

Subcutaneous immunoglobulin therapy given by subcutaneous rapid push vs infusion pump: a retrospective analysis

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ABSTRACT

Background: Administration of subcutaneous immunoglobulin (SCIG) via rapid push, an alternative to infusion pump delivery, can offer heightened simplicity and convenience for patients with primary immunodeficiency disease (PIDD).

Objective: To assess dosing and administration patterns, serum IgG responses, safety, and tolerability of the subcutaneous (SC) rapid push technique.

Methods: A retrospective medical record review captured data on 173 patients with PIDD (1,140 follow-up visits) who self-administered SCIG (16% or 20%) via infusion pump or SC rapid push.

Results: Serum IgG levels increased from a mean (SD) trough of 903.8 (285.4) mg/dL during intravenous immunoglobulin use to a steady-state mean (SD) of 1,121.6 (257.6) mg/dL on SCIG. Mean frequency of weekly SCIG administration was 2.3 days per week with pump and 2.8 days per week with SC rapid push. Mean serum IgG levels were higher among push vs pump users (1,164 vs 1,048 mg/dL). Mean (SD) SCIG volume administered per infusion site with SC rapid push was 15.0 (7.3) mL (maximum, 60.0 mL). Most patients using SC rapid push infused in 9 minutes or less; median pump infusion duration was 49 minutes. Use of 20% SCIG was associated with smaller mean weekly product volumes vs 16% SCIG (41.7 vs 51.0 mL) and fewer mean dosing days per week (2.0 vs 2.8 days). Adverse events, primarily local, were reported on fewer visits with SC rapid push (15.6%) than with infusion pump (20.7%).

Conclusion: The SC rapid push technique is a safe, viable alternative to an infusion pump, seemingly preferred by patients and offering more rapid administration.

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Introduction

For the past several decades, immunoglobulin replacement therapy has been a mainstay of treatment for patients with primary immunodeficiency disease (PIDD).¹ Traditionally, intravenous immunoglobulin (IVIG) has been administered as regular IV infusions given every 3 to 4 weeks, each infusion requiring several hours for administration at a medical facility. In addition to these convenience and technical issues, the dosing schedule of IVIG results in a pharmacokinetic profile characterized by initially very high serum IgG peak values, tapering off to lower trough levels before the subsequent dose.² Serum IgG concentrations typically vary by approximately 700 mg/dL around the mean between doses.²

Subcutaneous immunoglobulin (SCIG) provides greater ease and convenience than IVIG because it can be administered

according to the patient's schedule and can be infused at home, without requiring venous access.² Home-based SCIG therapy has been associated with statistically significant improvements in patient quality of life and treatment satisfaction.^{3–6} Studies have suggested similar efficacy with SCIG compared with IVIG in preventing infections in patients with PIDD.^{7–10}

There is evidence that the rate of IgG catabolism is proportional to its serum concentration, a phenomenon unique from other immunoglobulin classes.¹¹ Thus, the initially high peak concentration conditions associated with IVIG infusion might result in a higher rate of catabolic removal of IgG initially. With SCIG, which is generally given weekly or even more frequently, the dose of IgG is absorbed and redistributed much more slowly, with far less fluctuation in serum IgG levels.¹² The flatter serum IgG steady-state concentration curve with SCIG minimizes the potential for systemic adverse events (AEs) from high peak values or wearing-off effects from low values, phenomena that are associated with IVIG therapy.² In 2006, the first immunoglobulin product specifically approved by the Food and Drug Administration for subcutaneous (SC) administration became available (16% solution; Vivaglobin).¹³ A 20% solution of polyvalent human IgG for SC administration (Hizentra)¹⁴ was introduced in 2010, offering room temperature

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stability and lower total administration volumes.¹⁵ The conventional mode of SCIG administration has been via a programmable infusion pump. More recently, SC push using a syringe and a butterfly needle has emerged as an alternative technique that provides greater simplicity, more rapid drug delivery, and generally greater convenience.¹⁶ Our clinic offers patients with PIDD using immunoglobulin replacement therapy the choice of IVIG or SC administration via infusion pump or the SC rapid push method.

This was a retrospective medical record review designed to capture a large quantity of real-world data in patients with PIDD using SCIG via SC rapid push or infusion pump. The current analysis is an update of a previously published study of 104 patients, which was conducted before the availability of 20% SCIG.¹⁶ The primary objectives of the updated study were to assess dosing and administration patterns, characterize serum IgG levels before and during SCIG therapy, and evaluate the safety and tolerability of the SC rapid push technique. A secondary objective was to observe the effect of the 20% SCIG product compared with the 16% SCIG preparation on dosing and administration patterns.

Methods

Patients

Data for this retrospective analysis were gathered from a review of patient medical records at the author's practice in the Mid-western portion of the United States. Patients are referred to this clinic by physicians practicing within an approximate 300-mile radius. The medical record review included individuals of any age with a diagnosis of PIDD who received at least one course of SCIG between January 1, 2006, and November 2011.

Eligible patients were either naive to immunoglobulin therapy or were being switched from IVIG to SCIG (16% SCIG or 20% SCIG when it became available). The decision of whether to use SCIG was made by the patient. As part of their routine care, patients choosing SCIG therapy were further offered a choice of administration techniques: portable infusion pump or SC rapid push. Each delivery technique was demonstrated to the patient, with further training provided on whichever method was chosen. One nurse conducted in-hospital training for patients starting therapy in the hospital, and a second nurse trained outpatients at the infusion center. Most patients choosing SC rapid push were instructed in the use of a 12-mL syringe and a 25-gauge butterfly needle. Follow-up occurred via monthly telephone contact and clinic visits generally every 5 to 6 months.

When switching from IVIG to SCIG or from 16% to 20% SCIG, the standard policy at this clinic is a 1:1 dose conversion (IVIG dose per month divided by 4 equals the weekly SCIG doses). Patients were encouraged to divide up the total weekly SCIG dose according to their own preference and comfort level with regard to number and volume of infusions during each weekly interval.

Data Collection and Analysis

A standardized case report form was used to record demographic information and data relevant to each patient's SCIG treatment and previous IVIG regimen, if applicable. Eligible medical records were identified by the clinical staff of our clinic, and data were abstracted by an independent clinical research firm (Churchill Outcomes Research, Maplewood, New Jersey). Institutional review board approval was obtained from the Chesapeake Research Review (Columbia, Maryland), and informed consent was not deemed necessary. All patient information was kept confidential and de-identified in accordance with the Health Insurance Portability and Accountability Act Privacy Rule Section 164.514 and the Code of Federal Regulations, Title 45, Part 46, Protection of Human Subjects.

Data were reviewed and reported descriptively. Each visit was captured and analyzed according to the method and product in use at that specific visit. Patients were free to change administration method at any time, and most were transitioned at some point from 16% to 20% SCIG. Thus, individual patients could migrate among treatment categories over the data collection period.

Infusion duration estimates for SC rapid push dosing were provided directly by patients. Administration times for infusion pump were approximated based on recorded infusion site volumes and pump infusion rates. For infusion rates indicated as ranges (eg, 15–19 mL/h), the mean rate was used (17 mL/h in this example). In some instances, infusion rates were reported as a cutoff (eg, <5 mL/h or >60 mL/h); for these calculations, the less than and greater than signs were dropped, which may have led to slight overestimations or underestimations of infusion times for some patients.

Results

Study Sample

Data were gathered for 173 unique patients and 1,140 clinic visits during a mean follow-up period of 35.2 months. Table 1 summarizes the patients' demographics and baseline treatment characteristics. The population ranged in age from 45 days to 67 years at therapy initiation, with a mean age of 24.3 years. Most patients had hypogammaglobulinemia or common variable immunodeficiency, and just less than half of patients were previously being treated with IVIG. Approximately two-thirds of patients initially chose SC rapid push as their method of SCIG delivery. The exact number of infusions administered during the study interval could not be determined with complete accuracy, given the nature of retrospective data and occasional missing medical record entries. However, an estimation based on the overall reported mean frequency of SCIG administration and the typical 6-month interval between visits would suggest upward of 72,000 infusions in this cohort.

During the medical record review period, only 1 of the 173 patients (0.6%) returned to IVIG therapy. One patient discontinued SCIG for unspecified reasons, 1 patient died, 3 patients were "trialed off" immunoglobulin therapy by another physician, and 5 patients moved away or were lost to follow-up.

Table 1
Characteristics of study population

Characteristic	No. (%) of patients (N = 173) ^a
Age, mean (range), y	24.3 (0.1–67.0)
Sex	
Male	80 (46.2)
Female	93 (53.8)
Follow-up, mean (range), mo	35.2 (0–63.0)
Total No. of visits	1,140
Prior IVIG use	
Yes	74 (42.8)
No	99 (57.2)
Initial chosen method of SCIG delivery	
Infusion pump	60 (34.7)
Subcutaneous push	113 (65.3)
Diagnosis	
Hypogammaglobulinemia	83
CVID	66
Congenital hypogammaglobulinemia	6
Disorder involving the immune system	3
Severe combined immunodeficiency	2
DiGeorge syndrome	2
Selective IgM deficiency	1
Other selective immunoglobulin deficiencies	2
Other	5
Unspecified	3

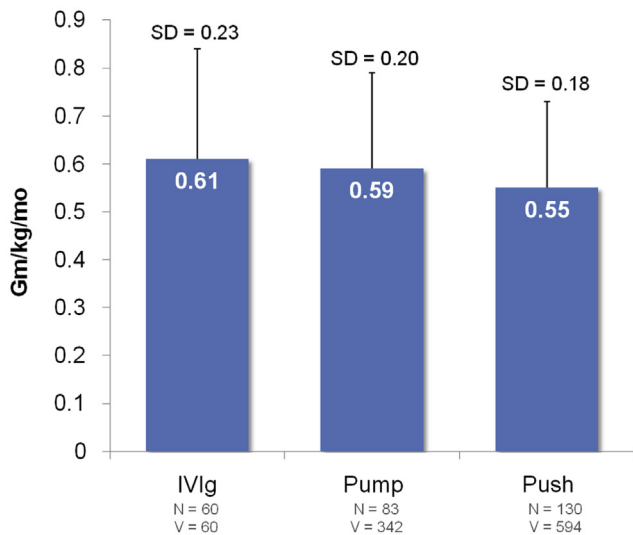
Abbreviations: CVID, common variable immunodeficiency; IVIG, intravenous immunoglobulin; SCIG, subcutaneous immunoglobulin.

^aData are presented as number (percentage) of patients unless otherwise indicated.

IVIG vs SCIG

Seventy-four patients (42.8%) had been using IVIG therapy before starting on SCIG. The mean monthly SCIG dose adjusted for weight (grams per kilogram per month) was similar, if not slightly lower than, the mean prior IVIG dose in both the pump and SC rapid push groups (0.61 vs 0.59 and 0.55 g/kg/mo, respectively) (Fig 1A). Mean serum IgG levels during pump infusion (1,048.0 mg/dL) and SC rapid push (1,163.9 mg/dL) use were higher than mean trough values measured during IVIG therapy (883.8 mg/dL) (Fig 1B).

A Ig dosing



B Serum IgG levels

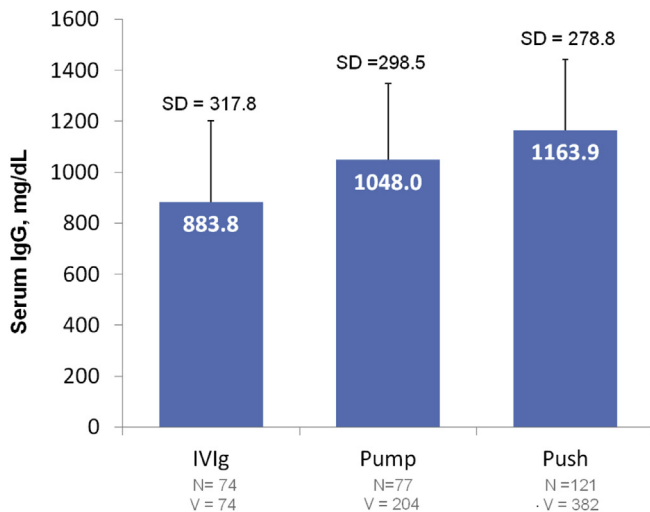


Figure 1. Mean monthly weight-adjusted immunoglobulin dosing (A) and mean serum IgG levels (B) during intravenous immunoglobulin (IVIG) and subcutaneous immunoglobulin administration (infusion pump or subcutaneous rapid push). The mean monthly weight-adjusted immunoglobulin doses were lower with subcutaneous administration but associated with higher serum IgG levels compared with intravenous administration. N indicates number of unique patients; V, number of visits (multiple visits per patient are possible). These numbers include all patients with relevant data for the particular outcome being presented, which varied depending on the variable. Data were categorized completely according to administration technique, while receiving subcutaneous immunoglobulin, patients had the freedom to switch administration technique at any time (eg, could migrate between categories); thus, N values are not identical for all variables.

Infusion Pump vs SC Rapid Push Administration

The mean monthly SCIG dose reported during SC rapid push use was slightly lower than that associated with infusion pump use (0.55 vs 0.59 g/kg/mo), yet mean serum IgG levels were higher during SC rapid push administration compared with infusion pump (1,163.9 vs 1,048.0 mg/dL), as already noted (Fig 1). Compared with infusion pump administration, SC rapid push dosing was characterized, on average, by more frequent days per week (2.8 vs 2.3 days), fewer infusion sites per dosing session (1.3 vs 1.7 sites), and a greater mean volume per infusion site (15.8 vs 13.8 mL). Figure 2 illustrates reported weekly dosing frequencies for both methods, indicating that most patients were dosing SCIG between 1 and 3 times per week, with a smaller percentage of patients dosing 4 or more times per week. There was a general trend observed toward more frequent dosing with higher doses, although there was a great deal of variability noted (data not shown). The mean (SD) SCIG volume administered per site, regardless of method, was 15.0 (7.3) mL, with a median of 20.0 mL per site. The maximum reported volume per site was 60.0 mL in an 18-year-old male patient with a body mass index of 24 (196 lb).

Most patients using SC rapid push were able to infuse their SCIG doses in 9 minutes or less (Fig 3). In comparison, the mean pump infusion duration was 49 minutes (median, 50 minutes).

AEs were reported as a percentage of visits in which an AE(s) was noted by the patient since the prior visit. The rate of reported AEs was lower among SC rapid push vs infusion pump visits (15.6% vs 20.7% of visits) (Table 2). Local injection site reactions were most common overall and also less frequent with SC rapid push vs infusion pump (recorded at 13.7% vs 17.6% of follow-up visits, respectively). Of nonlocal events, headache was reported most frequently and was noted with similar frequency between pump and push methods (1.0% vs 0.8% of visits).

Most patients continued using their initial chosen SCIG administration technique. Among patients initially choosing infusion pump, 78.3% either continued using the method or tried SC rapid push but returned to infusion pump. Among initial SC rapid push users, the corresponding rate of staying or returning was 83.1%. The remaining small percentages of patients switched SC delivery methods more than 2 times.

16% vs 20% SCIG

Mean monthly SCIG doses on a gram per kilogram basis were similar regardless of 16% or 20% SCIG use (0.57 vs 0.54 g/kg/mo, respectively), confirming a general 1:1 dose conversion when switching SCIG products. As expected, the use of 20% SCIG was

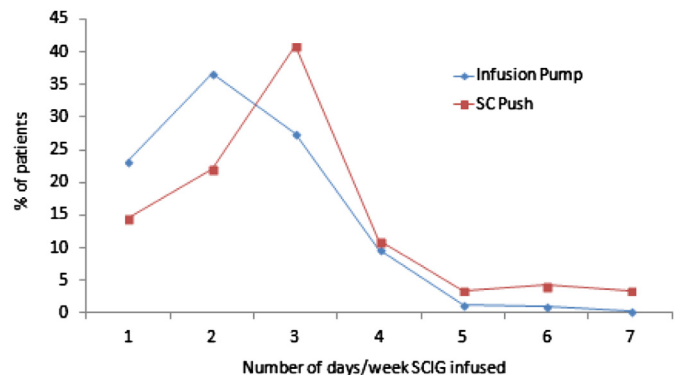


Figure 2. Distribution of patient-reported number of days per week administration of subcutaneous immunoglobulin (SCIG) with infusion pump (382 visits) or subcutaneous (SC) rapid push (655 visits). Most patients were dosing between 2 and 3 days per week.

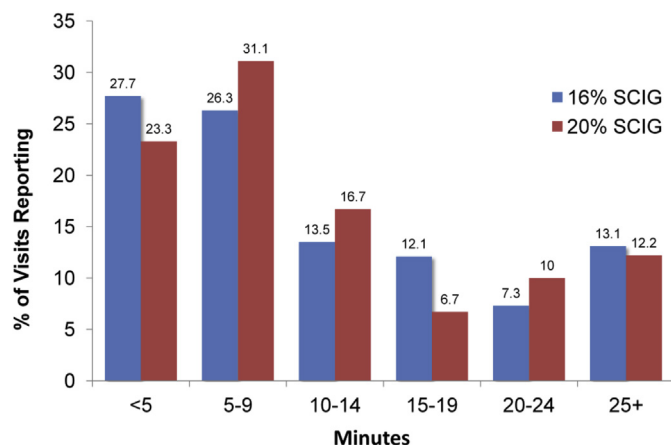


Figure 3. Distribution of reported frequencies of time required to administer subcutaneous immunoglobulin (SCIG) doses via subcutaneous push (percentage of visits; N = 3979 visits). Most patients were able to administer their subcutaneous (SC) rapid push doses in 9 minutes or less, regardless of formulation.

associated with smaller mean weekly product volumes compared with 16% SCIG (41.7 vs 51.0 mL), despite similar dosing regimens. This translated into fewer dosing days per week, on average (2.0 vs 2.8 days) (Fig 4). The mean number of infusion sites used per dosing session was similar between 16% SCIG (1.5) and 20% SCIG (1.4), yet mean SCIG volume per infusion site was higher with 20% SCIG vs 16% SCIG (17.5 ± 9.3 mL vs 14.4 ± 6.6 mL). The rate of reported AEs was lower with 20% SCIG (13.8% of visits) compared with 16% SCIG (18.0% of visits).

Discussion

This analysis describes the experience of a large number of patients with PIDD self-administering SCIG via SC rapid push or infusion pump during a mean follow-up period of almost 3 years. This is, to our knowledge, the largest analysis of SCIG administered via the SC rapid push technique.

There remains some controversy regarding dose conversion when transitioning patients from IVIG to SCIG. Official US dosing recommendations call for a 1:1.37 (16% SCIG) or 1:1.53 (20% SCIG) conversion ratio, guidelines that were based on study data comparing AUC values for the different methods.^{13,14} However, area under the curve has not yet been established as the best marker for evaluating immunoglobulin pharmacokinetics, and it has been argued that trough values may be more appropriate for correlation with clinical outcomes.¹⁷ European regulators support a 1:1 dose conversion, requiring only that trough serum IgG levels on SCIG be at least comparable to those noted during prior therapy.¹⁸ The general practice in our clinic is to transition patients from IVIG to SCIG using a 1:1 dose ratio, and our findings support previously published data demonstrating the adequacy of this approach.^{5,9,10,19,20} During IVIG therapy, serum IgG levels were drawn just before the next dose, thus

Table 2

Adverse event (AE) reporting frequency

AE	No. (%) of follow-up visits at which AEs were recorded	
	Infusion pump (n = 386 total visits)	Subcutaneous rapid push (n = 659 total visits)
Any AE	80 (20.7)	103 (15.6)
Local reaction	68 (17.6)	90 (13.7)
Headache	4 (1.0)	5 (0.8)
Rash	2 (0.5)	3 (0.5)
Other	7 (1.8) ^a	7 (1.1) ^b

^aIncluded leakage around needle, technical difficulties, variable energy levels, and darkening of skin around infusion site.

^bIncluded discomfort at infusion site, mild hives, fatigue, and jaw pain.

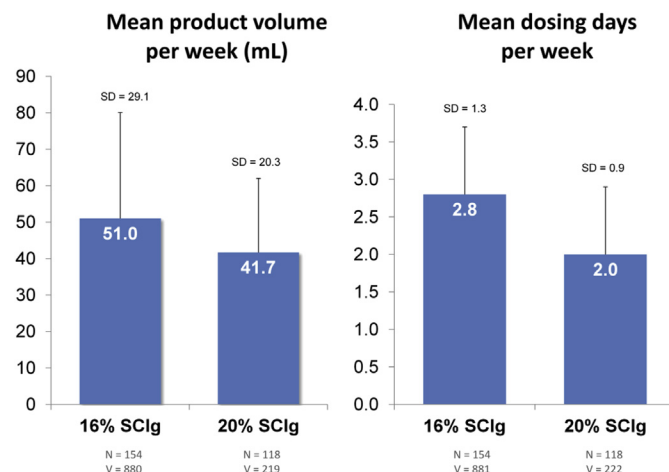


Figure 4. Comparative mean weekly product volume (A) and dosing frequencies (B) for 16% subcutaneous immunoglobulin (SCIG) vs 20% SCIG. The use of 20% SCIG was associated with lower volume per week and dosing on fewer days per week. N = number of unique patients; V = number of visits with relevant data

representing true trough values. Conversely, IgG level determinations while receiving home-based SCIG were more random in nature and could have been drawn at any point between infusions. Because SCIG was generally dosed only several days apart and because of the less variable pharmacokinetic profile with SC administration, these levels were believed to be good indicators of mean steady-state conditions. One of the intended advantages of SC push administration is shorter infusion time. Among our patients, more than half of SC rapid push users were able to administer SCIG doses in 9 minutes or less, and only 16% of users indicated needing longer than 25 minutes. In contrast, the mean duration of infusion using a pump was approximately 50 minutes. Despite a somewhat lower monthly SCIG dose associated with SC rapid push use compared with infusion pump, mean serum IgG levels were numerically higher during SC rapid push. Although the reason for this finding is only speculative, it may be related, at least in part, to the fact that the mean dosing frequency per week was slightly higher during SC rapid push use; a shorter interval between doses could have contributed to a somewhat flatter pharmacokinetic profile and the higher observed serum IgG levels. It is also possible that there are unique pharmacokinetic characteristics of SCIG administration via rapid push.

Although the medical staff in our clinic determines monthly SCIG dose requirements, the patients are given quite a bit of freedom in designing their particular weekly administration schedule. Even though official dosing recommendations for SCIG recommend once weekly administration,^{13,14} our population was typically dosing on multiple days per week by their own choice. There was a tremendous amount of variability observed in weekly dosing frequency patterns, confirming that individual patient preferences and priorities can differ greatly.

Although patient satisfaction with administration techniques could not be measured retrospectively, a high degree of satisfaction with the SC rapid push method was suggested by the fact that approximately two-thirds of patients chose to initiate SCIG therapy with this technique, and most continued using SC rapid push. A small number of patients reported switching methods several times during multiple visits. Our experience suggests that some patients who are trained on both SCIG methods will voluntarily alternate technique over time, depending on immediate life circumstances and personal priorities.

As expected, use of the higher concentration 20% SCIG product translated into more efficient dosing patterns compared with 16% SCIG, including lower total weekly volumes and fewer administration days per week. Even though mean infusion site volumes were slightly

higher with 20% SCIG, administration times for this preparation given via SC rapid push were still less than 10 minutes in most patients. Despite its higher concentration, the 20% solution has been shown to have a similar viscosity as the 16% formulation, with no reduction in infusion rate.²¹

A major limitation of these retrospective data is the inability to correlate AE frequency with individual infusions; AE data could only be quantified according to events reported in clinic visits, which were typically 5 to 6 months apart. As such, the clinic visit–reported rate of AEs is likely a substantial exaggeration of event rates if they could have been characterized per individual infusion. Yet, the data we were able to collect give at least a rudimentary comparison of safety between the 2 administration techniques, as well as an overview of the nature of events reported. Overall, AEs were reported at approximately 1 of every 5 to 6 visits and somewhat less frequently with the SC rapid push technique compared with infusion pump. As expected with SCIG infusion, AEs other than self-limited, local injection site reactions were rare.

Another limitation in the clinical interpretation of this study is the lack of infection rate or efficacy measures, outcomes that were not captured in the medical record review process. The mean steady-state immunoglobulin levels were in excess of 1,000 mg/dL for both SCIG administration techniques. To date, there are no clear cutoffs or population norms for determining immunoglobulin replacement adequacy according to serum IgG levels. A meta-analysis of IVIG data²² reported the pneumonia incidence among patients with PIDD to be progressively reduced up to an IgG trough level of at least 1,000 mg/dL. More recently, a similar meta-analysis of 13 SCIG studies analysis identified a significant inverse correlation between annual infection rate and serum IgG concentration.²³

This large medical record review suggests that immunoglobulin administration using an SC rapid push technique can be performed safely and quickly with a high degree of acceptability. Offering patients a choice of delivery options, along with freedom to tailor their weekly dosing patterns, increases the potential for greater treatment satisfaction and patient empowerment, which may support high levels of patient adherence.

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