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# Clinical Focus

ON PRIMARY IMMUNE DEFICIENCIES

# Subcutaneous IgG Therapy in Immune Deficiency Diseases

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# Subcutaneous IgG Therapy in Immune Deficiency Diseases

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## History

Purified IgG concentrates first became widely available during World War II, as fractionation of plasma was begun on a large scale to provide albumin as a treatment for shock on the battlefield (1). Clinical trials during the war had demonstrated the efficacy of human Immune Serum Globulin (ISG), as it was known, in preventing hepatitis; and studies on the home front demonstrated that ISG could prevent or ameliorate measles. Prophylactic administration of ISG to normal individuals at risk for specific infectious diseases was thus well established by the late 1940s. The popular practice of giving injections of ISG to premature babies probably actually represents the first use of ISG in the setting of (physiologic) immune deficiency. In 1952, Bruton described the use of subcutaneous injections of ISG to prevent infections in the first published case of "agamma-globulinemia," and demonstrated that these injections increased the content of γ–globulins in the boy's plasma as detected by electrophoresis (2). Janeway and Gitlin also had several patients with agammglobulinemia in Boston, but they treated their patients with intramuscular injections of ISG (3). This route was also used in a large study conducted by the MRC in the UK. The MRC study compared several different dosages, and concluded that 25 mg/kg/wk gave sufficient protection, while the higher dose of 50 mg/kg/wk was not sufficiently more effective to justify the increased pain and cost (4), and 25 mg/kg/wk or 100 mg/kg/mo IM became the standard treatment for antibody deficient patients worldwide.

It took many years of research to develop ISG preparations that were sufficiently free from contaminants, aggregates and active enzymes of the kallikrein-kinin and clotting systems to be safely given intravenously. Early attempts to give IgG intravenously resulted in very severe anaphylactoid reactions. The first IV preparations in the U.S. were licensed in the early 1980s. Before that date, however, my colleagues at NIH and I were confronted with a patient who did not keep appointments to get her IM shots because of the pain of the deep injections, and who had severe reactions to normal plasma, the major alternative route of IgG replacement at that time. Furthermore, the patient wanted to become pregnant, increasing the risk of severe consequences of infection, and increasing the amount of IgG required for adequate replacement. In order to accommodate the relatively large volumes of IgG that would be necessary, while avoiding the pain of the IM injections, we considered administering the IgG slowly, by the subcutaneous route. Reasoning that a major obstacle to giving ISG intravenously was complement activation caused by aggregated IgG in the preparations, we hypothesized that it would be preferable to give the IgG deeply in the subcutaneous fat rather than in or just below the skin, so there would be fewer mast cells that would be triggered by any C3a and/or C5a generated if complement was activated. We also reasoned that giving the IgG slowly would allow dissipation of any mediators released and allow homeostatic compensation to minimize the severity of any systemic adverse reactions. These goals were realized by using a small battery-powered syringe driver pump to give the 16% ISG through a 3/4 Butterfly® needle inserted at a 45 to 90 degree angle into the abdominal fat. Subcutaneous infusions of 10 ml of ISG over a few hours were well tolerated by the patient. Eventually, during the latter half of the pregnancy, she was taking as much as 20 ml (3.2 grams) per day (5). We soon recognized that these infusions were essentially free from systemic adverse effects as well as serious local reactions, and we allowed the patient to infuse herself at home. This markedly improved her adherence, and mother and baby both had serum IgG levels > 800 mg/dL at the time of birth (5). Subsequently, other groups adopted the slow subcutaneous method for administering ISG (6,7) and Welch and Stiehm reported that a patient who failed to tolerate any of the available ISG preparations by the IM route because of severe systemic reactions tolerated the same preparations quite well when given by slow subcutaneous infusion (8).

In the U.S., the new IV preparations were rapidly and widely adopted as standard therapy. In Sweden, large stocks of IM ISG were still available, and at considerably lower cost than the newer IV preparations. Partly for that reason, and partly due to the efforts of Gardulf and her colleagues in advocating subcutaneous therapy, the use of this mode of therapy continued in that country. Studies published more than a decade ago by that group demonstrated the remarkable freedom from systemic adverse events in over 33,000 infusions by the subcutaneous route (9). Together with the emerging problem of hepatitis C contamination of some of the IV preparations, these factors led to increasing use of subcutaneous IgG (SCIg) in Sweden and across Europe. A 2002 survey conducted by the European

**Figure 1A., 1B.**
**Serum IgG Levels in 34 year old Male with XLA**

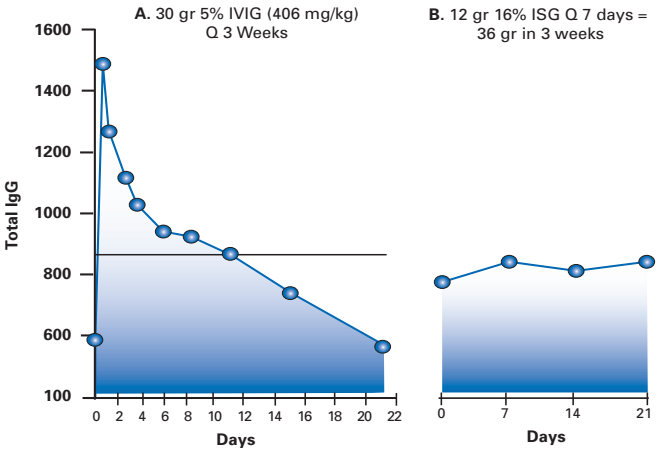
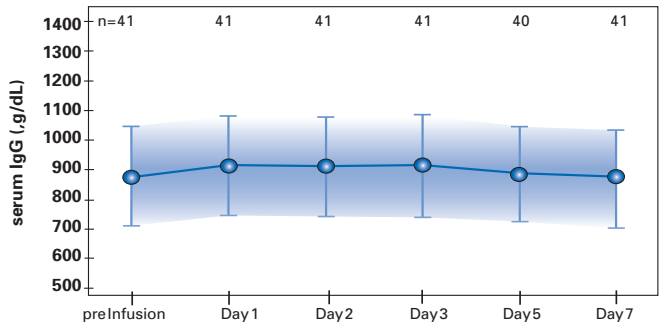



**Figure 1C.**
**Mean Serum IgG Levels Over Course of One Week During Steady-State Subcutaneous Therapy**




*Kinetics of Serum IgG Levels:*
*1A. IV infusion in XLA patient.*

*1B. Weekly subcutaneous infusions in same patient.*

*1C. Mean serum IgG levels in 41 patients in European Vivaglobin® trial. First value on left is "trough" just before weekly infusion was given.*

*All patients received a single subcutaneous infusion weekly. (A and B from Berger, ref 23, with permission of the publisher, C courtesy of CSL Behring)*

Society for Immunodeficiency (ESID) reported that 7% of European patients on IgG replacement received it by the subcutaneous route and more products have become registered for subcutaneous administration since that time (10).

Interest in SCIg continued slowly growing in the U.S., with reports that this route obviated the need for IV access in children (6, 7, 11) and facilitated treatment of patients with severe reactions to intravenous therapy (12).

## Pharmacokinetics of IgG Administered by the IV and Subcutaneous Routes

When a typical dose of IGIV is administered, the serum IgG level usually increases by as much as 1000 mg/dL by the end of the infusion, since the entire infused dose is in the intravascular space (Figure 1A). Over the subsequent 48 hours, some of the IgG diffuses out of the circulation into extravascular spaces, and eventually it equilibrates into a volume of distribution approximately equal to the total extracellular fluid (13). Following this equilibration phase, the IgG is catabolized with first order kinetics and a half-life of about 21 days. Thus, over the course of an average 3 or 4 week dosing interval, the range of IgG concentrations from peak to trough often varies by 250 to 300 % of the trough values (Figure 1A).

In contrast to the high peaks achieved after periodic IV infusions, most SCIg regimens fractionate the monthly dose into smaller increments which are given weekly or even more frequently. We assume that following a subcutaneous infusion, the equilibration of the IgG into its eventual volume of distribution is achieved by diffusion into the circulation from the local site, then out again into extravascular spaces throughout the body. As with the equilibration of IGIV out of the circulation, this equilibration also requires about 48 hours. The high peaks seen with intermittent larger IV infusions are thus markedly truncated. Once it equilibrates, the IgG again is catabolized with first order kinetics. However, before the concentration drops very much, the next fractional dose is given and the concentration is brought back up. Thus, with weekly or more frequent subcutaneous infusions, the range of serum IgG concentrations from peak to trough may vary by less than ±10% around the mean. In individual patients (Figure 1B) as well as in a study population (Figure 1C), this has been shown to result in essentially constant serum IgG concentrations over time.

This difference in the shape of the plots of serum IgG against time has potentially important implications for many patients. On the one hand, truncating the peak may obviate many infusion-related adverse effects such as chills, rigors, anaphylactoid reactions and peri- or post-infusion headaches. On the other hand, it has been proposed that achieving very high serum concentrations, even transiently, may help to get IgG into secretions, which could be important, particularly in IgA-deficient patients. Eliminating the high peak may reduce diffusion of IgG into some sites at which the IgG may play a role in regulating normal flora and colonization of epithelial surfaces with pathogens. On the other hand, maintaining higher trough levels by more frequent subcutaneous doses may also prevent periodic increases in susceptibility of the patient to invasive infections,

and seems to alleviate the fatigue, flu-like symptoms, myalgias and arthralgias experienced by many patients towards the end of their 3 or 4 week dosing interval on IGIV therapy.

There is little data upon which to evaluate the possible therapeutic importance of the high peaks achieved with IGIV vs. the higher troughs maintained by SCIg. A few studies have shown that patients on IGIV with higher troughs have fewer infections, but those higher troughs have usually been achieved by giving higher doses (14 - 16). Published data are not available on the effects of shortening the dosing interval and fractionating the dose of IGIV, which would give higher troughs without increasing the overall dose or raising the peaks. Furthermore, in patients with protein losing enteropathy or nephropathy, proportionally more IgG might be lost from the body while the serum IgG concentration is near its peak after an IV infusion, before the IgG has equilibrated out of the vascular compartment. In some cases, if the peak achieved by IV therapy is higher than the binding capacity of FcRn, the catabolic rate of IgG may increase disproportionately, this is felt to be an important mechanism by which high-dose IGIV ameliorates autoantibody mediated diseases (17).

## Regulatory Issues Surrounding Licensing of Subcutaneous IgG in the U.S.

The discussion in the preceding section illustrates the difficulty in determining which pharmacokinetic parameters would best allow regulatory agencies to determine if the properties of SCIg preparations meet existing requirements for integrity of IgG, and/or if administering this protein by the subcutaneous route alters its bioavailability. FDA guidelines for licensing of IGIV products mandate clinical trials of IGIV designed to examine 4 aspects of an IGIV preparation. These are:

1. Pharmacokinetic studies to determine if the IgG in the preparation has properties similar to those of native IgG;
2. Efficacy in preventing acute serious bacterial infections;
3. Tolerability (frequency and severity of infusion-related adverse events); and
4. Safety from severe adverse effects and transmission of blood-borne infections (18).

FDA scientists noted that most early trials of IGIV reduced the incidence of acute serious bacterial infections to <1 per patient per year, even at doses in the range of 100 - 150 mg/kg/mo. With time, physicians have realized that most patients generally do better with the higher doses that are facilitated by IV delivery, although exact criteria for that improved clinical status are lacking. Thus, recent licensing trials, which used starting doses of the investigational IGIV product based on the dose of the licensed product the patient had been using before enrollment, used mean IGIV doses of 400 - 450 mg/kg/mo. Most IgG licensing trials are only single arm studies, and it is inherently difficult to base conclusions about efficacy on historical controls. Therefore, FDA regulators were faced with the dilemma of not being able to assess conventional pharmacokinetic properties when evaluating a SCIg product which would be repeatedly dosed at intervals less than the half-life of IgG, and not having a satisfactory clinical/efficacy endpoint which actually reflected the goals of therapy with currently used doses of intravenously administered IgG (19). In addition, there are concerns that the bioavailability of IgG delivered subcutaneously might be lower than when it is given intravenously because of degradation of IgG in the tissues. Therefore, the FDA ruled that to assure the same efficacy beyond the minimal standard of <1 serious acute bacterial infection per patient per year, the total exposure to the IgG, as determined by the area under the curve (AUC) of serum IgG over time should be the same, regardless of the route of administration (19). To meet this requirement, the manufacturer of the first IgG to be tested for licensing for subcutaneous use in the U.S. (then known as Aventis-Behring) devised a study protocol in which a cohort of patients underwent a preliminary pharmacokinetic assessment on a stable regimen of a licensed IV preparation, then a repeat analysis while on a dose of subcutaneous test drug estimated to give an equal AUC, then a third analysis on an individually adjusted subcutaneous dose which was individually calculated to give the same area under the curve (20). Twenty-four patients completed this arduous regimen, and the mean of the individual dosage adjustments was 137% of the previous IV dose (20). Fifty-one patients completed a year of therapy with that adjustment. That calculated dose adjustment is now described in the prescribing information for Vivaglobin®, as the licensed product is known. It should be noted that European regulatory authorities did not impose similar requirements for registration of IgG products for subcutaneous administration in the EU. Their pharmacokinetic guidelines stipulate only that trough serum IgG levels on the subcutaneous product must not be less than those the same patient maintained on intravenous treatment (21).

**Efficacy:** Several studies suggest that IgG administered subcutaneously is equal in efficacy to IgG administered intravenously (22), even though there have not been direct comparisons of the same IgG preparation given by the different routes (rev. in 23). In the U.S., efficacy is currently judged by the incidence of acute serious bacterial infections (SBI) per patient per year (18). The FDA has posted standardized, rigorous criteria for diagnosing the infections fitting into this classification, which include bacteremia/sepsis, pneumonia, visceral abscess, osteomyelitis/septic arthritis, and bacterial meningitis (18). The minimal acceptable criterion for licensing of a new IgG product in

**Figure 2A. Mild Injection Site Reaction**

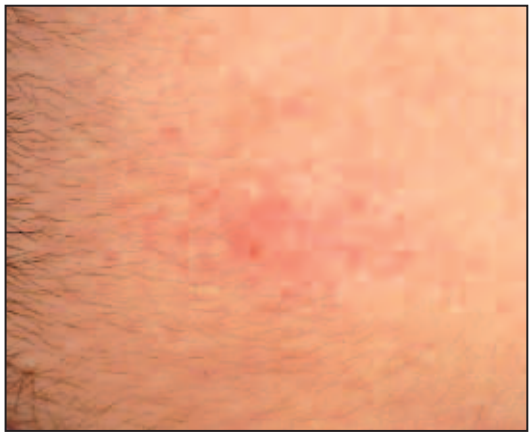
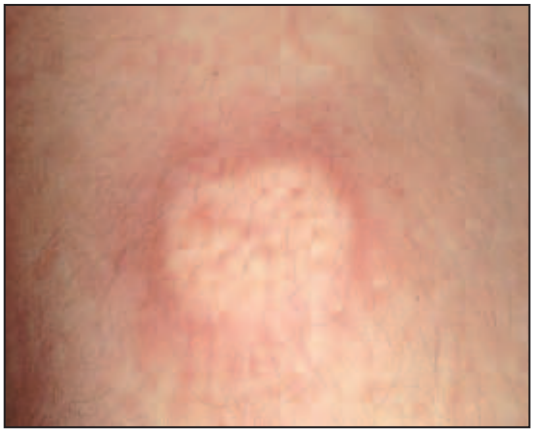


**Figure 2B. Moderate Injection Site Reaction**



*Grading of local site reactions in U.S. Vivaglobin® trial. 2A. Mild- note minimal erythema and swelling. 2B. Moderate- increased swelling with surrounding erythema. Pores are effaced giving skin appearance of skin of orange or grapefruit. (Photos courtesy of CSL Behring)*

the U.S. is that the upper bound of the 99% confidence interval around the mean for the annual incidence of these infections in patients with XLA and/or CVID must be <1 (18). In fact, for all of the IgG preparations licensed in the U.S. in the past 5 years, the highest mean incidence of acute serious bacterial infections is <0.16. In the Vivaglobin® licensing trial, the incidence of acute serious bacterial infection was only 0.04 per patient per year (20). Interestingly enough, a study of Vivaglobin® was performed in the EU and Brazil in the same time frame as the U.S. study described above, however the monthly dose of Vivaglobin® was the same as the dose of the IV preparation the patients had previously been receiving. In that study, the incidence of acute serious bacterial infections was also 0.04 per patient per year, the same as in the U.S. study in which the dose was increased in going from IV to the subcutaneous route (20). In these two studies, the incidence of infections other than SBI's was also very similar, at 4.4 infections/per patient per year in the U.S. study and 4.4/per patient per year in the EU/Brazil study (20). These results are also comparable to the rates of infections other than SBIs in the licensing trials of most of the IV preparations currently marketed in the U.S. The mean doses of IgG (given as one weekly subcutaneous infusion) in the two studies were 158 mg/kg/wk in the U.S. study and 89 mg/kg/wk in the EU study, with the ranges being 34 - 352 mg/kg/wk and 51 - 147 mg/kg/wk respectively (20). Long-term comparisons of the efficacy of different doses of SCIg in controlling/preventing progression of chronic lung and/or sinus disease in immunodeficient patients have not been reported.

It should be noted that SCIg has not been systematically studied as an alternative to high dose IV IgG in autoimmune/inflammatory diseases. The ability of patients to tolerate as much as 16 grams of IgG subcutaneously as a single infusion given in several sites over a few hours suggests that monthly doses in the range to 1 - 2 grams per kg could be achieved by administering such doses 2 or 3 times a week. The feasibility of achieving high monthly doses by frequent subcutaneous administration of readily tolerated doses of 16% IgG is illustrated by the immunodeficient woman in whom subcutaneous ISG was first used during pregnancy (5). During part of the third trimester, she was taking the equivalent of nearly 100 grams a month by infusing 20 ml (3.2 grams) daily. The use of frequent subcutaneous infusions to maintain high serum IgG levels was also described as far back as 1982 by Roord et al, who used this technique to treat an XLA patient with persistent echovirus infection (7). In different autoimmune/inflammatory diseases, the mechanisms of action of high dose IGIV are likely to differ, and we do not know if the extremely high peak serum IgG concentrations achieved by intermittent high dose IV infusions might be critically important for successful therapy in certain diseases.

## Adverse Events Associated with Subcutaneous Administration of IgG

One of the most striking aspects of subcutaneous IgG therapy is the very low frequency of systemic adverse effects. This was readily apparent from our first experience with subcutaneous IgG infusions, but those infusions were given very slowly. In addition, Welch and Stiehm had reported that a patient who could not tolerate any of the IM preparations available at that time because of serious systemic adverse reactions, routinely tolerated the

same preparations when given slowly by the subcutaneous route (8). Subsequently, Gardulf and her colleagues reported similar freedom from systemic reactions when the infusions were given faster and/or into multiple sites simultaneously (24 - 28). More recent studies also report very low incidences of systemic adverse effects. Indeed, there has been only one report in which the incidence of systemic adverse effects from subcutaneous IgG was greater than 1% (22). The National Health Service in the UK no longer requires patients who self-infuse IgG subcutaneously at home to have preloaded epinephrine injectors on hand (Ms. Janet Burton: Verbal communication).

The relative freedom from systemic effects of subcutaneously administered IgG is likely due, at least in part, to the slower equilibration of the IgG into the circulation. Even with "rapid" or "express" subcutaneous infusions, it is still likely that the infused IgG initially forms a depot from which systemic adsorption occurs more slowly. Regardless of how fast that depot is established, it is probable that the rate at which the IgG and/or any accompanying proteins or immune complexes reach the circulation is a more important determinant of the frequency of systemic adverse reactions.

In contrast to the freedom from systemic adverse effects, the incidence of local reactions at the infusion sites may be quite high, particularly when patients first begin to use the subcutaneous route. Rates of local reactions as high as 80 - 90% with initial subcutaneous infusions have been recorded in recent studies, although the incidence of these reactions falls below 30% within 1 - 2 months of continued weekly subcutaneous treatments (20). Local reactions (Figure 2) often include swelling, which in some cases may seem to be bigger than the volume of IgG infused, erythema, and a sensation of burning or itching. These are rarely considered painful or serious. Some patients may experience swelling without erythema, or vice versa (Figure 3). The swelling and erythema almost always dissipate completely within 24 hours after the infusion is finished. In most cases, by 72 hours, it is difficult to identify the site at which subcutaneous IgG was given. We presume that the swelling may be just osmotic, and/or due to the effects of locally released mediators from mast cells and/or leukocytes stimulated by immune complexes or IgG aggregates. Microscopic examination of biopsies of infusion sites taken during this type of reaction have not been reported. Curiously, the severity of these types of reactions and the incidence with which they occur has been reported to decrease dramatically as the patient continues with SCIg. The reasons for this are not clear. Certainly, there is some subjectivity in the patient's reporting of symptoms, and they may report decreased severity as they "get used" to these local reactions. However, objective signs of site reactions also seem to improve with time. Examination of patients who have used the subcutaneous route for many years fails to reveal any chronic local change in the tissues such as fibrosis or lipodystrophy. Some patients may develop isolated hard nodules or "pearls" below the sites of individual infusions but these are usually not tender, and seem to resolve with time. It is possible that the increased frequency of local adverse reactions when patients start on SCIg might be analogous to the increased frequency of systemic adverse reactions when patients start new IV products. Some studies have clearly documented that the incidence of adverse effects is highest with the first infusion of a new IV product but then decreases with subsequent infusions of the same product (29). We do not have similar data on what happens when patients using the subcutaneous route switch brands (preparations) of IgG, so we do not really know if the initially high incidence of local site reactions represents a reaction to the product itself, or to the route. The mechanisms by which patients apparently adapt over time to different IgG preparations are unknown, but could involve alterations in

**Figure 3A. Swelling With Little Erythema at Infusion Sites**

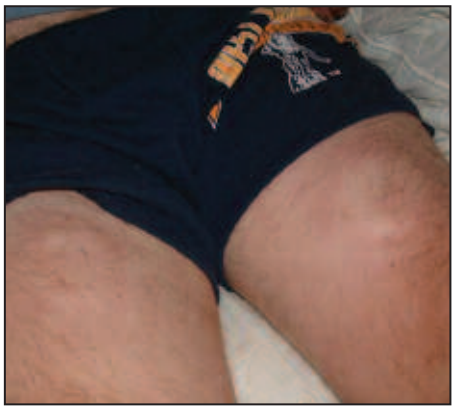


**Figure 3B. Erythema Without Much Swelling at Infusion Sites**

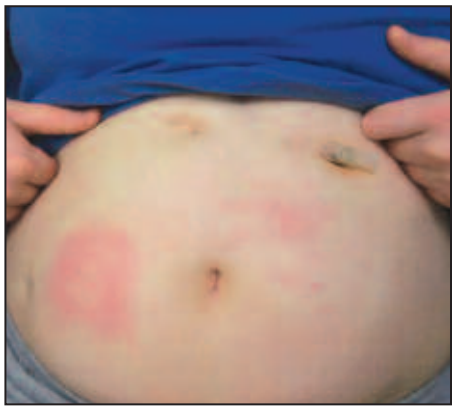


**Figure 3C. Slight Erythema and Swelling During Infustion**

*Reactions at sites of subcutaneous infusions. 3A. Swelling with minimal erythema at sites in thighs into each of which patient took 40 ml of 15% IgG. 3B. Erythema with minimal swelling at two abdominal sites. Note that patient has gastrostomy and scars from surgical procedures. This patient has been on subcutaneous IgG for several years with no long term local changes. 3C. Infant receiving subcutaneous IgG into site on left thigh. Note typical amount of swelling and erythema. Baby is not bothered by this and carries on playing. (Photo courtesy D. Sedlak, Duke University)*

**Table 1. Considerations in Selecting Route of IgG Therapy**

| Clinical Factors |
|---|
| ‹ Ability to establish IV access |
| ‹ Adverse effects during IV infusions or following peak |
| ‹ Adverse effects/suboptimal health at trough when IV infusion due |
| ‹ History of thromboembolic events |
| ‹ Risk of thrombosis, renal failure, hyperviscosity |
| **Life Style/Psychological** |
| ‹ Distance from/accessibility of infusion center |
| ‹ Availability of transportation |
| ‹ Patient's schedule |
| ‹ Availability of home nursing services |
| ‹ Ability to learn and perform infusions |
| ‹ Availability of partner/parent/"infusion buddy" |
| ‹ Home environment |
| ‹ Reliability of patient |
| ‹ Reimbursement issues |

immunoregulatory networks. It is certainly possible that mechanisms, like changes in production of anti-idiotypes, could contribute to the increased tolerance of subcutaneous as well as individual IV products over time. It is interesting in this regard that Sundin et al reported the induction of tolerance to IgA when previously sensitive patients were put on subcutaneous IgG (30).

**Safety:** As noted on the prior page, subcutaneous IgG administration has been remarkably free from systemic adverse events, and no long-term adverse effects on the subcutaneous tissues have been reported. There is only one preparation of IgG marketed for subcutaneous use in the U.S. at the present time, but there is another 16% ISG product available for IM use, and there have been multiple reports of the use of IV preparations by the subcutaneous route (12, 31, 32). Regardless of the intended route of administration, all polyspecific IgG products available in the U.S. are made solely from plasma collected from carefully screened and tested U.S. donors, and all of the manufacturing procedures include steps which have been shown to inactivate and/or partition multiple types of viruses. There is no evidence to suggest that the risk of acquiring blood borne viruses or prions varies with subcutaneous vs. intravascular administration, and none of the polyspecific IgG preparations currently available in the U.S. for administration by any route contains thimerosal or other mercury-containing preservatives.

**Effects on Quality of Life for Patients with Primary Immune Deficiency Disease (PIDD):** Because the volume of IgG that can be comfortably and conveniently infused at one time is limited, most SCIg regimens fractionate the total monthly IgG dose into 4 or more infusions, which are given weekly or more frequently. Since the subcutaneous route has a very low risk of serious systemic reactions, the combination of these two factors has led to a shift to self, partner or parent administration of SCIg at home. The freedom from dependence on trained medical personnel and/or special facilities for routine IgG treatments is appreciated by most patients. In a formal quality of life study, the transition from hospital or office based IV treatment to 12 months of home-based subcutaneous treatment was associated with significant ($p< 0.05$) improvements in "general health," "role-physical," "vitality" and "health transition" scales on formal quality of life evaluations using the SF-36 and PIDD life quality index tools (33). There were highly significant ($p< 0.0001$) reductions in the assessment of the degree to which treatment interfered with accomplishing daily tasks and the extent of "therapy-related problems," with a reciprocal increase in satisfaction with the therapy setting. Similar results were obtained in a study in Europe of children and adults switching from hospital-based IV treatment to home-based subcutaneous treatment (34). Patients switching to home therapy reported significant improvements in general health ($p=0.001$), improved school/social functioning ($p=0.02$) and fewer limitations in personal time/family activities (34). As compared to the hospital or office treatment group, patients already on IV treatment at home reported higher scores on most of these scales at baseline, without much additional improvement on switching from IV to subcutaneous therapy (33 - 35). The one exception to this was the

"general health" scale, on which even the group treated by the IV route at home before switching to the subcutaneous route reported a significant improvement ($p < 0.05$). In a study performed after subcutaneous IgG preparations were approved in Germany, it was found that patients on SCIg therapy reported increased flexibility and overall satisfaction. Only one patient on subcutaneous therapy later returned to the IV route. In contrast, when subcutaneous therapy was initially offered to patients already on IV infusions, half preferred to continue with IV treatment, for a variety of reasons (36). Taken together, these results suggest that major improvements in the quality of life are achieved by switching to home therapy, regardless of the route of IgG administration, but some additional increments could be attributed to the subcutaneous route of administration per se (33 - 35). To the extent that use of the subcutaneous route facilitates home treatment, it can help minimize the negative impacts of chronic disease on the patient's and family's activities, and improve the quality of life for a majority of PIDD patients.

**Patient Selection:** There are two sets of considerations which contribute to the decision as to which route of therapy might be best for any individual PIDD patient in any given set of circumstances (Table 1). The first set is comprised of clinical factors which might make SCIg preferable, such as problems in obtaining IV access, adverse effects from relatively large intermittent IV doses, and adverse effects/suboptimal clinical condition at the low trough just before an IV infusion is due. A history of thromboembolic events; and/or risk of hyperviscosity, thrombosis and/or renal disease in certain patients might also contribute to a preference for breaking up the monthly IV dose into smaller fractional doses given at shorter intervals by the subcutaneous route. The second set are factors which have more to do with the patients' living circumstances than with their clinical condition per se. These include accessibility of an infusion center, the patient's schedule and availability during business hours of infusion centers and/or home nursing agencies, reliability of the patient as assessed by the physician, ability of the patient to learn and perform the techniques used in subcutaneous infusions, safety, security and cleanliness of the home environment, and issues related to reimbursement vs. out-of-pocket costs. In the German study, apprehension about self injection and fear of having side effects at home were cited as major reasons why patients who chose to remain on IV therapy did not want to switch to SCIg (36). Patients who chose to remain on IV tended to be older and to be unemployed compared to those who switched (36). Decisions about which route to use and the actual regimen to be employed should be individualized based on each patient's medical condition(s), circumstances and feelings.

**Developing Individualized Treatment Regimens:** Our initial experience with subcutaneous IgG infusions showed that the freedom from serious adverse effects and lack of requirement for trained health care professionals allowed great flexibility in the choice of the exact treatment regimen to be used for any given patient. Gardulf and her colleagues further extended the range of possibilities by exploring the use of multiple pumps to infuse into several sites simultaneously, and by administering the infusions more rapidly (24 - 28). In the U.S. licensing study of Vivaglobin®, a single set of parameters was selected for the sake of uniformity (20), but parameters used in actual treatment regimens might vary considerably. In a review of regimens used for subcutaneous infusions by patients at our center compiled before Vivaglobin® became available, we found that variables including the time required for infusions, the size of the patient, the number of infusions per week and the number of needle sticks required for each infusion could all be adjusted in order to optimize the regimen for each patient (31). For example, some patients prefer taking infusions slowly into a single site while they sleep. Other patients prefer multiple sites and a short

**Table 2A. Inter-related Variables to be Considered in Selecting Regimen for Subcutaneous IgG Infusions.**

| | |
|---|---|
| 1. | Time for each infusion |
| 2. | Number of infusions per week or month |
| 3. | Number of sites per infusion |
| 4. | Volume per infusion |
| **Guideline:** 0.1 to 0.25 ml/kg/site/hr | |

**Table 2B. Use of "Rule of Twos"- Two Bottles, Two Sites, Two Hours. Vary Number of Infusions Per Month.**

| | |
|---|---|
| **For child:** two 10 ml vials = 3.2 grams per infusion | **For teenager or adult:** two 20 ml vials = 6.4 grams per infusion |
| = 12.8 gm/mo if once a week, 19.2 gm/mo if 6 per month | = 25.6 gm/mo if once a week, 38.4 gm/mo if 6 per month |
| = 500 mg/kg/mo for 25.6 kg 8 year old, 500 mg/kg/mo for 38.4 kg 12 year old | = 500 mg/kg/mo for 51.2 kg 15 year old, 500 mg/kg/mo for 77 kg adult |
| | If twice a week = 51.2 gm/mo = 500 mg/kg/mo for 102 kg adult |

duration of each infusion, while some prefer to use only one or two sites per infusion, but to take multiple infusions per week. In our series, we found that the relationship: 0.1 to 0.25 ml/kg/site/hr summarized most of their regimens (31). Some examples of the application of this relationship to regimens that suit different patients are shown in Table 2. Anecdotally, other colleagues report the use of different regimens such as infusing 10 ml/daily over 5 - 10 minutes without a pump (Ralph Shapiro in Minnesota and Hans Ochs in Seattle), and leaving catheters in place under the skin for 48 hours and infusing IgG on consecutive days (Charles Kirkpatrick in Denver). As can be seen, the limitation of 15 ml/site used in the Vivaglobin® licensing study is not necessarily observed by the patients under ongoing treatment conditions. In fact, at least four variables can be taken into consideration in developing a regimen to deliver any given monthly dose of IgG by the subcutaneous route. These are summarized in Table 3. In general, we prefer to use a unit-dose approach in which each infusion taken by the patient consists of a number of whole bottles of IgG, eliminating wastage. For a number of reasons, we prefer that the patient draw up the product into a syringe and use that syringe with an appropriate driver to take the infusion. Easy-to-use pumps which can drive 10, 20, 30, 50 and 60 ml syringes are available, and information on several of these with links to their manufacturers can be reviewed at the "Subcutaneous Ig Resource Center" available via the Rainbowbabies.org website (see below). It is also possible to use roller-type pumps to deliver product from reservoirs that can be filled by the patient or pharmacist. This can be very useful if precise dosing is desired and/or volumes greater than 60 ml are to be given at one time. Most patients are not likely to have multiple pumps at home. That approach has been used in Sweden to facilitate the use of multiple sites simultaneously. However, multiple branched tubing sets with subcutaneous needles at the ends are now available from several manufacturers and can be used to infuse simultaneously into multiple sites. The resistance at the different sites may vary a bit, resulting in unequal volumes going into different sites, but that should not pose significant problems for the patient. Considering the variables in Table 3 and the guideline discussed in Table 2 should provide flexibility to formulate a regimen that will suit any patient's needs and preferences.

**Table 3. Four Different Regimens for Delivery of Same Dose of SCIg.**

Sample regimens demonstrate flexibility of SCIg treatment plans in meeting patients' preferences. Note lack of maximum dose per site, and incorporation of time factor into plan. (Example: 70 kg adult receiving 500 mg/kg/mo IV = 35 gm/mo = 8.75 gm/wk. That would equal 55 ml of 16% IgG solution. To use whole 20 ml bottles, dose rounded up to 60 ml/wk = 9.6 gm/wk = 38.4 gm/mo = 548 mg/kg/mo.)

| Patient preference for regimen | ml/site | No of sites per infusion | Duration of each infusion (hours) | Number of Infusion (infusions/wk) |
|---|---|---|---|---|
| **Scenario 1:** Patient prefers one infusion into single site during sleep<br>60 ml into 1 site once a week using Freedom 60 pump and I site<br>over 6 hrs = 60 ml per site = 10 ml/site/hr = 0.14 ml/kg/site/hr | 60 | 1 | 6 | 1 |
| **Scenario 2:** Patient does not want infusion to take more than 1 hr.<br>30 ml into 2 sites twice a week using Freedom 60, or<br>10 - 30 ml syringe driver. 15 ml/site/hr = 0.21 ml/kg/site/hr | 30 | 2 | 1 | 2 |
| **Scenario 3:** Patient wants to complete infusions over 3 hrs on<br>Sunday afternoon while watching sports on TV:<br>30 ml into each of two sites once a week using<br>Freedom 60 pump = 10 ml/site = 0.14 ml/kg/site/hr | 30 | 2 | 3 | 1 |
| **Scenario 4:** Patient (Business executive) wants to use 1 site while walking around wearing pump at work. Will tolerate only limited swelling or itching at site. Will wear pump only for part of day, when not meeting clients.<br>20 ml into 1 site over 2.5 - 3 hrs, 3 x per week = 0.1 ml/kg/site/hr<br>20 ml Crono pump - easy to wear under jacket of business suit or on belt | 20 | 1 | 2.5 - 3 | 3 |

**Getting Started:** Several regimens have been used to transition between the IV and subcutaneous routes for PIDD patients already on established IgG therapy regimens. Many immunologists who are satisfied that their patient's condition is well controlled on their present dose of IGIV might choose to divide the monthly dose by 4 to get a weekly dose which will be given subcutaneously. Others might choose to increase the dose by 37%, as was done in the Vivaglobin® U.S. licensing trial, and/or to round-off each weekly dose higher so that full bottles of IgG are used and wastage is minimized. (Because they do not contain preservatives, most products must be infused within 24 hours of entering the vial, even if sterile technique is used.) The first weekly subcutaneous dose may be given within 7 to 10 days after the last IV dose, before the serum IgG level has dropped as low as the usual trough obtained with every 3 or 4 week IV infusions. That will result temporarily in higher serum IgG levels, which will converge on a steady mean as weekly subcutaneous infusions are continued. Waniewski et al and others have shown that administering 5 - 7 weekly doses on consecutive days is a satisfactory way to rapidly bring naïve patients' serum IgG levels up to the desired therapeutic range solely by the subcutaneous route (11, 37). If a patient is going to infuse at home, referral to a specialty pharmacy/home nursing service that will bill their insurance provider and deliver the IgG and infusion supplies may take weeks. The patient may continue on IV treatment or start on subcutaneous treatment in the hospital or office until all of the logistics and payment arrangements have been completed. If the physician or hospital pharmacy does not have an existing arrangement for obtaining a 16% product to administer subcutaneously, most 5 to 12% intravenous products currently marketed in the U.S. are likely to be well tolerated by the patient for initial training and transition to the subcutaneous route. However, in most cases, the 16% preparations are preferred for long-term subcutaneous use, because smaller volumes are required. Several manufacturers market 16% IgG products in the EU which are not currently available in the U.S., and newer preparations with concentrations as high as 20% are currently in clinical trials. We can thus look forward to a greater diversity of SCIg products and even greater flexibility in treatment regimens in the not too distant future.

Before beginning on subcutaneous infusions, it may be useful to have the patient/partner/parent insert subcutaneous needles to be sure they understand how this will feel and accept that they will be doing this themselves. The regimen to be used by the patient should be worked out in detail (although it can always be adjusted later). The number of needle sticks and time required for each infusion, as well as the number of infusions per week/month should be reviewed carefully to make sure the patient/parent understands the time commitment and how the schedule will fit into their daily/weekly routine. Because most patients can be active, ambulatory and in their preferred environment while they receive subcutaneous IgG, other activities can usually be performed while the infusions are running. Patients who switch from office-based IV to home subcutaneous infusion regimens usually report that the latter causes less interference with other activities and gives them more flexibility to complete tasks unrelated to their disease (33 - 35).

Once the regimen has been worked out and the orders submitted, the patient may be taught how to actually perform subcutaneous infusions while they are being "loaded" with repeated daily infusions, or by taking part of their IV dose and giving it subcutaneously while the remainder is being given intravenously. For training purposes, the fraction to be given subcutaneously can actually be divided into multiple small aliquots (of 5 - 10 ml each, for example) and given into different sites to allow a nurse or physician to demonstrate, and the patient to practice the correct technique under direct supervision. It may be very helpful to have a partner, close friend, or "infusion buddy" present to learn simultaneously, so that person can offer support and assistance when the patient gives the infusions at home. We prefer that once the patient receives the actual pump, tubing, product and other supplies and equipment they will use, they bring their paraphernalia into our clinic so that we may demonstrate the correct methods to them in detail, then have them demonstrate that back to us before allowing them to proceed independently at home. This follows the "see one, do one, teach one" approach many of us experienced in medical school. Many home care companies/specialty pharmacies have experienced personnel who can go to the patient's home to instruct them. It may be helpful to have a certification form listing each of the steps the patient has mastered, which can be initialed by the patient and the trainer. Although most of us take it for granted in our usual hospital/office environments, it is important to be sure to instruct the patient on proper disposal of medical waste and to assure that they have appropriate "sharps" containers and a way of disposing of them before the patient begins home infusions. Illustrated stepwise instructions are available in the Vivaglobin® package, on videos, and on several websites (listed on page 12). In addition, the patients may be given multiple copies of a paper checklist to assure that they have done every step properly for each infusion.

It is essential that the patient demonstrate proficiency, have an opportunity to ask questions, and express a feeling of comfort with all of the required steps. This usually takes only one clinic visit, but occasionally two or more office visits or sessions with an expert trainer employed by a home care provider who can instruct the patient in their own home may be necessary. We welcome this as a way of re-enforcing what the patient has already been taught in clinic. An alternative approach is used by Gardulf and her colleagues in Sweden, in which a cohort of patients goes through a several day training period together at the center. This provides a convenient opportunity for daily

infusions to "load" the patient, while also providing an excellent environment for educating patients about their disease and co-morbid conditions, and facilitates developing a peer support network with other patients/parents. The physician should make sure the patient has contact phone numbers, not just in case of emergencies, but also to answer questions; and if necessary, to "walk them through" the procedure when they are doing it independently. We find it helpful to have the patient bring their equipment and product back and self-administer an infusion in our clinic after they have taken several infusions at home, to assure that they have not incorporated any "bad habits" into their routine. Once the professional staff and patient are comfortable with all aspects of the regimen, follow-up can be planned as dictated by the patient's overall clinical condition. If necessary to re-enforce adherence, the patients may be given a voice-mail phone number to call when they are starting (or have completed) each infusion, and/or the patient may be asked to return the empty bottles of IgG to the clinic monthly, or at some other appropriate interval, to be sure the right dose is being taken over the right period of time. Serum IgG levels tend to become quite constant after a few months on subcutaneous treatment (Figure 1), so IgG levels can be measured at any time to help double check on adherence. It must be remembered, however, that dropping and/or low levels may also indicate GI or renal losses. As with intravenous IgG treatment, or any other use of blood products, the patient should record the lot number and expiration date of all bottles of IgG in a proper infusion log or diary.

**Conclusions:** Subcutaneous delivery of IgG has been shown to have efficacy equal to that of IGIV in patients with primary immune deficiencies. The volume of IgG that can be given with each infusion is limited as compared to the volume that can be delivered intravenously, so subcutaneous treatment regimens usually divide the typical monthly IV dose into weekly or twice-weekly fractional doses. Therapy by the subcutaneous route usually does not require trained medical personnel, and systemic adverse effects are extremely rare, so most patients are able to infuse at home. Subcutaneous IgG replacement may be particularly useful in patients who have experienced and/or are at risk for complications of IGIV treatment, and in patients in whom obtaining IV access is difficult. However, the use of this route for high-dose therapy in autoimmune and neurologic diseases has not been studied. Many patients appreciate the increased flexibility and autonomy conferred by home subcutaneous treatment and report increased quality of life. Independence from the office/infusion suite also places increased responsibility on the patient or parent.

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## For more information:

http://www.Rainbowbabies.org/Immunology then look on the left for Subcutaneous IgG Resource Center button. Has listing of pumps and needles used for subcutaneous IgG infusions, with links to manufacturers' sites, many other relevant links.

http://www.vivaglobin.com

http://www.clinimmsoc.org Teaching materials

http://www.ukpin.org.uk/Guidelines/3.01 Administration of SCIG

http://www.cc.nih.gov/cc/patient_education/pepubs/subq.pdf (Note understrike between patient and education) NIH Clinical Center Nurses' patient instructions on "How to give a subcutaneous injection"

# About the Immune Deficiency Foundation

The Immune Deficiency Foundation, founded in 1980, is the national patient organization dedicated to improving the diagnosis, treatment and quality of life of persons with primary immunodeficiency diseases through advocacy, education and research.

## Services for Medical Professionals

- Consulting Immunologist Program (877-666-0866) provides physicians with a free consult or second opinion on patients with primary immunodeficiency diseases
- LeBien Visiting Professor Program offers Grand Rounds and clinical presentations at medical institutions throughout North America
- United States Immunodeficiency Network (USIDNET). IDF administers this National Institutes of Health contract for research and mentoring for primary immunodeficiency diseases
- National Registries of Primary Immunodeficiency Diseases

## Services for Patients and Families

- Patient Advocacy – inquiries related to diagnosis, treatment, health insurance, peer support and literature requests
- IDF Educational Meetings – local and regional patient meetings, national conference
- IDF Volunteer Network – Peer Support, Grassroots Advocacy and Fundraising
- Student Scholarships – post-secondary education

## Educational Publications

- Patient & Family Handbook for Primary Immunodeficiency Diseases
- Our Immune System
- A Guide for School Personnel on Primary Immune Deficiency Diseases
- Diagnostic and Clinical Care Guidelines for Primary Immunodeficiency Diseases
- IDF Guide for Nurses on Immunoglobulin Therapy for Primary Immunodeficiency Diseases
- IDF Advocate – newsletter
- Primary Immune Tribune – e-newsletter

## Public Policy Initiatives

- Advocacy efforts on public policy issues at national and state levels by monitoring issues that are critical to patients
- IDF Grassroots Advocacy Program mobilizes the primary immunodeficiency community to contact their government representatives to promote healthcare legislation that will positively affect the community
- Advocacy for increased funding for research on primary immunodeficiency diseases
- Work with other organizations on quality of care initiatives for users of plasma products

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