

Subcutaneous Administration of Immunoglobulin Replacement Therapy in the Home Care Setting



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Subcutaneous administration of immunoglobulin (IgG) replacement therapy has emerged as an effective alternative to intravenous administration in both adult and pediatric patients. This monograph will review the results of several studies showing the efficacy and safety of the subcutaneous route of administration. In addition, the monograph includes a discussion of patient selection, dosage regimens, IgG preparations, pharmacokinetics, and considerations in managing patients receiving IgG therapy by the subcutaneous route.

Clinical Uses of Immune Globulin

IgG is a sterile preparation that contains antibodies used to treat patients with both inherited and acquired immune disorders, such as primary and secondary immune deficiencies. Clinical uses of IgG can be grouped into two main categories: replacement therapy and immune modulation therapy.

Primary immune deficiency diseases (PIDDs) are disorders in which part of the body's immune system is missing or does not function properly due to intrinsic or genetic defects in the immune system. By contrast, secondary immune deficiency disease is a condition in which the immune system is compromised by factors outside the immune system, such as viruses or chemotherapy. IgG is also used "off label" to treat a variety of neurological and autoimmune conditions, such as multiple sclerosis, Guillain-Barre' syndrome, and chronic inflammatory demyelinating polyneuropathy (CIDP).

In the last 20 years, the treatment of choice for both primary and most secondary immune deficiency syndromes has been the parenteral administration of IgG. Currently in the United States, according to the

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Immune Deficiency Foundation (IDF; www.primaryimmune.org), intravenous immune globulin (IGIV) therapy is the most common treatment option—70 percent of patients were treated with IGIV.¹ The majority of IGIV infusions are administered in the home (40 percent), although other treatment settings are used as well: hospital (30 percent), physician’s office (12 percent), and infusion center (11 percent).

Historically, the use of IGIV has been limited by the significant instances of side effects associated with its administration. With technological advances, IGIV tolerance has improved, but the product has yet to reach universal acceptance. In 1979, the first infusible IgG was produced. However, its use was restricted to passive immunity only. By the mid-1980s, manufacturers focused on developing products that were low in immune globulin A (IgA), which is also present in human plasma. IgA levels are of concern to those patients with IgA deficiency because they can develop antibodies to IgA, which can place them at increased risk for severe life-threatening reactions.

Additional concerns over carbohydrates, such as sucrose, glucose, and other stabilizers surfaced in the 1990s because of their potential to exacerbate renal disease in the elderly and in patients with underlying renal disease and other conditions. This led the U.S. Food and Drug Administration (FDA) to add a “black box” warning to package inserts for IGIV products containing these agents.²

By the mid-1990s, concerns over safety in the manufacturing process resulted in two popular IgG products being removed from the market after hepatitis C was transmitted to approximately 150 patients.³ Rigorous donor selection processes and registries were established as a result. Additional virus inactivation and elimination steps were mandated. Currently, solvent detergent, pasteurization,

Exhibit I
PHARMACOKINETIC SUMMARY IGIV vs SCIG

	IGIV	SCIG
n	17	17
Mean dose	120 mg/kg	165mg/kg
Mean IgG peak	1735 mg/dL	1163 mg/dL
Mean IgG trough	883 mg/dL	1064 mg/dL

Source: ZLB Behring, Vivaglobin® product information

and a variety of other methodologies, including nanofiltration and the addition of caprylate, are used in the manufacturing process to eliminate known viruses through validated processes.

Despite these improvements made within the IgG product pool, there is still a significant number of adverse reactions associated with the use of IGIV in both children and adults. Up to 15 percent of recipients experience some type of reaction. The severity of reactions can range from mild to severe, depending on the type.

Most reactions occur during the initial 30 to 60 minutes of the infusion and are typically mild and self-limited.¹ Pre-treatment with various medications can often reduce side effects and adverse reactions as well as reduction of infusion rates. While severe anaphylactic reactions are rare, patients with a significant history of atopic reactions and documented intolerances to protein-based therapies are at greater risk for an adverse reaction.

Subcutaneous Administration of IgG

Even with advances in the safety and tolerance of IGIV occur, certain subsets of patients have no vascular access, cannot physically tolerate IV administration, or, because of lifestyle issues or

other preferences, need other treatment options. In the U.S., subcutaneous IgG (SCIG) is quickly becoming an option for these patients.

The subcutaneous method has been a very common and accepted method of administration in Scandinavia and the United Kingdom for some time. Literature dating back as far as 50 years has documented its safe and effective use.⁴ Until recently, use of this method was considered very “off-label” in the U.S.

It was in 1980 that Berger and colleagues at NIH reported the use of a portable syringe driver to administer between five and 15 mL of IgG slowly to three adult patients.⁵ The authors concluded that the slow subcutaneous infusions of IgG were well tolerated and remarkably free from adverse reactions. This study began a parade of several others reporting similar positive results in adult and pediatric patients. In 1981, van der Meer and colleagues reported the safe and effective home administration of SCIG.⁶ Subsequent to this study others have reported similar successes.^{7, 8, 9}

However, the subcutaneous method of administration did not take hold, largely due to the advent of IGIV in the late-1970s. Additionally, there was no

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commercial product available specifically for SCIG administration and the longer, more frequent infusion times placed a time constraint on patients and health care workers. However, there is currently a renewed interest in SCIG administration in the U.S., due to a number of factors, including the January 2006 approval by the FDA of a 16-percent IgG designed and marketed exclusively for subcutaneous administration [immune globulin subcutaneous (human), VivaGlobin®, ZLB Bering].

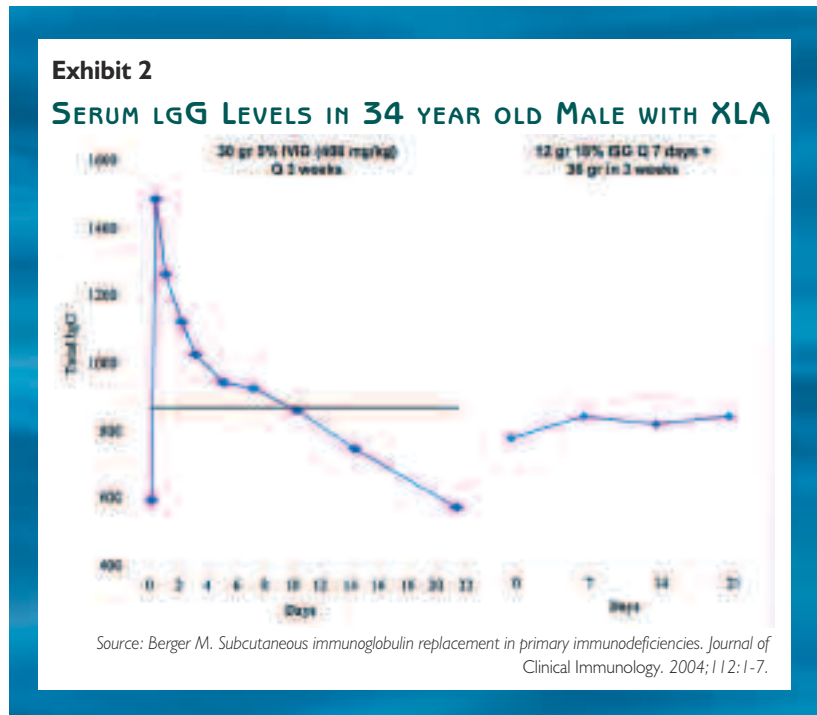
SCIG can be used when patients require more frequent infusions of IgG to maintain target levels. Numerous reports indicate a favorable pharmacokinetic profile when IgG is given subcutaneously. Exhibit 1 represents a summary of a U.S. and Canadian sub study that demonstrated that patients given SCIG maintained higher mean trough levels.

In addition, a 2004 study demonstrated that when a similar equivalent total IV dose per unit of time is given weekly as SCIG, higher trough serum levels were maintained. The author suggests that the significant differences between peak and trough ranges may be a factor in the differences in adverse reactions, such as headache, that are often associated with rapid changes in serum levels (see Exhibit 2).¹⁰ Several studies also demonstrated favorable improvement in infection rates, hospital admissions, and overall morbidity for patients on SCIG.^{7, 11, 12, 13, 14}

There are a variety of other clinical and patient preference advantages to administering IgG via the subcutaneous route. Exhibit 3 compares the advantages and disadvantages of IGIV versus SCIG administration.

Adverse Reactions to SCIG

It is important to consider that regardless of the route of administration, IgG therapy is the inoculation of a protein-based substance into the body.



Adverse reactions similar to those reported with other immunoglobulins administered differently may also occur. In a U.S. and Canadian study the most frequent adverse reaction was a local reaction at the injection site.¹⁵ Exhibit 4 lists other adverse reactions reported in clinical studies as a percentage of subcutaneous administrations for one formulation of SCIG.¹⁵

Patient Selection for Home Administration of SCIG

When assessing whether a patient is an appropriate candidate for home SCIG several factors need to be considered. Patients who have any contraindications to subcutaneous injections should not be considered for home SCIG therapy. The patient or their caregiver must be capable and committed to the management of the self-injected therapy. And, a non-remarkable compliance history must be evident. During assessment, clinicians should also:

- Determine if patients or their caregivers are willing and committed to perform administration independently.
- Evaluate patient/caregiver teaching and self-management abilities.
- Evaluate whether any social or compliance issues exist.
- Evaluate insurance coverage. Some payers will not cover self-administered therapies.
- Determine if there is a willing and capable health care provider for the SCIG and its associated supplies and equipment. Many providers have non-existent or limited experience with SCIG.
- Determine the specific IgG product that has been prescribed. Options may be restricted due to market availability and equipment to be used.
- Determine that the patient is willing to receive the initial treatment(s) in a controlled setting. If the patient is naïve to IgG or

SCIG treatment the first dose(s) should be given in a controlled medical environment with the appropriate supportive services in the event of an adverse reaction.

Subcutaneous administration of IgG

Historically the administration of SCIG has depended on using commercially available products that have been formulated either for IV or IM use. Concerns over using commercially available products not approved for subcutaneous use can include:

- For Standard IM IgG
 - ⌘ Limited efficacy for PIDD indication
 - ⌘ High viscosity
 - ⌘ Requires multiple vials
- For Lyophilized IGIV
 - ⌘ Must concentrate final solution
 - ⌘ Requires the additional step of reconstitution
- For Liquid IGIV
 - ⌘ Concentration is fixed resulting in a high subcutaneous volume
 - ⌘ Low pH may be irritating when given subcutaneously

Patients receiving SCIG require infusions at approximately one-week intervals into tissue spaces that have a limited volume capacity per rate of infusion. The final concentration of the solution is very important in order to deliver the appropriate therapeutic amount of IgG without exceeding volume requirements for subcutaneous administration. For example, a five-percent product contains 5 grams of IgG in 100 mL. If that same 5 grams were reconstituted to a 10-percent final concentration, the volume to be infused would only be 50 mL—a difference of 50mL.

For this reason, the IgG products available for subcutaneous administra-

Exhibit 3
SUBCUTANEOUS VS. INTRAVENOUS ADMINISTRATION OF IgG

Subcutaneous Advantages	Intravenous Advantages
No need for venipuncture	Large volumes can be delivered
Needle access much smaller and comfortable	Less frequent administration periods (21-28 days)
Slow systemic absorption serum swings decreases side effects, adverse reactions	Several manufacturers producing IV formulations
Consistent serum levels eliminates low trough levels	
Creates sense of patient-caregiver autonomy and control	
Low treatment cost model, payer friendly, lower co-pay (depending on plan)	
If self-administered, can relieve nursing burden during nationwide shortage	
Subcutaneous Disadvantages	Intravenous Disadvantages
Small volumes per infusion mean greater frequency of administration	Requires venous access
Requires competent and willing patient/caregiver	Increased potential for adverse reactions secondary to large shifts in IgG levels
Compliance and therapeutic monitoring more difficult	

tion have been limited. Most clinicians choose lyophilized products or a 16-percent solution designed for IM use [immune globulin (human), GamaS-TAN®, Talacris or Baygam®, Bayer]. The recent FDA approval of a 16-percent solution specifically designed and marketed for subcutaneous administration [immune globulin subcutaneous (human), VivaGlobin®, ZLB Bering] offers delivery of therapeutic amounts with less volume.

With subcutaneous administration, the IgG is infused through a small

needle just under the skin over several hours. Placement of the needle in the appropriate tissue—the subcutaneous fat layer—is very important to the tolerance to the infusion. Inadvertent intradermal injection of IgG could cause the release of mediators resulting in an adverse reaction via complement activation.¹⁰ Accidental placement of the needle within a subcutaneous vessel could lead to inadvertent IV administration, which can increase the incidence of an adverse reaction. It is generally recommended

Exhibit 4

**ADVERSE REACTIONS
FOR SUBCUTANEOUS
ADMINISTRATION OF IgG**

Adverse Reaction (n=3,656 infusions)	Frequency
Injection site reactions	49%
Non-injection-site reactions	
Headache	1.6%
Rash	0.2%
Nausea	0.2%
Nervousness	0.1%
Asthenia	0.1%
Gastrointestinal disorder	0.1%
Skin disorder	0.1%
Urine abnormality	0.1%
Fever	0.1%
Dyspnea	0.1%
Gastrointestinal pain	0.1%
Tachycardia	0.1%

Source: ZLB Behring, Vivaglobin® product information

to aspirate the needle set to ensure placement is not within a vessel.^{10, 15}

Needle set selection is often individualized; most clinicians experiment with several in order to determine the most comfortable set or ease of insertion option for each patient. Each set has specific unique advantages. For example, the Medtronic SoftSet® has a metal introducer that when removed, retains a soft plastic catheter in the subcutaneous site that can increase patient comfort.

Multiple subcutaneous sites can be used simultaneously for those patients who require larger volumes of IgG in order to maintain a weekly administration cycle. Common administration sites include the lower quadrants of the abdomen, inner and outer thighs, upper arm, and/or lateral hip. An excellent reference for site selection is www.cc.nih.gov/patient_education/pepubs/subq.pdf. If multiple punctures present a problem, for pediatric patients, for example, then a single site with a longer infusion time may be considered. Generally, no more than 20mL should be administered in any one site. In order to limit swelling, a rate of 20 ml/hour is suggested for rapid infusions; 4 ml/hour is suggested for longer infusions.¹⁰

There have been reports of rapid home infusions of SCIG.^{11, 16, 17, 18, 19} In order to prevent multiple pumps or syringe drivers during the multi-site simultaneous administration, clinicians can use a series of various male-male, female-female, and Y-site connectors distal to the infusion device. Recently Norfolk Medical introduced the ClearView MS™, which has two, three, and four infusion sets off of one single female luer lock.

Pump Selection

Syringe drivers or infusion pumps are most often used for SCIG because of the need to maintain a positive pressure against the subtle resistance within the subcutaneous space. Since small variances in infusion rates are of minimal consequence to the tolerability of SCIG, syringe drivers can be a patient- and caregiver-friendly means of administration. These devices also eliminate the need to transfer the solution into a cassette or empty sterile infusion bag because the infusion container is the syringe used to withdraw the immunoglobulin from its original container.

Dosing and Administration

The suggested initial weekly SCIG dose can be calculated by multiplying the previous IGIV dose by 1.37—a bioavailability correction factor—then dividing this dose into weekly doses based on the patient’s previous IGIV treatment interval (for example, if IGIV was administered every three weeks, divide by three). The SCIG dose will provide a systemic IgG exposure (AUC) comparable to that of the previous IGIV treatment.

For example:

- Typical intravenous monthly dose = 400mg/kg
- 70kg patient = 28gm = 7gm weekly
- SC bioavailability correction = 1.37 X 7gm = 9.6gm
- 60 ml (of a 16 percent SCIG) = 9.6 gm
- Divide into 15 ml per injection site X 4 sites

Weekly administration of this dose will lead to stable steady-state serum IgG levels with lower peak levels and higher trough levels compared to monthly IGIV treatment.^{5, 15} The recommended weekly dose of SCIG is generally considered to be 100 to 200 mg/kg body weight. Doses may be adjusted over time to achieve the desired clinical response and serum IgG levels. Because of differences in the half-life of IgG among patients with primary immune deficiencies, the dose and dosing interval of immunoglobulin therapy may vary.¹⁵

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