

Intravenous and subcutaneous immunoglobulin G replacement therapy

Francisco A. Bonilla, M.D., Ph.D.

ABSTRACT

Human polyclonal immunoglobulin G (IgG) for therapeutic use has been available for decades. This drug was developed for treatment of antibody deficiency (replacement therapy), although its use has expanded into many anti-inflammatory and immunomodulatory applications in recent years. This review focuses on IgG prescribing for replacement therapy. IgG for replacement is most often administered via the intravenous IgG (IVIG) or subcutaneous IgG (SCIG) routes. IVIG is usually administered every 3–4 weeks, and SCIG is usually administered weekly, although variations may be considered in all cases. Recently, a new product became available that uses hyaluronidase to facilitate absorption of large doses of SCIG less frequently (every 3–4 weeks, as with IVIG). There are important differences between the pharmacokinetics of these three routes of administration. IVIG therapy leads to high peaks and low troughs between infusions. IgG concentration fluctuates much less over time with SCIG. Hyaluronidase-facilitated SCIG is intermediate. SCIG may have lower bioavailability in comparison with IVIG and may require higher doses over time; this is not true for hyaluronidase SCIG. However, there are large variations in IgG half-life among individuals and with different products. Therefore, individualization of therapy is essential. Mild systemic “flu-like” adverse effects may affect up to 20–25% of patients who receive IVIG, smaller fractions may experience more-severe symptoms, whereas anaphylaxis is exceedingly rare. General flu-like systemic adverse effects are minimal with SCIG (intermediate with hyaluronidase SCIG), but transient (24 hours), mild, local inflammatory symptoms at infusion sites are relatively common with both forms. Additional rare but important complications of IgG therapy include thrombotic events and hemolysis that can be seen at high doses with any route of administration. Renal adverse effects may occur with IVIG as well. The variety of IgG products and routes of administration available today creates many opportunities for physicians to work with patients to find the optimal therapy for all.

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There are five classes or isotypes of human immunoglobulins, in decreasing order of blood concentration: immunoglobulin G (IgG), IgA, IgM, IgD, and IgE. Early measurements of human immunoglobulin pharmacokinetics were conducted by Waldmann and Strober¹ in the 1970s. They injected healthy volunteers with radioactively labeled immunoglobulins and measured the rate of their disappearance from the circulation. They found that IgG had a relatively long average half-life, of ~21 days, whereas all other isotype half-lives were on the order of 2–6 days. They also found that the half-life of IgG is inversely proportional to the

serum concentration. This is not true of any other immunoglobulin class. The basis of this half-life–concentration relationship is the regulation of IgG serum concentration by the neonatal Fc receptor expressed on the surface of vascular endothelial cells.² IgG is internalized by endothelial cells, and IgG bound to the neonatal Fc receptor is protected from degradation within the cell and is re-released into circulation. When the IgG concentration is high, the receptor system is saturated and a larger fraction of internalized IgG is degraded. When the IgG concentration is low, the opposite occurs. IgG is the only immunoglobulin class that interacts with the neonatal Fc receptor, thus, its half-life is extended in comparison with other isotypes.

Many primary and secondary immunodeficiencies involve an impaired ability to make specific antibody (antibody deficiency).³ Gammaglobulin is administered to these individuals to provide passive immunity and to protect the host, primarily from viral and bacterial respiratory, gastrointestinal, and more-invasive infections.^{4–6} Polyclonal human immunoglobulin for therapeutic use has been available since the 1950s. This is often referred to as gammaglobulin due to the electrophoretic mobility of serum IgG in the “gamma” peak. Early preparations were relatively crude and were suitable for intramuscular or subcutaneous (SC)

From the Clinical Immunology Program, Boston Children's Hospital, Boston, Massachusetts, and Department of Pediatrics, Harvard Medical School, Boston, Massachusetts

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Address correspondence to Francisco A. Bonilla, M.D., Clinical Immunology Program, Boston Children's Hospital, 300 Longwood Avenue, Boston, MA 02115

E-mail address: francisco.bonilla@childrens.harvard.edu

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administration. IgG administered by these routes are intramuscular IgG and SC IgG (SCIG), respectively. Intramuscular administration is painful and currently is rarely applied, with the exception of some specialty immunoglobulin products, *e.g.*, tetanus immune globulin. Newer immunoglobulin products have been refined and are suitable for intravenous (IV) administration, which is still the most popular route worldwide. SC administration is also convenient and is growing in popularity. This review focused on "low dose" or "replacement dose" gammaglobulin therapy for conditions of antibody deficiency. Larger doses of IgG may be administered for its immunomodulatory or anti-inflammatory effect in rheumatologic and other diseases of immune dysregulation, but these are not discussed.

ANTIBODY DEFICIENCY

The total body content of IgG is ~1 g/kg body weight. Approximately one-half is in the vascular compartment.¹ IgG is transferred across the placenta during gestation. As a result, the newborn has an adult level of IgG. While the immune system matures after birth, the IgG level falls to a nadir of ~300 mg/dL between ages 3 and 9 months, then slowly begins to gradually rise throughout childhood. For this reason, it is critically important to use age-adjusted normal ranges when evaluating children for possible antibody deficiency. The normal serum concentration in an adult ranges from ~600 to 1500 mg/dL, depending on the method of measurement and the laboratory.

Hypogammaglobulinemia alone is not an indication for IgG replacement. For example, some individuals may have abnormal loss of IgG through the gastrointestinal tract or by other routes but may still be capable of producing adequate antibody and having protective humoral immunity. A diagnosis of antibody deficiency also rests on demonstrating poor quantity and/or quality of antibody response to specific antigens encountered either *via* natural infection or immunization. Most such individuals will frequently be ill with viral and bacterial respiratory and gastrointestinal infections. Space does not permit a detailed review of the diagnosis of antibody deficiency. For a discussion of these issues, readers are referred to Gelfand *et al.*⁷ and references therein.

IgG REPLACEMENT

Among available IgG products, the measured serum half-lives range widely among clinical trials (Table 1). Note that these values are often different (usually longer) than the half-life measured by Waldmann and Strober.¹ This is most likely due to a combination of factors, including the estimation of half-lives when using total blood concentration and the presence of

Table 1 Measured serum half-lives of immunoglobulin G products in clinical use administered by the intravenous route*

Product	Mean $t_{1/2}$, days	Range, days	N
1	38	16–72	16
2	30	19–41	8
3	35	31–42 (95% CI)	57
4	41	23–84	47
5	28	22–33	3
6	45	15–88	15

$t_{1/2}$ = Serum half-life; CI = confidence interval; N = number of subjects.

*These data are from clinical trials for product licensure by the U.S. Food and Drug Administration and are presented in the prescribing information for each product.

varying amounts of residual IgG production in the patients who were immunodeficient and who were the subjects of these clinical trials (most of whom had either X-linked agammaglobulinemia or common variable immunodeficiency). Furthermore, the individual range of measured half-lives in these trials also varied greatly. Thus, it is absolutely essential to individualize the treatment regimen for each patient.⁸ Note also that it is always important to round an individual dose of IgG to the nearest appropriate unit dose available for any given product; this is to maximize the use of a life-saving and expensive biologic drug and prevent unnecessary waste.

IV ADMINISTRATION

Some IgG products are listed in Table 2. A typical blood concentration versus time curve for IV IgG (IVIG) administration is shown in Fig. 1. There is a rapid initial peak after infusion, followed by equilibration between intra- and extravascular spaces, then a slow decline over the remaining interval between doses.⁹ For the majority of patients, IVIG is administered every 3 or 4 weeks, rarely more or less frequently. Doses range from 0.3–0.5 g/kg every 3 weeks to 0.4–0.6 g/kg every 4 weeks (roughly 0.1–0.15 g/kg/wk). As noted, individualization of therapy is critical, and some patients may require more (or less) to remain clinically well. At initiation of therapy, a loading dose of ~1 g/kg may be given if the serum IgG is at or near zero. IV administration is generally performed by a trained professional in a health care setting or in the patient's home.

Mild systemic adverse effects with IVIG are common and may occur in 5–25% of patients, depending on their underlying diagnosis, the dose, speed of infusion (faster is worse), and time on therapy.^{10–12} Adverse effects are more frequent at the initiation of therapy,

Table 2 Immunoglobulin G products and routes of administration

Product	Concentration, %	Intravenous	Subcutaneous
Bivigam	10	Yes	No
Carimune	3–12	Yes	No
Flebogamma	5	Yes	No
Gammagard Liquid	10	Yes	Yes
Gammagard SD	5	Yes	No
Gammaked	10	Yes	No
Gammaplex	5	Yes	No
Gamunex-C	10	Yes	Yes
Hizentra	20	No	Yes
HyQvia	10	No	Yes
Octagam	10	Yes	No
Privigen	10	Yes	No

when an active infection is occurring, and when patients change from one product to another. Mild adverse effects include, *e.g.*, headache, fatigue, malaise, myalgia and/or arthralgia, and low-grade fever. More-severe adverse effects are less common (1–5% of patients) and include more severe forms of all of the above-mentioned adverse effects along with urticaria, wheeze, dyspnea, and rigors. Anaphylactic reactions are extremely rare (<1%). Thrombotic events may occur rarely in patients who receive IVIG, and all products carry this warning.¹³ The risk is greatest in individuals with inflammatory disorders (*e.g.*, vasculitides) or blood dyscrasias that predispose to thrombosis. This is thought to be due to activated clotting factor XIa that occurs as a contaminant in some IVIG preparations or possibly other contaminants as well. Hemolysis may also occur after high-dose IVIG infusions as a result of isohemagglutinins present in purified human IgG.¹⁴

Renal adverse events (interstitial disease) can also occur in some patients who receive IVIG.^{10–12} The risk of this is higher in patients with preexisting kidney disease and who receive large rapid infusions. The presence of sucrose in the IVIG product increases the risk, but these adverse effects can occur with any preparation. The potential thrombotic, hemolytic, and renal complications of IgG therapy are all exacerbated by higher doses and more rapid infusions. They are all more common with high-dose immunomodulatory therapy than they are with replacement therapy.

IVIG products also carry a warning regarding the possibility of anaphylactic reactions in patients with IgA deficiency (undetectable serum IgA).¹⁵ This has been attributed to high levels of IgG anti-IgA antibodies that may occur in a small minority of these patients, even though there is no conclusive evidence that the risk of anaphylaxis is higher in patients with IgA de-

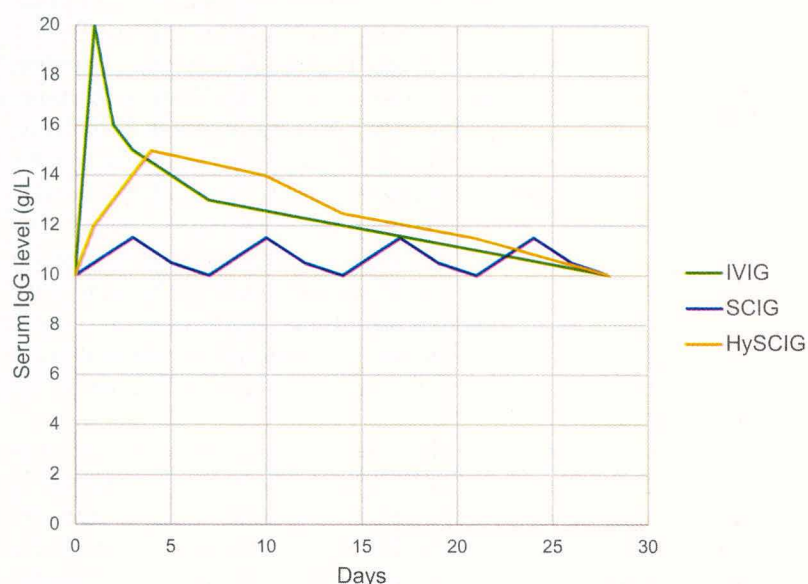


Figure 1. Representative plots of immunoglobulin G (IgG) serum concentration over time with intravenous IgG (IVIG), subcutaneous IgG (SCIG), and hyaluronidase-facilitated SCIG (HySCIG). In this diagram, IVIG and HySCIG infusions were given on day 0. Unfacilitated SCIG infusions were given on days 0, 7, 14, and 21.

efficiency overall (probably not, in fact) or that such antibodies have any role in the reaction. In any case, this risk seems to be nonexistent before adolescence and is an extremely rare event, in any case. IVIG therapy should never be withheld from a patient with IgA deficiency due to concern for this possible reaction; the risk is too low to warrant such a concern.

A meta-analysis of clinical trials of IVIG shows that the preinfusion (trough) serum concentration of IgG increases linearly with IVIG doses up to 0.6 g/kg per 28 days (slope, 121 mg/dL increase in trough IgG for every 100 mg per 28 days of dose increase).¹⁶ At the high end of the dose range, the trough level is usually >800 mg/dL. Furthermore, the pneumonia incidence decreases linearly up to a trough level as high as 1000 mg/dL, which indicates that, for a population of patients, and up to these doses and/or levels, there is no "point of diminishing returns" for IgG dosing with respect to preventing infections.

In general, IVIG should be dosed based on total body mass. Shapiro¹⁷ showed that clinically effective IVIG doses were the same in individuals with a body mass index (BMI) of >30 kg/m² and those with a BMI of <30 kg/m². Furthermore, there was no difference in trough IgG level between individuals with a BMI of >30 kg/m² and those with a BMI of <30 kg/m².

SC ADMINISTRATION

There are a few types of IgG products intended for SC administration.^{18,19} These include a 20% concentration product that can only be given SC (Hizentra) as well as products with 10% concentration that are licensed for both IV and SC administration (Gammagard Liquid and Gamunex-C). In general, SCIG has a lower bioavailability in comparison with IVIG by a ratio of 1.3. That is, to achieve the same bioavailable amount of IgG, SCIG must be dosed in a range 1.3 times the calculated dose of IVIG (or 0.13–0.2 g/kg weekly).¹⁸ The dose interval of SCIG may range from daily to every 2 weeks. Because SCIG is absorbed slowly into the circulation, the concentration varies very little over time (Fig. 1).⁹ When a 10–20% concentration IgG is infused SC, anywhere from one to six infusion sites may be required, depending on the amount given. A single infusion site may accommodate ~5 to 30 mL, depending on the amount of SC tissue, depending, in turn, on body location and BMI. Again, a loading IV dose may be given if pretreatment IgG is very low, and individualization of therapy is essential. SCIG is intended to be administered by the patient him- or herself or by an adult family member in the home. Note that, when therapy is given more frequently (even daily), the amount infused is small (~1 g or 5–10 mL). In this situation, the patient self-infuses in a single site by using a pump or by hand (push).^{20,21}

Systemic adverse effects are infrequent and much milder with SCIG than with IVIG.^{10,22} Local adverse effects at the site of infusion occur in the majority of patients but become less frequent and intense with continued therapy. These are, as might be expected, mild local inflammation with erythema, swelling, heat, and tenderness. These usually resolve within 24 hours after the infusion. Rarely are local reactions intolerable. Thrombotic reactions have also been described with SCIG; hemolysis is less likely but may occur with high doses.

A meta-analysis of SCIG clinical trials showed that the steady-state IgG level rises linearly with doses up to 800 mg/kg per 28 days, with levels generally >1200 mg/dL at the higher end of the dose range.²³ The slope of the increase was 84 mg/dL for each increase of 100 mg/kg per 28 days, which reflects, in part, the reduced bioavailability of SCIG in comparison with IVIG.^{18,23} As with IVIG, the rate of infection falls linearly with steady-state IgG levels up to 1300 mg/dL.²³ Also, as with IVIG, the SCIG should be dosed based on total body mass. In the study by Shapiro,¹⁷ the investigator also showed that clinically effective SCIG doses were the same in individuals with a BMI of >30 kg/m² and those with BMI of <30 kg/m². In addition, there was no difference in steady-state IgG level between individuals with a BMI of >30 kg/m² and of <30 kg/m².

The dosing guidelines for SCIG mentioned above are based on the fact that SCIG has two-thirds the bioavailability in comparison with IVIG.¹⁸ Not all authorities agree that it is necessary to use higher overall doses with SCIG to achieve the same clinical benefit in comparison with IVIG. However, there are data from trials that compared outcomes in patients who switched from IVIG to SCIG, which showed that outcomes were improved in those who received cumulative SCIG doses 1.3 times their IVIG dose in comparison with those who received equivalent cumulative doses of SCIG and ICIG. For example, two separate studies showed fewer days on antibiotics, fewer days missed from work or school, fewer days in the hospital, and a lower annual rate of infection in those who received the higher SCIG doses.^{23,24}

Seven separate studies of health-related quality of life in recipients of IVIG and SCIG showed improved quality of life in patients who received SCIG.²⁵ The dimensions in which they scored higher included Global/general health, Bodily pain, Role social/emotional/physical, Parental impact/emotional/time, Family activities, Vitality, Mental health, and Social functioning.

HYALURONIDASE-FACILITATED SCIG INFUSION

Another type of SCIG product uses recombinant human hyaluronidase to facilitate the infusion, which

permits doses of several hundred milliliters to be infused in a single site every 3 or 4 weeks (HyQvia).^{26,27} Hyaluronidase degrades hyaluronic acid in the extracellular matrix and makes tissues able to accommodate larger infusion volumes in a single area. The hyaluronidase activity disappears in a matter of hours and fibroblasts rapidly regenerate hyaluronic acid. Tissues revert to normal within 24–48 hours. This type of SCIG is considered to have equivalent bioavailability to IVIG, and dosing guidelines are as indicated above for IVIG.^{26,27} Systemic adverse effects with HyQvia are milder than with IVIG infusions but are somewhat more common than with SCIG without hyaluronidase. Mild local reactions are also common with HyQvia and diminish with continued use. HyQvia is also intended for infusion in the patient's home by him- or herself or with the assistance of an adult care giver.

HyQvia carries a unique warning related to a theoretical risk of impaired fertility in male or female recipients of the drug.^{26,27} Hyaluronidase is an important enzyme in the head of human sperm cells, and it is required for the sperm to penetrate the zona pellucida and fertilize an ovum. If a patient who is receiving infusions of hyaluronidase made neutralizing antihyaluronidase antibody, then this could impede fertilization. Thus far, there has been no evidence of production of neutralizing antihyaluronidase antibody in any recipients of HyQvia in clinical trials.²⁸ Approximately 20% of patients developed transient non-neutralizing antibodies detected in an extremely sensitive immunoassay. Some of these patients reacted on only a single measurement during the trial, and no patients had persisting antibodies after the end of the trial.

CONCLUSION

There are now a variety of IgG products available for both replacement and immunomodulatory use. These include products that range in concentration from 3 to 12% intended for IV use, and products from 10 to 20% concentration for SC use, including a product that can be infused SC in large doses in a single site by virtue of facilitation with human hyaluronidase. As a result of this variety of treatment options, it is very likely that a suitable IgG regimen may be crafted for any patient regardless of size, age, underlying or intercurrent disease, dose, problems with venous access, or problems with tolerability of a given product.²⁹ Continued technological development and innovation will likely lead to even further improvements in IgG yield, product purity, and convenience of dosage form and administration in the future.

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