[68] The ability to establish peripheral venous access that remains viable throughout the infusion can become progressively more difficult, and a central venous line may need to be inserted, carrying additional risks.[69] SCIg should always be considered before resorting to a port. Eliminating the need for venous access with SCIg therapy may also provide more treatment flexibility as patients are able to self-administer at a variety of locations at their own convenience, which may be even more beneficial in the context of the COVID-19 pandemic.

6 | ECONOMIC IMPACT AND FUTURE OF IgG THERAPY IN CIDP

Studies comparing the economic burden of SCIg vs IVIg in CIDP report mixed results and have primarily been conducted in European settings.[70–72] In general, studies agree that home-based infusions vs hospital-based result in cost reductions irrespective of the route of administration.[19,71,72] The primary cost driver is often the product itself and, in turn, the dose requirement. However, comparisons are complicated by the indirect costs associated with site of care, HCP resource, and long-term requirement for hospitalizations due to AEs or other disease-related complications. In reality, it is often unclear which route of administration will prove most cost effective, as the slightly more expensive cost of the SCIg product can eventually be offset indirectly by associated infusion cost savings and reduce productivity loss for patients as a result of hospital/infusion-related absenteeism.[28,73]

Currently, only one 20% SCIg solution is approved for use in adult patients with CIDP,[35] but other 10%–20% SC formulations are in various phases of development. In addition, an ongoing trial is exploring the tolerability and safety of hyaluronidase facilitated SCIg (fSCIg) in CIDP (NCT02955355). This method utilizes 10% SCIg and hyaluronidase in a two-step infusion, which can theoretically deliver volumes greater than 700 mL compared with the recommended maximum of 50 mL per site with conventional SCIg.[35,74] fSCIg allows infusions at similar rates and volumes to IVIg, but with potential reductions in systemic AEs comparable with SCIg. Data on long-term safety and cost comparisons for fSCIg are lacking and there is limited evidence to suggest any differences in QoL between SCIg and fSCIg in either CIDP or other neuromuscular disorders.[75–77]

To date, the United States has the highest IgG usage per capita, followed by Canada, Australia, and some European countries.[78] Uptake of SCIg stands at 15% of total IgG use in the US market (of which currently 61% is used in PID).[78] The use of IgG in neurological indications is growing and is anticipated to continue with high-dose neurological indications, such as CIDP. Given the expanding IgG therapy options in CIDP and the high cost of treatment, exploring opportunities for cost minimization are important.

To conclude, there is a role for both IVIg and SCIg in CIDP maintenance therapy. The most appropriate route of administration should be individualized and will be determined by the patient. Ensuring patients are familiar with the benefits of each route is important to aid in treatment optimization and provide a better chance of long-term adherence and success.

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CONFLICT OF INTEREST

Mazen Dimachkie serves, or recently served, as a consultant for ArgenX, Catalyst, Cello, CSL Behring, EcoR1, Kezar, Momenta, NuFactor, Octapharma, RaPharma/UCB, RMS Medical, Sanofi Genzyme, Shire Takeda, Spark Therapeutics and UCB Biopharma. Dr. Dimachkie received grants from Alexion, Alnylam Pharmaceuticals, Amicus, Biomarin, Bristol-Myers Squibb, Catalyst, Corbus, CSL-Behring, FDA/OOPD, GlaxoSmithKline, Genentech, Grifols, Kezar, Mitsubishi Tanabe Pharma, MDA, NIH, Novartis, Octapharma, Orphazyme Ra Pharma/UCB, Sanofi Genzyme, Sarepta Therapeutics, Shire Takeda, Spark Therapeutics, UCB Biopharma, Viromed/Healixmith & TMA. Namita Goyal has received research support from Brainstorm Cell Therapeutics, Cytokinetics, Fulcrum, Kezar, Octapharma, Orion, Orphazyme. Dr. Goyal has served on Advisory Boards for Acceleron, Alexion, Argenx, Biogen, CSL Behring, Cytokinetics, MT Pharma, Sanofi Genzyme, Sarepta. In relation to these activities, she has received travel reimbursement and honoraria. She has also served on the speaker's bureau for CSL. The remaining authors have no conflicts of interest. Kazim Sheikh has received personal compensation for speaking engagements from CSL Behring and research/grant support from the Department of Defense (W81XWH-18-1-0422) and the National Institute of Neurological Disorders and Stroke (R21NS107961). Chafic Karam has consulted for Acceleron Pharma, Inc; Akcea Therapeutics; Alnylam Pharmaceuticals, Inc; Argenx; Biogen; CSL Behring; and Sanofi Genzyme. Dr Karam has received personal compensation for speaking engagements from Akcea Therapeutics; Alnylam Pharmaceuticals, Inc; CSL Behring; and Sanofi Genzyme and research/grant support from Akcea Therapeutics and Sanofi Genzyme.

ETHICAL PUBLICATION STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

DATA AVAILABILITY STATEMENT

All data included in this manuscript is publicly available. The authors will consider requests for additional data from genuine researchers on an individual basis.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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