Review Article

Subcutaneous Immunoglobulin-G Replacement Therapy with Preparations Currently Available in the United States for Intravenous or Intramuscular Use: Reasons and Regimens

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Abstract

For patients who require replacement therapy for primary immunodeficiency, subcutaneous infusions of immunoglobulin G (IgG) may be preferable to intravenous infusions for several reasons. However, at present, there is no preparation marketed for use by this route in North America. In this article, we describe the reasons patients have selected this route of therapy and the range of treatment regimens used. Approximately 20% of our patients have chosen the subcutaneous route, mainly because of adverse effects from intravenous (IV) infusions or difficulties with venous access. Unit dose regimens using whole bottles of currently available 16% intramuscular preparations or sucrose-containing lyophilized preparations intended for IV use but reconstituted to 15% IgG for subcutaneous administration were individually tailored to each patient. In most cases, self-infusions or home infusions were administered once or twice a week, most commonly requiring two subcutaneous sites and 2 to 3 hours per infusion. On average, patients took 0.18 mL of IgG per kilogram of body weight per site per hour. There were no systemic adverse effects. In patients for whom comparative data were available, trough serum IgG levels were higher with subcutaneous therapy than with IV therapy.

Because immunoglobulin G (IgG) is distributed equally between the intravascular and extravascular compartments,[1] it seems logical to expect that IgG injected into tissue spaces will equilibrate into the vascular compartment and be redistributed throughout the body just as well as would IgG injected intravenously. Indeed, when IgG is administered to otherwise normal individuals for specific reasons—such as prophylaxis against measles, hepatitis, and other infectious diseases and to prevent Rh alloimmunization—it is generally given intramuscularly or subcutaneously. The first patient to be diagnosed with agammaglobulinemia was given IgG replacement by subcutaneous injections,[2] and intramuscular IgG injections were the standard of care for antibody deficiency diseases for many years.[3] In the late 1970s, Berger and colleagues introduced the use of small battery-operated syringe driver pumps to administer greater doses of IgG by the subcutaneous route than were tolerable by the intramuscular (IM) route.[4,5] In

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the early 1980s, however, IgG preparations that could be given safely by the intravenous (IV) route became available. For a variety of reasons, IV infusions given every 3 to 4 weeks rapidly became the most prevalently used method of IgG for replacement therapy for patients with antibody deficiency diseases in most Western countries. However, numerous patients have severe adverse reactions to immune globulin intravenous (IGIV) infusions. Stiehm and colleagues reported that patients who did not tolerate IM or IV infusions because of severe "anaphylactoid" reactions tolerated the same or similar products when given subcutaneously.[6,7] Gardulf and colleagues[8] and Berger[9] have also reported that the frequency of serious and/or systemic adverse effects is lower with subcutaneous administration than with IV administration.

Subcutaneous administration of IgG has continued to be very popular in Scandinavia, and a recent survey by the European Society for Immune Deficiencies suggests that this route is used by about 7% of all primary immunodeficiency (PID) patients in Europe.[10] Despite the prevalence with which the subcutaneous route of therapy is used in Europe, there are no preparations marketed for use by this route in the United States or Canada. However, problems with venous access, adverse effects of IV infusions, and the convenience of self-infusion at home have prompted many PID patients to seek this form of treatment. In addition, exposure of a cohort of PID patients in Canada and the United States to treatment by the subcutaneous route during a recent clinical trial of a subcutaneous IgG preparation has increased interest in the use of this route in these countries.[11,12] In this article, we describe a number of patients in our large referral practice who are routinely using the subcutaneous route with IgG preparations that are marketed for IV or IM administration. Our main purpose in this report is to describe the reasons that patients have selected this route for their IgG replacement therapy and the range of options that are available, although there is no preparation specifically licensed in North America for administration by this route at the present time.

Materials and Methods

This report is based on a retrospective review of patients' charts from our large university-based clinical immunology practice. Information was extracted from the records of those patients who receive IgG replacement by the subcutaneous route. Of about 110 patients who receive IgG for antibody deficiency, either in our clinics or at home, 20 are using the subcutaneous route.

Therapeutic regimens were established individually for each patient; in most cases, a major goal was the facilitating of self- or partner-administered IgG therapy at home. The exact regimen and the schedule for infusions were decided in a collaborative manner with input by the patient as well as the physician. The starting dose of IgG was based on the patient's previous IGIV regimen, or a range of 400 to 800 mg/kg/mo. During one or two visits to the clinic or hospital, all patients who intended to self-infuse at home were instructed in the preparation of the IgG product, use of the infusion pump, insertion of the needles, what local reactions to expect, and recognition of signs of adverse reactions. In each case, the patient was required to demonstrate the necessary skills to the physician and/or nurse before being allowed to continue at home. Although Gardulf and colleagues previously reported that they required patients to receive as many as six subcutaneous infusions under supervision in the hospital,[8] more-recent publications from that group have shown that after only two supervised infusions, patients were able to continue self-infusions at home.[13] We have found that one or two sessions with an experienced nurse-educator are sufficient to train most patients in self-administration. Patients on home infusion programs were asked to return to the clinic shortly after beginning their home program for inspection of the subcutaneous infusion sites and then at regular intervals for routine clinical follow-up or at least once a year as dictated by their clinical condition. Data collected at these visits and recorded on the patients' charts served as the source of the information reviewed for this report.

During this retrospective chart review, we recorded the reasons given by the patients for preferring the subcutaneous route. With one exception, all patients previously had been treated by the IV route. One patient was started on IgG supplementation at the age of 31 months because of recurrent infections and the lack of detectable antibodies against 10/12 serotypes of pneumococcus despite five injections of conjugated pneumococcal polysaccharide vaccine (Prevnar). His total IgG at 26 months of age was 484 mg/dL (normal level for this age is 335–975 mg/dL). The child's siblings had similar problems and had histories of disabling migraines after IGIV infusions although their specific antibody production eventually improved and IgG supplementation was no longer needed. When it became apparent that this young boy also required IgG supplementation, his therapy was initiated by the subcutaneous route. It should be noted that several of the patients sought out our center themselves or were referred specifically because they were having problems with IV therapy. In addition, several patients were referred to participate in a clinical trial of a subcutaneous preparation (ours was the closest participating study site). Information on age, weight, gender, immunologic diagnosis, previous treatment regimen, and complications of previous treatment regimens were recorded. In addition, serum IgG levels achieved on previous and current treatment regimens (if available) and details of the current subcutaneous regimen were recorded.

All patients gave informed consent for review of their medical records. This study was approved by the Institutional Review Board of University Hospitals of Cleveland/Case Western Reserve University.

Results

Demographics and Diagnoses

The 20 patients who are reported here ranged in age from less than 1 year to 84 years of age at the time of the chart review. Seven patients were 10 years of age or younger, four were between 11 and 20 years of age, and the remainder were more than 20 years of age. Eleven of the patients live outside of metropolitan Cleveland. Three of these came to our center to enroll in the clinical trial of subcutaneous therapy; one patient from our own practice also initially switched from IV to subcutaneous infusions as part of that trial. Eight patients were referred from other centres because of difficulties with ongoing IV treatment. Data for a mean of 21.6 months (median, 23 months) of subcutaneous therapy in each patient are summarized in this report.

The patients' diagnoses are listed in Table 1. One patient has confirmed X-linked agammaglobulinemia (XLA), and 10 have common variable immune deficiency (CVID) as defined by criteria established by the World Health Organization. Seven patients were diagnosed with selective IgG antibody deficiency after presenting with recurrent infections and failure to respond with, and/or to maintain, protective antibody titres after immunization with polysaccharides from *Haemophilus influenzae* and/or *Streptococcus pneumoniae*. Two patients were premature infant twins born at 27 weeks' gestation. The immunology service was consulted because one of the twins had recurrent infections while in the hospital. The IgG levels of both twins at 60 days of life were < 100 mg/dL, so IgG supplementation was begun by the IV route. Because of difficulty with repeated venous access, both were switched to the subcutaneous route.

Table 1 Patients Receiving Subcutaneous Immunoglobulin G, by Diagnosis

Diagnosis	No. of Patients
XLA	1
CVID	10
Selective IgG deficiency	7
Transient hypogammaglobulinemia of infancy	2
Total	20

Reasons for Choosing the Subcutaneous Route

The reasons these particular patients were given their IgG subcutaneously are summarized in Table 2. Note that some patients gave more than one reason for preferring this route. Almost half, including the prematurely born twins, had difficulties in establishing IV access for the infusions. One patient had numerous central venous catheters implanted just to facilitate IGIV administration; all the catheters had to be removed because of thromboses. The second most common reason for interest in subcutaneous infusions was adverse effects of IV infusions. These included chills and rigours during IGIV infusions and/or severe headaches, often with nausea and vomiting or other symptoms of migraine that occurred during IGIV infusion or within 48 hours of receiving an IGIV infusion. Four patients who were not previously dissatisfied with IGIV therapy and who did not have excessive adverse reactions to IGIV therapy were recruited into a study of subcutaneous IgG administration. On completion of the study, these patients requested to continue with the subcutaneous route but required a new regimen because the study product was no longer available. Three additional patients had been tolerating IGIV therapy with no problem but chose to switch to subcutaneous infusions because these better suited their lifestyles and/or work schedules.

Table 2 Patients' Reasons for Using Subcutaneous Immunoglobulin-G Therapy

Reason	No. of Patients
Poor venous access	9
Severe headache or systemic reactions	7
Continuation after participation in the study	4
Personal preference	3
Others (thrombosis secondary to IGIV therapy)	1

IGIV = immune globulin intravenous.

Dosage Regimens

With one exception, the patients were switched to subcutaneous treatment regimens with the understanding that this would involve more frequent treatment with smaller doses of IgG than the every-21- to 28-day IV regimens they had previously been using. It was anticipated, therefore, that the more frequent doses would be given at home by the patients themselves or by a partner or parent. To facilitate home or self-infusion without wasting the product, we adopted a "unit dose" approach that used either 10 mL vials of 16% immune serum globulin (1.6 g) intended for intramuscular use (BayGam® Bayer Health Care Inc.) or 6 g vials of sucrose-containing lyophilized IGIV (Carimune® NFZLB-Behring or Panglobulin® NF American Red Cross) as the unit doses. In most cases, the 6 g vials of lyophilized IGIV were reconstituted with 40 mL of sterile water for injection, resulting in a 15% IgG solution. For patients whose previous IV dosage was considered adequate, the weekly dose was calculated by dividing the IV dose by the number of weeks in the dosing interval. This was then rounded off to the nearest even number of unit dose vials as the weekly subcutaneous dose and/or multiplied by 4 to get the monthly number of unit dose vials. A few patients were considered to be on inadequate doses under their previous treatment regimens, so the dose given under our supervision was increased. Once the number of vials to be given to the patient each week or month was determined, the physician and patient worked together to arrive at a suitable frequency and regimen of infusions and to agree upon a schedule to be followed.

All of these patients used syringe driver-type pumps and were trained to (1) draw the 16% liquid from the 10 mL vials or reconstitute the lyophilized product in its container and then draw the resulting 40 mL of solution into an appropriate syringe, (2) attach the syringe to the pump, (3) insert the subcutaneous needle(s), (4) check to be sure they had not inadvertently inserted the needle into a vein, and then (5) attach the tubing and administer the infusion. Most patients used 27-gauge 6 to 8 mm Soft-Set plastic infusion needles (MiniMed, Northridge, CA) or Clearview infusion needles (Norfolk Medical, Skokie, IL). Because of our experience in this area, we were

able to direct patients to home nursing care companies and/or suppliers that would furnish the necessary equipment, supplies, and IgG preparations. Companies that are unfamiliar with subcutaneous regimens may present obstacles to supporting therapy by this route.

We do not have data on the costs of home subcutaneous therapy for these patients. It is likely that the cost of the IgG itself makes up 80 to 90% of the total costs of antibody replacement therapy, so the difference between IV and subcutaneous therapy is not likely to be great at the present time. This differs from the situation reported by Gardulf and colleagues at a time when the preparation used for subcutaneous therapy was much less costly than the IV form.[14] The total costs of self- or home infusion would be decreased to the extent that patients are billed for facility use and/or nurses' time because these costs would be obviated by self- or home infusion.

Twelve of the patients, including the three children under the age of 10 years, used the 10 mL vials of 16% immune serum globulin (ISG). This product is solvent/detergent treated and does not contain mercuric preservatives. These 12 patients' regimens are described in Table 3. Two of the children (designated "CK" and "PK" in Table 3) had been very-low-birth-weight premature babies whose own IgG production had been delayed; they each received a single 10 mL vial every other week, resulting in dosages of 320 and 271 mg/kg/mo, respectively. All patients with 10 mL of 16% ISG as their unit dose infused this into a single subcutaneous site. The time for each infusion varied between 1 and 3 hours for most patients. Two patients received their infusions while they slept at night. One of these (patient 8) took 10 mL of 16% ISG into a single site when she went to bed; the infusion actually took 4 to 5 hours, but the needle was not removed until the next morning. The other (patient 13) took 40 mL of a sucrose-containing IV product reconstituted to 15% IgG into two sites over approximately 8 hours.

The range of regimens and schedules worked out for the different patients is particularly well illustrated by patients 5, 6, and 7. These children, who were 10 to 12 years old, all used the same total

Table 3 Patients Using Liquid 16% Intramuscular Immune Serum Globulin*

Patient No.	Patient Name	Age (yr)	Weight (kg)	Monthly Dose		No. of Infusions		Details per Infusion				
				(g)	(mg/kg)	Per Week	Per Month	Dose (g)	Volume (cc)	No. of Sites	Duration (h)	mL/kg/h/site
1	CK	1	10.0	3.2	320	—	2	1.6	10	1	2	0.500
2	PK	1	11.8	3.2	271	—	2	1.6	10	1	2	0.424
3	JK	3	18.1	8.0	440	1	5	1.6	10	1	2–3	0.221
4	AP	10	19.5	9.6	492	1†	6	1.6	10	1	2	0.256
5	ML	10	27.8	19.2	690	3	12	1.6	10	1	1.5	0.347
6	TS	10	34.0	19.2	556	3	12	1.6	10	1	2	0.147
7	EE	12	36.2	19.2	530	1	4	4.8	30	2	1.5	0.276
8	SJ	13	39.0	16.0	410	2–3	10	1.6	10	1	8 (sleep)	0.032
9	DJ	51	70.7	51.2	724	2	8	6.4	40	2	4–6	0.056
10	NB	50	77.0	51.2	664	2	8	6.4	40	2	3	0.087
11	FW	46	88.6	48.0	558	3–4	15	3.2	20	3	3	0.250
12	NW	60	136.5	51.2	379	1	4	12.8	80	3	3	0.065

*BayGam, unit dose of 1.6 g.
†Once per week plus one extra infusion per month.

monthly dosage, 19.2 g, equal to 12 vials. This gave them 530 to 690 mg/kg/mo. Two of the patients took 10 mL infusions three times each week over 1.5 to 2 hours, with one subcutaneous site for each infusion. The third (patient 7) took 30 mL once a week, using two sites, but still required only 1.5 hours for that larger infusion. Several older children and adults (one of whom weighed 136.5 kg) also used this product to achieve monthly dosages of 379 to 724 mg/kg. Most of these patients combined multiple vials into two or three sites, taking infusions once or twice a week, with the exception of patient 11, who preferred to take 20 mL infusions every other day. The two prematurely born children (patients 1 and 2) each received the contents of one 10 mL vial of 16% ISG into a single site every other week (ie, twice a month).

Regimens based on 6 g as each unit dose are shown in Table 4. Most of these patients took an infusion of 6 or 12 g once a week, but two patients (patients 13 and 20) required one or two additional doses per month to achieve the prescribed total, and patients 18 and 19 took 6 g doses two to three times each week for a total of 12 and 10 doses per month, respectively. Monthly dosages varied between 24 and 72 g, which gave the patients 365 to 979 mg/kg/mo. Most patients split each infusion into two sites, but one patient preferred splitting each single 12 g infusion into four sites, just as he had been required to do during the clinical trial.

The mean monthly dosage of IgG for the patients listed in Table 3 is 503 mg/kg/mo. Since a 16% product was used, the mean volume infused was 3.14 mL/kg/mo. The patients listed in Table 4 received a mean monthly dosage of 654 mg of 15% solution per kilogram per month, which equals 4.3 mL/kg/mo. Individual's dosages of IgG had been determined previously on clinical grounds during IV therapy. A higher proportion of the patients listed in Table 4 were adults who may have been put on higher monthly doses because of chronic sinopulmonary infections.

No patient had any significant systemic adverse events from any subcutaneous infusion. One patient may have inadvertently administered the subcutaneous infusion intravascularly and developed local paresthesias and a red streak going

Table 4 Patients Using Lyophilized Preparations*

Patient No.	Patient Name	Age (yr)	Weight (kg)	Monthly Dose		No. of Infusions		Details per Infusion				
				(g)	(mg/kg)	Per Week	Per Month	Dose (g)	Volume (cc)	No. of Sites	Duration (h)	mL/kg/h/site
13	AT	15	40.0	30	750	1–2	5	6	40	2	8–9	0.059
14	CS	10	42.4	24	566	1	4	6	40	2	2–3	0.019
15	KA	14	65.8	24	365	1	4	6	40	2	2–3	0.121
16	LF	84	68.0	48	705	1	4	12	80	2	2–3	0.235
17	MC	22	70.9	60	845	1	4	12	80	4	2–3	0.112
18	WT	42	75.8	72	979	3	12	6	40	2	2	0.132
19	TSR	36	108.5	60	593	2–3	10	6	40	2	2	0.092
20	SR	49	124.0	54	433	1–2	5†	12	80	2	3–4	0.092

*Carimune NF or Panglobulin NF, unit dose of 6 g reconstituted with 40 cc of sterile water to give an immunoglobulin G concentration of 15%.
†One infusion per month is only 6 g.

down her leg from the infusion site in her thigh. The infusion was stopped, the patient took approximately 1 mg/kg of diphenhydramine orally, and the symptoms cleared rapidly and did not recur. No other infusion had to be interrupted. Local effects of the infusions included swelling and/or redness, but these cleared within hours of completing the infusions in all patients. Patients were taught to expect such local effects during their initial infusions, which were given under our supervision in the office or at the hospital. In nearly 2 years of follow-up per patient, no patient reported any increase in local effects with continued infusions; they all became accustomed to and/or experienced amelioration of any local redness or irritation at the sites of infusions as they continued with their treatment. No patient reported significant bruising or any long-lasting changes such as dimpling, lipodystrophy, nodulation, or long-lasting induration or fibrosis at any infusion site. In most cases, the exact infusion site was no longer identifiable within 12 or 24 hours after the infusion was completed.

Relation between Time and Number of Sites per Infusion

The starting regimen was selected by the physician and/or nurse, in collaboration with the patient. For example, patients taking 40 mL per infusion were commonly advised to start initially by dividing the 40 mL into two sites and allowing 2 to 3 hours for the infusion. However, the patients were allowed flexibility in modifying the regimen according to their own convenience and tolerance of local swelling or adverse effects at the infusion site(s), as long as they did not deviate from the prescribed monthly dose. Variables that could be adjusted included grams of IgG per infusion, number of infusions per month, and number of sites and duration of each infusion. With the exception of the two infants, the other patients selected combinations of these variables with which they were quite happy and on which they continued treatment for extended periods of time. Since local stretching of the skin, compression of subcutaneous structures, and local swelling are determined by (1) the total volume infused per site, (2) the rate at which it is infused into each site, and (3) the rate at which it is absorbed and/or diffuses away, we thought it would be of interest to characterize each patient's regimen by calculating the millilitres infused per hour per site. We also factored in the weight of the patient, as an indication of their size. The results of this calculation for each of the patients is given in the rightmost column of the tables. The mean for all of the patients, regardless of whether they used the 16% ISG or the lyophilized sucrose-containing solution adjusted to 15%, was 0.176 (standard deviation [SD], 0.134) mL/kg/h per site.

Serum IgG Levels Achieved on Subcutaneous versus IV Therapy

For only five of the patients could we find multiple serum IgG levels while they were on stable treatment with both IV and subcutaneous regimens and while they were clinically stable (which included maintaining a stable weight) so that we could compare the trough serum IgG concentrations achieved by the different routes. Trough serum levels for these five patients while on each route of therapy are shown in Figure 1. For these patients, the mean monthly dosage given by the subcutaneous route was 100% (SD, 14%) of the IV dose. This resulted in trough serum concentrations that were a mean of 16.9% higher (SD, 13%) on the subcutaneous route as compared to the IV route. The two former premature babies maintained serum IgG levels above 800 mg/dL but are not shown in the figure because their weights increased during the course of therapy.

Discussion

The introduction of immune globulin preparations that could be safely given by the IV route was clearly a major advance in the treatment of patients with primary immunodeficiencies. Compared to previous regimens with IM injections, IV therapy is better tolerated by most patients and allows convenient administration of larger doses of IgG.

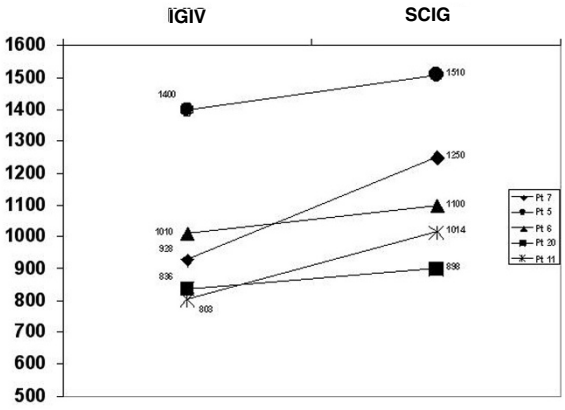

Figure 1 Trough serum immunoglobulin G (IgG) concentrations in clinically stable patients for whom comparable data were available. Each value shown is the mean for at least three determinations. Concentrations for a patient on immune globulin intravenous (IGIV) therapy are shown on the left, connected to the value for same patient on subcutaneous therapy, shown on the right. Patient numbers are shown in the box so that their infusion characteristics can be identified in Table 3 or Table 4. Overall, the mean trough IgG concentration for patients on subcutaneous therapy was 116.9% of that for patients on IV therapy.

Some patients, however, do not tolerate these large infusions at 3- to 4-week intervals and/or have difficult venous access. Subcutaneous injections of 16% ISG were used as the first specific treatment for primary immunodeficiency.[2] The introduction of small battery-powered syringe driver pumps to slowly administer ISG by the subcutaneous route greatly improved the tolerance for injections of the 16% ISG preparations and allowed greatly increased doses to be conveniently used by many PID patients.[9] Despite the popularity of subsequently introduced IV preparations, many patients require or prefer an alternate route and/or schedule for their IgG replacement. In Europe, the subcutaneous route has remained quite popular, but no preparation licensed for use by the subcutaneous route is available in North America. The lack of any preparation specifically marketed for use by this route in the United States has led us to develop regimens for the routine subcutaneous administration of preparations intended to be given by the IM or IV routes.

In this article, we describe the reasons a subset of patients in our practice prefers subcutaneous over IV therapy, and we also describe the regimens we have formulated to facilitate this method of IgG replacement. It should be emphasized that the results reported here are from a retrospective chart review, not a prospective study. There was no particular attempt to achieve any given type of regimen or rate of administration, nor to study the tolerance of any given IgG product in comparison with any other product. Nevertheless, we hope that the data reported here may help other immunologists to identify patients who may be satisfactorily (or even better) treated by the subcutaneous route rather than the IV route of IgG replacement and to formulate appropriate treatment regimens that use currently available products. The results illustrate the flexibility of IgG administration via the subcutaneous route and the fact that it can be carried out with different products and regimens. The preference for subcutaneous treatment by patients who previously experienced adverse effects with larger IV infusions at longer intervals highlights the decrease in adverse effects when smaller doses are given more frequently by the subcutaneous route.

The patients in our practice who are treated by the subcutaneous route represent a reasonable cross-section of those who might be receiving IgG replacement in any immunology referral practice. Most have CVID or some form of selective antibody deficiency; one is a young adult with X-linked agammaglobulinemia, and two are former premature babies with very low IgG levels. The reasons subcutaneous therapy is preferred generally fall into three categories: (1) difficult venous access, (2) adverse effects of intermittent IV infusions, and (3) personal preference or convenience. The babies, among others, have had venous access problems and we have chosen to suggest subcutaneous therapy rather than the implantation of access devices or indwelling central catheters. The use of the subcutaneous route to obviate anaphylactic and other severe reactions to IM ISG injections was initially reported by Welch and Steihm.[6] Subsequent large series have demonstrated the safety and freedom from systemic reactions with this route when compared with IV

therapy as well,[8,14,15] one report even suggesting that the use of the subcutaneous route has led to a loss of reactivity to IgA in patients who are deficient in that class of immunoglobulins.[16]

Several of the patients included in this report were referred to us and/or sought out our help specifically because of severe headaches, repeated chills and rigours, or other systemic reactions to IV preparations with which they had been previously treated. In some cases, the reactions were not life threatening but were temporarily debilitating and greatly interfered with work or school, such as migraine headaches occurring within 24 to 48 hours after periodic IV infusions. The ease of self-administration with the subcutaneous route allows these patients to fractionate the single large IV dose into multiple small doses, which are not followed by these types of adverse events. Overall, for these patients, the requirement for frequent self-dosing results in less overall disease-related morbidity or interference with normal activities. One-third of the patients sought to continue subcutaneous therapy after experiencing it in a clinical trial or sought out this method because it facilitates self-administration, which allows independence from fixed treatment schedules and/or the need to travel to fixed locations to receive IV treatment. The latter reason may be particularly important to patients whose careers require them to travel extensively or for prolonged periods. Gardulf and colleagues emphasized the increases in health-related quality-of-life scores that accompany the sense of autonomy achieved by patients in self-treatment programs (which are facilitated by the subcutaneous route) as compared to those who remain dependent on nurses or other providers for routine therapy.[17,18]

Some patients chose the subcutaneous route because adverse reactions to large doses that had been given intravenously suggested that fractionated doses might be preferable. In those cases, the frequent administration of fractionated doses is facilitated by the subcutaneous route. In contrast, for other patients such as those with difficult venous access, the subcutaneous route was preferred so that establishing venous access would be unnecessary. The choice of the subcutaneous route, in turn, suggested the use of smaller fractionated doses because the monthly dosage formerly given as a single large IV infusion might not be tolerated easily if given by the subcutaneous route. Regardless, in shifting patients from IV to subcutaneous therapy, dosing at least as often as once a week was preferred in most cases. This in turn suggested self- or home administration, which obviated the need to travel to the clinic or to have a nurse travel to the home for weekly or more frequent visits. To facilitate self- and home administration, we adopted a "unit dose" approach, using products with long shelf lives and which could be easily manipulated by the patients or a caregiver without extensive training or professional expertise, thus eliminating wastage of product. We have mainly used a 16% ISG preparation intended for IM use and available in 10 cc vials containing 1.6 g (BayGam) or lyophilized preparations that are available in 6 g vials (Carimune NF; or Panglobulin NF). The latter are readily reconstituted to approximately 15% IgG by the addition of 40 mL of sterile water, and the resulting solution is easily contained in a 60 mL syringe. These 10 mL and 40 mL doses, respectively (or multiples thereof), are easily drawn up in standard syringes, which may then be used with syringe driver pumps without the need for specialized reservoirs or filling equipment. In general, 1.6 g doses are preferred for children and 6 g doses are preferred for adults, although Table 3 shows that four of the adults were on regimens using 10 mL vials of 16% ISG, and Table 4 shows that patients as young as 10 years of age have used 6 g doses. The lyophilized preparations we recommended, when reconstituted to give 15% IgG, contain approximately 20% sucrose and are calculated to have an osmolality of 960 mOsm/kg[12]. Nevertheless, infusions of that mixture are well tolerated by the patients and do not seem to cause excessive local swelling or discomfort. We have seen no incidents of local injury or tissue breakdown with that solution. In most cases, within a few hours of completing the subcutaneous infusion, the site is no longer identifiable, and there have been no long-term adverse effects at the infusion sites. Our general plan is to recommend regimens based on approximately once-a-week dosing; the monthly IV dose is simply divided by 4 to get the weekly dose, and the nearest number of whole vials is recom-

mended for each dose. In several cases, one or two additional doses per month in addition to the weekly dose are required to get the desired total dosage from the unit dose vials. Several of the patients preferred to use smaller doses more frequently, and regimens were adapted so that they were quite acceptable to all of the patients who wanted to use the subcutaneous route. It should be noted that one of the patients reported by Berger and colleagues more than 20 years ago took 10 cc doses up to twice a day for several weeks to maintain her serum IgG level in the normal range during the third trimester of pregnancy.[5] This gave her the equivalent of nearly 100 g of IgG per month. Several patients described in this report (see Table 4, patients 17, 18, and 19) are routinely receiving 60 to 70 g of IgG per month via the subcutaneous route.

The original descriptions of the use of small pumps to give IM ISG emphasized slow administration, which was believed to be necessary to avoid local inflammatory reactions and/or the release of mediators from mast cells.[4,6,19,20] Subsequently, several groups showed that these infusions can be given much more rapidly and have reported rates as high as 20 mL per hour per site.[8,15,21,22] More recently, the use of "express" infusions as fast as 35 mL per hour per site has been described. At that rate, the use of multiple pumps allows 40 mL of 16% ISG to be given in 17 minutes.[13] In several trials, a fixed maximum volume per site (usually 15 mL or 20 mL) has been allowed. In developing regimens for the patients in this series, we assumed a relationship between the size of the patient and the volume that would be tolerated in any site over a given unit of time. Thus, patients who preferred to take their infusions while they slept could use very slow infusion into a single site whereas patients who wanted to complete their infusions much more rapidly could use multiple sites. The value for millilitres per kilograms per site per hour has been calculated for each patient and is shown in the rightmost column in Tables 3 and 4. The mean for all of the patients was 0.176 mL/kg per site per hour. This may be a useful "rule of thumb" for the initial design of individual regimens. For the average 70 kg adult, this equals 13.3 mL per site per hour, meaning that 6 g of 15% IgG solution could be divided into two sites and given over about 90 minutes. This can be easily achieved with a single pump and a tubing set with a "Y" connector. Again, an important feature of the subcutaneous route is its flexibility; of the patients in this series, two preferred slow infusions while a few successfully completed their treatment in 1 hour. A maximum of four sites per dose was used by these patients.

Several of the patients who are described in this series experienced significant problems with their initial attempts at IGIV therapy, or they may have been on insufficient doses or had their therapy interrupted before being referred to us for subcutaneous therapy. For these patients and several others (including the rapidly growing premature babies), we do not have stable baseline IgG levels, and so we are unable to compare serum levels achieved with subcutaneous therapy to levels achieved with IV therapy for most of the patients. For those five patients for whom multiple serum trough IgG levels drawn at the same intervals during IV and subcutaneous therapies were available, the mean monthly dose on subcutaneous therapy was 101.5% of the previous monthly IV dose, resulting in a mean trough serum IgG level on subcutaneous therapy that was 116.9% of that on IV therapy. As seen in Figure 1, all of the patients maintained higher trough levels on the subcutaneous regimens. This is consistent with previous reports suggesting that with more frequent fractionated doses, the variation of IgG levels around the mean is dampened and the trough is higher.[11,12] We performed no rigorous estimations of the incidence of fever or other signs of infection, the use of antibiotics, or days lost from work or school, but our general impression is that subcutaneous therapy is as efficacious as IV therapy.

Thus, this retrospective review has identified some of the reasons for which the subcutaneous route of IgG replacement might be preferred by patients with primary immunodeficiencies and has highlighted some parameters that may be useful in selecting and adjusting regimens for individual patients. It is hoped that IgG preparations specifically indicated for the subcutaneous route will soon be available in the United States and Canada, and the experience we have reported

herein may prove helpful as this mode of therapy becomes more widely used in these countries.

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