

Subcutaneous Immunoglobulin

Matching Treatments with Patient Needs

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KEYWORDS

- Immunoglobulin G • Intravenous IgG • Primary immunodeficiency disorders
- Subcutaneous IgG

KEY POINTS

- Subcutaneous immunoglobulin replacement in primary immune deficiency disease has advantages over intravenous replacement including lack of requirement for IV access, few systemic adverse reactions and stable serum IgG levels.
- Subcutaneous immunoglobulin allows patients with primary immune deficiency disease greater autonomy in their treatment.
- Dose conversion from and intravenous to subcutaneous immunoglobulin should be individualized to the patient based on serum IgG levels and clinical responses.

Immunoglobulin G (IgG) replacement therapy is the standard treatment for reducing susceptibility to potentially life-threatening infections in patients with primary immunodeficiency disease (PIDD). The range of IgG products available for administration by various routes has changed over the years, and perspectives on preferred therapeutic strategies have continued to evolve. Intravenous IgG (IGIV) preparations, introduced in the United States during the 1980s, largely supplanted older intramuscular (IM) preparations, which were associated with considerable disadvantages (eg, pain, poor adherence, difficulties in providing adequate dosing, suboptimal serum IgG levels, and inferior clinical outcomes).¹ Improved safety and efficacy led to IGIV becoming the major therapeutic modality for IgG replacement in patients with PIDD.¹ Nonetheless, IV products have not been without their shortcomings, such as the requirement for venous access as well as the risk of adverse effects due to fluctuations in IgG levels.² Such challenges have increased interest in the potential advantages of subcutaneous (SC) preparations.

IGIV AND IGSC: ADVANTAGES AND DISADVANTAGES

As noted, the introduction of IGIV in the United States overcame many of the limitations of IM injections. Unlike IM products, IGIV is generally well tolerated by most

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patients, can be given in large volumes per infusion so as to permit intermittent dosing (every 21–28 days), and can be used in individuals with bleeding disorders.¹ On the other hand, use of the IV route is problematic in some patients, especially children, and requires the involvement of trained personnel in most situations.¹ Furthermore, large shifts in IgG levels during IGIV dosing may cause adverse effects at or just after peak and during low troughs.¹ Infrequent dosing, in particular, may result in low trough levels. Serious adverse effects of IGIV include aseptic meningitis (occurring more frequently in patients receiving high-dose treatment and in patients with a history of migraine); renal complications (particularly with sucrose-containing products and in patients with diabetes, preexisting kidney disease, older age, or dehydration); and thromboembolic events (which are more common in patients with preexisting autoimmune disease and may also be related to increased blood viscosity, most often seen with lypophilized products).^{3–6} In light of these concerns, SC administration of IgG has drawn greater attention. Although IGSC has been widely used in Scandinavia and the United Kingdom for many years, the IV route has traditionally been preferred both in the rest of Europe and in the United States.^{1,7,8} In fact, the US Food and Drug Administration (FDA) did not approve an IGSC product until 2006.⁹

Advantages and disadvantages of IGSC versus IGIV are summarized in the **Table 1**.^{1,9} The SC route is an attractive alternative for a variety of reasons. Most patients with PIDD receive IGIV every 3–4 weeks, whereas IGSC is typically administered weekly.¹⁰ With more frequent administration of lower doses and slower absorption from the extravascular fluid space, fluctuations in peak and trough IgG plasma concentrations between infusions are minimized with SC preparations.¹¹ In addition,

Table 1
Advantages and disadvantages of IGSC and IGIV

	IGSC	IGIV
Advantages	• No requirement for venous access • Maintenance of more consistent IgG serum levels; elimination of low troughs • Low occurrence of systemic adverse effects • Facilitation of self- or at-home administration, increasing patient autonomy	• Well tolerated by most patients • Can be given in large volumes per infusion, allowing intermittent dosing (every 21–28 days) • Can be used in patients with bleeding disorders
Disadvantages	• Relatively small volume per infusion, requiring frequent dosing • Risk of local infusion-site reactions	• Requires venous access and trained personnel in most situations • Large shift in IgG levels during dosing; may cause adverse effects at or just after peak and during low troughs • Home infusion possible but more technically demanding than SC administration

Abbreviations: IGIV, intravenous immunoglobulin; IGSC, subcutaneous immunoglobulin.

Data from Berger M. Subcutaneous immunoglobulin replacement in primary immunodeficiencies. *Clin Immunol* 2004;112:1–7; and Moore ML, Quinn JM. Subcutaneous immunoglobulin replacement therapy for primary antibody deficiency: advancements into the 21st century. *Ann Allergy Asthma Immunol* 2008;101(2):114–21.

IGSC is associated with reduced systemic adverse reactions.^{7–9,12} Another benefit is that IGSC does not require vascular access and allows greater patient autonomy by permitting self-administration of therapy.¹³ Patients receiving IGSC are at risk of mild local infusion-site reactions, such as transient swelling, erythema, pain and itching.^{14–16} Notably, however, reactions at the site of administration are rarely severe and are more common on initiation of treatment, becoming increasingly less frequent over time (particularly during the first 8–10 weeks of therapy).^{7,14}

DOSING OF IGSC

When the first IGSC product was submitted for approval in the United States, the FDA required bioequivalence to IGIV as measured by the area under the curve (AUC) of serum IgG level versus time.^{10,17} To achieve this standard when patients are switched from one route to the other, 10% and 16% IGSC products must be dosed at 137% of IV doses, and the 20% IGSC product must be dosed at 153% of the IV dose.^{10,15,17} In contrast to the FDA standards, the European Medicines Agency mandates that IgG products produce trough serum levels comparable with those obtained with the same doses of other IGIV or IGSC products.¹⁸ This requirement is based on studies showing that similar steady-state and trough levels were attained when identical doses of IgG were administered via the 2 routes.¹⁹ Accordingly, in Europe, IGSC is dosed at 100% of the IGIV dose (calculated by dividing the full month's dose of IGIV by 4 to determine the weekly dose of IGSC). Many immunologists in the United States have adopted this practice as well. Nonetheless, other work has shown that if the weekly dose is kept constant when switching a patient from IGIV to IGSC, the steady-state IgG level is apt to be 12.7% higher with the SC product than with IV product.¹⁷ If the goal is to maintain a patient's steady-state IgG level on IGSC equal to the trough level on IGIV, the IGSC dose may need to be reduced to approximately 50% of the IV dose.¹⁷ With all these considerations in mind, commentators have advised, however, that the optimal approach is actually to individualize doses based on measured serum IgG levels and clinical responses in each specific patient, rather than relying on the reported mean pharmacokinetic parameters, when switching from an IV to an SC product.¹⁷

DELIVERY METHODS

A potential drawback to IGSC is the recommendation that the treatment be administered via a pump. A variety of pumps are available for delivery of IGSC at rates ranging from very slow to very rapid. Regardless of the design and capabilities, most pumps are cumbersome and can constitute barriers to the use of IGSC.

Our group has explored the use of manual, rapid-push administration of IGSC as an alternative to infusion by pump.¹⁹ This method simply uses a syringe and a butterfly needle to push the dose under the skin. The rapid-push technique offers the advantage of a great deal of flexibility in treatment schedules. Some patients choose once-daily administration, as they prefer a very small amount of IgG given very quickly. Others opt for 3-times-weekly dosing, and still others use multiple doses once per week.

Another issue of interest is the cost of therapy. Although there is no precise way to compare the costs of various options for IgG treatment, a number of economic studies have suggested that IGSC can yield significant cost savings when compared with IGIV.²⁰ Use of SC preparations is associated with lower costs for nursing time and administration. However, the requirement for tubing and pumps can be associated with considerable expense. In contrast, if one chooses the rapid-push method described above, the cost associated with the use of a syringe and butterfly needle is minimal.

SUMMARY

Experience to date with the treatment of PIDD suggests that the SC route may be a good alternative to IV therapy for IgG replacement. The use of IGSC can improve the care and quality of life of patients by maintaining more consistent serum IgG levels, reducing the occurrence of systemic side effects, while also providing more comfortable and convenient care. Patients who stand to derive particular benefit from IGSC include those who have poor venous access, have experienced severe systemic adverse effects when treated with IGIV, or desire greater autonomy in their treatment of PIDD. Certain drawbacks of IGSC may be overcome by rapid-push administration as opposed to infusion by pump.

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