Clinical Focus
ON PRIMARY IMMUNODEFICIENCIES

Subcutaneous Immunoglobulin Replacement

Authors
FRANCISCO A. BONILLA, MD, PhD
CARLA DUFF, CPNP, MSN, CCRP

Editor
MARK BALLOW, MD
This book contains general medical information which cannot be applied safely to any individual case. Medical knowledge and practice can change rapidly. Therefore, this book should not be used as a substitute for professional medical advice.

Immune Deficiency Foundation Clinical Focus on Primary Immunodeficiency: Subcutaneous Immunoglobulin Replacement

Copyright 2015 by Immune Deficiency Foundation, USA.

Readers may redistribute this article to other individuals for non-commercial use, provided that the text, html codes, and this notice remain intact and unaltered in any way. Clinical Focus on Primary Immunodeficiencies: Subcutaneous Immunoglobulin Replacement may not be resold, reprinted or redistributed for compensation of any kind without prior written permission from Immune Deficiency Foundation. If you have any questions about permission, please contact: Immune Deficiency Foundation, 110 West Road, Suite 300, Towson, MD 21204, USA; or by telephone at 1-800-296-4433.
Subcutaneous Immunoglobulin Replacement

Authors
Francisco A. Bonilla, MD, PhD
Carla Duff, CPNP, MSN, CCRP

1 Director, Clinical Immunology Program, Boston Children’s Hospital, Boston, MA
Associate Professor of Pediatrics, Harvard Medical School, Boston, MA

2 Advanced Registered Nurse Practitioner, University of South Florida, St. Petersburg, FL.

Address:
Boston Children’s Hospital
300 Longwood Avenue
Boston, MA 02115
Phone: (617) 355-8594
Fax: (617) 730-0310
Email: francisco.bonilla@childrens.harvard.edu

University of South Florida
601 5th Street South, 3rd Floor
St. Petersburg, FL 33701
Phone: (727) 727-4150
Fax: (727) 767-8532
Email: cduff@health.usf.edu

Introduction
The first published therapeutic use of human Ig appeared in the medical literature in 1952. Colonel Ogden Bruton gave subcutaneous infusions of Ig to a boy with agammaglobulinemia and showed that the serum electrophoresis gamma globulin peak became detectable and the frequency and severity of bacterial infections was diminished. Purified polyclonal human Ig for general therapeutic use has been available since the 1960’s.

Intramuscular injection of Ig is painful, and it is difficult to administer amounts of Ig intramuscularly sufficient for protection from infection. As Ig purification methods improved, Ig products suitable for intravenous administration (IVIG) became available in the 1980’s. These products are well-tolerated by a majority of patients. However, some patients have systemic side effects (discussed further below) during or after infusion. In addition, some patients experience the cyclical rise and fall of IgG levels between intravenous infusions as cyclical periods of relative malaise when IgG levels are low.

Subcutaneous administration of Ig (SCIG) is associated with minor local side effects and fewer systemic effects in comparison to IVIG. It is administered without the need for IV access and usually in smaller and more frequent doses so that the IgG level in the body remains relatively consistent, without the fluctuation characteristic of IVIG given every 3 or 4 weeks.

Use of SCIG has continued to grow slowly in the U.S. since the Food and Drug Administration (FDA) approved the first product intended for subcutaneous administration. Several products (described below) now have FDA approval for subcutaneous administration and SCIG accounts for an increasing fraction of Ig replacement therapy.

Ig products originally formulated for intravenous use can also be administered via the subcutaneous route, and some of these products have been approved by the U.S. Food and Drug Administration (FDA) for both routes of administration. Some products have been formulated specifically for subcutaneous use and cannot be administered IV. One of these products has entered the market very recently and represents a novel technique of subcutaneous administration facilitated by prior infusion of recombinant human hyaluronidase. In this guideline, any Ig administered by the subcutaneous route will be referred to as SCIG, with the exception of the hyaluronidase-facilitated product which will be referred to as Hy-SCIG.
Pharmacokinetics of Ig Administered by the Intravenous and Subcutaneous Routes

Immediately following an IVIG infusion of approximately 300-500 mg/kg, the serum IgG level increases 2-fold or more since the entire dose is in the intravascular space (Figure 1). Over the subsequent 48-72 hours, Ig diffuses out of the circulation into extravascular spaces, and eventually equilibrates into a volume of distribution approximately equal to the total extracellular fluid. Following this equilibration phase, the Ig is catabolized with first order kinetics and a half-life of about 21 days. Note that this is an average half-life of physiologic Ig in the circulation. Measured average half-lives of Ig in clinical trials are usually longer with significant variation between products ranging from 28-45 days, particularly in immunodeficient patients. It is also critical to note that there is tremendous variation between individuals. In clinical trials of IVIG, even with a single preparation, variation in serum Ig half-life between individuals can be as high as 6-fold (range 15-88 days).

IVIG is usually given at a 3 or 4 week dosing interval. During this period, the range of Ig concentrations from peak to trough usually varies by 250 to 300% of the trough values (Figure 1). In contrast to the high peaks achieved after periodic IV infusions, most SCIG regimens fractionate the monthly dose into smaller increments which are given every 1-14 days. Hy-SCIG is distinct; Hy-SCIG is designed to be used in regimens more similar to IVIG administered every 3-4 weeks.

Following a subcutaneous Ig infusion, the equilibration of the Ig into its eventual volume of distribution is achieved by diffusion into the lymphatics from the local site, into the vascular space, then out again into extravascular spaces throughout the body. Ig is absorbed from a subcutaneous infusion site over the course of a week, with most of the absorption occurring in the first 48 hours. Thus, the high peaks seen with intermittent larger IV infusions are markedly truncated. With weekly or more frequent SCIG infusions, the range of serum Ig concentrations from peak to trough may vary by less than ± 10% around the mean (Figure 1). This has been shown to result in essentially constant serum Ig concentrations over time. The pharmacokinetics of Hy-SCIG is intermediate between IVIG and SCIG, with a blunted broad early peak of concentration and a trough similar to IVIG (Figure 1).

The area under the curve of a plot of serum Ig concentration (Y-axis) vs time (X-axis) (Figure 1) is a measure of the bioavailability of an infused Ig product. The bioavailability of SCIG is approximately 2/3 in comparison to the same amount of Ig administered IV. This may be taken into account when prescribing an Ig replacement regimen. This will be discussed further below. The bioavailability of Hy-SCIG is approximately 93% of IVIG and they are considered bioequivalent.

Figure 1.

Kinetics of Serum IgG Levels
Efficacy, Safety, and Tolerability of Ig Administered by the Intravenous and Subcutaneous Routes

Efficacy
For replacement therapy for immunodeficiency, most Ig clinical trials focus on patients with XLA and common variable immunodeficiency (CVID). All FDA-approved Ig products meet a standard of efficacy. In the U.S., efficacy is judged by the incidence of acute serious bacterial infections (SBI) per patient per year. The FDA has defined rigorous criteria for diagnosing the infections fitting into this classification, which include bacteremia/sepsis, pneumonia, visceral abscess, osteomyelitis/septic arthritis, and bacterial meningitis. The minimal acceptable criterion for licensing of a new Ig product in the U.S. is that the upper bound of the 99% confidence interval around the mean for the annual incidence of these infections in patients with XLA and/or CVID must be <1 (in most trials it is much lower).

A meta-analysis of clinical trials of Ig replacement showed a number of important findings. First, trough IgG levels increase more or less linearly with cumulative dose up to approximately 1 g/kg/month. There is no plateau or diminishing slope with higher doses up to this limit. Even more important, there is a linear decrease in the incidence of pneumonia with increasing trough IgG level up to the same dose limit. There is no “point of diminishing returns” with respect to benefit with increasing dose. This likely reflects the fact that some individuals require relatively higher doses of Ig for clinical benefit in comparison to others. Higher dosing might be needed for other comorbidities such as bronchiectasis and protein losing enteropathies.

Several studies suggest that Ig administered subcutaneously is at least equal in efficacy to Ig administered intravenously, even though there have not been direct comparisons of the same Ig preparation given by the different routes. A meta-analysis of SCIG trials very similar to the study reported for IVIG above led to very similar conclusions. That is:

1) no plateau effect of steady-state IgG level in relation to cumulative dose, and
2) no plateau with respect to the decrease rate of all reported infections in relation to the steady-state IgG level.

Note that Ig is generally dosed according to total body mass. Retrospective studies indicate that this is appropriate. Individuals with high BMI do not have greater or lesser increases in IgG levels with IVIG or SCIG in comparison to those with low BMI when dosed according to total body weight. Thus, it is not appropriate to use ideal body weight or lean body mass as a denominator for Ig dosing. The retrospective studies cited suggest that such an approach would likely lead to under-dosing.

Safety
IV and SC products/routes are also generally equivalent with respect to safety (mainly lack of disease transmission). Several Ig products are FDA-approved for both IV and SC administration. Note that Hizentra® and HyQvia® are formulated only for SC use and cannot be given IV. All Ig products available in the U.S. are made solely from plasma collected from carefully screened and tested U.S. donors, and all of the manufacturing procedures include steps which have been shown to inactivate and/or partition multiple types of viruses. There is no evidence to suggest that the risk of acquiring blood borne viruses or prions varies with SC vs. IV administration. There are no reported cases of disease transmission by SCIG, and none with IVIG since 1994. None of the Ig preparations currently available in the U.S. contains thimerosal or other mercury-compound preservatives. However, contraindications, precautions and warnings can differ among products.

Rare cases of anaphylaxis during IVIG administration have been reported in association with IgG anti-IgA antibodies in patients with IgA deficiency. (Note that there is a single published report of anaphylaxis in association with IgE anti-IgA antibody.) SCIG contains small amounts of IgA, comparable to several preparations of IVIG. There are no published reports of anaphylaxis with SCIG in patients with IgA deficiency. In fact, patients who have had anaphylactic reactions with IVIG (whatever the mechanism may have been), have tolerated SCIG. Although all Ig products (IVIG and SCIG) carry the same warning related to use in patients with IgA deficiency, it should be
emphasized that anaphylaxis by any mechanism is a very rare event with any form of Ig therapy, including patients with IgA deficiency. This is a potential concern only in patients with absent IgA (i.e., below the limit of detection or <5-7 mg/dL) and who have high levels IgG of anti-IgA antibody18.

Thrombotic events are a rare complication of Ig therapy, occurring in approximately 0.1% of treated individuals overall19, 20. These occur more often with rapid high-dose IVIG infusions, but they have been reported with SCIG as well. This complication is thought to arise primarily from activated clotting factor Xlla which is a contaminant present to varying degrees in Ig preparations. Patients at highest risk have a history of prior thrombosis or vasculitis or other factor predisposing to risk of thrombosis.

Hemolysis may also occur in association with Ig therapy, either IV or SC21, 22. Clinically significant hemolysis is estimated to occur in approximately 1:10,000 infusions; recognition may be delayed >24 hr. Anemia can be severe enough to require transfusion. Hemolysis is seen with much greater frequency with IVIG in comparison to SCIG. Hemolysis is due to isoagglutinins present in therapeutic Ig, especially anti-A21. Risk factors include pre-existing hemolytic disease, inflammatory states, and rapid high dose infusions. Rare cases of acute renal failure and death have been reported. Current US and EU standards require isoagglutinin titers <1:6421.

**Tolerability**

Adverse events differ somewhat between IVIG and SCIG23, 24. Most patients tolerate IVIG without side effects and do not require pre-medication. However, in 10-25% of patients there are mild side effects that occur during or soon after infusion. These symptoms can include headache, back or abdominal pain, malaise, nonspecific or urticarial rashes, and cough. About 5% of patients have more severe symptoms that may mimic hypersensitivity reactions or flu-like illness with fever, myalgia/arthralgia, rhinorrhea, and wheeze. Perhaps 1% or fewer patients will have severe rigors, or a presentation similar to aseptic meningitis that appears 24-72 hours after infusion. The great majority of these symptoms are relatively easily controlled with pre-hydration, slow infusion, non-steroidal anti-inflammatory drugs, antihistamines, and occasionally corticosteroids. Anaphylaxis with IVIG is very rare (<1:10,000 infusions) and has not been reported with SCIG.

**Table 1**

Ig products and FDA-approved routes of administration

<table>
<thead>
<tr>
<th>Product</th>
<th>Intravenous</th>
<th>Subcutaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bivigam®</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Carimune®</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Flebogamma®</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Gammagard Liquid®</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Gammagard SD®</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Gammaked®</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Gammaplex®</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Gamunex-C®</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Hizentra®</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>HyQvia®</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Octagam®</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Privigen®</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>
Systemic symptoms are less frequent in patients receiving SCIG. The relative freedom from systemic effects of subcutaneously administered Ig is likely due, at least in part, to the slower absorption and equilibration of the Ig into the circulation. In contrast to the freedom from systemic adverse effects, the incidence of local reactions at the infusion sites may be quite high, particularly when patients first begin to use the subcutaneous route. Rates of local reactions as high as 80-90% with initial subcutaneous infusions have been recorded, although the incidence of these reactions falls below 30% within 1-2 months of continued weekly subcutaneous treatments.

Local reactions (Figure 2) often include swelling, which in some cases may seem to be bigger than the volume of Ig infused depending on distribution of subcutaneous tissue, and erythema. Sometimes there can be a sensation of burning or itching. These local reactions are rarely considered painful or serious. Some patients may experience swelling without erythema, or vice versa (Figure 3). Often, adjustment of ancillary supplies will mitigate site reactions (Figure 4). The swelling and erythema almost always dissipate completely within 24 hours after the infusion is finished. In most cases, by 72 hours, it is difficult to identify the site at which subcutaneous Ig was given.

The severity of these types of reactions and the incidences with which they occur have been reported to decrease dramatically as the patient continues with SCIG. The reasons for this are not clear. Certainly, there is some subjectivity in the patient’s reporting of symptoms, and they may report decreased severity as they “get used” to these local reactions. However, objective signs of site reactions also seem to improve with time. Examination of patients who have used the subcutaneous route for many years fails to reveal any chronic local change in the tissues such as fibrosis or lipodystrophy. Some patients may develop isolated hard nodules or “pearls” below the sites of individual infusions but these are usually not tender, and usually regress spontaneously over a few weeks or months. Infusion into sites with nodules should be avoided in order to hasten resolution. Local adverse effects of Hy-SCIG are comparable to SCIG. Systemic symptoms after Hy-SCIG are greater than with SCIG, but less than what is observed after IVIG.

Reactions at sites of Subcutaneous Infusions

Figure 2.
Slight Erythema and Swelling During Infusion
Infant receiving subcutaneous Ig into site on left thigh. Note typical amount of swelling and erythema. Baby is not bothered by this and carries on playing.

Effects on Quality of Life for Patients with Primary Immunodeficiency Disease (PI)

Because the volume of Ig that can be comfortably and conveniently infused SC at one time is limited, most SCIG regimens fractionate the total monthly Ig dose into 4 or more infusions, which are given weekly or more frequently. Volumes can vary dramatically based on frequency, concentration, and dosage with ranges from 1-50 mL with SCIG and from 50-600 mL per site with Hy-SCIG. Low dose daily infusions are also possible and preferred by some patients.

Since the subcutaneous route has a very low risk of serious systemic reactions, self, partner or parent administration of SCIG at home is routine. The freedom from dependence on trained medical personnel and/or

(Photo courtesy D. Sedlak, Duke University)
Reactions at sites of Subcutaneous Infusions

Figure 3.
Subcutaneous Infusion (SCIG)

0 minutes post infusion

8 hours post infusion

24 hours post infusion

(Reprinted with permission from CSL Behring, LLC)

Figure 4.
SCIG Initial Regimen

Initial SCIG regimen

Technical or clinical complaints?

NO

YES

Adjust ancillary supplies:
• Skin preparation
• Tape
• Transparent dressing

Consider administration parameters:
• Volume
• Flow rate
• Site of infusion
• Number of infusion sites

Continued complaints?

YES

YES

Adjust ancillary supplies:
• Subcutaneous needle set length and diameter
• Infusion pump device/syringe driver
• Change SCIG needle (length/gauge, type/brand)

Continue evaluation: tolerability generally increases over time
special facilities for routine Ig treatments is appreciated by most patients. Several quality of life studies have been performed in at least 7 such studies, quality was significantly better with SCIG compared to IVIG. Dimensions that were improved with SCIG included global/general health, bodily pain, role social/emotional and physical, parental impact/emotional and time, family activities, vitality, mental health and social functioning.

Studies are limited, but some suggest that SCIG may also be more cost effective than IVIG.

**Patient Selection**

There are two sets of considerations which contribute to the decision as to which route of therapy might be best for any individual patient with PI in any given set of circumstances (Table 2). The first set is comprised of clinical factors which might make SCIG preferable, such as problems in obtaining IV access, intolerability from relatively large intermittent IV doses, and suboptimal clinical conditions resulting from low Ig serum trough level (wear off effect). The second set includes factors which have more to do with the patients’ perception of their quality of life than with their clinical condition. Decisions for treatment options should be individualized based on each patient's medical condition(s) as well as patient input. Full involvement of patients in their treatment decisions has the potential to improve compliance and adherence resulting in improved quality of life and patient outcomes. A recent study by Samaan et al. demonstrated engaging the patient and empowering patient choice without preconceived opinions resulted in a high rate of compliance.

That said, when patients are given more control over their management and feel more empowered, they may also be free to make poor decisions about changes in their infusion schedules, or may be less adherent to their regimen, overall. Regular follow-up visits with specific questioning about any lapses or changes in the dose regimen together with more frequent monitoring of IgG levels are necessary to insure adherence.

**Table 2**

**Considerations in Selecting Route of Ig Therapy**

<table>
<thead>
<tr>
<th><strong>Clinical Factors Favoring SCIG</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Difficult IV access</td>
</tr>
<tr>
<td>• Systemic adverse effects during or after IV infusions</td>
</tr>
<tr>
<td>• Adverse effects/suboptimal health at trough when IV infusion due</td>
</tr>
<tr>
<td>• Risk for thromboembolic events or hemolysis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Lifestyle/Psychological Factors in Choosing Route of Administration</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Patient/family preference</td>
</tr>
<tr>
<td>• Distance from/accessibility of infusion center</td>
</tr>
<tr>
<td>• Patient/family schedule</td>
</tr>
<tr>
<td>• Availability of home nursing services</td>
</tr>
<tr>
<td>• Ability to learn and perform infusions</td>
</tr>
<tr>
<td>• Availability of partner/parent/&quot;infusion buddy&quot;</td>
</tr>
<tr>
<td>• Home environment</td>
</tr>
<tr>
<td>• Reliability of patient or parents</td>
</tr>
<tr>
<td>• Insurance/reimbursement issues</td>
</tr>
</tbody>
</table>
Developing Individualized Treatment Regimens

The decrease in systemic adverse reactions and lack of requirement for trained healthcare professionals allows great flexibility in the choice of the SCIG regimen to be used for any given patient. For example, some patients prefer taking infusions slowly into a single site while they sleep. Other patients prefer multiple sites and a short infusion time weekly or less. Others may prefer to use a small amount in a single site more frequently, even daily, etc. Considerations for SCIG regimens are summarized in (Table 3). Note again that the dosing regimens for Hy-SCIG are intended to be parallel with IVIG.

Ig Dose for Replacement

On a monthly basis, the “average” hypogammaglobulinemic patient requires between 300 and 800 mg/kg body weight via IV (or Hy-SCIG) infusion. Most patients do well in the 0.4-0.6 g/kg range, some can get by with less and others require more. The keys are to individualize the dose and titrate to clinical outcomes. Recall that Ig half-life varies greatly between individuals. It is critical to follow patients’ IgG levels and clinical course closely when initiating or modifying the regimen.

As mentioned above, the bioavailability of SCIG is less (about 2/3) in comparison to the same amount administered IV. Thus, when changing a patient established on IV therapy to SC, the monthly amount may be increased by a factor of approximately 1.3. However,

Table 3

Interrelated Variables to be Considered in Selecting a Regimen for Subcutaneous Ig Infusions.

<table>
<thead>
<tr>
<th>Cumulative monthly dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Initial therapy: 0.6-0.7 g/kg body weight</td>
</tr>
<tr>
<td>• Switch from IV: 1.3 X IV dose</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Infusion dose and interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Interval may range from daily to every 2 weeks</td>
</tr>
<tr>
<td>• Infusion dose depends on interval to make up monthly total</td>
</tr>
<tr>
<td>• ALWAYS USE UNIT DOSES!</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of infusion sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Depends on BMI</td>
</tr>
<tr>
<td>• Low BMI: 5-10 cc/site</td>
</tr>
<tr>
<td>• Medium BMI: 10-20 cc/site</td>
</tr>
<tr>
<td>• High BMI: 20-50 cc/site</td>
</tr>
<tr>
<td>• Larger volumes may be accommodated with longer (&gt;1 hr) infusion times</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Infusion time</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 5-20 min. for small infusions (5-20 cc)</td>
</tr>
<tr>
<td>• 30-60 min. for larger/multi-site infusions</td>
</tr>
<tr>
<td>• &gt;60 min. to accommodate larger volumes in fewer sites</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Infusion method</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Push by hand for small (5-20 cc) single-site infusions</td>
</tr>
<tr>
<td>• Pump for larger multi-site infusions</td>
</tr>
</tbody>
</table>
there is considerable variability in opinion about this, with many providers choosing to use the same dose that was given IV. When initiating SCIG therapy for a patient who has never received Ig before, consider a monthly dose of 600-700 mg/kg. Several studies suggest improved outcomes with higher SCIG doses. When a patient is initiating SCIG therapy and it is desired to bring the IgG level into a steady state as quickly as possible, one may consider administering (a) loading dose(s) either by IV or SC. A typical IV loading dose would be 1,000 mg/kg (roughly the total amount of IgG in a healthy adult). The replacement SCIG dose may be given on the same day, or within one week following the loading dose. Smaller loading SCIG doses may be given on 3-5 consecutive days to reach the cumulative 1 g/kg total loading dose followed immediately by the replacement regimen.

The dose interval for SCIG can be anywhere from 1-14 days. Note that therapeutic Ig is a precious commodity that should not be wasted, it is never appropriate to use a fraction of a unit dose and discard the remainder. The dose interval can always be adjusted, if necessary. With the variety of dosage forms available, almost any product can be used with great flexibility.

Areas of the body commonly used for infusion are those with some subcutaneous tissue such as the abdomen, inner thighs, flanks, buttocks, and the posterior upper arm. It is recommended to rotate the sites used with each infusion. The number of sites to use for infusion and the amount to infuse in each site are a function of the body mass index, the infused volume and the speed of infusion. A slender individual cannot accommodate a large subcutaneous infusion. A single site may only comfortably receive 5-20 cc. An overweight individual can tolerate up to 30-50 cc in one site. Smaller volumes may be infused rapidly in 15-30 minutes, larger volumes more slowly (1-2 hours or more). SCIG is appropriate for all ages. Neonates and infants can receive SCIG (SCIG products have not been studied in licensing trials below 2 years old; Hy-SCIG and Gamunex-C are licensed for use in adults only). In fact, SCIG may be preferable in infants, young children and geriatrics since IV access is not required. Administration of Hy-SCIG can be more complicated because of the two drug regimen and the different type of tubing needed. Just as Ig dosing must be individualized to achieve therapeutic clinical outcomes, so should the SCIG regimen be individualized to optimize frequency, infusion rate and site selection for best outcomes. Below are some examples of individualizing SCIG therapy.

**Examples**

1) A 10 kg child is starting SCIG at a dose of roughly 7 g Ig (700 mg/kg) monthly. This could be given as 1 g every 4 days, 2 g every 8 days, or 3 g every 12 days. Remember, use unit doses only! For an Ig product with a concentration of 20%, a 1 g dose has a volume of 5 cc and can be given in a single site over 30 minutes or less. Even a 2 g (10 cc) dose might be accommodated in a single site with a slower infusion time. The 3 g (15 cc) dose might need to be split into 2 sites, if the child is slender. If one is using a product with 10% concentration, then the volumes will be double for the same dose. In this example, the highest dose/volume would be 3 g or 30 cc which might need to be given in 3 sites, depending on the infusion time.

2) A 40 kg child is doing well on IVIG and wants to switch to SCIG. The current regimen is 20 g (500 mg/kg) monthly. You wish to give roughly 1.3 x 0.5 g/kg = 650 mg/kg or 26 g monthly. A 20% solution could be given as 5 g every 6 days or 10 g every 12 days. One could also choose to start at a lower cumulative dose such as 5 g weekly or 10 g every 2 weeks. This could even be given as 1 g daily on any 5 days per week. If the patient doesn’t do well, the dose can be increased to 6 g weekly or 12 g every 2 weeks, etc. Considerations of number of sites and volume per site again depend on concentration (double volumes for 10% solution), BMI, and rapidity of infusion, as discussed above.

3) A 70 kg adult is established on 35 g every 3 weeks IVIG, or approximately 44 g monthly. You switch to SCIG at a dose of roughly 1.3 x 44 = 57 g monthly. A 20% solution could be given as 2 g (10 cc) daily, 4 g (20 cc) every other day, 7 g (35 cc) twice per week, 14 g (70 cc) weekly, 20 g (100 cc) every 10 days or 28 g (140 cc) every 2 weeks. This patient decides that they like the daily dose because they can give it to themselves in a single site in 10-15 minutes.
SCIG Therapy in Practice

The management and treatment of PI is a complex process that may be difficult for some patients. Prior to initiating SCIG therapy, the treatment options including routes, frequency, volume, and brands as well as the advantages and disadvantages for each option need to be discussed with the patient. This should be a frank and open discussion without bias and allow for collaboration in the decision making. When patients are part of the decision making process, they are more likely to be compliant and have a positive outcome.

SCIG therapy has many advantages over IVIG including flexibility of administration, steady state Ig levels, and patient autonomy. As SCIG does not require IV access, the patient can perform the infusion anywhere, anytime. Since SCIG is gradually absorbed, systemic adverse reactions due to a large increase in Ig levels typically associated with IVIG (including headaches) are not as common with SCIG. The disadvantages associated with SCIG include more frequent dosing and whether the patient is willing or able to perform the infusion. As new products have emerged with different dosing intervals, SCIG can now be administered weekly, biweekly, and monthly, thus providing options for patients.

Before beginning SCIG, the patient must be informed of the benefits as well as the risk associated with Ig replacement therapy. Patients should be well informed about therapy benefits as well as Ig therapy risks mentioned earlier: All IVIG and SCIG products have similar warnings and contraindications such as possible renal failure, thrombotic events, aseptic meningitis, hemolysis, and anaphylactic reactions. Hy-SCIG has additional warnings regarding theoretical possible impact on male fertility of anti-hyaluronidase antibody. Note that there has not been any such demonstrated effect, but all relevant warnings for a particular product should be discussed with the patient before initiating therapy.

A discussion regarding expectations including infusion time, instructions for self-administration, necessary equipment and supplies, resources available, and common side effects including site reactions should occur before the patient begins therapy. Patients with realistic expectations tend to be more compliant and have more positive outcomes.

The patient should expect that an educated and experienced infusion nurse will be providing their SCIG training. In addition to discussing expectations, the nurse will provide education regarding self-administration skills and provide individualized learning tools for each patient receiving SCIG therapy. The patient will be expected to demonstrate proficiency to the infusion nurse, and it may take 3-4 training sessions for the patient to feel comfortable to perform the infusion alone.

During the training sessions, it may be helpful for a parent, partner, or friend to be present to learn the self-administration process to offer support and assistance when the patient performs the infusions. As patients must be proficient in infusion preparation, infusion set up and administration, and infusion supply disposal, the teaching steps for each section will be tailored to the individualized regimen for the patient. Patients must also demonstrate proficiency in hand washing, aseptic technique, proper use of equipment, proper storage and handling of medication and supplies, disposal of medication and supplies, and documenting the infusion in their therapy journal or electronic personal health record, such as the IDF ePHR, designed for patients with PI. A patient may be deemed proficient to self-administer when the patient can do a return demonstration without prompting or “teach” it back to the nurse. A detailed checklist of these skills should be provided to the patient as a reference tool (see Appendix 2).

The infusion nurse should provide the patient with continued support, including weekly phone calls, especially during the transition phase which typically lasts 3 months. If the patient should experience difficulty administering SCIG, a follow up visit to observe the administration technique may be warranted. A discharge instruction sheet detailing whom to call for any infusion related issues as well as a schedule for follow up visits with the provider should be provided to the patient. Most importantly, the patient should be informed that often the regimen or ancillary supplies will need to be adjusted and that they should contact the infusion nurse or their
provider to troubleshoot any SCIG infusion issues (see Appendix 1). There is a variety of educational materials and references available to the patient, infusion nurse, and provider (Table 4) to ensure that the patient is successful performing self-administered SCIG infusions.

**Summary**
SCIG is as efficacious as IVIG for treatment of primary immunodeficiencies. Clinical advantages include less systemic adverse reactions, particularly useful in patients who have experienced or are at risk for complications of IVIG treatment. SCIG is suitable for self-administration and does not require venous access; thus, patients no longer need to schedule an appointment for each infusion but instead have the flexibility to manage their therapy. SCIG allows patient input for designing an optimal therapy regimen. However, independence from the office/infusion suite also places increased responsibility on the patient or parents. SCIG regimens are very flexible with respect to frequency of infusions, and many patients appreciate the increased flexibility and autonomy conferred by home subcutaneous treatment and report increased quality of life.

**Table 4**
Reference and Educational Materials

<table>
<thead>
<tr>
<th>Reference and Educational Materials</th>
<th>wwwadresse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune Deficiency Foundation</td>
<td><a href="http://www.primaryimmune.org">www.primaryimmune.org</a></td>
</tr>
<tr>
<td>International Patient Organization for Primary Immunodeficiencies</td>
<td><a href="http://www.ipopi.org">www.ipopi.org</a></td>
</tr>
<tr>
<td>Jeffrey Modell Foundation</td>
<td><a href="http://www.info4pi.org">www.info4pi.org</a></td>
</tr>
<tr>
<td>Baxter International Inc.</td>
<td><a href="http://www.baxter.com">www.baxter.com</a></td>
</tr>
<tr>
<td>Bio Products Laboratory</td>
<td><a href="http://www.bpl.co.uk">www.bpl.co.uk</a></td>
</tr>
<tr>
<td>Biotest Pharmaceuticals Corporation</td>
<td><a href="http://www.biotestpharma.com">www.biotestpharma.com</a></td>
</tr>
<tr>
<td>CSL Behring</td>
<td><a href="http://www.cslbehring.com">www.cslbehring.com</a></td>
</tr>
<tr>
<td>Grifols</td>
<td><a href="http://www.grifols.com">www.grifols.com</a></td>
</tr>
<tr>
<td>Kedrion</td>
<td><a href="http://www.kedrionusa.com">www.kedrionusa.com</a></td>
</tr>
<tr>
<td>Octapharma</td>
<td><a href="http://www.octapharma.com">www.octapharma.com</a></td>
</tr>
</tbody>
</table>

**Disclosures**

Dr. Bonilla has been a consultant for Baxter, the Cowen Group, CSL Behring, the Gerson-Lehrman Group, and Grand Rounds Health. He also receives royalties from UpToDate in Medicine, and is a member of the Medical Advisory Committee and the Consulting Immunologist Program of the Immune Deficiency Foundation.

Ms. Duff has served as a nurse consultant for CSL Behring and Baxter Healthcare, is a member of the International Nursing Group for Immunodeficiencies (INGID), the Immune Deficiency Foundation Nurse Advisory Committee, National Association of Pediatric Nurse Practitioners (NAPNAP), and American Academy of Allergy, Asthma, and Immunology. She has received research support from CSL Behring.
References

1. Khan WN. Colonel Bruton’s kinase defined the molecular basis of X-linked agammaglobulinemia, the first primary immunodeficiency. Journal of immunology. 2012;188(7):2933-5.


Appendix 1

Nursing Guide for Troubleshooting SCIG Administration

Leaking at Site
- Assess catheter: is it fixed securely?
- Assess site location needle placement. Site location should not be subject to movement.
- Assess amount of subcutaneous tissue at injection site and, if appropriate, consider site with more tissue.
- Assess length of catheter: may be too short—can suggest catheter brand change.
- Assess volume being infused: may be too much volume per individual site. Adjust accordingly.

Local Irritation (Redness, Swelling, Itching)
- Educate patients and caregivers that local reactions are common and expected. Most are mild in nature.
- Assess size: mosquito bite, raised wheal, quarter, plum, peach, grapefruit—size should be consistent with volume being infused and amount of subcutaneous tissue on patient; thinner patients may have more prominent raised area; decrease amount of volume per site as necessary. Adjust site location accordingly.
- Assess length of catheter: may be too short; can suggest longer catheter length or brand change to avoid discomfort.
- Assess if tape allergy: change to paper/hypoallergenic tape.
- Assess if rotating sites appropriately: may decrease frequency of rotation.
- Decrease volume per site and/or increase infusion time
- When priming the subcutaneous needle sets, do not allow drops of IgG to cover needle.
  o Prime dry, leaving a small amount of air before needle. It has been suggested that the IgG tracked through the intradermal space can cause site reactions such as redness and itching.
- Advise use of gentle massage, warm or cool compress post infusion.
- Stop the infusion if generalized urticaria is present. Contact physician.

Extreme Discomfort with Needle
- Assess length: may be too long and irritating to abdominal wall.
- Consider topical anesthetic prior to insertion.

Blood Return Observed
- Do not infuse in site that has blood return. Hizentra should be infused into subcutaneous tissue only.
- Do not administer intravenously.
- In single-site tubing, remove and discard appropriately. Use new set. Notify supplier of need for replacement sets.
- In multisite sets, clamp off the tubing that shows the blood return and then remove the catheter from that site. Check with prescribing physician regarding selecting alternative for accommodating fewer sites:
  o Infuse the drug with the remaining appropriately located sites, thus increasing volume per site. May need to recalculate to a slower rate of infusion if appropriate. Consider previous history of site reaction and other factors.
  o Infuse the original amount of volume per site with the sites that are in place. When completed, repeat the infusion session with new site to accommodate the remaining volume from the site that had blood return.
- Change entire setup and start over.

Long Infusion Times
- Check patency of tubing, number of sites, volume per site. Check site location (do not inject into skin that has scar tissue).
- Assess infusion rate settings, correct selection of tubing size and length to match infusion rates, check pump function, battery function, etc.
- Arrange observation of patient technique (specialty pharmacy provider or office visit).
Appendix 1 continued

**Needle Contaminated by Touching, Dropping, etc.**
- Aseptic procedures require that supplies not be contaminated. Discard questionable needles in appropriate waste container and restart procedure.

**Infusion Pump Stops During Infusion**
- Check battery. Check for any line occlusion. Do not override occlusion alarm and increase psi delivered.
- Check sets for down-line occlusion. Multisite sets may cause occlusion alarm due to codependence of lines.
- Change catheter brands or use single independent lines that equally connect off a multiextension pigtail.
- Change gauge of catheter needle.
- Change type of infusion pump to simple syringe driver.
- Contact specialty pharmacy provider or supplier for further information.
- If necessary, maintain a closed system (leaving all connections intact), remove syringe, leave tubing attached to site and manually push plunger forward slowly to deliver remaining volume. Depending on volume, this may take some time.

**Difficulty with Manipulating Syringes for Filling**
- Lubricate the barrel of the syringe for easy manipulation by aseptically pulling back on the syringe, and moving it up and down before drawing up solution or filling with air.
- Pull back the amount of air to be infused into the vial and then attach the needle aseptically to the syringe.
- Mark the level of mL to which the syringe should be drawn back by placing tape on the outside barrel at the necessary level.
## Appendix 2

### Training Checklist for Home Administered Subcutaneous Immunoglobulin (SCIG) Infusion Treatment

Specific steps to be assessed prior to patient/caregiver considered competent to self-administer medication in a home setting. Number of training sessions can be individualized for patients.

<table>
<thead>
<tr>
<th>Patient Name:</th>
<th>Clinician:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Person Responsible for Infusion:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Patient Name:</td>
</tr>
<tr>
<td></td>
<td>Caregiver Name:</td>
</tr>
<tr>
<td></td>
<td>Guardian Name:</td>
</tr>
<tr>
<td>(Please Circle One)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient Skills</th>
<th>Introduced Date</th>
<th>Reinforced Date</th>
<th>Competency Demonstrated Date</th>
<th>Competency Mastered Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>C/NYC Initials</td>
<td>C/NYC Initials</td>
<td>C/NYC Initials</td>
<td>C/NYC Initials</td>
<td></td>
</tr>
</tbody>
</table>

- **Describe transportation & storage requirements of specific product**
- **Define SCIG administration and location of site of infusion**
- **Listing of appropriate infusion sites and understanding of rotation of sites**
- **Understanding and demonstrated care of infusion site**
- **Description of appropriate supplies necessary to complete procedure**
- **Understanding of pump usage and what to do when not working or if alarm sounds**
- **Understanding of “push” method as an alternative or when pump is unavailable**
- **Understanding of how to check product/prepare product and how to report wastage/unused product**
- **Ability to prepare infusion site and draw up product from single or multiple vials and prime tubing**
- **Demonstrated insertion of subcutaneous catheter /checking for blood/what actions to take if blood is present**
- **Demonstrates appropriate aseptic technique**
- **Demonstrates accurate administration of treatment, and removal and safe disposal of needle**
- **Demonstrates ability to accurately record infusion treatment information in diary**
- **Understanding of potential situations/reactions which could result from the infusion**
- **Understanding of correct management of any reactions to treatment**

*Form collated from contributions from Baxter, CSL Behring and Octapharma*
IDF Services for Healthcare Professionals
IDF offers services and resources for healthcare professionals. Visit www.primaryimmune.org/healthcare-professionals to learn more.

**IDF Consulting Immunologist Program:** A free service for physicians which provides the opportunity to consult with expert clinical immunologists about patient specific questions and obtain valuable diagnostic, treatment and disease management information regarding PI. Visit www.primaryimmune.org/consult

**IDF & USIDNET LeBien Visiting Professor Program:** Promotes improved knowledge by providing faculty at teaching hospitals with a Visiting Professor with expertise in PI and offers Grand Rounds and clinical presentations at medical institutions throughout the U.S.

**IDF Online Continuing Education Course for Nurses (English):** Primary Immunodeficiency Diseases and Immunoglobulin Therapy: A free, 5-hour, U.S. accredited course for nurses that provides an update on PI, immunoglobulin therapies and the nurse’s role with these therapies. Video Translations for Nurses in French, German, and Spanish are also available. www.primaryimmune.org/healthcare-professionals/continuing-education-course-for-nurses

**United States Immunodeficiency Network (USIDNET):** USIDNET is a research consortium established to advance research in the field of PI by maintaining a primary immunodeficiency disease registry, and providing education and mentoring for young investigators. USIDNET, a program of the Immune Deficiency Foundation (IDF), is funded in part by the National Institute of Allergy and Infectious Diseases (NIAID) and the National Institutes of Health (NIH) an agency of the Department of Health & Human Services.

**IDF Medical Advisory Committee:** Comprised of prominent immunologists to support the mission of IDF.

**IDF Nurse Advisory Committee:** Comprised of exceptional nurses to support the mission of IDF. Available as a resource for nurses administering immunoglobulin therapy or treating patients with PI.

**IDF Publications for Healthcare Professionals**
All publications are available at no cost, and they can either be ordered, or downloaded and printed. www.primaryimmune.org/idf-publications.

**IDF Diagnostic & Clinical Care Guidelines for Primary Immunodeficiency Diseases 3rd Edition**

**IDF Guide for Nurses on Immunoglobulin Therapy for Primary Immunodeficiency Diseases 3rd Edition**

**Clinical Focus on Primary Immunodeficiencies:**
- “Chronic Granulomatous Disease”
- “Clinical Update in Immunoglobulin Therapy for Primary Immunodeficiency Diseases”
- “Subcutaneous IgG Therapy in Immune Deficiency Diseases”
- “Primary Humoral Immunodeficiency Optimizing IgG Replacement Therapy”
- “The Clinical Presentation of Primary Immunodeficiency Diseases”
- “Treatment and Prevention of Viral Infections in Patients with Primary Immunodeficiency Diseases”
- “IgG Subclass Deficiency”
- “Immunization Of The Immunocompromised Host”

**IDF Resources for Patients and Families**
IDF has numerous resources on primary immunodeficiency diseases for patients and families, including publications, peer support programs, online networks and forums, educational programs, disease management tools, and much more. We encourage you to visit www.primaryimmune.org to see the full spectrum of our offerings, and we urge you to order and distribute our publications, all free of charge. If you have any questions or need additional information, please contact us at 800-296-4433 or info@primaryimmune.org.
The Immune Deficiency Foundation, founded in 1980, is the national patient organization dedicated to improving the diagnosis, treatment and quality of life of persons with primary immunodeficiency diseases through advocacy, education and research.