

Choices in IgG replacement therapy for primary immune deficiency diseases: subcutaneous IgG vs. intravenous IgG and selecting an optimal dose

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Purpose of review

Subcutaneous IgG (SCIG) is becoming more popular, but there is still uncertainty about efficacy and optimal dosing. This review discusses recent pharmacokinetic studies and applications of SCIG therapy, and its efficacy in the context of emerging understanding of the relationship between dosing and efficacy of both intravenous IgG (IVIG) and SCIG replacement therapy for primary immunodeficiency diseases.

Recent findings

Three preparations of IgG have been licensed in the US in the past year. Their bioavailabilities are 65–70% of that of IVIG. Pooled analyses show that the efficacy of SCIG in preventing infections is proportional to the steady-state levels achieved, and similar to that of IVIG. Pharmacokinetic studies allow estimation of doses that will yield desired serum levels with both IVIG and SCIG, and when switching from one route to another.

Summary

Pooled analyses show that at equivalent total doses, weekly SCIG results in steady-state levels 10–20% higher than troughs on monthly IVIG. For most patients, the choice between routes should be based on individual preference, and the regimen should be individualized to achieve the desired outcomes.

Keywords

IgG therapy, intravenous IgG, pharmacokinetics, primary immune deficiency diseases, subcutaneous IgG

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Introduction

The major fundamental differences between subcutaneous (sc) and intravenous (i.v.) administration of IgG are the lack of a requirement for venous access and the rate at which the IgG reaches the blood stream. Intravenous IgG (IVIG) is infused directly into the intravascular compartment, whereas with subcutaneous IgG (SCIG), the IgG must first diffuse into lymphatics, and it is then carried into the blood stream via the thoracic duct [1,2,3,4]. Thus, with SCIG, the intravascular IgG concentration increases more gradually, peaking at 48–72 h. Most other features of SCIG regimens are consequences of these fundamental differences. Since the rate at which the IgG enters the circulation appears to be the major determinant of systemic tolerability, the incidence of severe, and indeed all systemic adverse events is extremely low with SCIG. This freedom from adverse events and the lack of the need for venous access allow most patients (or parents/partners) to infuse SCIG at home. This frees the patient and family from costs and constraints involved in having nurses come to the home and

scheduling of, and travel to hospitals or other facilities where IVIG is usually given. Home infusion regimens are associated with improved health-related quality of life (QoL). Most home-based SCIG regimens employ weekly or more frequent dosing, which leads to steady-state IgG levels and may decrease ‘wear-off effects’ that commonly occur with monthly IVIG (Table 1).

Attempts at i.v. administration of early IgG preparations often resulted in severe systemic reactions resembling anaphylaxis or septic shock [5,6]. These reactions were attributed to impurities including endotoxin, aggregates which activated complement or cross-linked Fcγ receptors, and/or the presence of vasoactive proteins [5,6]. Initial successes with the use of small portable, battery-powered pumps to slowly administer intramuscular (i.m.) preparations by the subcutaneous route were attributed to decreasing the rate of production and/or release of the mediators of these adverse events [7]. In the 1980s, increasing purity of IgG preparations and the use of stabilizers which minimized aggregate formation allowed safe i.v. administration, ushering in a new era of treatment

for primary immune deficiency disease (PIDD) [5,6]. Despite relative freedom from severe or life-threatening reactions, up to 40% of IVIG infusions were still associated with systemic adverse events requiring monitoring by trained medical professionals, who were also necessary for establishing i.v. access. Most infusion-related adverse events can be ameliorated by limiting the rate at which the IVIG is administered and/or premedication with NSAIDs, antihistamines and/or corticosteroids [8]. Thus, most patients reasonably well tolerate IgG replacement therapy by the i.v. route. Monthly IVIG is considered advantageous by some patients because all they have to do is 'show up and roll up their sleeve' once a month. For a small fraction of patients, i.m. injections and/or i.v. infusions are just not tolerable, and subcutaneous therapy is a necessity [9]. For many more patients, the subcutaneous route is more convenient because i.v. access is not necessary and self-infusions at home are more easily adaptable to the patients' lifestyle. Dividing the monthly IgG dose into weekly fractions results in steady-state serum IgG levels, and many patients report that they feel better overall when they no longer experience the ups and downs in IgG levels that accompany intermittent IVIG infusions.

Pharmacokinetics of IgG administered by the subcutaneous and intravenous routes

The major pharmacokinetic difference between SCIG and IVIG is the rate at which the IgG enters the blood stream. With IVIG, the concentration in the bloodstream peaks immediately upon termination of the infusion, frequently reaching concentrations more than twice as high as the trough level just before the infusion [1,2]. With SCIG, absorption of the IgG into the lymphatics is slower, and then the IgG must be delivered into the blood

Key points

- Differences in pharmacokinetics of subcutaneous IgG (SCIG) vs. intravenous IgG (IVIG) result in decreased systemic adverse effects, and the ease of subcutaneous vs. intravenous access makes home SCIG treatment regimens practical for most patients.
- At similar total monthly doses, weekly SCIG will result in steady-state IgG levels approximately 10–20% higher than troughs on monthly IVIG, with similar efficacy in preventing infections.
- Choice of the route of IgG therapy should be individualized according to preferences and lifestyle choices of each patient.
- With both SCIG and IVIG, the frequency of infections decreases as the dose and serum IgG level increase, with no apparent plateau in efficacy.

stream by lymph flow. Thus, the peak serum IgG level does not occur until approximately 48 hrs or more after the infusion. Furthermore, because some of the IgG administered subcutaneously is already equilibrating into the total extracellular fluid even before all of the infused IgG has gotten into the bloodstream; and because of binding and/or degradation of IgG in the subcutaneous tissues (see 'Bioavailability of SCIG' subsection, below), the maximum serum concentration of IgG is, on average, only 61% of the peak achieved with i.v. infusions. In three recent studies [10^{••}–12^{••}] comparing IVIG and SCIG in PIDD patients, the mean peak serum IgG level (C_{max}) immediately after i.v. infusions was 2303 mg/dl. In contrast, the mean peak with SCIG was 1410 mg/dl and the interval (t_{max}) between beginning an SCIG infusion and the peak IgG concentration was 62.6 h (2.61 days) [3[•],13,14]. The slower rate of rise towards the peak

Table 1 Features of subcutaneous and intravenous routes of IgG delivery which may be important in choice of therapeutic regimens

Subcutaneous	Intravenous
Subcutaneous infusion sites easy to find and access	i.v. site access usually requires trained personnel and even then may be difficult
Self-treatment at home usually practical	Home treatment usually requires nurse visit
Home treatment at patient's own convenience is most common regimen	Hospital or office-based infusion regimens with infusions during normal work hours most common
Increased autonomy improves quality of life in many cases	Some patients prefer 'to be taken care of' and/or enjoy infusion center ambiance - social contact
Requires reliable patient and monitoring of adherence to prescribed regimen and clinical status of patient	Office-based infusions facilitate physician follow-up and monitoring of associated conditions
Lack of facility and administration fees may make overall costs lower	Facility and professional fees may make overall costs higher
Total amount of IgG administered per dose limited by volume	Large dose can be administered in single infusion
Multiple sites often necessary, infusions may be weekly or more frequent	Single site per infusion, usually once every 3–4 weeks
Slow systemic adsorption alleviates adverse effects (AEs) related to peak	Immediate rise in serum IgG may be helpful in some cases, but can also cause AEs
Very low frequency of systemic AEs	Systemic AEs may require premedication and monitoring
Local reactions may be problematic but are usually transient and tolerable	Injection site reactions rare but may include phlebitis, bleeding and/or thrombosis
Frequent dosing eliminates 'wear-off' effects	Low trough levels contribute to 'wear-off' effects
Decreased bioavailability may lead to higher doses	Standard of 100% bioavailability
Importance of any given factor should be considered in each individual case.	

and the truncation of its height are believed to be responsible for the much lower incidence of systemic adverse events with SCIG. This is consistent with observations that many adverse events of IVIG infusions are rate-related [8], and has been repeatedly confirmed [1,10^{••},15]. No differences have been reported in the half-life ($t_{1/2}$) of IgG given by the subcutaneous vs. i.v. routes. With modern preparations of IgG, $t_{1/2}$ s have generally been reported to be about 30–35 days [2]. With weekly SCIG, only about 4.4 days elapse between the $t_{\max}$ of one dose and the administration of the next dose, suggesting that only about 10–20% of the administered IgG is metabolized before the serum level starts to rise again. In contrast, with IVIG dosing intervals of 3–4 weeks, approximately 36–48% of the IgG may be metabolized by the time the next dose is due. These differences in the dosing intervals used in most SCIG vs. IVIG regimens result in increased trough ($C_{\min}$) serum IgG levels with SCIG. Pooled data from seven studies in which equivalent monthly IgG doses were given as subcutaneous infusions weekly vs. i.v. infusions every 21–28 days showed that trough serum IgG levels were 10–20% (mean = 12.7%) higher with weekly SCIG than with the same total monthly IVIG dose [3[•]]. After 6–12 weekly infusions, SCIG results in near-steady-state IgG levels, with differences between $C_{\min}$ and $C_{\max}$ only 5–10% of the overall mean. (This steady state can also be achieved by ‘loading’ the patient with five or six consecutive daily infusions of what will then be the weekly SCIG dose [16,17[•]].) In contrast, with IVIG this trough-to-peak difference is often greater than 50% of the overall mean [1,2,4]. In other words, the longer the interval between doses, the lower the trough level and the greater the difference between peak and trough levels are likely to be, regardless of the route of administration [4]. In a 2003, US Immune Deficiency Foundation survey, before SCIG was licensed in the USA, 68% of respondents answered that they could ‘usually’ or ‘sometimes’ feel the effects of their IVIG ‘wearing off’ before the next dose was due [18]. By making frequent (i.e. weekly or even more often) administration of IgG convenient, SCIG regimens are thus able to eliminate the low troughs associated with less frequent IVIG regimens. In turn, maintenance of near-steady-state IgG levels seems to eliminate or minimize these ‘wear-off’ effects, presumably contributing to an increased sense of well being and freedom from symptoms of subclinical/chronic infection with SCIG therapy.

Bioavailability of subcutaneous IgG

The area under the curve (AUC) of serum concentration vs. time of a drug after a single i.v. infusion is defined as 100% bioavailability. The bioavailability of the drug when given by any other route is generally lower. These concepts are most commonly applied to the ‘oral

bioavailability’ of small molecule drugs, which is usually less than 100% due to incomplete absorption from the gastrointestinal tract and/or ‘first-pass’ metabolism in the liver. On the basis of arguments that i.m. administration of IgG resulted in significant local degradation, animal studies showing decreased bioavailability of SCIG vs. IVIG, and human studies of subcutaneous vs. i.v. infusions of therapeutic monoclonal antibodies and fusion proteins containing the Fc portion of IgG [13], it was expected that polyclonal SCIG would also have lower bioavailability than IVIG. This decreased bioavailability may involve degradation in the tissues and/or local binding in the intercellular matrix. Because of this expectation, several studies were designed to directly determine the bioavailability of SCIG as compared to IVIG.

Although the European Medicines Agency (EMA) requires only that the trough levels achieved with new SCIG preparations are noninferior to those obtained with already-licensed products [14], the US FDA requires that the dose of SCIG be increased to compensate for its decreased bioavailability [19]. To meet this requirement, the first US study of an IgG specifically intended for SCIG use included a preliminary pharmacokinetic study in which the AUC of IVIG was calculated for individuals, who were then started on an SCIG dose equal to 120% of the previous i.v. dose. After stabilizing on SCIG, the AUC was measured again; then the subcutaneous doses were individually adjusted to give AUCs noninferior to those measured on IVIG. After 12 weeks on the new SCIG dose, the AUC was measured again [3[•],15]. The mean individual adjusted dose was equal to $137 \pm 21\%$ of the original i.v. dose, giving a mean AUC which was 94.5% of that on IVIG [3[•],15]. The bioavailability is equal to 100 divided by the dose adjustment times the ratios of the AUCs, which in this case would be $100/137 \times 94.5/100 = 68.9\%$. In a similarly designed study of a 20% SCIG product, the individual dose adjustment required to achieve a noninferior AUC was $153 \pm 15.6\%$ of the monthly equivalent of the i.v. dose, giving a mean AUC which was 100.2% of the AUC on IVIG. Thus, for that 20% product, the subcutaneous bioavailability is $100/153 \times 100.2/100 = 65.5\%$. Recent studies of two already licensed IVIG products showed subcutaneous bioavailabilities of 64.9 and 69.3%, respectively [10^{••},11^{••}].

Dosing and efficacy

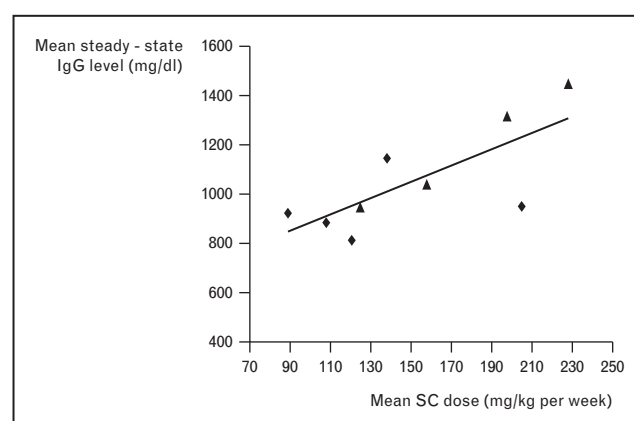
The relative contributions of different kinetic and dosing parameters to the efficacy of IgG replacement regimens in PID are not clear, and it has not yet been possible to define an ‘optimal’ dose of IgG replacement therapy by either the i.v. or s.c. route [20]. Variables including overall dose; interval; peak, trough, or mean serum IgG levels; and AUC have all been considered, but there is no consensus on the importance of any given parameter as

a determinant of efficacy. Furthermore, there is not even agreement on how 'efficacy' should be measured. The US FDA has established the annual frequency of acute serious bacterial infections (aSBIs, <1 per patient per year) as its main criterion of efficacy [21]. However, other outcome measures such as infections other than aSBIs, exacerbations of chronic/recurrent sinus and/or pulmonary disease, days of fever, episodes or days of hospitalization, days of parenteral antibiotic therapy, days lost from school/work/usual activities, and rate of decline of pulmonary function are also of concern. Obviously, all of these measures are not equally important in all patients. Furthermore, effects of IgG therapy on outcomes such as the incidence of malignancy and the incidence/severity of autoimmune disease are even less well defined.

Most studies suggest that higher doses result in higher serum levels and greater freedom from infection. Bonagura *et al.* [22] suggested that each individual PIDD patient has a 'biological trough level' above which he or she remains free from infection and Lucas *et al.* [23**] reported that periods of freedom from infection are more likely with higher trough serum IgG levels. A recent meta-analysis of IVIG studies by Orange *et al.* [24**] suggests that the incidence of pneumonia decreases by 27% with each 100 mg/dl increment in trough IgG level. Similarly, a pooled analysis of seven SCIG studies found an inverse linear relationship between the incidence of infections and the steady-state serum IgG level [25**]. Neither of these analyses shows any plateau in the relationship between the incidence of infection and the serum IgG level, but rather both suggest that the incidence of infection decreases continuously as the trough or steady-state level increases. However, it is not clear that optimal therapy requires the complete absence of nonserious infections, nor that control of acute episodes of infection equates with lack of progression of chronic infection. This may be especially true for PIDD patients with bronchiectasis and/or other chronic lung diseases. Lucas *et al.* [23**] found that patients with bronchiectasis require higher doses of IgG to reach the same trough levels as patients without bronchiectasis, but Chen *et al.* [26*] report that the rate of decline in forced expiratory volume in 1 second in PIDD more closely correlated with the monthly IgG dose than the trough level. Taken together with differences in which efficacy outcome variables that may be most important in any given patient, these results suggest that regardless of the route, IgG doses should be individualized for each PIDD patient.

In most recent studies of SCIG, the steady-state serum IgG levels were in the range of 900–1200, and the annual rates of nonserious infections were 3.4–4.3 per patient per year [25**]. Two additional studies with mean steady-

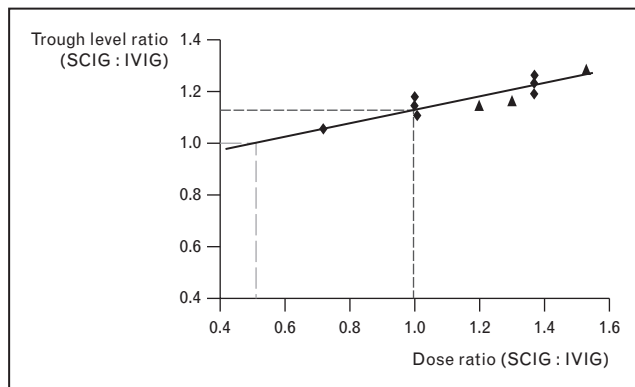
Figure 1 Steady-state serum IgG Level (y-axis) as a function of weekly subcutaneous IgG dose (x-axis)



Each point represents the mean of a different study (see [3*] for individual citations). Correlation coefficient by linear regression ($r = 0.752$, $P = 0.02$). IVIG, intravenous IgG; SCIG, subcutaneous IgG. Reproduced with permission from [3*].

state IgG levels of 810 and 1250 mg/dl reported infection rates of 5.2 and 2.8 per patient per year, respectively [25**]. Thus, the incidence of infection decreases linearly as the level increases. Similarly, recent IVIG studies show that trough IgG levels in the range of 900–1150 are associated with annual rates of infections of three to four per patient per year. Thus, with doses sufficient to give trough (with IVIG) or steady-state (with SCIG) serum IgG levels in the range of 900–1200 mg/dl, there seems to be little significant difference in the incidence of aSBIs or other infections, regardless of the route. Figure 1 shows the relationship between the weekly dose of SCIG and the resulting steady-state serum IgG level from seven SCIG studies [3*]. A weekly SCIG dose of 100 mg/kg results in a steady-state IgG level of approximately 875 mg/dl and a weekly SCIG dose of 150 mg/kg results in a steady-state serum IgG level of approximately 1050 mg/dl. Orange *et al.* [24**] presented a similar analysis relating IVIG doses and trough serum levels, which suggests that the mean trough level increases approximately 120 mg/dl with every 100 mg/kg increase in monthly IVIG dose. Berger *et al.* [3*] also provide a graph of the change in trough level in going from IVIG to SCIG as a function of the percentage of the previous IVIG dose given by the subcutaneous route (Fig. 2). This shows that to achieve a steady-state serum IgG level equal to the trough on IVIG therapy, the weekly SCIG dose should give the equivalent of 50% of the previous monthly IVIG dose (red dashed lines). Conversely, a weekly SCIG dose which results in the same total dose as monthly IVIG will result in a mean steady-state IgG level equal to 113% of the trough level on the previous IVIG regimen. Together, these three graphs allow estimation of the dose of SCIG required to yield any given steady-state level, the dose of

Figure 2 Relationship between subcutaneous IgG: intravenous IgG trough level ratios (y-axis) and subcutaneous IgG: intravenous IgG dose ratios (x-axis)



Each point is the mean value of a different study (see [3^{*}] for individual citations). Correlation coefficient by linear regression ($r=0.894$, $P=0.0002$). Red dashed line shows that steady-state serum IgG level on SCIG would be equal to trough on IVIG (1.0 on y-axis) when SCIG dose is equal to 0.496 of the IVIG dose. Blue dashed line shows that steady-state serum IgG level on SCIG would be 113% of the trough on IVIG when the monthly IVIG and SCIG doses are equal (with the SCIG divided into four weekly increments). IVIG, intravenous IgG; SCIG, subcutaneous IgG. Reproduced with permission from [3^{*}].

IVIG required to yield any given trough level, and the changes in total monthly dose necessary to achieve any desired IgG level when switching from IVIG to SCIG, or *vice versa*.

Local reactions associated with subcutaneous IgG

Recent studies of SCIG have allowed volumes of up to 30 ml per site at rates up to 20–30 ml/site/h, and at least 50 ml/h overall. Multiple sites are often used simultaneously, so the total weekly dose can be given in 90 min or less. In most patients, infusion of 20–30 ml of IgG solution into a single site in less than 2 h causes some swelling, which may be accompanied by redness and/or a sensation of burning or itching. These ‘reactions’ generally resolve over 12–24 h, do not require any treatment, and are subjectively graded by patients as ‘mild’ or ‘moderate’. Several studies reported high rates of local reactions initially, which decreased over time [11^{••},13]. The decrease over time is more likely due to the eventual recognition by the patients that some swelling and redness was routine, rather than to actual physiologic changes in the subcutaneous tissues or IgG metabolism. If patients are instructed to recognize and expect these injection site phenomena, they rarely complain [27]. More severe reactions are extremely rare and may be due to poor technique and/or contamination of the infused drug. Very few patients on SCIG ask to return to IVIG treatment because of local or systemic reactions to SCIG, and most patients who try SCIG prefer to

remain on SCIG [10^{••}–12^{••},13,28]. Long-term changes at infusion sites are extremely rare, and many patients have tolerated SCIG for years. Rotating the sites used for consecutive infusions seems prudent, but is not absolutely necessary. A few studies have reported using multiple sites and pumps to give ‘express infusions’ of the whole weekly dose in 17 min [29]. Conversely, infusion of the whole weekly dose into a single subcutaneous site at a very slow rate (i.e. up to 8 h), while the patient is sleeping has also been described [30]. Many patients prefer regimens in which the total weekly SCIG dose is divided into multiple increments such as 10 ml, which can be drawn up into a single syringe and ‘pushed’ without a pump into one or two sites over a few minutes, several days a week [31^{••}]. With 20% SCIG, for example, 10 ml three times per week will deliver 24 g per month; and 20 ml four times per week will deliver 64 g per month. Thus, the flexibility of SCIG administration allows development of a regimen ideally suited to almost any individual.

Studies have shown injection of a relatively small amount of recombinant human hyaluronidase into the subcutaneous site just before infusion of IgG allows greater volumes to be infused per site with more rapid uptake into the systemic circulation and increased bioavailability compared with infusion of the same preparation without the hyaluronidase [32]. The hyaluronidase breaks up some of the interconnections in the subcutaneous matrix, allowing more rapid spreading of the infused material, but these changes are rapidly repaired as part of a normal turn-over mechanism. This agent has thus far only been studied with 10% IVIG solutions, but its use with SCIG solutions as concentrated as 16 or 20% may allow much higher doses of IgG to be given by the subcutaneous route with minimal local reactions.

Quality of life and psychological considerations

Because IgG replacement therapy is generally required for the whole lifetime of a PID patient, the effects of IgG infusions on the QoL must be considered. Formal studies of the health-related QoL using validated instruments such as the SF-36 and PF-50 showed that home-based SCIG regimens result in considerable improvement as compared with office or hospital-based i.v. regimens [33,34]. However, home-based i.v. regimens scored almost as highly as home-based subcutaneous regimens, suggesting that shifting the site of therapy to the home, with concomitant increases in the patients’ autonomy and convenience to the family, is more important than the route of administration *per se* [33]. An interesting German study [35] reported that older, retired patients preferred IVIG because of apprehension about sticking themselves with needles and changing their long-term i.v. regimens. In contrast, younger patients were more willing to try

something new and were less anxious about self-treatment.

Studies of SCIG in children, and infants under 2 years of age have shown no basic differences in safety or efficacy of SCIG compared to studies in older children and adults under 65 years of age [36,37[•]]. No particular problems are associated with home infusion of babies by their parents [37[•]]. A recent study [38[•]] reported that most elderly patients (>65 years of age) can infuse SCIG at home by themselves or with assistance from a family member. Despite concomitant medical conditions or treatment with anticoagulant or antiplatelet drugs, the elderly did not experience any increase in local or systemic adverse events with SCIG therapy [38[•]].

Pharmacoeconomics

The major cost of IgG replacement is for the IgG itself. In the US, the only product labeled solely for subcutaneous use, 20% Hizentra, is manufactured by the same process as its 10% i.v. counterpart, so its cost should not be very different. Two brands of 10% IgG are labeled for both subcutaneous and i.v. use, so again, their cost should not differ with the route of infusion. Most subcutaneous regimens use portable pumps, which are purchased or leased by the patient. These may cost anywhere from a few hundred to several thousand US dollars, but that cost is expected to be amortized over several years. I.V. infusion pumps are often more expensive than small portable subcutaneous pumps, but since they are used only 1 or 2 days a month, they are usually owned by the infusion center or home care service rather than the individual patient. Costs of tubing/needle sets and other supplies used for SCIG infusions may also vary from a few to over a hundred dollars per infusion. Pooling bags, tubing, i.v. catheters and other supplies for i.v. infusions are usually slightly less expensive than supplies for SCIG. However, since IVIG is generally given only once a month, whereas SCIG is generally given once or twice a week using multiple sites, yearly costs of supplies for SCIG may be five to 10 times more than for i.v. infusions. These costs are usually more than offset by nursing and facility fees associated with i.v. infusions. Patients and/or families performing home infusions generally experience significant savings in costs of transportation, parking and time lost from work. A Canadian government assessment concluded that i.v. infusions at home would be the least expensive form of replacement therapy, with SCIG at home only slightly more expensive, but with office or hospital-based i.v. infusions most expensive [39^{••}]. A recent comparison of the actual costs accrued during patients' last year on IVIG vs. the following year on SCIG showed that costs of pumps and supplies for SCIG were almost exactly offset by facility and administration costs for IVIG. However, when travel and time lost from

work were included, SCIG was less expensive than IVIG by \$(US) 2830 per year/patient ($P < 0.01$) [40^{••}].

Conclusion

There is little difference in the overall efficacy of IVIG vs. SCIG, but there are fewer systemic adverse events with the latter. For a few patients, difficult venous access or severe intolerance of IVIG may dictate a preference for SCIG. For the majority of PIDD patients, however, the choice of SCIG vs. IVIG comes down to personal preference based primarily on convenience and lifestyle issues. The direct costs to payors should be about the same for both routes, but there may be significant savings in travel costs and time lost from work for patients who self-infuse at home. In turn, self-infusion at home is facilitated by SCIG: most patients/parents can easily learn to administer SCIG after a few instructional sessions with an infusion nurse or doctor. Regardless of the route of administration, doses and treatment intervals should be individualized based on each patient's clinical condition and response.

Acknowledgements

Conflicts of interest

This manuscript was prepared while M.B. was a salaried employee of CSL Behring with equity interest. Figs. 1 and 2 are reproduced from [3[•]] with permission of the publisher.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

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