Patient Preference and Adherence

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REVIEW

Patient Preferences for Faster Home-Based Subcutaneous Immunoglobulin Infusion Therapy and the Effect on Adverse Events

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Abstract: Patients have expressed a preference for home-based subcutaneous immunoglobulin infusion therapy, often citing the time savings from not having to commute, as well as the flexible scheduling that home-based treatment provides. In this review of evidence, the opportunity to decrease time spent during infusions is explored, as well as the contrast between subcutaneous and intravenous infusion therapy. How decisions are made is also explored. Stakeholders include patients, their caregivers, and medical professionals supervising their care. Costs associated with various treatment options have been explored in the literature, in some depth. One element of cost that is often omitted, however, is the cost of time to patients and caregivers. A conclusion that there is a substantial opportunity to save patient and caregiver time is warranted. There is an opportunity to improve infusion protocols using existing devices. Evidence suggests that the mean savings per infusion is 38.94 minutes with optimized infusion protocols, saving more than one and one-half days of waking hours over the course of a year. More research in this domain is warranted.

Keywords: SCIG, PIDD, home, adverse events, flow rates, patient preferences

Introduction

Subcutaneous immunoglobulin (SCIg) therapy has emerged as a highly effective treatment option for patients with primary immunodeficiency disorders.[1] SCIg therapy involves periodic infusions of immunoglobulin (Ig) into subcutaneous tissue, where it replaces deficient or absent antibodies in individuals with primary immunodeficiency disorders. The efficacy of SCIg therapy has been well-established in several clinical trials.[2–4] These trials have shown that it can prevent infections,[5] reduce infection frequency and severity, and improve a patient's quality of life.[6] Due to its convenience, flexibility in dosing, and reduced systemic side effects compared to intravenous immunoglobulin (IVIg) therapy, SCIg has become increasingly popular among patients and clinicians managing their care.

Despite SCIg therapy benefits, there has been historical concern about potential adverse events, including concerns associated with increasing SCIg infusion flow rates. However, recent studies suggest that increasing SCIg therapy flow rate does not necessarily increase adverse event risk. This has important implications for physicians using SCIg therapy in their practice, because a downward adjustment of SCIg therapy flow rate may do little or nothing with respect to minimizing adverse event risk. Moreover, longer infusions are costly to patients in terms of treatment time.

This paper reviews evidence regarding the relationship between SCIg flow rates and adverse events, with particular focus on SCIg therapy efficacy and safety in patients with primary immunodeficiency disorders. SCIg and IVIg therapies can effectively manage a broad range of disorders, including chronic inflammatory demyelinating polyneuropathy (CIDP), multifocal motor neuropathy (MMN), and diverse autoimmune neuromuscular conditions.[7,8] Nonetheless, a detailed review of their use in these disease states lies beyond the scope of this paper. Instead, this paper concentrates

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on the time-saving and cost-reducing advantages that non-facilitated SCIg therapy can provide to patients with primary immunodeficiency disease (PIDD).

The First Choice: SCIg or IVIg: Who Chooses? How and Why?

Immunoglobulin replacement therapy is a common treatment used to manage primary immunodeficiency disorders (PIDDs). Two forms of this therapy, intravenous immunoglobulin (IVIg) and subcutaneous immunoglobulin (SCIg), are highly effective in replacing deficient or absent antibodies in the body. Whereas both treatments achieve the same goal, there are key differences.

The primary and most obvious difference between IVIg and SCIg is administration method. IVIg is delivered intravenously; the immunoglobulin solution is injected directly into a vein through a catheter or needle. In contrast, SCIg is delivered subcutaneously; the immunoglobulin solution is injected under the skin using a small needle or needles, often in the abdomen, or sometimes in the thigh. Another difference is the frequency of administration. With IVIg, the immunoglobulin solution is injected every 3–4 weeks, while in SCIg the solution is typically delivered once a week or every two weeks. This difference provides a more consistent level of immunoglobulin in the body with SCIg. This makes SCIg a preferred option for some patients.

IVIg infusions can take several hours to complete, while SCIg infusions can sometimes be completed in a few minutes. Adverse events associated with IVIg and SCIg can also differ.[2] IVIg has a higher risk of systemic adverse events, such as headache, fever, nausea, anaphylaxis, and thrombotic events. SCIg, in contrast, has a higher risk of local adverse events such as redness, swelling, and pain at the injection site. Another difference is that SCIg can be administered at home by the patient or their caregiver, whereas IVIg is typically administered in a hospital or infusion center.[6]

There are several factors that physicians consider when determining whether IVIg or SCIg therapy is more suitable for a particular patient. These factors include:

1. Patient's medical history: A patient's medical history and any pre-existing conditions may influence the choice of therapy. For instance, patients with a history of thrombotic events may be better suited for SCIg therapy due to its lower risk of systemic adverse events such as thrombosis.
2. Frequency and duration of treatment: The frequency and duration of treatment can play a role in determining the optimal therapy. SCIg is administered more frequently than IVIg. This can be beneficial for patients requiring consistent immunoglobulin levels.
3. Route of administration: The route of administration can also be a decisive factor in selecting the optimal therapy. Patients preferring to receive home treatment and patients who have difficulty traveling to an infusion center may be better suited for SCIg therapy. SCIg therapy is often administered at home by the patient or their caregiver. Home-based IVIg therapy is not as common.
4. Adverse event profile: The adverse event profile of each therapy can influence treatment choice. Patients who have experienced adverse events with IVIg therapy may be better suited for SCIg therapy, because it has a lower risk of systemic adverse events.
5. Cost: The cost of treatment is also a consideration. IVIg therapy is typically more expensive than SCIg therapy. This may be a deciding factor, especially for patients with limited financial resources.[9]

Patient preference for SCIg therapy is a significant factor driving the switch from IVIg to SCIg. One study found that younger patients tend to prefer SCIg and older patients were more likely to opt for IVIg therapy.[10] This may be related to their history of IVIg therapy and a reluctance to change a method that has worked for them in the past. During a study where the intent was to shield patients from Covid-19 infection, 41 patients aged 19 to 88 were switched from IVIg to SCIg at home. They transitioned easily. Although a third of patients in this study wished to return to IVIg, eventually the percentage wishing to remain on SCIg increased from 22% to 59%.[11]

A pediatric study found no difference with respect to quality-of-life measure between children who were treated at home with SCIg therapy compared to those who were treated at home with IVIg; however, it did find an increase in

quality-of-life scores for children who switched from IVIg to SCIg.[12] Accordingly, caregivers should consider switching from home-based IVIg to home-based SCIg because evidence indicates that this switch will be viewed favorably by children in their care.

Cost savings is another factor driving a switch from IVIg to SCIg. Significant cost savings have been identified in The United Kingdom,[13] Australia,[14] Canada[15–17] and the United States.[18] One significant reason SCIg costs less than IVIg is because it requires less time from medical professionals, especially nurses.

Ultimately, the choice between IVIg and SCIg therapy will depend on the patient's individual needs and preferences, as well as the advice of their healthcare provider. Physicians must consider multiple factors when selecting the most appropriate therapy to achieve optimal outcomes for their patients.

Determining SCIg Flow Rates

The recommended flow rate for SCIg replacement therapy is usually determined by the prescribing healthcare provider and may vary depending on dose, drug prescribed, the patient's age, weight, underlying medical conditions, overall health status, and history of tolerating treatment. Each drug on the market has specified limits to their respective flow rates and maximum volume per needle site. These limits are typically lower when the patients are acclimating to SCIg treatment.[5,19] Clinicians will take these flow-rate limits into consideration when choosing an SCIg drug and treatment protocol for their patients.

It should be noted that the flow rate may also be adjusted from infusion session to infusion session, based on the patient's response to treatment. To administer SCIg replacement therapy, a healthcare provider typically uses an infusion pump. The pump provides precise control of the flow rate. The infusion pump delivers the immunoglobulin solution into the subcutaneous tissue at a steady rate over time. Flow rate is also adjusted by selecting the number of needle sites, needle gauge, and tubing.

Training and instruction on using infusion pumps and SCIg administration are essential to ensure safe and effective treatment delivery. Patients should be monitored closely during and after infusion to identify any potential adverse reactions.

In the United States, several SCIg drugs are currently licensed for use, including Hizentra®, Gammagard Liquid®, Gamunex®-C, Gammaked®, Hyqvia, Cuvitru®, Cutaquig®, and Xembify®.[20] These drugs are effective in reducing infection severity and frequency in patients with primary immunodeficiency diseases (PIDD). Note that each drug has different recommended flow rates and administration guidelines. For example, the flow rate for Gammagard Liquid depends on the patient's weight, Hizentra® varies depending on the patient's number of infusions received, while the flow rate for Gamunex®-C is 20 mL/hr/site. See Table 1.

Table 1 Selected SCIg Drugs Licensed in US (2024)

Product Name/Drug (Manufacturer)	Infusion Schedule	Administration Method
Hizentra® (CSL Behring)[21]	PIDD: First infusion ≤15 mL/hr/site. Subsequent doses ≤25 mL/hr/site as tolerated.	Infusion pump or rapid push
Gammagard Liquid® (Takeda)[22]	40 kg BW and greater: First infusion 30 mL/ site at a rate of 20 mL/hr/site. Subsequent doses may be increased to 30 mL/site at a rate of 20–30 mL/hr/site. Maximum flow rate not to exceed 240 mL/hr for all sites combined. Under 40 kg BW: First infusion 20 mL/site at a rate of 15 mL/hr/site. Subsequent doses may be increased to 20 mL/ site at a rate of 15–20 mL/hr/site. Maximum flow rate not to exceed 160 mL/hr for all sites combined.	Infusion pump or rapid push
Gammaked® (Kedrion)[23]	20 mL/hr/site (max of 8 infusion sites)	Infusion pump or rapid push
HyQvia® (Takeda)[24]	Initial and max rate is based on weight and number of infusions received. Infusion rates may be increased every 5–15 mins as tolerated. Initial rate range: 5–10 mL/hr/ site. Max rate: 300 mL/hr/site. Every 3–4 weeks infusion.	Infusion pump

(*Continued*)

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Table 1 (Continued).

Product Name/Drug (Manufacturer)	Infusion Schedule	Administration Method
Cuvitru® (Takeda)[25]	May administered in up to 4 sites simultaneously. First 2 infusions:<40 kg administer ≤20 mL/site at rate of 10–20 mL/hr/site ≥40 kg administer ≤60 mL/site at rate of 10–20 mL/hr/site; Subsequent infusions (all weights): Administer ≤60 mL/ site at rate of ≤60 mL/hr/site.	Infusion pump or rapid push
Cutaquig® (Pfizer)[26]	Adults ≥17 years: Infusions 1–2: ≤20 mL/hr/site. Subsequent Infusions: Gradually increase as tolerated by approximately 10 mL/hr/site every 2–4 weeks up to a maximum of 52 mL/hr/site.	Infusion pump or rapid push
Xembify® (Grifols)[27]	May administer up to 6 infusion sites simultaneously at a maximum rate of 25 mL/hr/site.	Infusion pump or rapid push

Notes: Data from these package inserts.

It is always best to consult with a healthcare provider for specific recommendations. The pharmacokinetics of Ig is variable from patient to patient, and while influenced by weight, weight alone is not a reliable predictor of how a drug will perform in an individual patient.[28,29] Therefore, consultation and monitoring by a healthcare professional is required.

Are Patients Going Fast Enough? Why or Why Not?

Minimizing infusion time is an area of interest for researchers, professionals, caregivers, and patients. There is currently interest in rapid SCIg infusions[30,31] and hyaluronidase facilitated SCIg (facilitated SCIg, or fSCIg).[3,32] fSCIG is in contrast to the classic SCIg infused every 3 to 4 weeks (vs every week) and an infusion pump is mandatory for the administration. When treatment is administered at home, patients and caregivers have a favorable view of avoiding travel to a hospital or clinic.[6]

Recent drug developments and ongoing research in drug delivery have produced several methods to reduce infusion time. These methods include increasing drug concentration by volume,[33] and by increasing flow rates.[33,34] Several manufacturers provide a variety of pumps, tubing, and needle sets that provide the practitioner with options allowing optimization of flow rate tailored to an individual patient's needs. Major manufacturers include KORU Medical Systems, Inc. and EMED Technologies. There is also an ongoing switch from syringes that patients fill themselves from a vial to prefilled syringes, which saves time. In one study one patient used 2 pumps to speed infusion time.[35]

Little research has been done on minimizing infusion time by altering an existing protocol while dose and drug is held constant. By changing the tubing used, the needle gauge used, and increasing the number of needle sites, it is possible to reduce SCIg infusion time. A recent study found that very few protocols used in 97 patients were optimized with respect to time in simulations; a mean of 38.94 minutes could be saved per infusion by changing tubing, needle gauge, and number of sites.[36] The savings over the course of a year was substantial, with mean savings ranging from 10 hours and 34 minutes to 1 day, 12 hours, and 17 minutes, depending on the drug infused. With optimization one patient could save 8 days, 22 hours, and 56 minutes a year in a simulation using the KORU Freedom Flow Rate Calculator.

Patient Preference for Home Infusion

Perhaps the primary preference driving SCIg is the ability to infuse at home, and the ability to schedule the infusion at a convenient time. One advantage cited by patients is the ability to avoid time commuting to a clinic or hospital.[6] One study compared patients who switched to home-based SCIg therapy after receiving IVIg therapy in a hospital (Group A) and at home (Group B). Both groups preferred the SCIg therapy to IVIg. In Group A the preference for SCIg therapy was 81% and the preference for home therapy was 90%. In Group B, 69% preferred SCIg to IVIg and 92% preferred home-based therapy.[37]

It seems reasonable to extend this time-saving preference to the individual infusion event. Home treatment is the most common reason cited for either SCIg or home-based IVIG treatment. Home treatment contributes to patient autonomy, participation, and perceived health; caregivers and professionals view home treatment positively.[6]

Adverse Events Associated With SCIg

SCIg therapy is an effective treatment option for PIDDs; however, it can also cause adverse events, some of which are more common than others. There is evidence that a common side effect of IVIg therapy—headaches—can be reduced or eliminated by switching to SCIg therapy.[38] The most frequently reported adverse event associated with SCIg therapy is a local reaction at the injection site, such as redness, swelling, and pain. These reactions are generally mild and self-limiting, but they can persist for several days after the injection.[6]

Other common adverse events associated with SCIg therapy include fatigue, headache, and gastrointestinal symptoms such as nausea and diarrhea. Adverse reactions tend to diminish over time as a patient acclimates to the therapy.[4] Most drug manufacturers recommend a ramp-up period when SCIg is introduced, to allow the patient to acclimate to the treatment and to assure that any adverse reactions can be addressed. In a study of 65 patients, 3656 infusions were studied. Of these, 2,584 infusions were associated with an adverse event (71%); however, 96% were mild or moderate with a short duration and required no treatment.[38] In this study, 91% experienced an infusion-site reaction, 32% experienced headache, 11% experienced nausea, 6% experienced a rash, 5% experienced asthenia (weakness), and 5% experienced gastrointestinal disorder. No treatment-related serious adverse events were reported.

Less common adverse events associated with SCIg therapy include systemic reactions such as fever, chills, and muscle pain. These systemic reactions are more common in IVIg, and IVIg can be associated with thromboembolic events including stroke, pulmonary embolism, and myocardial infarction.[39,40] With SCIg, systemic reactions are generally mild and self-limiting, but they can occur during or shortly after the infusion and may require medical attention. Severe adverse events associated with SCIg therapy, such as anaphylaxis and thrombotic events, are rare but can occur in patients with pre-existing risk factors.

Examining the Data With SCIg Flow Rates and Potential Effect on Adverse Events

Several studies have investigated the relationship between SCIg flow rates and adverse reactions. While some studies have suggested that a faster infusion rate may be associated with a higher incidence of local reactions, such as redness, swelling, or pain at the infusion site, there are also studies that have found no significant difference in adverse events between slower and faster infusion rates.

One study published in the *Journal of Clinical Immunology* found that patients who received SCIg at a faster infusion rate (greater than or equal to 25 mL/h) experienced a higher rate of local reactions compared to those who received treatment at a slower rate (less than 25 mL/h).[35] However, the study did not find a significant difference in the rates of systemic reactions, such as headache, fever, or nausea, between the two groups.

In contrast, a study published in the *Journal of Clinical Immunology and Allergy* found a lower incidence of adverse events between patients who received SCIg treatment at a faster infusion rate (with a rapid push method) compared to those who received treatment at a slower rate (with a conventional pump).[41]

Accordingly, it is important to note that the relationship between SCIg flow rates and adverse events is not fully understood. Adverse events may vary depending on the individual patient and the specific delivery products being used. Healthcare providers typically monitor patients closely during and after SCIg infusion to identify any potential adverse reactions, regardless of the flow rate used. If a patient experiences adverse events during SCIg infusion, then the healthcare provider may adjust the infusion rate or take other measures to manage the symptoms and ensure the safe and effective delivery of treatment.

Patient Preferences for Faster Flow Rates

Interest in reducing infusion time has started to generate new studies. In an in-vitro study, warming the Immunoglobulin fluid has been studied to reduce viscosity and increase flow rate.[42] In addition, a simulation study was performed showing that infusion time can be substantially reduced using current infusion devices.[36] Patient interest in reducing infusion time has not been extensively studied, but preliminary findings suggest that this variable is of interest to patients.

Conclusion

Patients with primary immunodeficiency disorders are interested in reducing infusion time when it comes to their necessary regular infusions of immunoglobulin. Two main reasons that SCIg is gaining popularity over IVIg infusions is because it eliminates the time used to commute to a hospital or clinic and it reduces the costs associated with receiving an infusion in a clinical setting.

Work has just begun in this field to study the methods that can be used to speed up flow rates with equipment that already exists. In-vitro and mathematical simulations have been performed showing that the potential to reduce infusion time—substantially—does exists. Very little attention has been devoted to assessing patient preference for reducing infusion time, so more studies are needed to quantify patient preferences and to quantify the impact on quality-of-life variables before and after reducing infusion time.

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