

Chapter 28

Immunoglobulin Replacement Therapy

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Immunoglobulin (Ig) replacement therapy is one of the most important and successful therapies for people with primary immunodeficiency diseases (PI) that affect antibody production. The therapy is both lifesaving and often lifelong, and it plays a huge role in the lives of many people with PI. The first commercial Ig for intravenous use was approved in 1981 for people with antibody immune deficiency.

What Is Immunoglobulin Replacement Therapy?

There are several specific medical therapies available for people with PI involving antibody deficiencies. Antibody deficiencies account for more than 50% of the disorders. These illnesses, such as Common Variable Immune Deficiency (CVID), X-linked Agammaglobulinemia (XLA), and other disorders, are characterized by a lack of and/or impaired antibody function.

Immunoglobulin or Ig, also known as gamma globulin or immune globulin, refers to the liquid plasma component of blood that contains immunoglobulins or antibodies. These antibodies have the important role in the immune system of neutralizing bacteria and viruses, and enhancing the phagocytosis and destruction of bacteria, certain viruses, and other pathogens.

When antibody molecules recognize a microorganism as foreign, they physically attach to it and set off a complex chain of events involving other components of the immune system that work to eventually destroy the infection. Antibodies vary with respect to their specialized functions in the body. These variations are determined by the antibody's chemical structure, which in turn determines the class of the antibody (or immunoglobulin). There are five major classes of antibodies (IgG, IgA, IgM, IgD and IgE). IgG has four

different subclasses (IgG1, IgG2, IgG3, IgG4). IgA has two subclasses (IgA1 and IgA2). Only the IgG is purified from plasma in the production of therapeutic Ig products, so Ig used for treatment contains 95-98% pure IgG with only small amounts of other plasma proteins including some IgA and IgM.

It is important to understand that the Ig given to people with PI partly replaces what the body should be making, but it does not stimulate the individual's own immune system to make more Ig. Since Ig only replaces the missing end product but does not correct the person's defect in antibody production, Ig replacement therapy is usually necessary for the individual's lifetime. In addition, the Ig only provides temporary protection. Most antibodies, whether produced by their own immune system or given in the form of Ig replacement, are used up or metabolized by the body and must be constantly replenished. Approximately half of the infused antibodies are metabolized over three to four weeks, so repeat doses of Ig are required at regular intervals. Ig replacement therapy reduces the susceptibility to infections, can optimize health, and improve quality of life. As with any treatment, however, individual risks and benefits should be discussed with a healthcare provider.

Before starting Ig replacement therapy, it is important that the provider completes all the immune studies to demonstrate that the individual's immunoglobulins

are not only low but also that the individual does not make specific antibodies. People who do not have antibody disorders normally make antibody during and after natural infections and in response to immunization with vaccines. Immunologists generally use tetanus toxoid and pneumococcal vaccines (Pneumovax® or Prevnar®) to test the ability of the person to make specific antibodies. Blood is drawn before giving the vaccine to measure the vaccine specific antibody levels. After vaccination, a second blood sample is drawn four to six weeks later to determine how well specific antibodies are made to these vaccines. It is important that the individual completes this second blood draw to determine the response to the vaccine within this four to six-week timeframe. These results provide important information about the individual's immune condition and insurance companies often review this information before approving Ig replacement therapy. Once Ig replacement therapy is started, it is not possible to get accurate results for these important tests without stopping Ig treatment for a few months.

History

Gamma globulin derived from human plasma was first introduced as a treatment option in 1952 when gamma globulin was injected intramuscularly (IM) to treat people with recurrent infections who had antibody immune deficiencies¹. Dosing was very difficult because only small amounts of gamma globulin could be given in each painful shot. Much scientific investigation in the 1960s and 1970s finally led to a suitable gamma globulin product that could be used intravenously in the early 1980s. People with antibody disorders have been successfully treated with intravenous immunoglobulin replacement therapy (IVIG) for over 30 years.

With the discovery of well-tolerated preparations of IVIG in the 1980s, the suboptimal, painful IM administration was no longer used². This shift to IVIG changed the face of PI treatment. In primary or secondary hypogammaglobulinemia (low IgG), Ig replacement therapy protects against infections by providing an adequate amount of IgG in the blood³. Human immunoglobulin plays an important role in the treatment of many diseases, including diseases for which there is no other alternative treatment^{3,4}. Currently, more than 100 inflammatory and autoimmune disorders are also treated with IVIG.

Route of Administration

Ig replacement therapy is generally administered either intravenously (abbreviated IVIG), or subcutaneously (abbreviated SCIG). SCIG can be given in two ways: conventional or facilitated. The facilitated method uses an additional enzyme medication to increase the amount of Ig that can be delivered during each subcutaneous infusion. The individual with PI or caregiver and the prescriber should have a discussion about which route of administration is most appropriate. There are advantages and disadvantages for each route of administration (see Table 28:1). IVIG has allowed infusion of higher doses over a short time and historically has been the standard route of administration. It must be administered by a healthcare professional.

SCIG was utilized as early as the 1970s⁵, but it did not gain approval from the Food & Drug Administration (FDA) in the U.S. until 2006. This therapy does not require venous access and is associated with the slow release of Ig from the subcutaneous tissues into the blood, which enables IgG levels to remain consistent and steadier between infusions⁶.

Currently, among those receiving Ig replacement therapy in the U.S., approximately 50% use IVIG and 50% use SCIG. The individual with PI or caregiver and the prescriber need to make a decision on the route of therapy that is best for the individual person. All options are clinically effective. All therapies, regardless of route, must be individualized to meet the individuals' needs.

Manufacturing

There are more than 25 different Ig preparations available worldwide. The preparations vary in a number of ways, including the distribution of IgG subclasses, stabilizers, and infusion details. All Ig products are made from human source plasma. Source plasma is different than recovered plasma, which is collected through whole blood donation where plasma is separated from its cellular components. This source plasma is pooled from thousands of plasma donations by a process called plasmapheresis in which the liquid part (plasma) is separated from the red and white cells. The red and white cells are then returned to the patient. This allows a specific donor to return to the plasmapheresis center monthly.

Considerations for Choosing a Route of Administration for Ig Replacement Therapy

Table 28:1

	Intravenous Immunoglobulin (IVIg)	Facilitated Subcutaneous Immunoglobulin (fSCIg)	Subcutaneous Immunoglobulin (SCIg) (Conventional)
Frequency of Dosing	Every three to four weeks.	Every two, three, to four weeks.	From daily to every 14 days.
IgG Level	Achieves an initial high concentration of IgG that decreases gradually over approximately 21 days.	There is an initial peak (day 4), although not as extreme as with IVIg, and decreases gradually over 21 days.	No variation in IgG level once steady state is achieved; level stays constant.
Access	Requires intravenous (IV) access (NOT a port).	Does not require IV access. Individual can do their therapy independently once appropriately trained.	Does not require IV access. Individual can do their therapy independently once appropriately trained.
Needle Sticks	Usually one (to establish IV access).	One to two.	One to four or more, depending on dose and preference.
Time of Infusion	Usually three to four hours.	Usually three to four hours.	Variable. Data supporting safe, rapid (less than 30 minute) infusions and individuals who manually push their dose as rapidly as tolerated.
Ancillary People	Requires healthcare professional to establish IV access and monitor infusion.	Individuals can establish their own subcutaneous access once trained, but therapy requires a committed individual with PI or caregiver.	Individuals can do their own SCIg once trained.
Intra-infusion Systemic Side Effects	Possible, including chills, rigors, blood pressure changes, nausea/vomiting, aches.	Possible, but to a lesser degree than with IVIg.	Usually no systemic effects but localized burning or itching is possible.
Pre-medication	Sometimes necessary.	Sometimes necessary.	No, as drug is not biologically available for 24-36 hours.
Intra-infusion Local Side Effects	Not usually, unless IV infiltrates.	Sometimes some itching and burning.	Sometimes some itching or burning.
Post-infusion Side Effects	Systemic side effects possible.	Both local and systemic post-infusion side effects are possible.	Redness and swelling at the site of the infusion which decrease with subsequent infusions.
Cost	Cost for drug and nursing/infusion center.	Cost for drug and supplies.	Cost for drug and supplies.

Usually a pool or lot of Ig product is derived from approximately 10,000 donors. This ensures that a pool or lot of Ig contains a broad spectrum of specific antibodies that are found in the general population which then provide protection to people with PI. The product contains at least 90% intact IgG molecules. All Ig products licensed in the U.S. must be made from source plasma that has been collected in the U.S.

Safety

There are multiple safety steps in the production of Ig: donor screening, viral removal, and inactivation of viruses.

All plasma donors undergo a very rigorous screening process that includes a detailed history of infections and risk behaviors, and testing of their plasma for certain viruses using very sensitive techniques. Donors cannot give their plasma unless they pass this screening. Donors are asked specific questions about risk factors that could affect the safety of the donation and are excluded from donation if risk factors are identified. Plasma centers can look at the donation history for each donor. The FDA also requires blood centers to maintain lists of unsuitable donors to prevent further donations from these rejected donors. As an added protection, donors must return to donate within a set timeframe for rescreening. If a donor does not return within that timeframe, their prior plasma donation is discarded.

After donation, the individually donated plasma is tested for infectious agents before being pooled with plasma from other donors. Once the plasma is pooled, the entire pool is tested for the markers of HIV and hepatitis A, B, and C viruses. The pooled plasma is then divided up and different methods of fractionation and filtration help to separate out the IgG molecules. At multiple times throughout this process, the pool is tested for viral safety before additional safety measures are implemented.

In the mid-1990s, rare clusters of non-A, non-B hepatitis (now called hepatitis C) were documented after the use of some IVIG products. This prompted the addition of an extra viral inactivation step in the manufacturing process. Now multiple safety measures, including pasteurization, low pH, low pH with pepsin, and solvent detergent help dissolve the lipid enveloped viruses, including hepatitis C. An additional safety step is chromatography, a technique widely used to obtain pure ingredients from mixtures. More recently, a final ultrafiltration or depth filtration step has been added to remove the possibility of

transmission of prion related diseases (mad cow disease). Transmission of HIV, which is destroyed in the first ethanol fractionation step in the production of Ig, has never been documented with the use of any Ig replacement therapy.

Dosing

Ig replacement therapy is typically dosed based on the recipient's weight. Many factors, however, are considered when the medication is prescribed. Typically, a starting dose is between 400 to 600mg/kg/month. Doses are adjusted for clinical efficacy, with the expectation of minimizing the frequency and severity of recurrent infections while minimizing side effects of the medication. IgG levels are usually monitored over time and correlated with the response to therapy.

With SCIG, there is a steady level of IgG present in the bloodstream due to the more frequent dosing regimens (Figure 28:1) and slower rate of absorption.

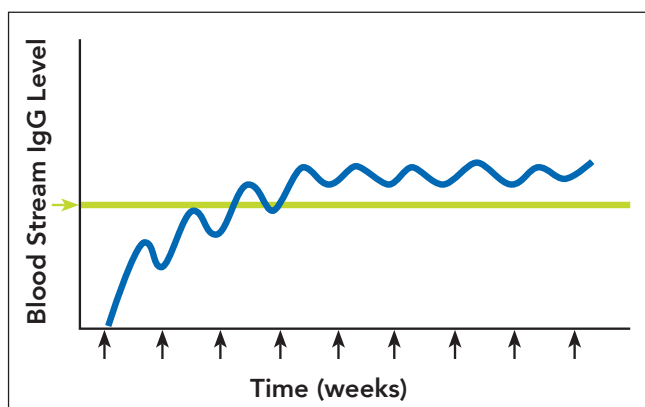
With IVIG, the dosing at longer intervals may cause peaks and valleys, called troughs (Figure 28:2). The goal is to keep the levels of Ig in the blood stream above a certain level even when the level is at its lowest (the trough level) right before the next infusion is due.

Intravenous Immunoglobulin (IVIG) Replacement Therapy

Uses: IVIG is given through a vein. Most immunologists strongly discourage the use of central catheters to administer IVIG due to the increased risk of serious blood infections and the development of blood clots. Placing a central venous catheter, also known as a port, due to poor venous access increases the risk of infections and blood clots, and it should be strongly discouraged. Given the very serious risk involved with the use of implantable ports, individuals should instead consider switching to the subcutaneous route of administration (SCIG) if there is a vein access problem.

IVIG is typically given every three-four weeks at a dose determined by the prescriber. Infusions can be given in various settings including an inpatient or outpatient infusion suite, physician office, or in the home. IVIG is administered by a healthcare professional, and the procedure is scheduled in advance. In special extenuating circumstances, individuals can be instructed to self-infuse this therapy after they are stable on the treatment as long as IV access can be established. The medical

Figure 28:1



professional should, however, stay with the individual for the length of the infusion because of the risk of serious side effects, such as anaphylaxis.

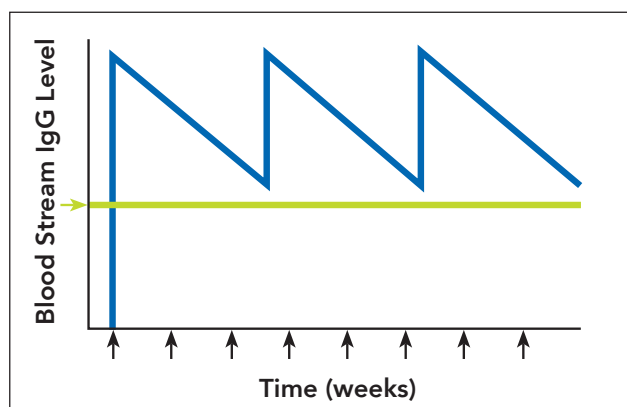
The following are considerations for switching from IVIG to SCIG administration:

- Extreme prematurity (mainly infants born before 30 weeks)
- DiGeorge (22q11.2 deletion) syndrome
- Jacobsen syndrome

Side Effects: Although IVIG has been safely and effectively administered since the early 1980s, IVIG can cause adverse effects, both localized and systemic. Systemic reactions to IVIG infusion occur in approximately 3% to 15% of individuals receiving treatment. The side effects are usually self-limiting and can be avoided by decreasing the rate of the infusion, good hydration, and/or making sure that the product is at room temperature when it is infused.

Individuals may be at increased risk for developing an adverse reaction if they have never received IVIG, have active infections or pre-existing conditions (such pneumonia or bronchiectasis), or are switching products. Individuals with a history of migraine headache may be at risk for a post-infusion headache reaction. The prescriber of the therapy can modify IVIG dosing by decreasing the rate of infusion or adding other medications to the prescription. Medications such as acetaminophen, diphenhydramine, non-steroidal anti-inflammatory drugs, or corticosteroids can help prevent side effects during and after an infusion. It is important to know, however, that repeated use of corticosteroids used to manage IVIG side effects may lead to long-term problems associated with repeated steroid use. While IVIG brands differ by manufacturer, the

Figure 28:2



listed side effects are virtually identical on each package insert. Some common infusion reactions are headache, nausea, fever, chills, flushing, wheezing, vomiting, backache, muscle aches, joint aches, or chest tightness. Side effects experienced during an infusion of Ig are almost always related to the rate of the infusion, such as infusing too fast, or relate to the temperature of the product. Stopping or slowing the infusion is usually the only intervention needed to alleviate these symptoms. Sometimes a switch in product is successful in alleviating these side effects as some may simply tolerate one brand better than another.

Some side effects can happen up to 72 hours after an infusion of Ig. These delayed symptoms are not usually associated with the rate of infusion. Some rare side effects include:

- Aseptic meningitis (inflammation of the meninges, the membranes that surround the brain and spinal cord) has been seen up to 72 hours after infusion of IVIG and may be more prevalent in people with a history of migraine headaches. Hydrating prior to IVIG may protect from this side effect. It is important to note that every person who develops a post-infusion headache does not necessarily have aseptic meningitis. A prescriber should be notified if the individual experiences severe headaches that do not respond to standard medications such as acetaminophen or non-steroidal anti-inflammatory drugs, like ibuprofen.
- Anaphylaxis is very rare and may be associated with anti-IgA IgE antibodies (there are no labs that can test for these IgE antibodies) in some people who have totally absent IgA. The role of anti-IgA antibodies in causing anaphylaxis in people with IgA deficiency receiving Ig

replacement therapy is still controversial⁷. The newer liquid IVIG products have low concentrations of IgA. In addition, reactions due to anti-IgA antibodies do not occur with SCIG, and SCIG has been safely given to people with PI suspected of having anti-IgA IgE antibodies.

- Acute renal failure has been seen after infusion of IVIG; 90% of these cases, however, are associated with sucrose-based products, which are no longer in use and are not necessarily associated with the timing of the infusion. Individuals over age 65 or who have pre-existing kidney disease may be at an increased risk of adverse effects on the kidney.
- Blood clots, such as thrombotic side effects and embolisms, have been associated with IVIG infusions. The relationship between IVIG infusion and an increased risk of blood clots is thought to be due to a plasma contaminant (Factor XIa) that all manufacturers test for in the final product and eliminate, if present to reduce this risk. Risk factors for blood clots include heart disease, advanced age, previous thrombotic event, clotting disorder, hypertension, diabetes, high cholesterol, renal disease, obesity, and immobility⁸. Adequate hydration prior to administering the IVIG is very important as is not exceeding the recommended rate of infusion.
- Hemolytic anemia is a rare but reported side effect of IVIG. The risk of significant hemolysis (breakdown of blood cells) appears greater in those who receive high dose IVIG for autoimmune disorders than in those who are receiving replacement therapy.

What Side Effects to Report to the Prescriber:

The individual with PI or caregiver is responsible for reporting any side effects or discomforts experienced during or after an infusion of IVIG to the prescriber of the therapy and to the nurse administering the therapy.

Side effects to report include but are not limited to:

- Headache
- Body aches
- Fever/chills
- Diarrhea
- Muscle cramps

- Nausea and vomiting
- Symptoms of infection

Optimized Infusion Experience: A nurse trained in the administration of this therapy and the appropriate place of administration for IVIG is important. Many of the side effects that happen during an infusion are related to rate. The nurse should be experienced in infusing this medication and aware of when to slow down the rate of infusion or stop the infusion if necessary. If individuals are aware of steps that they can take to prepare for each infusion, the infusion process will be much smoother. It is important to be well hydrated going into an infusion of IVIG. This will not only help the nurse get an IV started, but it will decrease the risk of headache and other side effects after each infusion. Prescribed pre-medication is designed to prevent side effects. It is important to take the pre-medication as prescribed. Individuals or caregivers should record the infusion experience on a calendar or journal so that any adverse experience can be reported to the nurse and the prescriber prior to the next infusion so that adjustments can be made to the rate, pre-medications, dose, etc.

Monitoring: Routine lab tests may be ordered by the prescriber to monitor IVIG treatment. This may include measuring IgG levels just before the next infusion is due. It is also necessary to monitor other blood levels such as total blood counts and measures of kidney and liver function. Most importantly, the prescriber will want to monitor the person for infections to make sure IVIG is having the desired effect of decreasing serious infection.

Subcutaneous Immunoglobulin (SCIG) Replacement Therapy

Subcutaneous immunoglobulin replacement therapy (SCIG) has gained popularity in the U.S since the 2000s. SCIG has increased the options available for people needing Ig replacement therapy for PI and certain neuromuscular diseases. Currently, there are several products available that can be administered subcutaneously using a number of regimens. These products differ based on concentration, stabilizers, and infusion specifics.

SCIG Regimens: Greater flexibility in the dosing and an increase in the number of products available has contributed to the expanded use of SCIG. The following are currently available for subcutaneous use: 10% preparations, 20% preparations, and

facilitated SCIG (a 10% SCIG preparation plus an enzyme called hyaluronidase). In general, SCIG regimens require the individual with PI or caregiver to learn how to self-administer at home. Both forms of SCIG allow for self-administration at home. Facilitated SCIG may be administered at home or in-office administration with a nurse, depending on insurance coverage and preference.

SCIG is usually infused under the skin, into the subcutaneous layer of the abdomen, thighs, or outer buttocks at one or multiple sites, depending on the volume being infused (Figure 28:3). The total monthly dose is calculated by the prescriber, then divided according to the interval between infusions (usually weekly or biweekly for conventional SCIG and every three-four weeks for facilitated SCIG). The number of needle sticks (sites) is also calculated for the individual depending on the volume and the concentration of the SCIG to be infused. Larger intervals between infusions require larger volumes of product to achieve the same total dose. Conventional SCIG can be given daily, weekly, every two weeks, or multiple times per week, as long as the total monthly dose is divided appropriately. Dosing daily involves subcutaneous injection of small volumes without the need for a pump, using only a syringe. Facilitated SCIG can be given every three-four weeks to deliver the total monthly dose at once into the subcutaneous space. This is facilitated by the use of human bioengineered hyaluronidase. Hyaluronidase is a naturally occurring enzyme in the subcutaneous tissues that is injected into the subcutaneous space before the Ig to expand the subcutaneous space and allow more medication to be infused into each site. The effects of the hyaluronidase enzyme are very short lived, and the tissues revert back to normal in 24 to 48 hours. The benefit of this therapy is a decrease in the frequency of infusions as it allows for an entire three or four-week dose to be administered at one time.

Figure 28:3 Sites for infusion of SCIG



The length of the infusion varies depending on the volume infused, but generally takes up to one to two hours (or less). For SCIG, some of the standard (less concentrated) 10% IVIG preparations can be used via the subcutaneous route. Currently there are several 20% (more concentrated) preparations indicated for subcutaneous use only that allow for smaller volumes to deliver the same dose with fewer needle sticks. With the 20% preparations, site volumes can range from 30ml to 60ml per site depending on the individual's tolerance. In facilitated SCIG, about 300-600ml can be delivered in one site or divided into two or more sites as tolerated.

In general, SCIG is delivered using a small needle attached to tubing and a syringe that is placed in either an automatic mechanical pump or an electric programmable pump. Both pumps are portable. Alternatively, some individuals may prefer or better tolerate SCIG delivered by subcutaneous push, meaning that a small amount of SCIG is injected daily under the skin without the use of a pump. The Ig products come in a variety of vial sizes depending on the manufacturer. Several needle and tubing sizes are available, and troubleshooting problems with SCIG often involves reviewing that the equipment being used, such as needle sets, tubing, pump, etc., are appropriate for the individual receiving the therapy.

Dosing: As in IVIG, the typical starting dose is between 400 to 600mg/kg/month. The monthly dose is divided into infusions daily, weekly, or every two weeks. In contrast, facilitated SCIG enables the whole monthly dose to be infused every three to four weeks. Doses are adjusted to clinical effect, with the expectation of minimizing the frequency and severity of recurrent infections. IgG levels are monitored over time, correlated with clinical outcomes, and the dose is adjusted as necessary. With SCIG, there is a steady level of IgG (no peaks or troughs like IVIG) present in the bloodstream due to the more frequent dosing. With facilitated SCIG, there are peak and trough levels but the peak levels are not as high and trough levels are not as low, as with IVIG.

Optimized Infusion Experience: Several variables involved with SCIG allow optimization of the infusion experience. Some of these variables include number of needle-sticks, infusion sites, volume infused/site, needle length, and pump type. The number of needle-sticks may be reduced by increasing the volume infused per site. Fewer sites are needed with the more concentrated 20% products. Conversely, more sites may be needed if the less concentrated solutions are used. With facilitated SCIG, which delivers the whole month's

dose at once, the dose can be divided between one to two sites, depending on how the infusion is tolerated. If the individual is experiencing discomfort using the abdomen, other sites such as the thighs can be used. If the individual prefers to dose every month rather than weekly or every two weeks, then facilitated SCIG using one to two sites may be the best choice. For those who have issues with tolerating infusions, smaller volumes of SCIG daily may be needed. Several needle lengths are also available that can be tried; the important thing is to use a needle long enough to insure that the Ig is being administered into the subcutaneous tissues rather than the skin. A variety of infusion pumps are available ranging from a simple and portable mechanical pump to more complicated programmable pumps. Most importantly, SCIG can provide freedom of scheduling for those who self-infuse, resulting in fewer school and workday losses.

Side Effects: In general, SCIG is associated with fewer systemic adverse events than IVIG. SCIG is an option to consider when IVIG is not well tolerated, when there is poor venous access, or when the individual's lifestyle is more compatible with SCIG than IVIG. SCIG can be considered for children, adults, pregnant women, the elderly, and for individuals with IgA deficiency secondary to having antibodies against IgA (very rare). Systemic side effects are usually mild. Severe reactions rarely occur, but individuals who have had severe reactions to IVIG might be at a higher risk. Pre-medication is usually not required for SCIG. The most common adverse reaction reported is local redness, swelling, and irritation at the injection site. Usually these mild localized reactions improve with repeated infusions. In rare cases, the injection site reactions can be severe. To improve or avoid the infusion site reactions, and decrease the chance of other problems, individuals need thorough training to ensure that proper technique is used to access the subcutaneous tissue. Local skin reactions may be due to inadequate needle length preventing the Ig from being infused into the subcutaneous tissue. For those with fear of needles, a topical numbing medicine or ice can be applied to the skin prior to the subcutaneous infusion.

Monitoring: With SCIG, there is a steady state level of IgG in the circulation due to more frequent infusions of smaller doses and the fact that the Ig is more slowly absorbed. Peak and trough levels are not as extreme, and the level is more consistent on a daily basis. Routine lab work including blood

counts and markers of liver and kidney functions should be monitored. None of the currently available products for SCIG, are stabilized with sucrose, making renal complications less likely. Smaller doses given subcutaneously also minimize risks due to fluid overload.

Practical Considerations: Many practical considerations should be taken into account when deciding if SCIG is the right choice. SCIG requires more frequent administrations (daily, weekly, every two weeks), unless the facilitated SCIG route is chosen (every three to four weeks). Medical supervision is not required for home infusion, so the ability of the individual to adhere to the treatment regimen is an important consideration. If there is a fear of needle-sticks, training strategies for self-infusion including numbing creams should be considered. Manual dexterity, or the ability to make coordinated hand and finger movements to manipulate objects, is also required to draw up SCIG and manage the pump. SCIG provides the freedom to administer Ig at home or anywhere else at any time of day. This flexibility and control have been shown to enhance the quality of life for many individuals⁹. SCIG is associated with a lower rate of systemic side effects, making this route of administration a good option for those experiencing unwanted adverse effects from IVIG. Administration of more frequent, smaller volumes provides a steady level of Ig, avoiding high peak levels that may be associated with side effects of IVIG, such as headaches and symptoms of wear-off. SCIG should be given serious consideration for college students and those individuals whose jobs require frequent travel. Individuals should remember that there are many options available for therapy and that they should thoroughly discuss these options with their prescribers.

Summary

The goal of Ig replacement therapy for antibody disorders—no matter the route of administration—is to provide protection from infection. An individual's adherence to therapy is paramount to achieving this goal. Any barriers to therapy, real or potential, need to be addressed appropriately.

It is also important to remember several things when considering Ig replacement therapy:

- **Not all infections can be prevented.** After starting Ig replacement therapy, individuals may still get infections. It is hoped, however, that

Table 28:2

	Intravenous Immunoglobulin (IVIG)	Facilitated Subcutaneous Immunoglobulin (fSCIG)	Subcutaneous Immunoglobulin (SCIG) (Conventional)
Who?	Indicated for adult and pediatric individuals with PI.	Indicated for adult and pediatric individuals with PI.	Indicated for adult individuals with antibody deficiencies.
How?	Usually administered by a nurse.	Self-administered.	Either self-administered or given by a nurse.
Where does it go?	Infused directly into the bloodstream through a vein.	Infused or injected under the skin into the subcutaneous tissues of the arms, belly, outer buttock or the thighs.	Infused under the skin into the subcutaneous tissues of the belly, outer buttock or the thighs.
When?	Usually given every three-four weeks.	Can be given on a flexible schedule from daily to every two weeks.	Can be given every three-four weeks.
How long?	Can take two-six hours to infuse.	Can take five minutes to two hours to infuse or inject.	Can take one-2 hours to infuse.
Where is it given?	Can be infused at home, in a hospital or an outpatient infusion center depending on insurance and patient preference.	Usually administered in a home setting after the patient is trained to be independent.	Can be infused at home or in an outpatient infusion center depending on insurance and patient preference.
Side effects?	Individuals can have side effects that are often related to the rate of infusion and can be treated and prevented with other medications, given before or after the treatment.	Skin can be red and irritated at the site of injections. This often improves with each injection.	Skin can be red and irritated at the site of injections. This often improves with each injection. The volume per injection is larger than standard subcutaneous (under the skin) injection, so the volume is more visible under the skin, and may take 48-72 hours to totally absorb.

the frequency and severity of infections will be significantly decreased so that permanent organ damage, like bronchiectasis can be prevented

- **“One size does not fit all.”** An individualized Ig replacement therapy regimen must be developed for each individual and modified as necessary to achieve treatment goals and the needs of each person.
- **Once a diagnosis of PI involving antibody production and/or function has been made, Ig replacement therapy will probably be needed lifelong.** In some instances, reevaluation of the diagnosis may be undertaken. This must be done cautiously as Ig replacement therapy must be stopped for four months to obtain accurate repeat lab tests.

The following chart (Table 28:2) is designed to facilitate a discussion between individuals and caregivers living with PI and their healthcare providers when immunoglobulin (Ig) replacement therapy is determined to be the treatment of choice and is deemed medically necessary. Decisions on which therapy is best should be made with some of these factors in mind. For more information, refer to the IDF Guide to Ig Therapy that contains frequently asked questions and troubleshooting SCIG therapy.

Resources

Information regarding the Ig products currently licensed in the U.S. is available from each specific manufacturer via the individual corporate websites. Companies who manufacture Ig replacement therapy offer a wealth of valuable information for individuals and families living with PI. Learn more about the companies, their products, general information about PI and/or reimbursement assistance programs on their websites.

For a complete, updated list of Ig products, manufacturers, and details, visit the IDF website: www.primaryimmune.org/ig-products. Please note that manufacturers and products are subject to change.

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Adapted from: Chapter 24 Immunoglobulin Therapy and Other Medical Therapies for Antibody Deficiencies. IDF Patient & Family Handbook for Primary Immunodeficiency Diseases 5th Edition. 2013.