

Subcutaneous Administration of IgG

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KEYWORDS

- IgG • Primary immune deficiency
- Subcutaneous • IgG • Efficacy
- Pharmacokinetics • Quality of life
- Adverse effects

Systemic availability of exogenous antibodies injected subcutaneously (SC) into humans was recognized more than 100 years ago, when immune animal sera were used as the major treatment of diphtheria and tetanus.¹ Indeed, the characteristics of adsorption of IgG from SC sites were well understood even then: “A certain time must elapse from the injection...until its healing activity in the infected parts of the body can develop... (Antibody) injected under the skin does not pass straight into blood vessels but first into the lymphatic vessels. From here it takes several hours before passing gradually into the blood stream and further time still is needed before it is diffused not only everywhere in the blood stream but also in the extra-vascular fluids.”¹ Despite the slower kinetics of adsorption and distribution of IgG given by the SC, as opposed to the intravenous (IV), route, SC administration of the exogenous antisera was preferred because of its freedom from the severe and often life-threatening systemic reactions that accompanied IV injections of animal proteins. Decades later, similar freedom from systemic adverse reactions prompted the use of slow SC infusions of human IgG concentrates in patients who had primary immune deficiency diseases (PIDD) and poor tolerance of intramuscular (IM) injections or the newly developed IV preparations.^{2–6} Several studies have shown that subcutaneous immunoglobulin (SCIg) has similar efficacy to intravenous immunoglobulin (IVIg) in preventing infections in PIDD patients. The freedom from systemic adverse effects and the ease with which SC can be administered at home has led to its increasing popularity in recent years, and to documented improvement in quality of life for PIDD patients.

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EFFICACY

Although several studies suggest that SCIG treatment is comparable to IV treatment in preventing infections in PIDD patients, few direct comparisons have been made. Chapel and colleagues⁷ used a composite score for “major” and “moderate” infections in a crossover study comparing the two routes, and reported slight, but not significantly different, decreases in infection in patients on SC treatment. The number of days lost from work or school due to illness showed no difference in the two groups.⁷ This study included 24 subjects who completed 1 year of treatment on each route, but different IgG preparations were used for the different routes.⁷ Pac and Bernakowska⁸ reported a nearly 50% reduction in episodes of infection and days of antibiotics on 13 months of SC as opposed to the preceding year of IV treatment in the same patients. Gardulf and colleagues⁹ showed a reduction in days in hospital per year due to infection in PIDD patients on SC versus those on IV treatment, but the statistical significance of this difference was not reported. In a recent study in Germany in which patients on SCIG were asked to compare retrospectively their previous IVIG with current SCIG treatment regimens, the reported incidence of infection dropped from 2.8 ± 2.0 days in 6 months on IV to 1.9 ± 1.9 days in 6 months on SC ($P = .021$).¹⁰ The author and his colleagues recently completed a randomized, crossover study in the United States, in which 11 patients received the same monthly dose of a single preparation of IgG by the IV and SC routes for 6 months each. Thirteen episodes of infection occurred during the IV phase versus only 9 episodes during the SC phase.¹¹ In one of the largest and most closely monitored studies of SCIG, which included 51 patients in the United States in a 12-month efficacy period, Ochs and colleagues¹² reported 0.04 serious infections and 4.4 nonserious infections per patient per year. In a 6-month study of 47 patients on the same SC preparation in the European Union and Brazil, the annualized incidence of serious infections was also 0.04 per patient per year and the incidence of nonserious infections was 4.3 per patient per year.¹³ These results are comparable to the overall mean of 0.068 serious infections per patient per year and 3.02 nonserious infections per year in the licensing trials of all IVIG preparations licensed in the United States since 2000. Thus, the results indicate that SCIG is equal in efficacy to IVIG in preventing infections in PIDD patients.

Although it may be postulated that elimination of periods with low IgG levels toward the end of IVIG dosing intervals (see later discussion) might result in better long-term freedom from morbidity due to chronic sinus or lung infection in PIDD patients, data are not available that would allow comparison of the long-term effects of SC versus IV IgG administration on the development of bronchiectasis or other changes on CT scans, nor on deterioration of pulmonary function in patients who have PIDD. Similarly, no data are available comparing the efficacy of SC versus IV IgG on the persistence or progression of chronic sinus disease in PIDD patients with that problem, or on other complications of PIDD.

PHARMACOKINETICS

Few published data report traditional pharmacokinetic parameters for IgG administered by the SC route in immunodeficiency patients. Studies in rabbits have shown that the peak serum IgG concentration is reached 3.2 days after SC injection of human IgG and that the bioavailability of IgG given IM or SC is less than that of IgG given IV.¹⁴ In another rabbit study, using a preparation of IgG currently marketed in the United States for IV use, more than 120% of the IV dose was necessary to achieve the same area under the curve (AUC) of IgG versus time for SC versus IV administration.¹⁵

The Food and Drug Administration (FDA) criteria for approval of new IgG preparations for IV administration include the requirement that pharmacokinetic parameters for the new preparation be similar to historical values for previously licensed IV preparations.¹⁶ The parameters to be reported include the volume of distribution; plasma concentration time curve, including the time at which the maximum concentration is reached and the maximum concentration that is achieved; AUC; half-life; and elimination rate constants.¹⁶

Partly because of the preclinical data mentioned earlier, partly because of data received by the FDA showing that monoclonal antibodies and therapeutic Fc fusion proteins have lower bioavailability when given by the SC or IM as compared with IV route, and partly because of uncertainty regarding which pharmacokinetic parameters are most relevant for the use of IgG in PIDD patients, the FDA faced a quandary in formulating criteria for licensing IgG preparations to be given by the SC route.¹⁷ To be sure that patients being given SCIG were at least as well protected as those receiving IV preparations, the FDA took the “conservative” position that the AUC for SC IgG must equal the AUC for the previous IV regimen given to the same patient.¹⁷ In contrast, European regulators require only that the “trough” serum IgG level on SC IgG exceed that achieved on IVIG.¹⁸ For the one IgG preparation currently licensed for SC use in the United States, the requirement for equivalence of the AUCs resulted in a “dosage penalty” of 37%.¹² That is to say, to achieve the same mean AUC for IgG given SC as compared with IV, an average of 37% more IgG had to be given by the SC route. It is not clear from published studies that equivalence of the AUC is necessary for therapeutic equivalence, and results of a European study in which the same dose was given by the IV and SC routes showed no difference in rates of infection (efficacy) from the North American study in which the SC dose was raised by 37%.^{12,13} In that European study, the mean “steady-state” serum IgG concentration achieved on SC IgG was 11% higher than the mean trough IgG concentration with the same total monthly dose being given once every 3 to 4 weeks by the IV route. In contrast, in the North American study with the 37% dosage increment, the mean steady-state IgG level on SC therapy was 32% higher than the mean IgG trough level on IV therapy.¹² Data from these and other studies comparing IgG levels achieved by the IV and SC routes are presented in **Table 1**.

The systemic adsorption of IgG from SC sites is considerably slower than that of IV-injected IgG. Sample pharmacokinetic curves for each route of administration are shown in **Fig. 1**. As seen on the left, an IV infusion of 406 mg/kg of IVIG into a patient who had X-linked agammaglobulinemia rapidly raised the serum IgG level by more than 900 mg/dL. The peak IgG typically decreases somewhat over the next 48 hours as the IgG redistributes into the total extravascular volume, then continues to decline with first-order kinetics and a half-life of about 22 days.^{19,20} Thus, patients on typical regimens of IV infusions every 21 to 28 days are never really at a steady state. During the course of each dosing interval, their serum IgG concentration typically varies by more than 700 mg/dL around the mean (in this case, 850 mg/dL). In contrast, when the IgG dose is fractionated into three or four equal doses given SC at weekly intervals, the slow systemic adsorption from the injection site or sites increases the serum IgG even as the IgG is diffusing out of the circulation elsewhere in the body. Thus, the peak is markedly truncated. Fractionating the usual 21- or 28-day IV dose into SC doses given weekly, or even more frequently, can result in a true steady state, in which the IgG being adsorbed from SC injection sites essentially replaces that fraction of the previous dose that has been metabolized. The right side of **Fig. 1** shows data for the same patient maintained on a weekly SC dose equal to 40% of the previous 21-day dose; in other words, a monthly dose 20% higher than on IV therapy. The

Table 1 Comparison of serum IgG concentrations on intravenous and subcutaneous therapy							
Author (Y)	(N)	IV Dose (mg/kg/mo)	Mean IV Trough (mg/dL)	Mean SC Dose (mg/ kg/wk)	SC Dose (as % of IV)	Mean SC trough (mg/dL)	% Δ in Trough (SC/IV – 100%) ^a
Chouksey (2003)	5	553	997	138	101.5	1144	14.7
Ochs (2006)	51	465	785	158	136.0	1040	32.0
Gardulf (2008)	47	—	836	89	101.0	922	11.0
Desai (2008)	10	551	1051	138	100.0	1168	11.1

^a Mean of individual percent changes.

maximum variation around the mean serum IgG concentration of 816 mg/dL is only 50 mg/dL.

Fig. 2 shows mean serum IgG levels in 47 patients midway through a 6-month study in which they received an average weekly dose of 89 mg/kg IgG given SC on days 0 and 7 of the time period shown. Again, it is readily apparent that a near-steady state is achieved, with little variation in the IgG level over the 14-day interval sampled here.²¹

In a much earlier study of 23 adult CVID patients by Waniewski, and colleagues,²² it was reported that weekly SC infusions of 100 mg/kg maintained steady-state IgG levels, with little variation around the mean for more than a year. The time to reach this steady state was also examined in that study. One group of 6 patients, naïve to IgG therapy, with a mean baseline IgG concentration of 220 ± 140 mg/dL, was started on 100 mg/kg IgG SC once a week. After 6 months of weekly infusions, these patients

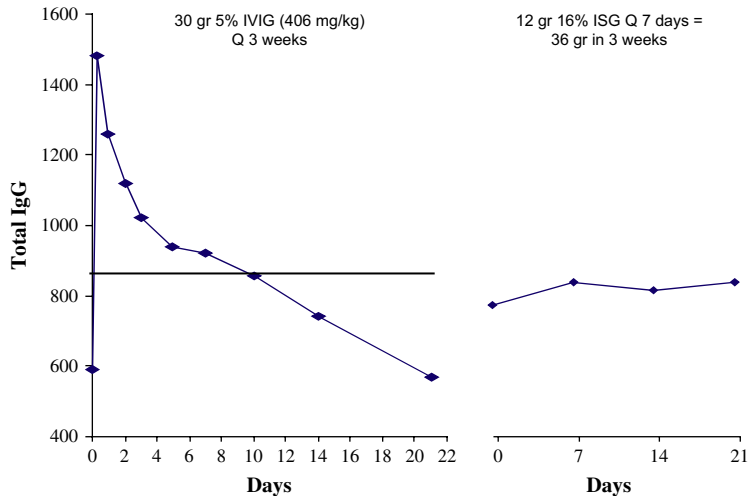


Fig. 1. (Left) Serum IgG levels in a 34-year-old X-linked agammaglobulinemia patient while on a regimen of 30 g IVIG (406 mg/kg) every 3 weeks. (Right) After a few months on 12 g SCIG once a week.

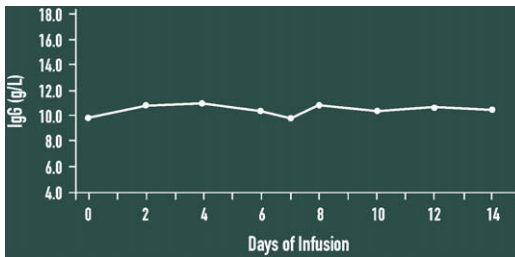


Fig. 2. Mean steady-state IgG levels in a group of 47 patients receiving weekly SC infusions on days 0 and 7.

had a mean serum IgG level of 820 ± 180 , which was still lower than the apparent steady state of 990 ± 60 mg/dL achieved at 12 months of therapy.²² That concentration then remained fairly constant over 6 months of further treatment with the same weekly dose of SCIG.²² To obviate the slow and gradual rise in the serum IgG level observed in naïve patients given only one infusion a week, Waniewski and colleagues²² gave another group of patients 100 mg/kg infusions daily for 5 consecutive days. That group of patients achieved a steady state of approximately 1200 mg/dL by the end of that 5-day course of treatment, and had mean levels of 1150, 1110, and 1120 at 6, 12, and 18 months later, respectively. It may be important to note, however, that the later group of patients had received IM or IV IgG treatment at unspecified times before beginning on SC treatment, and that they had a mean IgG level of 670 ± 280 mg/dL just before beginning SC therapy. Nevertheless, many immunologists consider five to seven daily infusions of 90 to 120 mg/kg each satisfactory for quickly bringing up the serum IgG level of a newly diagnosed antibody-deficient patient, so that the patient can then continue on weekly infusions alone.²³

In the recent pivotal study of an IgG preparation now licensed by the FDA for SC administration in the United States, patients who were already on stable IGIV treatment regimens were given their initial SC infusion 7 to 10 days after their most recent IV infusion; then, SC infusions were continued on a weekly basis. That schedule results in initially higher IgG levels for the next several weeks, which trend downwards over time to a new steady state. Desai and colleagues¹¹ have also completed a recent study using that interval between the patient's last IV and first SC infusions, followed by weekly SC infusions of one quarter of the previous monthly IVG dose (on a mg/kg basis). In those patients, the mean steady-state serum IgG concentration on SC infusions was 11% higher than the mean trough level had been on IV therapy, and that steady state was reached after 10 to 12 weeks of SC treatment.

ADVERSE EFFECTS

Systemic Adverse Effects

The difference between the shapes of the pharmacokinetic curves illustrated above for SC versus IV IgG administration underlies one of the most important differences between current IV and SC regimens. Many of the adverse effects associated with IV infusions, such as headaches, fever, and anaphylactoid reactions, occur during the infusion or within 48 hours of it, while the serum IgG concentration is rapidly increasing or is still near its peak. Elimination of the sudden, rapid increases and transient peaks in the serum IgG concentrations is believed to be responsible for the marked amelioration in systemic adverse effects experienced by patients who transition from IV to SC regimens.²⁴ One of the original rationales for using slow infusions

when the IM preparations were given SC was that if large injections of IgG induced the release of mediators such as prostaglandins or cytokines, which produced chills, fever, and other remote systemic adverse effects, then slow administration might decrease the rate at which these putative mediators were released and would decrease their concentrations at any point in time,² which, in turn, would allow compensation by normal homeostatic mechanisms. Indeed, many of the systemic adverse effects associated with IV infusions are considered “rate related” and may be obviated by slowing the rate of the IV infusion.²⁵ With SC administration, a depot is created in the tissues, from which the IgG reaches the blood stream much more slowly than if it was infused directly into a vein. Furthermore, the serum IgG level remains nearly constant on SC regimens. Hence, rapid release or dramatic systemic effects of any mediators are unlikely to be produced when the exogenous IgG comes into contact with Fc receptors or antigens.

The freedom from systemic adverse effects with SC administration was apparent when the first few reports of slow SC infusions of IM immune serum globulin (ISG) appeared in the early 1980s,²⁻⁶ and continues to characterize SC administration.²⁴ In the reports of Gardulf and colleagues^{9,26,27} in the early to mid-1990s, systemic adverse reactions were reported with less than 1% of SC infusions, as opposed to 46% with the IV preparations available in that era. Pac and Bernakowska⁸ reported a series in which 15 patients received 780 SCIG infusions over a 13-month period. Systemic adverse effects were experienced by only 1 patient, a child who had required steroids and other premedications before IVIG infusions. Although that patient tolerated the SC infusions for months with no problems, she subsequently suffered systemic reactions at two consecutive SC infusions, and was switched back to her previous regimen of IV premedication before standard IVIG doses. None of the other patients had significant systemic adverse effects and none switched back to IV therapy.⁸

In only two major studies has the incidence of systemic adverse effects accompanying SC infusions been reported as greater than 1%. Chapel and colleagues⁷ reported that 3.3% of SC infusions were accompanied by systemic adverse effects, as compared with 5% of IV infusions. Ochs and colleagues¹² reported that headaches occurred during, or within 48 hours following, 1.6% of SC infusions, but only 35% of these headaches were considered “severe,” requiring prescription medications. Only 3 subjects out of 68 withdrew from that year-long study because of infusion-related adverse effects; no infusion-related serious systemic adverse reactions occurred.¹²

Local Adverse Effects

Most patients experience some kind of local reaction, at least transiently, at the sites of SC infusions. These reactions may include swelling, redness, and a sensation variously reported as “itching” or “burning.”^{11,12,24,28} The swelling may exceed that expected from the volume of fluid injected at the site, but that is unusual. Pruritis, when it occurs, is not usually severe. The patient’s sensation is often more just an awareness of the presence of an area of swelling or redness, rather than true discomfort. In the trial of Ochs and colleagues,¹² these reactions occurred initially in nearly 90% of patients, and were mostly considered “mild” or “moderate” (**Fig. 3**). Only 3 patients out of 68 discontinued participation in that study because of local site reactions. In almost all cases, local swelling or redness dissipates within hours (**Fig. 4**). Occasionally a small, pearl-sized nodule or knot may persist for 1 or 2 days. Examination of patients who have infused IgG SC in the same region of the body (ie, anterior abdominal wall, flanks, or upper thighs) for years has not revealed any long-term changes such as fibrosis or fat necrosis. In most studies, the incidence of local reactions has been reported to decrease over several months of continuing SC



Fig. 3. Local site reactions in a SC IgG licensing trial. (Top) “Mild” reaction; slight erythema with minimal swelling. (Bottom) “Moderate” reaction; significant swelling. Swollen area is blanched and surrounded by a ring of erythema few millimeters in width.

therapy, as illustrated in the data of Ochs and colleagues (**Fig. 5**). Most of the data on which that and similar curves are based are recorded by the patients in diaries they keep at home. Therefore, it is likely that a major contribution to the recording of the reactions is subjective. As the patients get accustomed to the local phenomena that accompany SCIG infusions, they are less likely to report a small degree of local swelling as a “reaction.” It is possible that the decreased rate of local reactions associated with SC infusions might represent some kind of accommodation of the patient to the specific product, which might be analogous to the increased rate of reactions associated with switching to a new IV preparation reported in some studies. Biopsy studies of SC IgG infusion sites at various times after the injections have not been reported.

“Wear-Off” or Trough Effects

As opposed to acute adverse effects associated with the high peaks of IgG in the serum that accompany bolus IV administration, many patients who receive IVIG infusions every 21 to 28 days report general malaise, fatigue, arthralgias or myalgias, and increased susceptibility to infections during the last 7 to 10 days of each dosing interval. Most patients on IV treatment regimens report that they can feel their IVIG “wearing off” before their next infusion is due.²⁹ Often, patients will report that they have “run out of gas” or “feel punk” at the end of the IV dosing interval. It is apparent from the graphs that these low serum IgG levels are obviated by weekly or more frequent SC infusions. **Table 1** summarizes the changes in “trough” serum IgG level on SC versus IG therapy reported in several recent studies. As patients achieve stable steady-state serum IgG levels on SC regimens, they frequently report alleviation of



Fig. 4. Clearing of local site reactions after SC IgG administration. A 14-year-old girl has just finished infusing approximately 22 mL of a 15% solution of Carimune into each of two abdominal sites sequentially. The infusion into the first site (to the patient's left of umbilicus) was given over about 1 hour and ended 1 hour before the picture was taken. The site of the needle is still visible, as is some diffuse swelling, but the redness has almost completely dissipated. The infusion into the second site (to the patient's right of umbilicus) was just completed before this picture was taken. Note the mild central swelling surrounding the needle site, and several centimeters of redness, but no induration per se. The patient was infused with 6 g of 15% Carimune solution made by pushing 40 mL of sterile water for injection into a 6-g bottle of lyophilized IgG. Note that indented scars are from surgical drains or other procedures, not from IgG infusions.

the symptoms they previously experienced as their serum IgG levels approached their nadir. This improvement, in turn, may lead to an overall more continuous feeling of good health, which likely contributes to the increased quality of life reported by most PIDD patients who switch from IVIG to SC.^{27,30–32}

QUALITY-OF-LIFE EFFECTS

Several formal studies have been done of the health-related quality of life of PIDD patients on different modes of therapy, mostly performed by Gardulf and colleagues in Sweden. European and North American patient populations have been surveyed for these studies. PIDD patients in the United States have also been surveyed by the Immune Deficiency Foundation (IDF), but that survey was completed before any SC product was licensed in the United States. Several sources of dissatisfaction expressed by patients in the 2003 IDF survey are directly related to the sites, timing, or frequency of IV infusions. The specific sources of dissatisfaction with IV regimens resonate with the results of the studies of Gardulf and colleagues, and can be affected by switching from IV to SC therapy. Most importantly, although 64% of PIDD patients surveyed by the IDF reported that they were somewhat or very satisfied with the convenience of the location of their IVIG treatments, satisfaction was reported by 96% of patients infused at home, as compared with only 51% of those infused in doctors' offices and 48% of those infused in hospital outpatient clinics. Among those infused in other locations, only 39% reported that the location was "very convenient." Sixty-nine percent of the patients reported receiving their IVIG infusions on weekdays between 9 AM and 5 PM, and only 64% considered that "very convenient." Eighty-eight percent of patients reported receiving IVIG infusions at intervals of 3 weeks or longer,

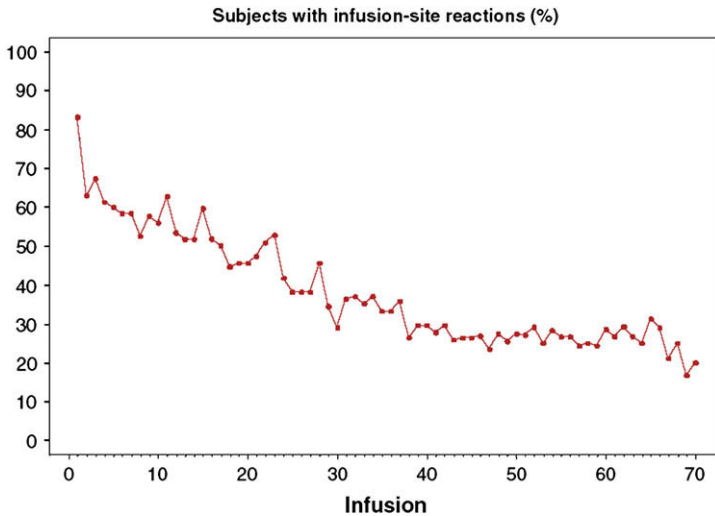


Fig. 5. Incidence of local site reactions during SCIG therapy. (Data from Ochs HD, Gupta S, Kiessling P, et al. Safety and efficacy of self-administered SC immunoglobulin in patients with primary immunodeficiency diseases. *J Clin Immunol* 2006;26:265.)

but 68% reported that usually or sometimes they could feel the effect of their IgG “wearing off” before their next infusion. Over the course of a patient’s lifetime, these sources of dissatisfaction can become major burdens, with significant emotional consequences.^{27,32} Many of the sources of dissatisfaction with IV treatment regimens can be alleviated by switching to SCIG. Because of the safety of SCIG and the fact that IV access is not required, most patients can be infused at home, either by a parent or partner, or by self infusion, and assistance by trained medical professionals is not routinely required. Infusions can therefore be given on a schedule of the patient’s own choosing. Because the infusions in most SC regimens are given weekly or even more often, and a true steady state is achieved, “wear-off” effects are also obviated.

In their 2004 study of patients in Europe receiving SC IgG infusions at home, Gardulf and colleagues³⁰ used standardized instruments for recording health-related quality of life. These included the “child health questionnaire–parental form 50” for children and the “short form 36” for adults. In addition, a “life quality index” form was developed to examine the patients’ perceptions of the impact of their IgG treatment on their daily activities.^{30–32} Among children previously receiving IVIG infusions in the hospital, significant ($P < .01$) improvements in 6 out of the 14 subscales were reported after 10 months on weekly SC infusions at home. Of these, improvement reached significance within 6 months of home therapy on the scales measuring general health perception, emotional impact, family activities, and global health.³⁰ For adults who had previously been on IV therapy in hospital, the switch to SCIG at home resulted in improvements in the “vitality,” “mental health,” and “social functioning” scales. Treatment satisfaction increased in both children and adults, and all the children and 73% of the adults preferred SC over IV treatment.³⁰ In a similar study applying the same survey instruments to North American patients, children and adults who had been on IV infusions in hospitals or doctors’ offices before switching to weekly SCIG at home recorded significantly ($P < .01$) higher scores for scales measuring “role–physical” (extent of limitation in normal activities [schoolwork and so forth] due to physical problems), general health, vitality, and health transition (improvement) after 12 months on SCIG at

home.³¹ Even more dramatic ($P < .001$) changes were reported in treatment satisfaction, including decreased interference of treatment with other activities, decreased problems related to receiving therapy, and increased satisfaction with the treatment setting.³¹ In contrast, among patients who were receiving IV treatment at home before entering the study of SCIG, significant improvement in only one scale, "general health," was reported. These results suggest that major improvements in quality of life are achieved when PIDD patients are treated at home rather than in hospitals or doctors' offices. SC infusions facilitate a transition to home care because of their freedom from adverse effects and the lack of a requirement for trained medical personnel. Elimination of the low trough levels just before monthly IV treatments, which obviate periodic increases in susceptibility to infection, is probably responsible for the increase in general health reported by all patient groups on switching to SCIG, regardless of the location at which the treatment was administered. These conclusions are further supported by the patients' preferences: 76% of the patients in the North American study expressed a preference for SC rather than IV therapy, whereas 91% of the patients preferred home treatment.³¹

Despite the apparent advantages of home SCIG treatment for most PIDD patients, not all patients are interested in switching from IV to SC treatment, and not all patients want to switch from hospital or office to home treatment. In Germany, where home SC has been offered as an alternative to IV treatment since 2003, demographics and attitudes were recorded from 32 adult patients who chose SC therapy and were compared with those recorded by 28 adult patients who chose to remain on IV therapy.¹⁰ Patients who chose SC treatment were younger (37 ± 9 versus 51 ± 14 years of age, $P < .001$) and a higher percentage were employed (69% versus 28%). The predominant reasons patients on IV refused to try SCIG were perceived inconvenience (48%), anxiety about adverse reactions at home (31%), and anxiety over needle sticks (6%). In contrast, the major reasons patients on SC gave for preferring that route were flexibility (50%), decreased side effects (17%), and constant IgG levels (17%).

Thus, in considering which route and location of therapy might be most appropriate for any given patient, it is important to consider the individual patient's life situation and attitudes toward self versus assisted treatment, and the medical advantages and disadvantages of each route for that individual patient. Although SCIG may be preferred by many PIDD patients, it is not necessarily the best choice for everyone.

PATIENTS WHO HAVE SPECIAL CONDITIONS

Only a few reports exist of the use of SCIG in PIDD patients presenting unique challenges for IgG therapy, including pregnancy, IgA sensitization, and bleeding disorders. The author and his colleagues' original motivation for using ambulatory pumps for slow SC delivery of IgG was to facilitate adequate IgG replacement in a pregnant patient who did not tolerate IM injections or plasma transfusions. At times during the third trimester, that patient self administered 140 mL of 16% IgG per week, equaling 22.4 g per week.⁵ The patient gave birth at term by a spontaneous vaginal delivery, and neither mother nor baby suffered any complications of the therapy or delivery, nor any postpartum problems. Mother's and baby's IgG levels were 620 mg/dL and 880 mg/dL, respectively, on day 2 after birth.⁵ Gardulf and colleagues³³ subsequently reported a series of 11 pregnancies in nine immunodeficient women who self infused 100 mg/kg/wk at home throughout the pregnancies, using a rapid infusion protocol. No complications or serious infections occurred, and in all cases, the cord blood IgG concentration was equal to, or higher than, the mother's. No reports have been published describing large series of infants who had antibody deficiency treated

with SCIG, but several pediatric centers have been administering IgG in this way because the difficulty of obtaining IV access, which is common in babies under 2 years of age, is obviated with the SC infusions. The author and his colleagues have treated several patients in this age group with SCIG, and have found weekly doses in the range of 1 mL of 16% IgG (160 mg) per kg, up to 10 mL, are easily tolerated in the thigh. Although some parents may be hesitant to poke their baby, once they see how well the babies tolerate the small prick of a single 27- or 28-gauge needle, they are quickly relieved. Especially if previous attempts at IV therapy have required multiple sticks or the use of scalp-vein infusions, the advantages of the SC route are readily apparent.

Many physicians and patients inquire about the use of the SC route in patients who have bleeding disorders or anticoagulant therapy. Heparin is commonly self administered at home by the SC route and, although some local bruising may occur, bleeding from the sites is usually not a significant problem. Arora and colleagues³⁴ have reported the use of SCIG in a patient who had von Willebrand's disease with no special precautions or problems, and anecdotal reports exist of the successful use of SCIG in boys who have classic hemophilia.

Another concern that is frequently voiced about IgG treatment of PID in general, both IV and SC, is the potential for problems associated with administering IgA-containing IgG preparations to IgA-deficient patients. Although a risk for anaphylaxis exists if preparations containing IgA are given to patients who lack that protein, in practice this event is extremely rare. Anaphylaxis due to SC injection of IgA-containing preparations has not been reported, and this procedure is generally regarded as safe in PID patients, most of whom have some IgA or also lack the capacity to produce IgE (ie, Bruton's agammaglobulinemia). Sundin and colleagues³⁵ have reported that administration of IgA-containing IgG preparations SC was well tolerated by patients who had detectable anti-IgA antibodies, although the isotypes of the anti-IgA antibodies were not reported and none of the patients were specifically tested for IgE against IgA. Four of the anti-IgA-positive patients lost their anti-IgA activity after weeks to months of weekly treatment with an IgG preparation containing up to 5 mg/mL of IgA.³⁵ Induction of a state of unresponsiveness to IgA was inferred from the absence of IgA-containing complexes in the patient's sera and the lack of reemergent anti-IgA activity, even after switching to low-IgA preparations.³⁵ The presence or absence of partial IgA deficiency does not seem to correlate with local reactions to SCIG, or with the amelioration of these reactions over time. Because of the theoretic risk for anaphylaxis, anaphylactoid reactions, and other severe adverse effects, it is recommended that the initial doses of SCIG always be given in a clinical setting equipped to treat acute severe reactions in the unlikely event they occur.²¹

COST

Comparisons of the costs of SC versus IV therapy regimens in the early 1990s reported that substantial savings were achieved by the use of IM preparations by the SC route.²⁶ Analysis of that data suggests that the savings were mainly due to decreased cost of the stocks of IM ISG compared with the (at that time) new IV preparations. In the current era, the major cost of any IgG treatment regimen is the product itself. In turn, the single biggest contribution to the cost of the products is the cost of the starting plasma itself. Although marketing and distribution expenses vary, in general, the costs of SC and IV products supplied by most manufacturers are, and will likely continue to be, in the same range. Typical regimens for self-SC administration at home generally use one or more pumps, which may have purchase prices ranging from a few hundred to a few thousand US dollars each. Depending on arrangements

for purchase or leasing of the pump or pumps, service charges or amortization of the purchase price may add as much as \$50 to \$100 a month to the cost of SC regimens. Several popular pumps require special, proprietary syringes or tubing sets, which may add \$5 to \$25 to the cost of each infusion, and elaborate multibranching tubing sets with special SC needles may also drive up the per-infusion costs. Because infusions are typically given once or twice a week, the cumulative annual costs of some regimens may be considerable. In contrast, many IV regimens include facility fees or bed charges, and charges for the nurse or other health professional who starts the IV and monitors the infusion. IV infusions are frequently given using pumps for precise control of the infusion rates, which may add an equipment charge or purchase price to the cost of the IV regimen. Because IV regimens typically involve infusions that are given only once every 3 or 4 weeks, those costs may not accumulate as rapidly as the cost of the supplies associated with SC regimens. Indirect costs, such as for transportation to a hospital or infusion center, parking, and time lost from work, should also be considered in comparing the total costs of home SC versus hospital- or office-based IV treatment regimens.

A recent study performed by the Canadian Government Agency for Drugs and Technologies in Health (CADTH) concluded that home IV treatment would be the least expensive program for PIDD patients in that country, with home SC a close second. The estimated direct yearly per-patient costs for treating an "average" adult who has IVIG in hospital was C\$ 21,777; IVIG at home (self administered, without a nurse) was C\$19,891; and SC at home was C\$ 20,416. When indirect costs, such as transportation and time lost from work were included, the costs were C\$ 23,037 for hospital-based IV, C\$ 20,302 for home IV (assuming this would be self administered, without a nurse), and C\$ 21,033 for self-administered home SCIG. However, when the decrease in adverse effects and increased quality of life with SC versus IV treatment were included in the calculations, the conclusion was reached that SCIG "dominates" because of "greater expected benefits at lower expected costs" per quality adjusted life-year.³⁶ Overall, if the 75% Canadian PIDD population now receiving IgG treatment switched from IV to SC therapy, the CADTH estimated that the savings to the government would be approximately C\$ 9,000,000/y.³⁶ This analysis assumed the same price per gram of IgG regardless of the route by which it would be administered.

A similar analysis in Germany, using actual data on payments by insurance companies for PIDD patients receiving IgG by both routes, showed that the average price per gram for IgG to be given by the SC route was only 46% of that for IgG to be given by the IV route. Overall, the budget impact analysis from that study, independent of any adjustment for improvement in quality of life measurements, showed that yearly savings for the German statutory health insurance would be 17 to 77 million Euros annually if 60% of current PIDD patients switched from IV to SCIG.³⁷

PRACTICAL CONSIDERATIONS IN SUBCUTANEOUS IMMUNOGLOBULIN THERAPY FOR PRIMARY IMMUNE DEFICIENCY DISEASES

Selection of Infusion Regimens

The author and his colleagues' initial attempts to give SC IgG infusions were performed using 16% ISG preparations in a patient who previously had demonstrated poor tolerance for IM injections of the same preparations.² Other early patients were usually also chronically infected. To avoid local or systemic adverse effects, they administered the ISG slowly, initially at 1 to 2 mL per hour.^{2,5} Furthermore, because the ISG was generally provided in 10-mL vials, that was the usual volume infused into a single site. As other investigators began to use this method in a wider

spectrum of patients, it became clear that much faster rates and increased volumes per infusion site could be tolerated. In their 1991 study of 25 PIDD patients routinely receiving SCIG infusions for 1.25 to nearly 4 years, Gardulf and colleagues⁹ reported that those patients who had higher body mass indexes were receiving higher doses at each infusion, and using two pumps with up to four sites in the abdomen or thighs for each infusion. The mean volume per infusion was 42.8 mL (range 28–60), and the mean duration of the infusions was 75.8 minutes (range 45–120 minutes). Each patient's initial infusion was given at a rate of 10 mL/h into each site. After several infusions, the rates were increased by 1 mL/site/h every few weeks according to each patient's tolerance, until the above rates were achieved.⁹ Although 36% of those patients had previously suffered severe reactions after IM injections, no severe or moderate reactions were observed after the SC infusions, and only 0.9% of SC infusions were accompanied by mild systemic symptoms.⁹ Subsequently, Gardulf and colleagues^{26,38} continued treating patients with these "rapid" infusions at 20 to 40 mL/h. Similarly, Gaspar and colleagues³⁹ reported the routine use of 20 mL/h, usually into two sites simultaneously. Hansen and colleagues⁴⁰ then reported that most patients tolerated "express" infusions at rates up to 35 mL/h/site, such that 10 mL could be delivered per site in 17 minutes. Using multiple syringe drivers to deliver IgG into four sites simultaneously, these investigators reported that 40 mL (6.4 g of IgG) doses were routinely tolerated in as little as 17 minutes.⁴⁰

In the only licensing trial of SCIG that has been reported in the United States, limits were set at 20 mL of IgG per hour with a maximum of 15 mL/site.¹² In studies of this type, conservative regimens are often selected for fear that adverse effects, if they occur, will have a negative impact on the regulatory authorities. It is therefore likely that similar rates and volumes per site will also be selected in future pivotal studies. In contrast, when IgG preparations marketed for IV or IM use were used "off label" for SC infusions using drivers that could accommodate syringes as large as 60 mL, a much broader range of regimens could be used, and the flexibility of the SC route could be exploited more fully. Taking into consideration the patient's preference as to the number of needle sticks (sites) per infusion and the time he/she is willing to spend, it becomes readily apparent that these two variables have a reciprocal relationship. That is, if more sites are used, the overall time for infusing a given total dose will be decreased as compared with giving the same dose into fewer sites. Additionally, it becomes readily apparent that fully grown adults can tolerate greater volumes per individual site than small children, and that it is likely that patients who have greater amounts of SC tissue (ie, higher body mass index or obese individuals) will also tolerate more IgG per site than lean individuals. If infusions are given slowly, then the infused IgG may be diffusing away even as more is being given, so that more volume can be put into an individual site without increasing the local discomfort or severity of any possible reaction. Before any SC preparation was licensed in the United States, the author and his colleagues reviewed the SC regimens being used by their patients, most of whom had been referred because of adverse effects with IVIG. These patients were receiving SC infusions of an IM ISG preparation, or a lyophilized preparation reconstituted to yield a solution with an IgG concentration of approximately 15%.^{41,42} Regimens ranged from 10 mL into one site in less than 1 hour in children, to 40 mL over several hours into one site (usually taken at night while the patient was sleeping), to 40 to 60 mL given into multiple sites simultaneously in short times. The spectrum of regimens eventually selected by the patients, who ranged in age and size from preemies initially weighing 5 kg to adults weighing over 130 kg, was broad but could be inclusively summarized by calculating the rate in mL of IgG per site per hour per kg body weight. The mean was found to be 0.176 mL/site/kg/h,

with a standard deviation of 0.134,⁴² which is approximately equal to 12 mL/site/h in an “average” 70-kg adult, or 3.5 mL/site/h in an “average” 20-kg 6-year-old child.

The flexibility illustrated by the regimens discussed above suggests that the patient should have a major input into designing his/her own regimen, according to his/her preferences, tolerance at the local sites, and lifestyle choices. The patient’s priorities for the number of infusions per month, number of needle sticks, and time per infusion can be easily accommodated if the regimen is selected thoughtfully. A useful algorithm is to determine the total IgG dose to be delivered per month and to ask if the patient already has firm ideas about the regimen he/she would like to use. If the patient does not, a good starting point is to divide the total volume of IgG to be infused during the month by four and to start with the assumption that one infusion per week will be preferred. The volume to be infused weekly can be rounded off to the nearest multiple of whole vials of IgG product, so that the patient can be taught to draw up each dose without wasting any of the IgG and without requiring a pharmacist to be involved. The number of pumps that will be available to the patient should then be considered. In most cases in the United States, a patient is likely to have only one pump at home, whereas in the United Kingdom, it is common for the National Health Service (NHS) to provide two pumps to each patient.⁴³ In Sweden, up to four pumps are frequently used for each infusion. Dividing the volume to be given in each infusion by the number of pumps narrows the choices of the size of the syringe that will be used for each pump, which, in turn, is a major factor in determining which pumps might be used for that particular patient.⁴⁴ The number of sites to be used for each infusion and the time can then be calculated based on the patient’s preferences. The calculated value given above, 0.18 mL/kg/site/h, can serve as a useful guide and starting point. The product manufacturer’s recommendations in the prescribing information can be used in the same way, but it should be remembered that such information has usually been selected in an arbitrary way to facilitate uniform data collection during clinical trials. Once an initial regimen plan is formulated, it should be reviewed carefully with the patient to be sure it is acceptable and the patient does not foresee any problems in complying with it. If the time, number of sites, or volume per site in the planned regimen seems excessive, splitting the dose into two or more infusions per week should be considered. Orders can then be written and the appropriate equipment obtained. As the patient becomes experienced with the infusion regimen, it can be modified. In many cases, the patient’s tolerance of local site reactions increases with repeated infusions, and the time for each infusion can be shortened or the volume of IgG infused per site can be increased.

The paragraph above describes a reiterative process that may be used to arrive at an optimal regimen, individualized for each patient, and is based on the experience in the author’s clinic with various patients and multiple different IgG products over many years. Each of the parameters in **Box 1** may be considered independently, and varied to reach a regimen that fits easily into each patient’s individual lifestyle and preferences. Some investigators have explored options at the extremes of the above regimens. For example, Shapiro in Minnesota and Ochs in Seattle have reported anecdotally that many patients prefer to increase the parameter of the number of infusions per month out to 20 to 30, by giving “daily pushes” of 10 mL each, which is done conveniently by repeatedly pushing 1 to 2 mL from a 10-mL syringe without any mechanical pump at all. Daily doses of 10 mL (1.6 g, if a 16% IgG solution is used) are easily given over 5 to 10 minutes in this way, and are well tolerated by many patients. Infusing 1.6 g every weekday gives a monthly dose of 35.2 g, and the patient does not have to take infusions on the weekends. In contrast, if the patient takes a 1.6-g infusion every day, the total monthly dose will be 48.8 g per month.

Box 1**Establishing an optimal subcutaneous immunoglobulin regimen for any individual patient**

1. Predetermination: dose of IgG in mg/kg/mo. Start with estimated dose of 500 mg/kg/mo, use current monthly IV dose, or use current monthly IV dose $\times$ correction for bioavailability if desired.
2. Parameters that should be selected in accordance with patients preferences. Note that any individual parameter in this list can be prioritized and set as the most important variable, which will influence the choices for the other parameters.
 - Number of infusions per week or month
 - Volume per infusion
 - Number of sites per infusion
 - Volume per site
 - Total time for each infusion
 - Decision to use multiple sites simultaneously or sequentially
 - Number of pumps

At another extreme, patients may prefer only a single needle stick per week and might choose to infuse a large volume into a single site, which may be accomplished over a long time using a pump that can drive a large (60-mL) syringe, or with a roller-type pump and a reservoir. Examples of this type of regimen include the author and his colleagues' patients who infuse up to 60 mL at rates of 8 to 10 mL per hour while they sleep, and regimens reported by Dr. Charles Kirkpatrick of the University of Colorado, in which a single SC needle with a short "pigtail" tubing that can be closed and capped, is kept in place overnight. IgG is infused into that single site over 2 consecutive days, which would easily allow doses of IgG as great as 120 mL (19.2 g) to be tolerated by most patients each week. Another variation on a "standard" weekly dosing regimen was recently reported by Gustafson and colleagues,⁴⁵ in which doses of 200 mg/kg were given SC every other week rather than 100 mg/kg every week. Trough IgG levels on the two regimens were not compared directly, but no increase in adverse effects (AEs) or infections was reported.⁴⁵

An alternative approach is to adopt a simplified regimen using a "rule of twos": "two bottles into two sites over 2 hours." For the average 70-kg adult, an infusion composed of two 20-mL vials of 16% IgG given in this way equals 10 mL per site per hour, or 0.143 mL/kg/site/h, well within the range described above. For a 35-kg child, the same rate per site is achieved if two 10-mL vials are used. These regimens provide 6.4 g or 3.2 g of IgG per infusion, respectively. The desired total monthly dose can then be achieved by varying the number of infusions per month. For example, two 40-mL infusions per week would provide 51.2 g per month, and two 20-mL infusions per week would provide 25.6 g per month. Given that any level of activity short of rigorous exercise or total immersion in water is possible while taking these SC infusions, 2 hours per infusion is easily tolerated once or twice a week by most patients, most of whom spend many more hours than that every day sitting at a desk or in front of a television or computer, doing housework, or walking at a moderate pace.

Site Selection and Specific Procedures

Numerous resources describe in detail exact procedures to be used in selecting and preparing sites and actually administering the infusions.^{43,46-49} SC injections are most

frequently given in the anterior abdominal wall out to the flanks, the anterior or inner thighs, and the backs of the upper arms; these are diagrammed in the cited literature. A useful and easy-to-remember guideline is to be able to “pinch an inch” of SC tissue at any intended site. A key to successful SC infusion is to place the needle sufficiently deep to avoid intradermal administration. Initially, the author and his colleagues used .75-inch 25-gauge butterfly needles inserted at a 45° to 90° angle to the skin. Now, various needles specifically designed for SC use, with the needle itself mounted at 90° to the “wings” or gummed disk and tubing are available.⁴⁴ Except in the leanest patients, needles of 11 to 15 mm in length are preferable, to be sure the infusion is given into SC fat, and to minimize leakage from the site. When leakage or excessive redness occurs, it is often because needles that are too short (only 6 mm) have been used. Various stainless steel and silastic catheters in the range of 25 to 28 gauge and 6 to 15 mm in length are now marketed, attached to tubings of various lengths, with as many as four branches attached to one hub,⁴⁴ for infusing into multiple sites simultaneously. For most patients, a simple antiseptic wipe with alcohol or chlorhexidine is all that is needed to prepare the site. Extensive scrubbing is not usually necessary, and repeated use of iodine-containing antiseptics such as Betadine may actually be irritating or cause sensitization. A eutectic mixture of local anesthetics (EMLA) has been successfully used with children and with adults who may have anxiety about sticking themselves, but it is generally not needed because the needles are so small and precise placement, as with IV catheters, is not necessary. Excessive or irritating tape should be avoided; many patients have more erythema and itching from the tape than they do from the SCIG itself. The most important precaution is that the patient should draw back from the needle with a syringe before starting the pump or “pushing” the product, because high-concentration IgG solutions intended for SC or IM use may not necessarily be free from dimers or larger aggregates, which can cause adverse reactions if injected intravascularly. Providers should remember to instruct patients in the proper disposal of “sharps” and other medical waste, and should make sure that proper containers are available and appropriate logistics have been arranged.

Initiating Subcutaneous Therapy/Teaching the Patient

Various publications and other resources are available for instructing patients to self administer SCIG, including illustrated brochures on Ig manufacturer’s Web sites,^{46,47} a monograph available from the IDF,⁵⁰ a small pamphlet prepared by the National Institutes of Health Clinical Center nursing staff on how to give a subcutaneous injection,⁴⁸ and additional information specifically written for patients that is available on the Web.^{43,49} Several organizations, including the American Academy of Allergy, Asthma, and Immunology, Case Western Reserve University/University Hospitals of Cleveland, and CSL-Behring, offer courses for physicians, nurses, and pharmacists, to assist with development of expertise within individual practices, institutions, and home care companies/specialty pharmacies.

Centers in different countries have developed different approaches to actually starting SCIG therapy and teaching the patient, parent, or partner to perform the infusions when that is appropriate. Several of these are described in the book, “Subcutaneous Ig Training and Education Program.”²³ Frequently, logistics, including the time necessary for obtaining approval from the patient’s insurance company and identifying the appropriate home nursing service/specialty pharmacy (when that is necessary), play a major role in determining the approach to be used in any given case. Most patients who have been referred to the author and his colleagues have already been on IVIG. Many other patients are newly diagnosed but not hospitalized, and it is desirable to get

their IgG supplementation going without delay. In these situations, the author and his colleagues will submit the necessary paperwork for SC therapy while they start or continue the patient on IV infusions at their center. One or two 10-mL aliquots are removed from the total volume of IVIG to be administered, by drawing that amount out with one or more 10-mL syringes. These aliquots are then infused SC while the main part of the dose is being given IV. Anecdotal and published reports^{42,51} suggest that most IV preparations are well tolerated by the SC route. The nurse instructs the patient in how to administer the SC infusion and demonstrates as he/she starts it. The patient then experiences the sensation at the infusion site, and is given the opportunity to confirm that he/she would like to switch to the SC route. Another SC infusion is then started at a different site, and again, the nurse explains each step. That infusion may be stopped after 3 or 5 mL have gone in, and the patient is invited to start a new infusion at a different site using the IgG remaining in the syringe. In many cases, this step can be done two or three times during the course of a single IV infusion. After he/she has completed an instructional program and observed a nurse starting the infusions several times, the patient should demonstrate proficiency back to the nurse/physician. A checklist the nurse can initial to document that the patient has successfully mastered each step can be used to provide documentation that all necessary techniques were taught correctly. Medicare and Medicaid now have billing codes that will allow reimbursement for the time involved in starting and administering SCIG infusions (obviously, one cannot bill for SC and IV infusions at the same visit), and preapproval for the SC product and involvement of a specialty pharmacy are not necessary because the patient is actually receiving an IV product. Teaching the procedures for SC infusions is continued in the same way at subsequent IV infusion visits until the patient receives the pump, syringe, and product he/she will actually use at home for self/parent/partner infusions. When that occurs, the author and his colleagues ask the patient to bring those materials into their clinic so they can be instructed with the actual supplies they will use themselves. At that visit, it is not necessary to bill for the product, supplies, or pump because that has all been arranged and provided by the home care company/specialty pharmacy. The next time the patient is due for an SC infusion, usually 1 week later, the home care nurse is asked to go to the patient's home and observe/instruct the patient on self infusion. More than one visit may be necessary, but that is not usually the case because the patient has already been instructed by the author's office staff. It may be helpful if the home care nurse or someone from the physician's office confirms that he/she will be accessible by telephone during the patient's first several infusions at home, to provide reassurance or "talk the patient through" any step at which he/she has questions or difficulties. Finally, the author and his colleagues ask the patient to return to their clinic after he/she has taken a few infusions at home without a nurse present. The patient brings his/her product, pump, and supplies and gives him/herself an infusion under observation, to be sure all questions are answered, everything is being done in a sterile and safe way, and no problems are evident. After that, the patient continues on home infusions, and follow-up visits are scheduled as indicated by the patient's medical condition.

Other approaches include starting naïve patients on IgG replacement by giving five to seven daily infusions in the hospital and using each day's infusion as an opportunity for instructing the patient. This approach need not be limited to inpatients. Gardulf and colleagues in Sweden have had good success with conducting a 6- to 8-day course of instruction that covers not only the techniques for home SCIG administration but also basic information about PIDD, helpful instruction in hygiene for PIDD patients, and other relevant matters. This course is given to small cohorts of newly diagnosed

patients who come together at the referral center when the course is given. The patients within the cohort have the ability to bond with each other, and then they continue as a support group for each other after the formal instruction period is completed. In other settings, 24-hour availability of an on-call nurse or pharmacist accessible by a toll-free phone number, or identification of an “infusion buddy,” who either takes his/her own infusion together with another patient or is available by phone, will provide an additional level of comfort and confidence to patients who have any degree of anxiety or hesitation about proceeding at home.

It is important, particularly for patients who are used to being seen by the physician at every visit when IV infusions are given in the office setting, to be instructed carefully about potential problems with their infusions and complications of their underlying PIDD that should cause them to contact their physician urgently, or when to go to an emergency room or urgent care facility. Although most practices in the United States will prescribe preloaded epinephrine injectors (such as an Epi-pen) for patients who infuse IgG at home, in fact, these are rarely needed for patients using the SC route. The United Kingdom NHS now no longer provides these for home SC patients because they were so rarely actually needed. Finally, patients who are self infusing at home should use special medical waste (biohazard or “sharps”) containers and should discard needles or other used medical equipment cautiously. In addition, provisions for collecting and appropriate disposal of the waste containers must be arranged.

Assuring Adherence to Subcutaneous Regimens

In many cases, patients on home SCIG regimens will be seeing the physician or other health care professionals less often than previously, especially if the patient had been receiving IGIV in the physician’s office and a “check-up” at each infusion visit. Patients should be carefully evaluated for reliability and insight before they are allowed to have the degree of independence possible with home SCIG regimens. As with all other users of blood products, patients should keep a logbook in which the infusion date, lot number, and expiration date of all vials of IgG are recorded. If the patient wants to keep this log electronically, it should be carefully backed up onto a disc or other memory device separate from the computer itself, or forwarded to a central memory service. Inspection of the logbook or computer record by the physician or nurse at regular intervals should be an important part of each patient’s follow-up. An additional precaution may be to ask the patient to mark the label of each vial of IgG with the date on which it was used, and then to return the empty vials to the physician’s office.

Because the serum IgG concentration tends toward a true steady state if SCIG is given weekly or more often, the patient’s serum IgG can be drawn randomly, and should serve as an indicator of compliance with the prescribed regimen. However, changes in metabolism accompanying different disease states, or protein losses, for example, due to nephropathy or enteropathy, may be the cause if low levels are observed. In growing children, the dose or regimen may need to be altered every few months as the child gains weight.

SUBCUTANEOUS IMMUNOGLOBULIN IN OTHER CONDITIONS

Although the SC route has proved to be useful for delivering the doses of IgG used for replacement therapy in PIDD, few studies have been carried out of the use of this route in autoimmune and inflammatory diseases for which doses in the range of 1 to 2 g/kg are given over 2 to 4 days once a month. It should be obvious from the data in [Fig. 1](#), in which a hypogammaglobulinemic patient sustained an increase in his serum IgG

concentration of more than 800 mg/dL when he was given 400 mg/kg of IGIV, that patients receiving doses in the range of 1000 to 2000 mg/kg over 1 to 4 days will reach extremely high IgG concentrations. These IgG levels can significantly increase blood viscosity and may be associated with increased risks for ischemic, thromboembolic, and renal adverse effects.⁵² Fractionating the same monthly dose into 10, 20, or even 30 aliquots, which could be given at 1- to 3-day intervals throughout the month, might be expected to decrease the maximum IgG level and the alterations in blood rheology and might, therefore, be safer. Furthermore, patients who are receiving "high-dose" IGIV therapy are usually monitored closely during their infusions, so they are frequently treated in hospitals or infusion centers rather than at home. It therefore seems likely that SC infusions would be particularly preferable for many patients in terms of safety and convenience.

Multiple mechanisms of action have been proposed to account for the efficacy of high-dose IGIV in autoimmune/inflammatory diseases, and it seems likely that different mechanisms are important in different disease states, depending on their pathophysiology.⁵³ In any disease state in which an extraordinarily high peak is not required, the SC route would seem likely to offer distinct advantages for many patients. Even in the author's initial experience with SCIG in the early 1980s, it became obvious that a motivated patient (a young woman who wanted to safely carry a pregnancy through to term) could take two 10-mL SC infusions every day, yielding a monthly dose of nearly 100 g.⁵ Current regimens for PIDD frequently have patients taking as much as 60 mL of 16% IgG (9.6 g) over 1 to 2 hours while they are performing normal activities. Because this regimen is well tolerated, or even preferred over IV infusions, by most patients, no *a priori* reason seems to exist as to why multiple infusions in that dose range could not be given several days per week. Few studies have been carried out of SC dosing in this range for the treatment of autoimmune/inflammatory diseases. In one report of SCIG in patients who had well-documented chronic idiopathic demyelinating polyneuropathy (CIDP), one patient who could not be successfully treated with immunosuppressive medications and had only transient responses to IGIV doses of 800 mg/kg was successfully transitioned to SCIG. This patient, a 73-year-old woman weighing 75 kg remained stable with good strength for more than 8 months on a regimen of 16 g of IgG per week, given as five separate infusions of 3.2 g (20 mL) over 2 hours each. The other patient, a 53-year-old man who also could not be successfully treated with immunosuppressive and IGIV therapy, has been successfully managed for more than 2 years with only 6.4 g of IgG per week, given as a single infusion of 40 mL of 16% SCIG.⁵⁴ Neither of these patients had any side effects from the SC infusions other than local swelling; no systemic adverse effects were reported at all.⁵⁴ In the first patient, the cost savings associated with the use of SCIG rather than IGIV was estimated at 30,000 Euros per year. Cost savings were not estimated for the other patient.

Koller and colleagues⁵⁵ have reported on three patients who tried the SC route to receive IgG for neuromuscular diseases. One patient developed a systemic exanthem after 9 weeks on SCIG and refused further treatment by that route. Another patient, with biopsy-proven CIDP persisting for more than 2 years, previously suffered multiple relapses despite corticosteroids and IGIV. He was successfully managed with weekly infusions of 100 mg/kg of SCIG and showed marked reduction in disability scores over the 6 months described in the report. No further relapses occurred and his steroid dose could be reduced. The third patient had multifocal motor neuropathy that had responded in the past to IGIV. He was also successfully managed with 100 mg/kg of SCIG per week and did not require any other therapy. It thus seems clear that, although SCIG cannot be widely recommended for use in autoimmune/inflammatory

diseases at the present time, reason for optimism exists, and additional studies in these conditions should be performed.

FUTURE DEVELOPMENTS

In the next few years, we are likely to see continued evolution of SCIG therapy in the United States. Multiple IgG products are already marketed for SC use in Europe. Clinical trials are now underway in the United States using a “next generation” 16% solution and with two 10% IgG products currently marketed for IV use. In addition, one manufacturer already has a 20% IgG solution in clinical trials for SC treatment in PIDD, and another has published a method for generating and reconstituting 20% IgG solutions that are easily given through 28-gauge needles.⁵⁶ Clinical trials of that type of preparation have not yet been initiated. It is likely that the availability of 20% solutions of IgG for SC use will provide further impetus for the use of this route to deliver high-dose IgG for autoimmune and inflammatory diseases. The availability of 20% solutions may also provide advantages for some patients using conventional doses of IgG for PIDD, because less volume will be needed to administer the same amount of IgG. However, studies that show that high-concentration products are tolerated as well as the alternatives must be completed before they come in clinical practice.

Another approach to giving larger volumes of IgG SC is the injection of recombinant hyaluronidase to loosen the SC tissues by temporarily breaking down hyaluronic acid in the extracellular matrix of adipose and connective tissue. Apparently, the matrix is repaired rapidly, so the tissues are not changed permanently. Recombinant and other forms of hyaluronidase have been in clinical use in humans for some time for various indications, including enhancing the effects of local anesthetics, facilitating hydration by clisis, and in ophthalmic and plastic surgery.⁵⁷ A recent study has shown that intradermal injections of a formulation of a recombinant human hyaluronidase was free from allergic reactions in 100 normal subjects.⁵⁸ Preliminary reports suggest that an SC injection of hyaluronidase just before an infusion of IgG into the same site allows SC delivery of volumes of 10% IgG similar to those used for monthly IV treatment of PIDD patients in the same time that would be required for IV administration.⁵⁹ Obviously, the ability to infuse larger volumes faster by the SC route, without the need for multiple sites, would be a distinct advantage for many PIDD patients. However, the ability of the weekly SC infusions now used by many patients to raise the “trough level” and eliminate “wear-off” effects would not be expected if the whole monthly dose was given at one time. Results of currently ongoing studies are anxiously awaited, to assess the safety and tolerance of these regimens and to determine how hyaluronidase-facilitated SC infusions will affect the treatment of PIDD. The results of the current studies are also likely to lead to further studies of SCIG in autoimmune and inflammatory diseases.

SUMMARY

The efficacy of SC administration of antibodies followed by purified IgG was recognized and used by von Behring and Bruton. The availability of IgG preparations that could be administered safely by the IV route was a long-sought goal that was finally achieved in the early to mid-1980s. IVIG revolutionized the treatment of PIDD and led to the discovery of the therapeutic value of high-dose IgG in autoimmune and inflammatory diseases not associated with PIDD. Improved therapy has improved outcomes and expectations, and most PIDD patients can lead fully active and productive lives. Administration of IgG by the SC route is effective and safe, overcomes obstacles

to the use of IVIG in some patients, and provides important quality-of-life advantages to others. The coming years will see increased use of SCIG in PIDD, which will be facilitated by advances leading to higher-concentration IgG products and easier delivery. Additional clinical research and the effects of these advances are likely to lead to increased use of SCIG in autoimmune and inflammatory diseases, in addition to more widespread use in PIDD.

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