

# Differentiating Characteristics and Evaluating Intravenous and Subcutaneous Immunoglobulin

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## Intravenous and Subcutaneous Immunoglobulin Treatment Options

Immunoglobulin (Ig) has provided lifesaving therapy for a range of primary immunodeficiency diseases. With the introduction of subcutaneous immunoglobulin (SCIG) products, treatment options have expanded for patients with several conditions, such as primary immunodeficiency diseases or chronic inflammatory demyelinating polyneuropathy (CIDP), that require Ig therapy. In addition, recombinant human hyaluronidase-facilitated SCIG (fSCIG) is an option with primary immunodeficiency diseases, which allows for easier entry of large volumes of fluid through the extracellular matrix.<sup>1</sup> **Table 1**<sup>2-9</sup> lists the currently available intravenous immunoglobulin (IVIG) and SCIG products. IVIG and SCIG products are manufactured from the plasma of healthy donors. Plasma pools are derived from a minimum of 1000 donors as mandated by the FDA but typically include a larger number.<sup>10</sup> Generally, a batch of Ig will include plasma from approximately 15,000 donors.<sup>11</sup> The volume of the plasma pools in production typically ranges from 2000 kg to 4000 kg.<sup>12</sup> Ig products sold in the United States are derived solely from US donor plasma, although the final Ig product may be manufactured in FDA-approved facilities outside of the United States.<sup>2</sup> These supply factors impose an inherent limit of source material that can cause supply chain issues, such as frequent product shortages, and is reflected in the product cost. The limited supply of product puts a premium on the importance of clinically appropriate therapy, including the decision to use the intravenous (IV) or the subcutaneous (SC) route of administration. SCIG products are currently only approved for the treatment of primary immunodeficiency, with the exception of immunoglobulin subcutaneous ( Hizentra ), which is also approved for CIDP<sup>13</sup>; IVIG products are indicated for several other disease states (Table 1<sup>2-9</sup>).<sup>2,14</sup> Clinicians and managed care professionals should also be aware that physicians often prescribe Ig products, particularly IVIG, for off-label uses, and payers do reimburse (often denied, and need appeal) for such uses.<sup>15</sup> Although those off-label uses, which may number more than 150,<sup>16,17</sup> are outside the scope of this paper, they represent a very important component of Ig therapy; readers are encouraged

## ABSTRACT

Clinicians have a range of options for treating patients with disease states that require the use of immunoglobulin (Ig). Traditionally, intravenous immunoglobulin (IVIG) administration has provided effective therapy for a variety of disease states. More recently, subcutaneous immunoglobulin (SCIG) administration has become available for patients with primary immunodeficiencies and chronic inflammatory demyelinating polyneuropathy (CIDP). Ig is used as replacement therapy in patients with primary or secondary immunodeficiencies and has been shown to reduce morbidity due to bacterial infections associated with antibody deficiency. The mechanism of action for use of Ig in the treatment of autoimmune disorders is complex and partially understood, but immunomodulatory effects have been suggested in CIDP and multifocal motor neuropathy. The available IVIG and SCIG products differ in their pharmaceutical properties (eg, pH, osmolality, IgA content, sodium content, and stabilizer), which can affect safety and tolerability in some patients. The pharmacokinetics of Ig also differ based on the route of administration. With IVIG administration every 3 or 4 weeks, peak concentrations are greater and trough concentrations are lower, which can increase the propensity of systemic adverse effects (AEs) and impact tolerability of therapy. SCIG infusions are typically administered more frequently (ie, biweekly, weekly, and even daily based on patient need), resulting in steady state concentrations with fewer fluctuations in Ig plasma levels. The route of administration plays a major role in the types of AEs seen in patients receiving Ig therapy, with systemic AEs associated with IV administration and local reactions more commonly seen with SC administration. By understanding the differences in IVIG and SCIG products, which are not interchangeable, and the patient characteristics that guide product selection, clinicians and managed care providers can better serve patients with immunodeficiency disorders and other disease states.

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For author information and disclosures, see end of text.

to refer to the findings of a work group of the American Academy of Allergy, Asthma, and Immunology (AAAAI) for their review and categorization of the evidence for the use of Ig for a wide range of disorders.<sup>14</sup>

### Choosing the Right Patient for the IV and SC Routes of Administration

The AAAAI established a list of 8 guiding principles to help clinicians make quality decisions regarding IVIG for patients with primary immunodeficiency.<sup>18</sup> These principles provide a framework for the clinically appropriate use of IVIG. Although the AAAAI's principles are directed at IVIG for primary immunodeficiency, many points also translate to SCIG therapy and other FDA-approved indications, such as CIDP or multifocal motor neuropathy. Site of care, route of administration, and product characteristics are principles that apply globally when considering the effective use of Ig. The AAAAI states that the decision to infuse Ig in a hospital, hospital outpatient, community office, or home-based setting must be based on clinical characteristics of the patient and a discussion between the healthcare providers and the patient. Ultimately, the route of administration of Ig should be based on patient characteristics, as the IV and SC routes have demonstrated efficacy based on appropriate dosing regimens.<sup>19</sup> Lastly, Ig is not a generic drug, and Ig products are not interchangeable based on the variability of key components in each product. When making the clinical decision regarding an Ig product, clinicians should be aware that some products may be designed for a single route of administration, whereas others may be approved for multiple routes of administration (refer to Table 1<sup>2-9</sup>). For example, immune globulin (Flebogamma DIF) is approved only for IV administration,<sup>4,5</sup> and immune globulin with recombinant human hyaluronidase (HyQvia) is approved only for SC administration.<sup>20</sup> Other products, such as immune globulin (Gammagard Liquid 10%) and immune globulin injection, caprylate/chromatography purified (Gamunex-C 10%), are approved for IV and SC administration.<sup>21,22</sup>

It is recommended that payers and institutions keep an open Ig formulary because a

**TABLE 1.** IVIG and SCIG Products and Their Indications<sup>2-9,a</sup>

| Product  | Indications  |
|--|--|
| <b>IVIG Products</b>   |  |
| Immune globulin (Asceniv) 10%  | <ul style="list-style-type: none"> <li>Primary humoral immunodeficiency</li> </ul>   |
| Immune globulin (Flebogamma DIF) 5%, 10%                                     | <ul style="list-style-type: none"> <li>Primary humoral immunodeficiency</li> <li>Immune thrombocytopenic purpura</li> </ul>  |
| Immune globulin (Gammagard S/D) 5%, 10%                                      | <ul style="list-style-type: none"> <li>Primary humoral immunodeficiency</li> <li>B-cell chronic lymphocytic leukemia</li> <li>Immune thrombocytopenic purpura</li> <li>Kawasaki disease</li> </ul>           |
| Immune globulin (Gammaplex) 5%, 10%  | <ul style="list-style-type: none"> <li>Primary humoral immunodeficiency</li> <li>Chronic immune thrombocytopenic purpura</li> </ul>  |
| Immune globulin (Octagam) 5%, 10%  | <ul style="list-style-type: none"> <li>Primary humoral immunodeficiency (5%)</li> <li>Chronic immune thrombocytopenic purpura (10%)</li> </ul>   |
| Immune globulin (Panzyga) 10%  | <ul style="list-style-type: none"> <li>Primary humoral immunodeficiency</li> <li>Chronic immune thrombocytopenic purpura</li> </ul>  |
| Immune globulin (Privigen) 10%   | <ul style="list-style-type: none"> <li>Primary humoral immunodeficiency</li> <li>Chronic immune thrombocytopenic purpura</li> <li>Chronic inflammatory demyelinating polyneuropathy</li> </ul>               |
| <b>IVIG/SCIG Products</b>  |  |
| Immune globulin (Gammagard Liquid) 10%                                       | <ul style="list-style-type: none"> <li>Primary humoral immunodeficiency (IV/SC)</li> <li>Multifocal motor neuropathy (IV)</li> </ul>   |
| Immune globulin injection, caprylate/chromatography purified (Gammaked) 10%  | <ul style="list-style-type: none"> <li>Primary humoral immunodeficiency (IV/SC)</li> <li>Idiopathic thrombocytopenic purpura (IV)</li> <li>Chronic inflammatory demyelinating polyneuropathy (IV)</li> </ul> |
| Immune globulin injection, caprylate/chromatography purified (Gamunex-C) 10% | <ul style="list-style-type: none"> <li>Primary humoral immunodeficiency (IV/SC)</li> <li>Idiopathic thrombocytopenic purpura (IV)</li> <li>Chronic inflammatory demyelinating polyneuropathy (IV)</li> </ul> |
| <b>SCIG Products</b>   |  |
| Immune globulin (Cutaquig) 16.5%   | <ul style="list-style-type: none"> <li>Primary humoral immunodeficiency</li> </ul>   |
| Immune globulin (Cuvitru) 20%  | <ul style="list-style-type: none"> <li>Primary humoral immunodeficiency</li> </ul>   |
| Immune globulin (Hizentra) 20%   | <ul style="list-style-type: none"> <li>Primary humoral immunodeficiency</li> <li>Chronic inflammatory demyelinating polyneuropathy</li> </ul>  |
| Immune globulin with recombinant human hyaluronidase (HyQvia) 10%            | <ul style="list-style-type: none"> <li>Primary humoral immunodeficiency</li> </ul>   |

IV indicates intravenous; IVIG, intravenous immunoglobulin; SC, subcutaneous; SCIG, subcutaneous immunoglobulin.

<sup>a</sup>Carimune NF and Vivaglobin have been discontinued in the United States as of the date of publication, although some products may still be available on the market. Bivigam was previously discontinued but has been reapproved as of May 2019.

**TABLE 2.** Pharmaceutical Properties of Select IVIG, IV/SCIG, and SCIG Products<sup>2,6-8</sup>

| Product                               | Osmolality (mOsm/kg)        | Sodium Content | pH      | IgA (mcg/mL) | Stabilizer                            |
|---------------------------------------|-----------------------------|----------------|---------|--------------|---------------------------------------|
| <b>IV Products</b>                    |                             |                |         |              |                                       |
| Asceniv 10%                           | N/A                         | 100-140 mEq/mL | 4.0-4.6 | ≤200         | Polysorbate 80, glycine               |
| Flebogamma DIF 5%                     | 325 ± 4.8                   | <3.2 mEq/mL    | 5.6±0.1 | <3.1         | Sorbitol                              |
| Flebogamma DIF 10%                    | 343 ± 6.4                   | <3.2 mEq/mL    | 5.5±0.1 | <3.1         | Sorbitol                              |
| Gammagard 5% S/D                      | 636                         | 146 mEq/mL     | 6.4-7.2 | <1           | Glycine                               |
| Gammagard 10% S/D                     | 1250                        | 292 mEq/mL     | 6.4-7.2 | <2           | Glycine                               |
| Gammaplex 5%                          | Not <240, typically 420-500 | 30-50 mEq/mL   | 4.8-5.1 | <10          | Sorbitol, glycine, and polysorbate 80 |
| Gammaplex 10%                         | Not <240, typically 280-288 | ≤5 mEq/mL      | 4.9-5.2 | <20          | Polysorbate 80, glycine               |
| Octagam 5%                            | 310-380                     | ≤30 mEq/mL     | 5.1-6.0 | <200         | Maltose                               |
| Octagam 10%                           | 310-380                     | ≤30 mmol/L     | 4.5-5.0 | 106          | Maltose                               |
| Panzyga 10%                           | 240-310                     | Trace          | 4.5-5.0 | 100          | Glycine                               |
| Privigen 10%                          | 240-440                     | Trace          | 4.6-5.0 | ≤25          | Proline                               |
| <b>IV or SC Products</b>              |                             |                |         |              |                                       |
| Gammagard Liquid 10%                  | 240-300                     | None added     | 4.9-5.2 | 37           | Glycine                               |
| Gammaked 10%                          | 258                         | Trace          | 4.0-4.5 | 46           | Glycine                               |
| Gamunex-C 10%                         | 258                         | Trace          | 4.0-4.5 | 46           | Glycine                               |
| <b>SC Products</b>                    |                             |                |         |              |                                       |
| Cutaquig 16.5%                        | 310-380                     | ≤30 mmol/L     | 5.0-5.5 | ≤600         | Maltose                               |
| Cuvitru 20% solution                  | 208-292                     | None added     | 4.6-5.1 | 80           | Glycine                               |
| Hizentra 20%                          | 380                         | Trace          | 4.6-5.2 | ≤50          | Proline                               |
| HyQvia 10% solution (+ hyaluronidase) | 240-300                     | None added     | 4.6-5.1 | 37           | Glycine                               |

IgA indicates immunoglobulin A; IV, intravenous; IVIG, intravenous immunoglobulin; NaCl, sodium chloride; SC, subcutaneous; SCIG, subcutaneous immunoglobulin.

patient may not tolerate a certain product and may require options based on product and patient characteristics. Specific Ig products need to match with patient characteristics to ensure patient safety; a change of Ig product should only occur with the active participation of the clinicians and other members of the healthcare team.

Another pertinent resource for clinicians is the *Immunoglobulin Therapy Standards of Practice* published by the Immunoglobulin National Society (IgNS), which is in its second edition.<sup>2</sup> The IgNS document comprehensively covers many aspects of Ig therapy, with practice criteria accompanying each standard. Recognizing the collaborative approach that is necessary to properly treat patients who are receiving Ig therapy, IgNS emphasizes the interdisciplinary aspects of patient care that includes prescribers, pharmacists, nurses, and many other healthcare professionals.<sup>2</sup>

### Patient Factors and Formulation Factors

The primary and active component of Ig products is immunoglobulin G (IgG). However, formulations of Ig can vary in many different respects: IgG monomer, dimer, and aggregate concentrations;

IgA and IgM content; stabilizers; additives; and levels of impurities.<sup>2</sup> When multiple products are being considered for a specific patient, clinicians must weigh the impact of these pharmaceutical formulation factors, as they contribute to differences in safety and tolerability.<sup>23-27</sup>

Osmolality of IVIG, IV/SCIG, and SCIG products ranges from 208 mOsm/kg to 1250 mOsm/kg. Most of the products are within the range of physiologic osmolality of approximately 290 mOsm/kg (Table 2<sup>2,6-8</sup>). Products that deviate substantially from physiologic osmolality levels may put the patient at risk for various infusion-related adverse effects (AEs), such as thrombotic events and aseptic meningitis, particularly in elderly or neonatal patients, patients with cardiometabolic impairment, and patients with renal dysfunction.<sup>2,24</sup> Similarly, the same patient populations may be sensitive to the sodium content of Ig products, which is reported in a variety of units (eg, mmol/L, mEq/mL, mg/mL). If the pH of an injectable product is substantially below physiologic levels, localized reactions at the site of injection may result. With the pH of Ig products ranging from a low of 4 to 7.2 (see Table 2<sup>2,6-8</sup>), a slow infusion time

may be advisable for products with pH levels toward the lower end of the range.

Although Ig products primarily contain IgG, they also contain varying amounts of IgA (<1 mcg/mL to ≤200 mcg/mL for IVIG products and 37 mcg/mL to 80 mcg/mL for SCIG products).<sup>2</sup> Early research indicated that rare but severe anaphylactic reactions to Ig products were most likely to occur in patients who were severely deficient in IgA and also had IgE-type anti-IgA antibodies present. However, the administration of a low-IgA product has been shown to be effective in preventing severe allergic reactions in a small number of IgA-deficient patients who have previously experienced such reactions. Because SCIG therapy has a slower release of product into the general circulation, there are also a number of reports in the literature suggesting that SCIG therapy may be used successfully in IgA-deficient patients who experience adverse drug reactions (ADRs) to IVIG products.<sup>2</sup>

Stabilizers are included in the product formulations to prevent IgG aggregation, which may increase the risk of certain AEs, such as anaphylaxis.<sup>19</sup> Glycine is the most commonly used stabilizer, whereas D-sorbitol, glucose, maltose, L-proline, and polysorbate 80 are included in some formulations. Ig products containing glucose should be avoided in patients with diabetes when it is feasible as they can potentially raise serum glucose levels. Furthermore, products that contain maltose as a stabilizer should be used cautiously in patients with diabetes as some blood glucose monitoring systems (glucometers) may return falsely elevated glucose levels, which could lead to the unnecessary administration of insulin and result in hypoglycemia. Fortunately, most glucometers exhibiting this interference have been phased out of the market.<sup>19</sup>

Volume is also a significant consideration when choosing an Ig product, whether it is IV or SC. IVIG products are available as 5% or 10% solutions. One product is available as a lyophilized powder that can be reconstituted into a 5% or 10% solution using sterile water. When considering an IVIG product to select for a patient based on volume, it is very important to keep the clinical picture of the patient in mind. Extra volume could be beneficial in those patients who do not maintain adequate oral

hydration and could also help minimize ADRs. In contrast, the extra volume could worsen underlying clinical conditions, such as congestive heart failure, hypertension, and renal dysfunction. Furthermore, the additional volume of low concentrated products may take longer to infuse and increase nursing time. SCIG products are commercially available as 10%, 16.5%, and 20% solutions. Although a 10% product may be better tolerated in some patients,

**TABLE 3.** Advantages and Disadvantages of IVIG and SCIG Therapy<sup>2,32</sup>

|               | IVIG   | SCIG   |
|---------------|--|--|
| Advantages    | <ul style="list-style-type: none"> <li>• Less frequent dosing</li> <li>• History of efficacy</li> <li>• Safety profile and risk mitigation strategies are well known</li> <li>• Frequent contact with healthcare professionals during administration can mean better clinical monitoring and early identification of problems</li> </ul> | <ul style="list-style-type: none"> <li>• Self-administration feasible for patients with cognitive and fine motor ability</li> <li>• Smaller infusion volumes allow gradual absorption and steady state IgG levels</li> <li>• No venous access needed</li> <li>• Common AEs are localized at the infusion site</li> </ul> |
| Disadvantages | <ul style="list-style-type: none"> <li>• Requires venous access</li> <li>• Skilled personnel typically needed for administration</li> <li>• Peaks and troughs of PK profile may affect efficacy and safety</li> <li>• Systemic AEs</li> </ul>  | <ul style="list-style-type: none"> <li>• Often requires more frequent infusions and multiple SC infusion sites and needlesticks</li> <li>• Lack of direct patient monitoring when self-administered to evaluate technique</li> <li>• Patient adherence may decrease</li> <li>• Localized site reactions</li> </ul>       |

AE indicates adverse effect; IgG, immunoglobulin G; IVIG, intravenous immunoglobulin; PK, pharmacokinetics; SC, subcutaneous; SCIG, subcutaneous immunoglobulin.

**TABLE 4.** Local Adverse Drug Reactions With SCIG Therapy and Mitigation Strategies<sup>2</sup>

| Local Reaction  | Mitigation Strategies   |
|---|---|
| Leaking at the infusion site  | <ul style="list-style-type: none"> <li>• Ensure needle placement and security</li> <li>• Ensure adequacy of SC tissue</li> <li>• Ensure appropriate needle length</li> <li>• Ensure appropriate volume infused per site</li> <li>• Ensure appropriate rate of infusion</li> </ul>   |
| <p>SCIG: Reaction at the infusion site should be consistent with volume of drug infused and is expected to appear raised and quarter-sized in diameter.</p> <p>fSCIG: Reaction at the infusion site is expected to appear as a soft, diffuse pancake.</p> | <p>If greater reaction is seen, the following may be considered:</p> <ul style="list-style-type: none"> <li>• Decrease the volume per site</li> <li>• Change site of infusion</li> <li>• Ensure appropriate needle length</li> <li>• Administer lower doses more frequently</li> <li>• Assess sensitivity to adhesive</li> <li>• Consider slowing infusion rate</li> <li>• Ensure good dry priming needle technique in SCIG tubing and needle sets</li> <li>• Consider gentle massage or using a warm or cold compress post infusion</li> </ul> |

fSCIG indicates facilitated subcutaneous immunoglobulin; SC, subcutaneous; SCIG, subcutaneous immunoglobulin.

the greater volume of product that needs to be infused means more SC infusion sites and frequent administrations. The rate of infusion and volume per site is individualized for each product and must be taken into consideration, in addition to patient tolerability.<sup>2-8</sup>

When writing a prescription for Ig, some prescribers may specify a brand, and some payers impose limited formularies that require the use of a specific Ig product. If the prescribed or reimbursed product is not ideal for the patient based on these clinical characteristics, it is incumbent upon the Ig clinician to advocate for other options with the prescriber or payer if warranted.<sup>2</sup> The potential interactions between patient factors and pharmaceutical formulation factors must be considered by clinicians when making IVIG or SCIG product choices and must be assessed on an ongoing basis.

### Individual Patient Ability and Preference

Patient preference for one form of administration is an important factor to consider when choosing between IVIG and SCIG. In addition, it is important to understand and consider options that are available for the site of care. Options for the site of care include the following<sup>2</sup>:

- Hospital inpatient with prescriber/nurse supervision
- Hospital outpatient with prescriber/nurse supervision
- Physician office with prescriber/nurse supervision
- Free-standing infusion suite with prescriber/nurse supervision
- Home-based infusion with nurse supervision
- Home-based infusion without nurse supervision (SCIG only)

Patients often prefer the convenience of home-based Ig administration,<sup>28,29</sup> and studies suggest that home administration is feasible for certain patient populations. Factors that must be considered by clinicians when determining the site of care include the patient's medical history and comorbidities, age, ability to travel, home environment, previous experience with Ig, access to emergency medical services or 911, availability of a caregiver, third-party payer restrictions, financial burden, and preference. In addition, when evaluating the appropriateness for SCIG therapy, the Ig clinician must assess the patient's ability to learn how to successfully perform self-administration and to adhere to dosing regimens.<sup>2</sup>

Studies reviewing patient preferences of site of care have revealed a mixed picture; the site of care and route of administration need to be a patient-specific consideration. In the VISAGES study, Bienvenu et al observed that approximately 70% of patients who received hospital-based IVIG preferred hospital-based administration. Of 12 home-based patients who received IVIG, just 1 patient preferred hospital-based administration. All patients who received home-based SCIG preferred that arrangement compared with the option of hospital-based therapy.<sup>30</sup> In a survey study with 300 respondents, Espanol and colleagues determined that a majority of respondents (76%) were satisfied with their current treatment arrangement,

either IVIG or SCIG.<sup>28</sup> In a smaller study, Hoffmann et al observed that 92% (n = 22) of adult patients preferred SCIG over IVIG, and 83% (n = 20) preferred home-based therapy over the alternative.<sup>31</sup>

### Ig Treatment Options, Risks, and Benefits

Determining the best Ig treatment option for a given patient requires an assessment of the risks and benefits of each product. As outlined previously, patient considerations may dictate a particular route of administration. When an initial assessment has been completed and it is found that IVIG and SCIG would both be feasible for a patient, additional factors, including AE profiles, dosing frequency, and pharmacokinetics (PK), can be considered. **Table 3**<sup>2,32</sup> summarizes the advantages and disadvantages of each route of administration, which are described in detail throughout this paper.

The number of indications for IVIG and SCIG therapies preclude listing all the corresponding dosing recommendations. What follows is a summary of dosing recommendations for common indications. In primary humoral immunodeficiency, the IVIG dose is 300 mg/kg to 800 mg/kg every 3 or 4 weeks, and the SCIG dose is adjusted from the adjusted IVIG dose every 1 to 14 days. For CIDP, an IVIG loading dose of 2 g/kg is given in divided doses over 2 to 5 consecutive days with a maintenance dose of 1 g/kg every 3 weeks administered over 1 day or divided into 2 doses of 500 mg/kg given on 2 consecutive days (modified according to patient response). Alternatively, SCIG may be utilized for maintenance dosing in some patients at 0.2 g/kg to 0.4 g/kg weekly. For immune thrombocytopenic purpura or idiopathic thrombocytopenic purpura, the IVIG dose is 1 g/kg for 1 to 3 doses. Patients with multifocal motor neuropathy would receive a loading dose of 400 to 500 mg/kg daily for 5 days, followed by a maintenance dose of 0.5 to 2.4 g/kg/month based on clinical response.<sup>2</sup> The information provided is from the IgNS Standards of Practice; note that it is not based on the individual package inserts, but includes other dosing recommendations from the published literature. Please refer to individual prescribing information for specific product dosing.

### IVIG: Unique Considerations

Besides patient and formulation factors, the choice between IVIG and SCIG often hinges on dosing frequency, which is highly dependent on PK differences between the routes of administration. IVIG introduces Ig directly into the circulatory system via venous access. After IVIG administration, the IgG serum concentration shows an initial sharp rise followed by a rapid decrease for 1 to 4 days after the infusion and then a gradual decrease over the next 21 to 28 days.<sup>33</sup> Steady state is achieved between the fourth and sixth infusion of IVIG in a naïve patient who is usually dosed every 3 to 4 weeks. Once steady state is reached, a pre-infusion trough level can be obtained, but the utility of monitoring trough levels is indication-specific. In primary immunodeficiencies, dose and interval are titrated to

achieve an IgG trough level of greater than 500 mg/dL. For patients with common variable immune deficiency, many prescribers target an initial serum IgG level equal to that of the patient's pretreatment level plus 300 mg/dL. However, as the IgNS Standards of Practice indicate, Ig dosing should be based on a combination of clinical response and appropriate trough levels rather than trough levels alone, which is a clinical practice supported by the literature.<sup>2,34-38</sup> Patients who receive IVIG therapy for immunodeficiencies appear to have an increased risk of infection as IgG trough levels are approached. This phenomenon, sometimes referred to as wear-off, may increase the risk of infection by 26% for patients on a 3-week administration cycle and 55% for patients on a 4-week administration cycle.<sup>39</sup> IVIG dosing in autoimmune disorders is even more variable following the initial recommended starting dose, and it is customarily based on the individual patient's clinical response.

Overall, Ig therapy is safe and well tolerated in most patients. AEs in patients undergoing IVIG therapy tend to be systemic in nature.<sup>40,41</sup> Such AEs are observed more commonly in treatment-naïve patients and may occur up to 34% of the time with the first infusion.<sup>32</sup> Other estimates point to similar (eg, up to 40%) rates of AEs with IVIG infusion. Whenever possible, the goal should be to prevent ADRs from occurring, and this can usually be achieved by proper product selection and administration.<sup>2</sup> If ADRs do occur, it is important to note that many of the systemic AEs associated with IVIG can be attenuated by reducing the infusion rate of IVIG, ensuring adequate hydration, and/or premedicating the patient with nonsteroidal anti-inflammatory drugs, corticosteroids, and antihistamines.<sup>14,19,42,43</sup>

### SCIG: Unique Considerations

One of the often-mentioned advantages of SCIG is the option to administer required doses at a time and place of the patient's choosing. Although many patients receiving IVIG can use home infusion services, the option to receive treatment that does not require a skilled healthcare professional is an advantage of SCIG. However, the advantage of home-based administration may be mitigated to some degree by the more frequent dosing schedules often required for SCIG, as well as the need to self-infuse using needle sets, SC infusion pumps, and syringes.<sup>42</sup> With more frequent dosing schedules, patients may be advised to vary the site of injections as well as limit the volume per site based on SCIG product used.<sup>6,13,20-22</sup> The dosing frequency for SCIG is predicated on PK principles and varies between SCIG and fSCIG.

When Ig is administered SC, it must first diffuse through the SC space into the lymphatic system before entering the circulatory system via the thoracic duct.<sup>19</sup> This results in a decreased peak concentration compared with IVIG. With more frequent dosing (eg, daily, weekly, or biweekly), trough levels with SCIG are not as severe as IVIG and a steady state concentration is achieved.<sup>32,44,45</sup> The

absorption process inherent with SCIG administration reduces the bioavailability of Ig by approximately 30% to 35%.<sup>46</sup> Based in part on potential differences in bioavailability, the IgNS recommends consulting with the prescriber to determine what conversion factors, if any, are used when switching patients from IVIG to SCIG.<sup>2</sup> This is similar to practices in other parts of the world where dose adjustments between IVIG and SCIG are not typically required but may be individualized for patients based on PK and clinical response.<sup>47</sup> However, fSCIG has some of the properties of SCIG and IVIG regimens, resulting in hybrid PK profiles for fSCIG. Although the bioavailability of fSCIG products is similar to that of IVIG products, peak serum IgG levels are typically lower than those encountered with IVIG infusion; thus, fSCIG retains an AE profile closer to that of SCIG.<sup>1</sup>

Given the PK parameters, SCIG therapy has the advantage of few systemic AEs, which may occur in fewer than 5% of patients who receive SCIG. One meta-analysis determined that the systemic AE rate for SCIG was 0.43%.<sup>42</sup> On the other hand, patients who receive SCIG therapy are more likely to experience local site reactions (eg, erythema, swelling, warmth, induration, and soreness), which may occur in up to 75% of patients.<sup>42</sup> See [Table 4<sup>2</sup>](#) for a summary of local ADRs that can occur with SCIG products, along with suggested mitigation strategies.

### Conclusions

Whether administered via the IV or SC route, successful Ig therapy depends on expert clinical knowledge and experience, as well as a collaborative healthcare environment.<sup>2</sup> IV and SC are both clinically appropriate modes of administering Ig to patients with primary immunodeficiency disorders and other autoimmune disease states. Each mode of administration has advantages and disadvantages but remains a patient-specific choice.<sup>2,32</sup> Many factors must be considered when choosing between IVIG and SCIG, including patient characteristics, pharmaceutical formulation factors, patient preference, and patient lifestyle and abilities, among others. ■

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