REVIEW ARTICLE

Practical Aspects of Transitioning from Intravenous to Subcutaneous Immunoglobulin Therapy in Neuromuscular Disorders

Deepak Menon, Evelyn Sarpong, Vera Bril

ABSTRACT: Recent evidence shows that subcutaneous immunoglobulin (SCIG) is as efficacious as intravenous immunoglobulin (IVIG) and has a better safety profile and acceptance rate among patients with neuromuscular disorders who require maintenance IVIG treatment. Awareness of the practical aspects of patient selection, enrollment, dose calculation, administration, and follow-up would help physicians coordinate a smooth and seamless transition from IVIG to SCIG. SCIG is ideally offered to patients having intolerable side effects during IVIG or wearing-off effect and in those keen for treatment autonomy. The weekly dose of SCIG is calculated by multiplying the maintenance dose of IVIG by the dose adjustment factor and dividing by the interval between IVIG in weeks and is initiated 1 week after the last dose of IVIG. The physician places the order for the SCIG and the clinic nurse or the physician refers the patient to the home care nursing program for further education and training. The necessary supplies are dispatched to the patient who would also collect the SCIG from the transfusion center of the nearest hospital. The patient is educated on assembling and administering the infusion, and home visits are continued until the patient or caregiver is confident. Regular follow-up with the patient is maintained to assess treatment response and side effects if any. With a smooth transition, most patients have excellent tolerance to SCIG and in our experience seldom request switching back to IVIG. Transitioning patients from IVIG to SCIG offers several advantages and thus, in general, is preferable for multiple stakeholders.

RÉSUMÉ : Aspects pratiques du passage des IgIV aux IgSC dans le traitement des troubles neuromusculaires. D'après des données récentes, l'administration d'immunoglobulines par voie sous-cutanée (IgSC) est aussi efficace que l'administration d'immunoglobulines par voie intraveineuse (IgIV), tout en offrant un meilleur profil d'innocuité et un taux plus élevé d'acceptabilité chez les patients atteints de troubles neuromusculaires ayant besoin d'un traitement d'entretien par les IgIV. Le fait de connaître les aspects pratiques de la sélection des patients, de l'inscription, du calcul de la dose, de la voie d'administration et du suivi devrait faciliter la tâche des médecins dans le passage en douceur des IgIV aux IgSC. Ces dernières devraient, en principe, être réservées aux patients qui éprouvent des effets indésirables intolérables du traitement par les IgIV, qui connaissent une diminution de l'efficacité des médicaments ou qui tiennent vraiment à acquérir une certaine autonomie dans le traitement. On calcule la dose hebdomadaire d'IgSC en multipliant la dose d'entretien d'IgIV par le facteur d'adaptation de la dose, et en divisant le produit par le nombre de semaines entre les doses d'IgIV; l'administration des IgSC débute une semaine après celle de la dernière dose d'IgIV. Le médecin prescrit alors les doses d'IgSC, et l'infirmière ou l'infirmier de clinique ou le médecin dirige le patient vers le programme de soins infirmiers à domicile en vue d'une formation théorique et pratique sur le traitement. Les fournitures nécessaires sont remises au patient, qui devrait aussi se procurer les IgSC au centre de transfusion de l'hôpital le plus près de chez lui. Le patient reçoit une formation sur l'assemblage du matériel et l'administration des perfusions, et les visites à domicile se poursuivent jusqu'à ce que le patient ou l'aidant se sentent à l'aise dans cette nouvelle façon de faire. Il faut effectuer un suivi régulier des patients afin d'évaluer la réaction au traitement et la production possible d'effets indésirables. La tolérance aux IgSC est excellente chez la plupart des patients lorsque le passage se fait en douceur et, d'après l'expérience des auteurs, seul un petit nombre de malades demande à retourner au traitement par les IgIV. Le passage des IgIV aux IgSC offre plusieurs avantages aux patients et, de ce fait, se présente en général comme la formule à privilégier à de nombreux égards.

Keywords: Intravenous immunoglobulin, Subcutaneous immunoglobulin, Therapy, Transition, Neuromuscular

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Introduction

High-quality evidence demonstrates the efficacy of intravenous immunoglobulin (IVIG) in patients with autoimmune or inflammatory neuromuscular disorders.[1,2] Synthesized from pooled human plasma obtained from a large number of healthy donors, the main component of IVIG is intact Immunoglobulin G (IgG) molecules and is marketed for intravenous (IV) infusions.[3] Several immunomodulatory mechanisms for IVIG including actions on B and T cells, macrophages, complement, and cytokines have been proposed.[4] The treatment of chronic

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neuromuscular disorders such as chronic inflammatory demyelinating polyneuropathy (CIDP) and myasthenia gravis (MG) require long-term immunomodulatory maintenance therapy. However, despite being efficacious, there are several practical limitations that make long-term IVIG maintenance less attractive both from the patient and health care delivery perspective. In this regard, subcutaneous immunoglobulin (SCIG) has several advantages over IVIG. Although most data are on primary immunodeficiency syndromes, recent meta-analysis and the results of the PATH study which was a double-blind, placebo-controlled trial have shown SCIG to be as efficacious as IVIG with a significantly better safety profile in CIDP, and similar outcomes have been noted with multifocal motor neuropathy with conduction block and MG.[5–10] Based on these evidence, SCIG has been approved for the maintenance treatment for CIDP. In this review, we discuss the practical aspects of transitioning a neuromuscular patient from IVIG to SCIG therapy. We also highlight the workflow in our unit, which is essential for a smooth and seamless transition from IVIG to SCIG.

Difference in Formulations and Pharmacokinetics between IVIG and SCIG

IVIG is available as 50 mg/ml (5%) or 100 mg/ml (10%) formulations, while SCIG is available currently in 10% and 20% concentrations stabilized with L-proline. Generally, the IV and subcutaneous formulations cannot be interchanged though there are exceptions with certain brands. After IVIG infusion, there is an initial rapid rise in the first day followed by decline of immunoglobulin (Ig) levels over the first 3 days to 50%, and further slow decline with a half-life of around 22 days. With IVIG therapy, there is a significant fluctuation of serum Ig levels, and a wearing-off effect prior to the next infusion is reported by many patients.[8,11] SCIG, on the other hand, is characterized by a slow, steady absorption from the subcutaneous space and the lymphatic system, producing lower peak levels, but higher trough levels and a steady serum concentration without the major fluctuations in serum Ig levels observed with IV administration.

Advantages and Disadvantages of SCIG over IVIG

The rapid rise of serum Igs, increased serum viscosity, and complement activation are suspected to be responsible for most of the side effects of IVIG.[4] With a lower rate of increase, reduced peak serum levels and a steady state, SCIG has significantly lower risk of adverse reactions.[8,12–14] Moreover, a typical maintenance dosage of IVIG consists of 1g/kg every 3 to 4 weeks infused over 6 to 8 h in a hospital day unit, while in the case of SCIG administration amounts to one or two infusions per week averaging 1.5 h per infusion at the patient's convenience. During SCIG infusion, the patient can continue with their other activities and this route affords much greater flexibility.[15] Although the cost of SCIG may be slightly higher than IVIG, budget impact models show that the overall health care system cost with SCIG is significantly lower due to fewer hospital visits and shorter nursing time required for infusion.[16,17] Equally importantly, several studies show improved patient satisfaction and quality of life on switching from IVIG to SCIG and SCIG scored better when compared to home-based IVIG as well.[18–20] Table 1 summarizes some of the main advantages and disadvantages of SCIG.

Table 1: Summary of the main advantages and disadvantages of SCIG over IVIG

SCIG
Advantages
Does not require vascular access and hence obviates need for hospital day unit admissions
Adverse reactions are rare and tend to be milder
Self-administered with 3-month supplies allowing freedom to travel and hence increased patient convenience and satisfaction[22,23]
Reduced health care costs
Disadvantages
More frequent treatments and needle pricks
Mostly patient-driven, requires training, competency, and family support
Self-administration challenging for patients with hand weakness and impaired dexterity
Contraindicated in patients on anticoagulation and bleeding diathesis[4]
Infusion site reactions, but usually mild and tolerated well[9]

SCIG = subcutaneous immunoglobulin.

Selecting the Patient

SCIG is a treatment option for any patient with a neuromuscular disorder for whom IVIG maintenance treatment is indicated. Although there is some evidence for its direct use in mild to moderate exacerbations in MG and also for as first-line therapy in treatment naïve patients with CIDP, the evidence for initial SCIG in acute situations is limited, and considering its pharmacokinetic profile, we suggest IVIG be used first in most situations.[21,14] We seldom initiate a patient on SCIG and offer transition to SCIG in those patients who respond well to IVIG and are stable on Ig therapy, and for those on IVIG with intolerable side effects or wearing-off with symptoms re-emerging before the next dose. It is necessary to counsel the patient about the advantages and disadvantages of SCIG, and this therapy is better offered to patients who are comfortable with handling the instructions for self-infusion, who are keen for autonomy, and who do not have a needle phobia. Since anticoagulation and bleeding diathesis are contraindications to SCIG, patients with these conditions are not selected for this therapy.

Patient Counseling

In-depth patient counseling is vital for compliance. Patients should have clear explanations about the reasons, advantages and disadvantages of transitioning, where it can be done, how long it takes, where and how to inject, how to procure the supplies, people involved in treatment, and contact numbers and emails for support to respond to any concerns that arise. Figure 1 shows the workflow in our unit for transferring a patient from IVIG to SCIG.

Dose Calculation

Most of the data on pharmacokinetics and dose conversions involving SCIG are from studies in primary immunodeficiency

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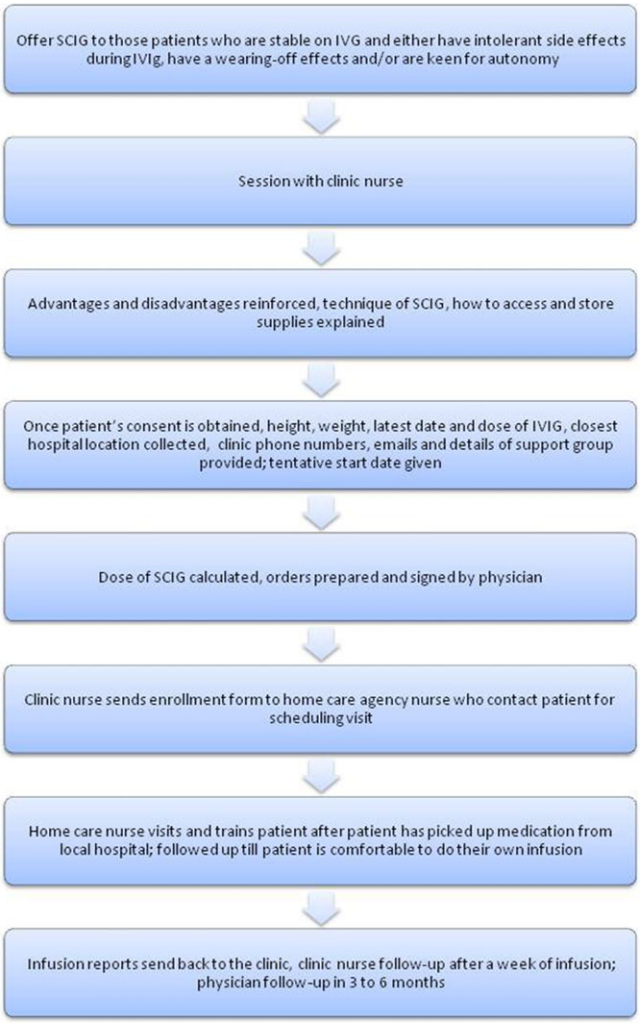

Figure 1: *Flow chart depicting the workflow in our clinic in transitioning a patient from IVIG to SCIG.*

diseases, and recommendations have been extrapolated for neurological indications. The differences in the pharmacokinetics mean that at equivalent doses, the peak serum IgG levels after weekly SCIG are 31% lower and the trough levels are 10%–20% higher compared to monthly IVIG, while the bioavailability calculated by the area under the serum concentration–time curve (area under curve, AUC) is lower.[20,21] Based on pharmacokinetic studies, to ensure non-inferiority as far as the bioavailability was concerned, a mean dose adjustment of 137% to 153% of the IVIG doses was recommended for different 20% SCIG formulations.[20,22,23] Subsequently, the US prescribing authorities recommended that patients switching from IVIG to 20% SCIG are treated with at least 1.37 times their previous IVIG dose.[24] On the other hand, clinical trials from Europe have based their comparisons of efficacy on the IgG trough levels. Since, even with an equivalent dose conversion, the IgG trough levels are higher with SCIG, the European recommendations are for a 1:1 dose adjustment when switching from IVIG to 20% SCIG.[25–27] The Canadian Blood Services also recommend an equivalent dose switch followed by titration to achieve an IgG trough level of at least the lower limit of the age-specific serum IgG reference range, or as needed to achieve clinical effectiveness.[28] Several trials in primary immunodeficiency found comparable results between the two dose adjustment methods, but there were certain factors such as reduced rate of missed work or school days and length of hospital stay caused by infection that were found to favor the higher conversion coefficient.[27,29,30] From the neurological perspective, it remains uncertain whether the treatment response depends on the IgG trough or peak levels or the total bioavailability and which pharmacokinetic parameter determines the treatment response. In the PATH extension study, a higher dose of SCIG was associated with lesser relapse of CIDP. To protect against underdosing, especially during the initial switch from IVIG to SCIG, we adjust the dose by a factor (DAF) of 1.37, and further adjustments are made based on the clinical response.

The weekly dose of SCIG in grams is therefore calculated with the following formula:

Weekly dose of SCIG (g) = Maintenance dose of IVIG (g) x DAF/number of weeks between IVIG doses. Then, the calculated dose in grams is multiplied by a factor of 5 for 20% SCIG formulations or by 6.25 for 16% formulations giving the total volume of SCIG in milliliters to be infused in 1 week. This can be divided into 2 or 3 doses per week. In the few patients who may be receiving 2 g/kg of IVIG every 3 or 4 weeks as maintenance therapy, a 1:1 replacement is suggested, since higher SCIG doses raise concerns about increased dose-related side effects. IgG levels are used by certain centers to guide further dose adjustments, but the reliability of these levels in any given patient is open to question, and we suggest using the patient's clinical status when deciding on further dose modifications.[31,32] On rare occasions when a patient is directly initiated on SCIG, the dose is calculated after determining the dose of IVIG required based on the patient's ideal body weight.

Table 2: Components of the SCIG infusion system

SCIG vials
Antiseptic wipes or alcohol swabs to sterilize preparation surface, immunoglobulin bottles
Mini-spike dispensing pin or 18-gauge needle for extracting product from bottles
Needle administration sets 2–4 needles per patient (available in 6-, 9-, and 12-mm sizes)
Manual infusion pump
Occlusive dressing to secure needle administration set
Sharps container standard plastic transportable hazard bin
Logbook used to log infusions and keep immunoglobulin tracing numbers

SCIG = subcutaneous immunoglobulin; mm = millimeters.

Supplies Needed for SCIG Infusion

Supplies for SCIG infusion include a mechanical infusion pump; needle administration sets (6–12 mm size), and dispensing pins/needles for extracting SCIG; an infusion rate regulator, which enables the patient to use a dial to regulate flow rate; a 60-ml syringe; a dispensing pin (spike); occlusive dressing or tape; alcohol swabs; immunoglobulin vials; a sharps container; and a patient diary or logbook (Table 2, Figures 2 and 3).

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Figure 2: *Components of the subcutaneous infusion system: (A) vial containing SCIG, (B) spike used to draw SCIG into the syringe from the vial, (C) ambulatory infusion pump, (D) 60-ml syringe with the spike attached to draw SCIG from the vial, (E) flow rate controllers, (F) ambulatory infusion pump with a syringe attached, (G) infusion tubing with multi-needle set (H) magnified view of the 6-mm subcutaneous needle, (I) occlusive dressing, and (J) sharp container.*

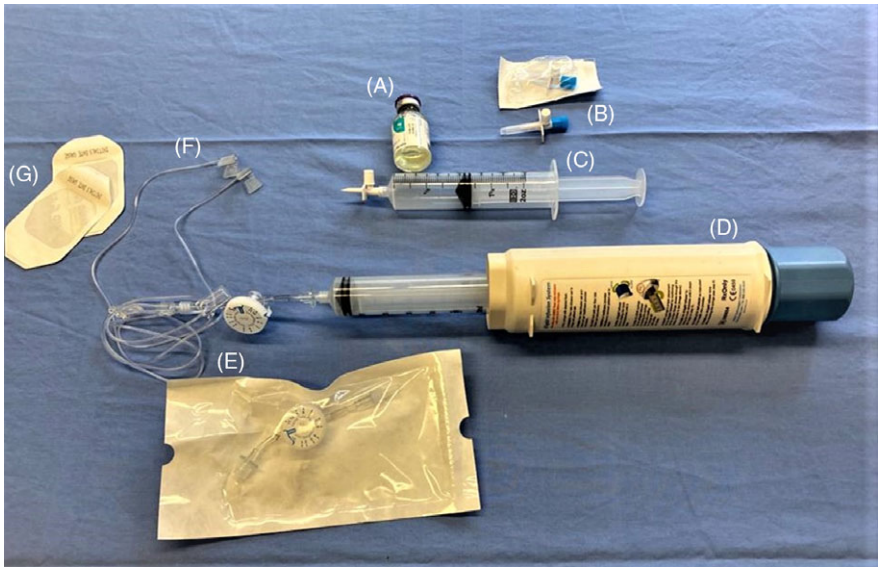

Figure 3: *SCIG infusion system. (A) vial containing SCIG, (B) spike used to draw SCIG from vial into the syringe, (C) syringe with spike attached, (D) infusion pump with a syringe attached, (E) flow controller attached to the syringe at one end and tubing at the other, (F) tubing with the multi-needle unit, (G) occlusive adhesive dressings.*

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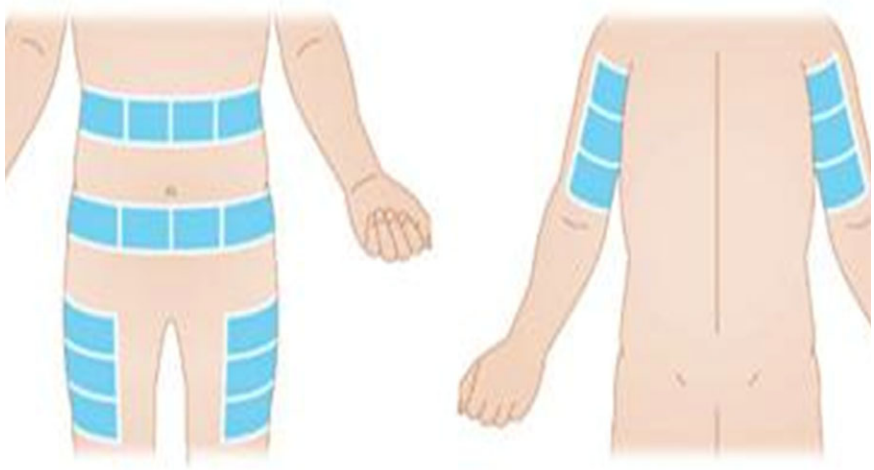

Figure 4: *Diagram depicting the ideal sites for needle placement for SCIG infusion.*

Technique of Infusion

The SCIG dose is initiated 1 week after the last dose of IVIG. The site of infusion can be abdomen, thighs, lower back, or upper arms, and most patients prefer the abdomen or thighs. (Figure 4) Multiple sites can be infused simultaneously if needed, but the sites should be at least 2 inches apart. The desired amount of SCIG is drawn into the 60-ml syringe and is fixed into the infusion pump, connected to the regulator, tubing, and the subcutaneous needle. The needle is selected based on the thickness of the subcutaneous fat and ranges from 6 to 12 mm, much smaller than IV needles. After the site is cleaned thoroughly with an alcohol swab, the skin with the subcutaneous fat is pinched with one hand and the needle inserted with the other and fixed in place with an occlusive dressing. The regulator can then be set for a rate of infusion which can be started at about 20 ml/h and later increased to 25–30 ml/h. The optimal volume of 20–30 ml per site, but this can be increased gradually up to 40–50 ml depending on patient tolerance. In general, for a smooth and successful transition, a gradual escalation in dose and number of sites is advised. The patient is advised to note the details of the infusion in the logbook, including any adverse reactions. After the infusion, the pump is cleaned and stored, and the needles and tubing discarded in a suitable sharps container.

Home Care Nursing Support Program

Each manufacturer of SCIG has established a home support program providing nursing services for this therapy. Once the distributer's nursing support group receives the enrollment forms, they contact the patient to schedule a home visit which is made after confirming that patient has all the necessary supplies. The components for the infusion system are dispatched by the respective manufacturer to the patient's address, while the SCIG is collected by the patient or caregiver from their closest blood bank, to which the dose and orders for SCIG have been put in by the clinic nurse. The clinic nurse coordinates the visit and contacts both the patient and the home visit nurse. During the visit, the home care nurse trains the patient or care giver on how to prepare the infusion, choose the infusion site, insert and fix the needle, discard the sharps, and maintain the logbook. Generally, four sessions of training and infusion will be supervised by the home visit nurse unless the patient desires further sessions. SCIG is always ordered by the clinic nurse for the patient to pick up from their local hospital blood bank. The home nurse sends infusion reports to the clinic and does follow-up visits with the patient at regular intervals. In those clinical settings where the services of a dedicated clinic nurse are not available, the physician introduces the transition, performs the dose calculation of SCIG, orders at the most convenient blood bank for the patient, and introduces the home support program to the patient. The home support program nurse then fully trains the patient and also may order further SCIG doses, depending on the specific SCIG.

Potential Adverse Effects and Comparison with IVIG

The adverse effects with immunoglobulin treatment can be immediate such as flu-like symptoms (80%), dermatological (6%), and rarely hypotension and transfusion associated lung injury; or delayed which include thrombotic events such as stroke or myocardial infarction (MI) (1%), aseptic meningitis (0.6%–1%), hemolysis (1.6%), and rarely renal dysfunction.[33] The different pharmacokinetic properties and the slow rate of absorption mean that the chances of these systemic adverse effects are significantly lower with SCIG. The meta-analysis comparing IVIG and SCIG in patients with primary immunodeficiencies clearly showed a better safety profile for SCIG with an odds ratio of adverse effects of 0.5 compared to IVIG.[32] Another meta-analysis comparing these two agents in inflammatory neuropathies found a relative risk reduction by 28% in moderate and/ or systemic adverse effects with SCIG.[6] The frequency of adverse effects in the SCIG group in neuropathies was 5% and might be slightly higher compared to other patient populations with reported rates of 0%–3%, since the dose of SCIG tends to be higher for chronic neuropathies.[6] The most common adverse effects of SCIG are local infusion site reactions which include itching, burning sensation, leakage from the infusion site, and mild redness and/ or swelling which usually subsides over 12 to 24 h. There is a wide range in the reported incidence of local adverse reactions from 0.003 events /infusion to 0.58 events / infusion, and this variability may be related to differences in

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reporting and recording.[34,35] The intensity of local reactions tends to subside with subsequent infusions and seldom leads to discontinuation of treatment. Starting with low volumes and a slow infusion rate with gradual escalation, use of appropriate size needles and the use of ice packs after infusions can help to relieve the majority of local reactions.[33]

Transitioning Back to IVIG

In general, few patients request return to IVIG after having been on SCIG. Patients' attitudes and personality traits can also influence this decision.[36,37] Younger people who are actively employed and desire flexibility in their life style and who are more stable and self-confident and less susceptible to psychological stress prefer SCIG.[37] Some patients find the increased treatment frequency and responsibility of self-treatment to be overwhelming and request switching to IVIG therapy.[15] A lack of information about the benefits, misconceptions about the technical demands of self-infusions, and a paradoxical perception of "lack of freedom" could be other considerations. Despite being on SCIG for 12 months, about 20%–30% of patients do not show a clear preference for SCIG.[38,39] Some other reasons for returning to IVIG include clinical worsening or perceived lack of benefit on switching from IVIG to SCIG and infusion site reactions. While there is no data on the dosage regimen for switching back to IVIG, a logical recommendation would be to return to the previous dose of IVIG followed by further titration based on clinical response.

Future Trends

The volume of SCIG that can be infused at a single site is a limiting factor which necessitates frequent infusions or the use of multiple needle punctures and infusion sites. Use of recombinant human hyaluronidase (rHuPH20) with 10% SCIG – also called facilitated SCIG (fSCIG) – may help overcome the volume issue as this form of SCIG breaks down the subcutaneous extracellular matrix and facilitates absorption and thus allows infusions of larger volumes and better bioavailability. This affords infusion volumes of up to 600 ml with rates of infusion titrated up to 240 ml/h. This therapy has been approved for primary immunodeficiency diseases, and a phase III randomized controlled study is underway to examine the efficacy, safety, and tolerability of fSCIG in patients with CIDP.[36]

Conclusion

Transitioning patients from IVIG to SCIG offers several advantages in terms of fewer side effects, better quality of life, increased patient independence, and lower health care costs. Therefore, it is generally advantageous for multiple stakeholders to switch patients from IVIG to SCIG. Appropriate patient selection, fulsome patient counseling, and a collective effort between the physician, clinic nurse, and home visit nurse all ensure a smooth and successful transition from IVIG to SCIG.

Disclosures

The authors have no conflicts of interest to declare.

Statement of Authorship

DM was involved in reviewing literature and drafting and editing the manuscript; ES was involved in review of literature and editing the manuscript; and VB was involved in concept and design, critically revising, and final approval of manuscript.

References

1. Patwa HS, Chaudhry V, Katzberg H, Rae-Grant AD, So YT. Evidence-based guideline: intravenous immunoglobulin in the treatment of neuromuscular disorders: report of the therapeutics and technology assessment subcommittee of the American Academy of Neurology. Neurology. 2012;78:1009–15.
2. Perez EE, Orange JS, Bonilla F, et al. Update on the use of immunoglobulin in human disease: a review of evidence. J Allergy Clin Immunol. 2017;139:S1–46.
3. Barahona Afonso AF, João CMP. The production processes and biological effects of intravenous immunoglobulin. Biomolecules. 2016;6:15.
4. Jacob S, Rajabally YA. Current proposed mechanisms of action of intravenous immunoglobulins in inflammatory neuropathies. Curr Neuropharmacol. 2009;7:337–42.
5. Alcantara M, Sarpong E, Barnett C, Katzberg H, Bril V. Chronic immunoglobulin maintenance therapy in myasthenia gravis. Eur J Neurol. 2021;28:639–46.
6. Racosta JM, Sposato LA, Kimpinski K. Subcutaneous versus intravenous immunoglobulin for chronic autoimmune neuropathies: a meta-analysis. Muscle Nerve. 2017;55:802–9.
7. Bourque PR, Pringle CE, Cameron W, Cowan J, Chardon JW. Subcutaneous immunoglobulin therapy in the chronic management of myasthenia gravis: a retrospective cohort study. PLoS One. 2016;11:e0159993.
8. Salameh JS, Deeb W, Burawski L, Wright S, Souayah N. Safety and efficacy of subcutaneous immunoglobulin in the treatment of neuromuscular disorders. J Clin Neuromuscul Dis. 2016;17:110–9.
9. van Schaik IN, Mielke O, Bril V, et al. Long-term safety and efficacy of subcutaneous immunoglobulin IgPro20 in CIDP. Neurol Neuroimmunol Neuroinflammation. 2019;6:e590.
10. van Schaik IN, Bril V, van Geloven N, et al. Subcutaneous immunoglobulin for maintenance treatment in chronic inflammatory demyelinating polyneuropathy (PATH): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Neurol. 2018;17:35–46.
11. Rojavin MA, Hubsch A, Lawo J-P. Quantitative evidence of wear-off effect at the end of the intravenous IgG (IVIG) dosing cycle in primary immunodeficiency. J Clin Immunol. 2016;36:210–9.
12. Geng B, Piracha F, Rashid H, Rigas M. Intravenous versus subcutaneous immunoglobulin in primary immunodeficiency: real world evaluation of safety efficacy and patient perceptions. J Clin Cell Immunol. 2020;11:589.
13. Berger M. Subcutaneous IgG in neurologic diseases. Immunotherapy. 2013;6:71–83.
14. Markvardsen LH, Sindrup SH, Christiansen I, et al. Subcutaneous immunoglobulin as first-line therapy in treatment-naive patients with chronic inflammatory demyelinating polyneuropathy: randomized controlled trial study. Eur J Neurol. 2017;24:412–8.
15. Rasutis VM, Katzberg HD, Bril V. High-dose subcutaneous immunoglobulin in patients with multifocal motor neuropathy: a nursing perspective. J Infus Nurs Off Publ Infus Nurses Soc. 2017;40:305–12.
16. Martin A, Lavoie L, Goetghebeur M, Schellenberg R. Economic benefits of subcutaneous rapid push versus intravenous immunoglobulin infusion therapy in adult patients with primary immune deficiency. Transfus Med Oxf Engl. 2013;23:55–60.

https://doi.org/10.1017/cjn.2021.56 Published online by Cambridge University Press

17. Vaughan LJ. Managing cost of care and healthcare utilization in patients using immunoglobulin agents. Am J Manag Care. 2019; 25:S105–11.
18. Bienvenu B, Cozon G, Hoarau C, et al. Does the route of immunoglobin replacement therapy impact quality of life and satisfaction in patients with primary immunodeficiency? Insights from the French cohort "Visages". Orphanet J Rare Dis. 2016;11:83.
19. Hadden RDM, Marreno F. Switch from intravenous to subcutaneous immunoglobulin in CIDP and MMN: improved tolerability and patient satisfaction. Ther Adv Neurol Disord. 2015;8:14–9.
20. Cocito D, Peci E, Lauria Pinter G, et al. Feasibility of switching from intravenous to subcutaneous immunoglobulin in CIDP: PATH trial and clinical experience. Clin Neurophysiol. 2019; 130:e12.
21. Beecher G, Anderson D, Siddiqi ZA. Subcutaneous immunoglobulin in myasthenia gravis exacerbation: a prospective, open-label trial. Neurology. 2017;89:1135–41.
22. Berger M, Rojavin M, Kiessling P, Zenker O. Pharmacokinetics of subcutaneous immunoglobulin and their use in dosing of replacement therapy in patients with primary immunodeficiencies. Clin Immunol. 2011;139:133–41.
23. Wasserman RL, Melamed I, Nelson RP, et al. Pharmacokinetics of subcutaneous IgPro20 in patients with primary immunodeficiency. Clin Pharmacokinet. 2011;50:405–14.
24. Berger M, Ochs H. Conversion from intravenous to subcutaneous immunolgobulin therapy: relationship between dose, serum trough IgG concentration and infection rate in patients with primary immune deficiency diseases. J Allergy Clin Immunol. 2006;117:S109.
25. Krishnarajah G, Lehmann J-YK, Ellman B, et al. Evaluating dose ratio of subcutaneous to intravenous immunoglobulin therapy among patients with primary immunodeficiency disease switching to 20% subcutaneous immunoglobulin therapy. Am J Manag Care. 2016;22:S475–81.
26. Kobrynski L. Subcutaneous immunoglobulin therapy: a new option for patients with primary immunodeficiency diseases. Biol Targets Ther. 2012;6:277–87.
27. Gardulf A, Nicolay U, Asensio O, et al. Rapid subcutaneous IgG replacement therapy is effective and safe in children and adults with primary immunodeficiencies–a prospective, multi-national study. J Clin Immunol. 2006;26:177–85.
28. Fadeyi M, Tran T. Calculating the dose of subcutaneous immunoglobulin for primary immunodeficiency disease in patients switched from intravenous to subcutaneous immunoglobulin without the use of a dose-adjustment coefficient. Pharm Ther. 2013;38:768–70.
29. Immune Globulin Products [Internet]. Professional Education; 2016. Available at: https://professionaleducation.blood.ca/en/immune-globulin-products; accessed January 2021.
30. Haddad E, Berger M, Wang ECY, Jones CA, Bexon M, Baggish JS. Higher doses of subcutaneous igg reduce resource utilization in patients with primary immunodeficiency. J Clin Immunol. 2012;32:281–9.
31. Orange JS, Belohradsky BH, Berger M, et al. Evaluation of correlation between dose and clinical outcomes in subcutaneous immunoglobulin replacement therapy. Clin Exp Immunol. 2012;169:172–81.
32. Bonilla FA. Pharmacokinetics of immunoglobulin administered via intravenous or subcutaneous routes. Immunol Allergy Clin North Am. 2008;28:803–19.
33. Guo Y, Tian X, Wang X, Xiao Z. Adverse effects of immunoglobulin therapy. Front Immunol. 2018;9:1299.
34. Shabaninejad H, Asgharzadeh A, Rezaei N, Rezapoor A. A comparative study of intravenous immunoglobulin and subcutaneous immunoglobulin in adult patients with primary immunodeficiency diseases: a systematic review and meta-analysis. Expert Rev Clin Immunol. 2016;12:595–602.
35. Ballow M, Wasserman RL, Jolles S, Chapel H, Berger M, Misbah SA. Assessment of local adverse reactions to subcutaneous immunoglobulin (SCIG) in clinical trials. J Clin Immunol. 2017;37:517–8.
36. Baxalta now part of Shire. A Phase III Study to Evaluate the Efficacy, Safety, and Tolerability of Immune Globulin Infusion 10% (Human) With Recombinant Human Hyaluronidase (HYQVIA/HyQvia) and Immune Globulin Infusion (Human), 10% (GAMMAGARD LIQUID/KIOVIG) for the Treatment of Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP). clinicaltrials.gov; 2020 [Report No.: NCT02549170. Available at: https://clinicaltrials.gov/ct2/show/NCT02549170; accessed January 2021.
37. Kittner JM, Grimbacher B, Wulff W, Jäger B, Schmidt RE. Patients' attitude to subcutaneous immunoglobulin substitution as home therapy. J Clin Immunol. 2006;26:400–5.
38. Jiang F, Torgerson TR, Ayars AG. Health-related quality of life in patients with primary immunodeficiency disease. Allergy Asthma Clin Immunol. 2015;11:27.

https://doi.org/10.1017/cjn.2021.56 Published online by Cambridge University Press