Current treatment options with immunoglobulin G for the individualization of care in patients with primary immunodeficiency disease

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Summary

Primary antibody deficiencies require lifelong replacement therapy with immunoglobulin (Ig)G to reduce the incidence and severity of infections. Both subcutaneous and intravenous routes of administering IgG can be effective and well tolerated. Treatment regimens can be individualized to provide optimal medical and quality-of-life outcomes in infants, children, adults and elderly people. Frequency, dose, route of administration, home or infusion-centre administration, and the use of self- or health-professional-administered infusion can be tailored to suit individual patient needs and circumstances. Patient education is needed to understand the disease and the importance of continuous therapy. Both the subcutaneous and intravenous routes have advantages and disadvantages, which should be considered in selecting each patient’s treatment regimen. The subcutaneous route is attractive to many patients because of a reduced incidence of systemic adverse events, flexibility in scheduling and its comparative ease of administration, at home or in a clinic. Self-infusion regimens, however, require independence and self-reliance, good compliance on the part of the patient/parent and the confidence of the physician and the nurse. Intravenous administration in a clinic setting may be more appropriate in patients with reduced manual dexterity, reluctance to self-administer or a lack of self-reliance, and intravenous administration at home for those with good venous access who prefer less frequent treatments. Both therapy approaches have been demonstrated to provide protection from infections and improve health-related quality of life. Data supporting current options in IgG replacement are presented, and considerations in choosing between the two routes of therapy are discussed.

Keywords: dosing regimens, immunoglobulin replacement therapy, intravenous immunoglobulin, primary immune deficiency disease, subcutaneous immunoglobulin

Introduction

Severe primary antibody deficiencies (PAD) require lifelong immunoglobulin (Ig)G replacement therapy [1–3]. Throughout the 1980s and 1990s, intravenous IgG (IVIG) administration was the most common method of replacement in most countries [1,2], but subcutaneous IgG (SCIG) has become established as a well-tolerated and effective treatment, which is preferred by many patients and their families [1,4–14]. Treatment regimens incorporating IVIG and SCIG products now allow physicians, nurses and the parents/care providers to support patients with widely different clinical backgrounds and lifestyles.

Sufficient data have been accumulated to suggest that the choice of IgG therapy for a patient with PAD is no longer simply a binary decision between monthly IVIG and weekly SCIG regimens. Variables which impact the choice of a regimen in any given patient with PAD include total monthly IgG dose, frequency and route of administration, the device used for administration, volume and rate of infusion, recommended IgG level at the end of an infusion cycle (trough level), number of infusion sites, the product and/or formulation used, site of care and administration of IgG,
education and training of the patient and family, the administration support system, and the occurrence and management of adverse events (AEs), including the need for pre- or post-medications (i.e., for prophylaxis or treatment of post-IVIG headaches, 'wear-off' or end-of-dose fatigue and other symptoms; Fig. 1). The availability of weekly, bi-weekly or more frequent SCIG regimens with 16 or 20% products, in addition to every 2-, 3- or 4-weekly intravenous administration of 5 or 10% preparations or hyaluronidase-facilitated SCIG (fSCIG) have significantly expanded choices for patients.

Overall, higher IgG levels are associated with increased resistance to infection. This has long been suggested for IVIG, but has also been documented for SCIG [15,16]. However, studies suggest great variability in the IgG levels required for different individuals to remain free from infection and in the dosing regimens needed to maintain the necessary serum IgG levels [17–20], and thus the association can only be drawn at the population level. Recent advances to be considered in formulating the best treatment approach for each patient are discussed.

**Aim of IgG replacement therapy**

The goal of long-term IgG replacement therapy is to reduce the incidence and severity of infections and prevent long-term deterioration in organ function [1,3,21]. Usually, this requires normalization of serum IgG levels. Optimized replacement IgG therapy may delay or abrogate the progression and development of complications in PAD, such as bronchiectasis, autoimmune disorders or digestive tract disorders, and retard development of progressive lung disease [1,3,22]. The treatment also aims to improve the self-perceived health-related quality of life (HRQoL) of children, adults and elderly people with PAD [12,21,23–29].

The importance of accurate diagnosis to identify those patients most likely to benefit from IgG replacement therapy is of initial and paramount importance. Unsatisfactory laboratory methods and the incorrect interpretation of results can lead to institution of IgG replacement therapy that is neither appropriate nor effective [30]. For example, careful interpretation of antibody responses to the 23-valent pneumococcal vaccine, with repeated determinations over time, may be necessary to determine the need for long-term IgG replacement therapy [30,31]. In some cases, an empirical trial of IgG may be indicated even when an underlying PAD has not been diagnosed clearly. In other cases, it may be appropriate to offer a patient a trial of discontinuation of an established IgG treatment regimen to allow wash-out and reassessment of the patient’s ability to maintain antibody levels and to mount protective vaccine responses.

The approach to the variables and goals of IgG therapy may change at different stages of a patient’s life: living circumstances, degree of exposure to infectious diseases and the onset of complications necessitating changes in therapy.

**Routes of administration: IVIG and SCIG for individualized therapy**

The choice of administration route should consider a range of clinical and patient parameters. Although IVIG replacement therapy has been used for many years, there have been more than 25 years of accumulated experience with SCIG therapy in Europe, especially in the Nordic countries. SCIG is now widely available in Europe, the United States and a steadily growing number of other countries [24,32–37].

From a pharmacokinetic viewpoint, the principle difference between the subcutaneous and intravenous routes is the slower rate at which IgG reaches the bloodstream following subcutaneous administration [38] and the frequency of administration. The pharmacokinetics of IgG can be described by a two-compartment model, with IgG in equilibrium between the vascular and extravascular compartments [39,40]. IVIG is infused directly into the intravascular compartment, immediately achieving high levels, which fall very rapidly over the next several days as the IgG is distributed into the extravascular compartment. The overall extracellular volume is about twice that of the intravascular compartment, so the IgG level re-equilibrates to about half the peak level. Catabolism then causes the level to drop more slowly over subsequent weeks. SCIG infusions form an initial depot at the local site(s), after which IgG is transported from the subcutaneous tissue into the lymph and then into the bloodstream [41]. The lack of the rapid attainment of a high peak IgG concentration with SCIG (Fig. 2) is associated with a substantially reduced incidence of systemic and severe AEs [38]. In addition, the near steady-state serum IgG levels achieved with weekly or more

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**Fig. 1.** Variables in immunoglobulin (Ig)G therapy. Akin to using pure colour paints to create a complex image, there are numerous variables in IgG therapy that can be applied to optimize the approach to any given patient. Some variables, for which at least some data exist supporting their adjustment in individual patients to improve outcomes, are listed as paints on the painter’s palette.
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**Fig. 2.** Serum immunoglobulin (Ig)G concentrations achieved with intravenous Ig (IVIG) and subcutaneous Ig (SCIG). Serum IgG concentrations for IVIG are from the pharmacokinetic study of Privigen® in primary antibody deficiency (PAD) \((n = 25)\) [99], those for SCIG are from the pharmacokinetic study of Hizentra® \((n = 18)\) [100]. Mean values are shown.

Frequent SCIG administration confer comparable protection against infections [5,11,12,34,42–44]. In contrast, recent pooled analyses showed that the incidence of infection increases as the IgG level falls towards the end of each 3- or 4-week IVIG dosing cycle [45]. It is not possible to achieve the near steady-state IgG levels with weekly SCIG [46–48] using IVIG.

The reduced incidence of systemic AEs and the comparative ease of the subcutaneous infusion facilitate home-based self- or family-administered SCIG regimens. However, this treatment option requires a reliable, committed individual and an experienced educator.

Most currently available IVIG formulations are associated with low rates of systemic AEs, which are generally tolerable and related mainly to the rate of infusion. These are more likely to be encountered during the first or second infusion of a given product (or if there is a concurrent infection) [38,48,49]. However, in some patients, lower trough IgG levels prior to the next dose of IVIG may cause ‘wear-off’ effects such as increased risk of infection, fatigue and/or a sense of feeling ill in some patients [15,38]. For these patients, either an increased IVIG dose, a shorter interval between IVIG infusions or substitution for weekly or more frequent SCIG infusions may be preferable [50]. In specific clinical situations such as PAD-associated immune-mediated cytopenia, IVIG may be more effective in quickly raising the platelet or white blood cell count, owing to the established immunomodulating effects. Conversely, patients with gastrointestinal or renal protein loss might benefit from the more gradually absorbed, smaller doses usually used with SCIG.

In some countries, specific insurance or payor policies regarding product, route, dose, and/or trough levels may restrict the provider’s ability to optimize the treatment regimen. However, a well-reasoned and referenced proposal or a 3–6-month therapeutic trial to establish efficacy may offer a way forward [3,51].

**IgG therapy and health economics**

Multiple factors, including product, method of delivery (i.e. with or without a pump) and whether a dose adjustment coefficient is used, may determine the relative cost of SCIG compared with IVIG therapy. As SCIG is self-administered by most patients, costs for facilities and health-care professionals should be reduced or eliminated. Swedish, German, and Canadian studies have shown an economic advantage in administering SCIG at home compared with hospital-based IVIG therapy [7,52–55] and also a 50% reduction in costs for the patients/families [7]. In Quebec, patients and parents spent less time away from home or other activities for SCIG therapy than for IVIG, and the total medical and non-medical costs were significantly lower for SCIG than IVIG \((P < 0.001)\) [54]. In British Columbia, the cost to the health-care system was reduced by CA$5736 per patient over 3 years by using SCIG compared with previous IVIG therapy [55]. An additional benefit for patients using SCIG is the possibility to do something else during the subcutaneous infusion. According to a recent survey of the International Patient Organization for Primary Immunodeficiencies (IPOPI), the average time for performing a SCIG infusion is less than 2 h, compared with approximately 2–6 h for an IVIG infusion [13,56]. Thus, the total time spent for SCIG infusions in a month may be longer than the time for IVIG infusion, but it is not perceived as ‘lost’ from other activities [13], and the time required for transportation to the hospital or infusion centre is also regained by the patient. There are hardly any studies comparing the costs of home- and hospital-based IVIG therapy. A review of the available literature concluded that the difference in therapy costs between IVIG and SCIG is due mainly to home therapy [27]. Home-based IVIG therapy may thus be expected to be similarly less costly than the equivalent hospital-based regimen and also not require the pumps needed for SCIG; however, the corresponding costing models are complex, with country- and service-specific variation.

**Dosing regimens**

**Dose**

IgG trough levels are a useful aid to monitor the adequacy of therapy and guiding care, but should be used in conjunction with a range of other clinical and laboratory findings to individualize therapy. These include infection frequency, antibiotic requirement, bronchiectasis, time lost from school or work, underlying diagnosis [X-linked agammaglobulinaemia (XLA) versus common variable immunodeficiency (CVID)], the presence of IgA, inflammatory markers, beta-2 microglobulin, imaging [57], potentially the measurement of individual antibody levels to specific pathogens [58], and, currently in a research setting, Fc
receptor polymorphism [3]. Even though a trough serum IgG level of 5 g/l has been used by some as a minimal target level, it is quite clear that different individuals require different IgG levels to remain free from infection and different dosing regimens to achieve and maintain those levels [59]. According to recent studies and in the authors’ experience, currently recommended average lower limits have increased to 7–8 g/l [7,15,32,60,61], with each patient treated individually. Lucas et al. have reported that patients with bronchiectasis require higher doses of IgG to achieve the same serum levels as those without bronchiectasis and that patients with XLA may require higher IgG levels than those with CVID [19]. At the University Hospital of Wales (Cardiff, UK), higher doses of IgG are given to patients with end organ damage or XLA. These findings and many authors’ clinical experience emphasize the need for individualized IgG therapy.

Starting IgG doses currently tend to be 400–600 mg/kg per 3 or 4 weeks for IVIG or 100–150 mg/kg per week for SCIG [15,16,51,62,63]. Bonagura et al. suggested a biological trough level for each patient to remain free from serious acute infection, rather than establishing an arbitrary mean based on the normal population [20]. Following regular monitoring (which might include spirometry, lung diffusing capacity and/or high-resolution computed tomography scans), dose adjustments should be made based on clinical outcomes and best practice for monitoring home therapy [37]. However, the minimization of acute infections may not necessarily prevent chronic infection (i.e. bronchiectasis) and its complications.

Dose intervals

Regimens should allow the treatment to be integrated into the patient’s specific life situation without causing undue adverse effects or sacrificing clinical efficacy. Any infusion frequency is feasible, from once every 4 weeks for IVIG to several times per week for SCIG. Currently, for patients receiving IVIG, administration every 2–4 weeks is used depending on the clinical outcome [35,64]. In a survey conducted by the US Immune Deficiency Foundation in 2007, 56% of patients received IVIG every 4 weeks, 27% every 3 weeks and 11% every 2 weeks; only a small proportion of patients used intervals longer than 4 weeks [64]. Recent treatment recommendations in the United States and Europe are similar: in a 2010 survey, 87% of the American Academy of Allergy, Asthma and Immunology (AAAAI) members recommended a 4-weekly dose interval, whereas the European Society for Immunodeficiency respondents used 3- and 4-weekly intervals [35]. For SCIG treatment, once-weekly has generally been preferred, but regimens ranging from daily to bi-weekly have been used in children and adults [5,13,42,44,62,64–67]. Diverse regimens can be tailored to require minimal number of infusions or sites per infusion depending on the patient’s tolerance, preference and available time (Table 1). In one author’s experience, patients with PAD experiencing joint pain or body aches may prefer to use daily or every-other-day SCIG infusions.

The usual practice of switching from IVIG to SCIG therapy in Europe has been to use the equivalent monthly IgG dose split into four equal weekly doses (1:1 dosing) [68,69]. Despite the recommendation of the US Food and Drug Administration to use a dose adjustment coefficient to achieve similar total exposure to IgG (non-inferior area under the curve of serum IgG concentration plotted versus time) [16], studies of clinical practice in the United States suggest that physicians are not necessarily heeding that recommendation, as there was no difference in the total monthly doses used by the intravenous and subcutaneous routes [70,71]. The impact of equivalent IVIG and SCIG dosing on frequency of infection and long-term outcomes remains to be seen, but available data suggest that even within the ‘normal’ range of serum IgG levels, higher levels provide better protection [16].

Infusion rate

Many of the systemic, infusion-related AEs with IVIG, such as headache, chills and/or malaise, can be alleviated by adjusting the infusion rate according to the individual patient’s tolerance and/or by reducing it when symptoms occur [72]. More than 60% of the responders of the First National Immune Deficiency Foundation Survey in 2002 and of a Swedish survey reported experiencing infusion rate-related AEs with IVIG [56,73]. Among current intravenous products, the newer 10% liquid IVIG formulations can be administered at infusion rates of up to approximately 5 ml/kg/h [74,75] or even 7.2 ml/kg/h [72]. For SCIG 16% products, the maximum recommended infusion rates are 10–20 ml/h. The maximum recommended rate for SCIG 20% is 15 ml/h/site for the first infusion and 25 ml/h/site for subsequent infusions, but these have largely been chosen to avoid side effects during registration trials that did not aim to determine the maximum rate or volume per site tolerated. ‘Express’ rates of up to 70 ml/h have been used successfully in some centres [8,47,48]. It has been shown that an infusion rate of 35 ml/h does not create more local AEs than 20 ml/h [8]. However, AEs (e.g. local pain or pronounced swelling and/or persisting local reactions) associated with very high infusion rates or volumes should be avoided when adjusting therapy for individuals.

Infusion volume

IVIG infusions are seldom limited by volume concerns, although volume may be an issue in some patients with cardiac or renal disease. In contrast, with SCIG, the volume infused per site and the number of sites per infusion should be limited to what can be tolerated comfortably by the
Table 1. Regimens for infusing different doses with minimal number of sites per infusion and longest infusion interval.

<table>
<thead>
<tr>
<th>Patient, weight</th>
<th>SCIG 0·4 g/kg/month, q2w</th>
<th>SCIG 0·5 g/kg/month, ×2 per week</th>
<th>SCIG 0·6 g/kg/month, ×2 per week</th>
<th>IVIG 0·4 g/kg/month, q4w</th>
<th>IVIG 0·5 g/kg/month, q3w</th>
<th>IVIG 0·6 g/kg/month, q3w</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infant, 12 kg</td>
<td>12 ml/site</td>
<td>6 ml/site</td>
<td>3·8 ml/site</td>
<td>4·5 ml/site</td>
<td>48 ml</td>
<td>36 ml</td>
</tr>
<tr>
<td></td>
<td>1 site</td>
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<td>1 site</td>
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<td>1 site</td>
</tr>
<tr>
<td></td>
<td>0·6 h</td>
<td>0·3 h</td>
<td>0·19 h</td>
<td>0·23 h</td>
<td>0·83 h</td>
<td>0·63 h</td>
</tr>
<tr>
<td>Child, 23 kg</td>
<td>11·5 ml/site</td>
<td>11·5 ml/site</td>
<td>7·2 ml/site</td>
<td>8·6 ml/site</td>
<td>92 ml</td>
<td>69 ml</td>
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<tr>
<td></td>
<td>2 sites</td>
<td>1 site</td>
<td>1 site</td>
<td>1 site</td>
<td>1 site</td>
<td>1 site</td>
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<tr>
<td></td>
<td>0·58 h</td>
<td>0·58 h</td>
<td>0·36 h</td>
<td>0·43 h</td>
<td>0·83 h</td>
<td>0·63 h</td>
</tr>
<tr>
<td>Adolescent, 50 kg</td>
<td>25 ml/site</td>
<td>25 ml/site</td>
<td>16 ml/site</td>
<td>19 ml/site</td>
<td>200 ml</td>
<td>150 ml</td>
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<tr>
<td></td>
<td>2 sites</td>
<td>1 site</td>
<td>1 site</td>
<td>1 site</td>
<td>1 site</td>
<td>1 site</td>
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<tr>
<td></td>
<td>1·25 h</td>
<td>1·25 h</td>
<td>0·78 h</td>
<td>0·94 h</td>
<td>0·83 h</td>
<td>0·63 h</td>
</tr>
<tr>
<td>Adult, 1, 60 kg</td>
<td>15 ml/site</td>
<td>15 ml/site</td>
<td>19 ml/site</td>
<td>23 ml/site</td>
<td>240 ml</td>
<td>180 ml</td>
</tr>
<tr>
<td></td>
<td>4 sites</td>
<td>2 sites</td>
<td>1 site</td>
<td>1 site</td>
<td>1 site</td>
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<tr>
<td></td>
<td>0·75 h</td>
<td>0·75 h</td>
<td>0·94 h</td>
<td>1·13 h</td>
<td>0·83 h</td>
<td>0·63 h</td>
</tr>
<tr>
<td>Adult, 2, 70 kg</td>
<td>17·5 ml/site</td>
<td>17·5 ml/site</td>
<td>22 ml/site</td>
<td>13 ml/site</td>
<td>280 ml</td>
<td>210 ml</td>
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<tr>
<td></td>
<td>4 sites</td>
<td>2 sites</td>
<td>1 site</td>
<td>2 sites</td>
<td>1 site</td>
<td>1 site</td>
</tr>
<tr>
<td></td>
<td>0·88 h</td>
<td>0·88 h</td>
<td>1·09 h</td>
<td>0·66 h</td>
<td>0·83 h</td>
<td>0·63 h</td>
</tr>
<tr>
<td>Adult, 3, 90 kg</td>
<td>22·5 ml/site</td>
<td>22·5 ml/site</td>
<td>28·2 ml/site</td>
<td>17 ml/site</td>
<td>360 ml</td>
<td>270 ml</td>
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<tr>
<td></td>
<td>4 sites</td>
<td>2 site</td>
<td>1 site</td>
<td>2 sites</td>
<td>1 site</td>
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<tr>
<td></td>
<td>1·13 h</td>
<td>1·13 h</td>
<td>1·41 h</td>
<td>0·84 h</td>
<td>0·83 h</td>
<td>0·63 h</td>
</tr>
</tbody>
</table>

Regimens for different doses, with minimal sites per infusion and longest intervals are presented for different patients. Calculations for subcutaneous Ig (SCIG) regimens are based on a 20% SCIG product and an hourly rate of 20 ml/h for each site. Calculations for intravenous Ig (IVIG) regimens are based on a 10% IVIG product and an hourly rate of 4·8 ml/h/kg for each site. Author recommendations (shading) are based on a dose of 0·4 g/kg/month and refer to the regimen only; if clinical outcomes necessitate higher dose, the regimen could be reassessed.
patient and may be influenced by the product, dose and duration of each infusion. While IVIG is generally available as a 5 or 10% formulation, SCIG is available in 10, 16, 16.5, or 20% solutions. The availability of 16–20% SCIG solutions allows larger doses to be administered in smaller volumes. When using SCIG, larger volumes can be accommodated using several simultaneous sites per infusion and/or more frequent infusions. Total doses of as much as 50 ml infused simultaneously into two to three sites can be tolerated easily by most adults, even elderly patients [76]. In the authors’ experience, up to 80 ml into a single site can be tolerated. It is important to choose a comfortable infusion rate and volume per infusion site in each patient when individualizing the SCIG therapy. However, increasing both variables at the same time may complicate resolving potential local tissue AEs.

**Number of infusion sites**

The number of subcutaneous infusion sites used during each infusion differ widely. Up to four sites are used by most patients [7,9,42,76,77], either sequentially or simultaneously [11,69], but as many as six to eight sites have been used for single infusions. The flexibility of using different number of sites, volumes per site, infusion duration, and interval allow infusion regimens to integrate with the lifestyle of individual patients (Table 1). Portable infusion pumps and bifurcated or more highly branched tubing sets can be used to facilitate any desired regimen, and can limit the total time required for SCIG treatment.

**SCIG treatment of patients previously untreated with IgG**

If the subcutaneous route is chosen, initiation of therapy in previously untreated patients sometimes includes a ‘loading’ phase. Initial loading with 100 mg/kg daily for 5 consecutive days [12] increases serum IgG levels to target levels of more than 5 g/l within 1 week (Fig. 3) and also provides a good opportunity for effective training for subsequent self-infusion at home [47]. Weekly SCIG raises the IgG more gradually, reaching levels >5 g/l after 3–4 weeks [65], with steady-state levels reached after 6 months. In the US registration trials and in patients in whom serum IgG levels must be raised rapidly, IVIG is given first, followed by a switch to SCIG therapy for maintenance [48].

**Experience in specific patient subpopulations**

**Pediatric populations**

Rapid SCIG infusion therapy [9] was adopted for use in children in the 1990s [78]. Optimal treatment of children and infants aged less than 2 years is particularly important in order to prevent the development of chronic lung infec-

![Fig. 3. Serum immunoglobulin (Ig)G levels in previously untreated patients. Loading 1 included administration of 100 mg/kg daily for 5 days (n = 18); the maintenance regimen was 100 mg/kg once weekly thereafter [12]. With loading 2, patients (n = 13) received 100 mg/kg twice a week for 2 weeks; the maintenance regimen was 100 mg/kg once weekly [101]. Mean values are shown.](image)

tion. Although trough IgG levels are generally targeted in the same way and in the same range as for older children and adults, early rigorous treatment may favor better clinical outcomes and minimize lung complications [62,79]. Overall, all studies in pediatric patients indicate that management of primary immunodeficiencies with IVIG therapy begun early in life is well tolerated, effective, and improves patients’ HRQoL [62,79,80].

The ease of administration and good tolerability of SCIG in children allows maintenance of adequate IgG levels and successful management of infections, resulting in fewer days in hospital and days missed from school or day care [12,43,69]. Similar results were observed in studies evaluating the HRQoL of pediatric patients on SCIG therapy [5,21,81]. Home therapy with weekly SCIG resulted in greater independence, reduced the periods of absence from school and social activity, enhanced freedom to travel, decreased disruption of daily activities, improved therapy convenience and comfort, and provided better treatment flexibility as opposed to hospital-based IVIG treatment [5,21]. Psychological preparation and play therapy during the nurse-led training for IgG replacement in children is important to assist the child and family. For occasional pediatric patients with family situations that preclude home therapy, SCIG administration in a clinic or hospital day unit may be the preferred option.

**Elderly patients**

As a patient group, elderly people are more likely to have co-morbid conditions, such as impaired cardiovascular and/or kidney function, and to be receiving concomitant medications that might be considered to potentially increase the risk and/or severity of AEs. Age-related changes in the circulatory system, subcutaneous and connective tissues might also be expected to affect the dynamics and/or tolerability of SCIG [76]. Further, reduced dexterity, lack of
self-confidence or an infusion partner and resistance to change may make self-infusion at home more challenging in elderly patients. For these reasons, some elderly patients prefer IVIG infusions administered by trained professionals at a clinic or infusion centre.

However, travel to the office or infusion centre might be challenging for some elderly patients. Studies have shown that home-based SCIG appears to be well tolerated, effective and practical in patients aged more than 65 years [76]. Moreover, none of the patients, including patients with diabetes and patients who received anti-coagulant or anti-platelet therapy, experienced problems with local reactions such as bruising, bleeding or skin breakdown [76]. The lack of local site complications in patients on concomitant anti-coagulant or anti-platelet therapy has also been confirmed in a wider age range (3–89 years, median 70 years) of patients with PAD receiving maintenance SCIG therapy [82]. SCIG treatment every 2 weeks (bi-weekly) was also tolerated well by elderly patients [42].

IgG use during pregnancy

In a study of pregnant women with PAD, weekly SCIG infusions were well tolerated and effective in nine women during 11 pregnancies [83]. During pregnancy, women switched infusion site from the abdominal wall to the thigh for convenience reasons. IgG dose is usually increased in the last trimester to compensate for placental IgG transfer, but can also be adjusted based on the increased weight during the pregnancy. This gradual increase of the dose may be more convenient for the woman [83]. After more than 400 infusions, no systemic AEs or marked local tissue reactions were observed. Gestation was normal in all cases and all babies were born in a healthy condition with normal serum IgG levels and IgG subclasses, with no requirement for additional IgG therapy following birth.

Patients with obesity

SCIG (16 or 20%) administered by infusion pump or push administration was effective and well tolerated in obese patients, providing a practical alternative to IVIG without the need for special dosing adjustments [77]. Dose to serum IgG level ratios were similar in obese and non-obese patients, consistent with equivalent bioavailability regardless of body mass index (BMI): there was no evidence supporting a need for SCIG dose adjustments in obese patients with PAD [77]. Nevertheless, treatment guidelines in Australia, Canada, and the United Kingdom have suggested dose adjustments in obese patients based on lean body weight – mainly in the context of immunomodulatory IgG doses – as a potential cost-saving mechanism, although there is little published evidence to support this approach [84]. Rates of AEs, mostly of injection-site reactions, were slightly lower among obese (15.8% of visits) compared with non-obese (17.6% of visits) patients [7,77].

Administration practicalities

Devices for administration: pump, syringe

Individual patient preferences, cost and local policies may all be considered in deciding whether to administer SCIG using small portable infusion pumps (‘pump’) or simply pushing the IgG from a syringe. Volumes of less than 20 ml can be pushed directly, with only one or two sites per infusion. This often necessitates more frequent dosing, but each infusion usually takes much less time. A retrospective analysis in 104 patients found that for push administration using a syringe, volumes of 3–20 ml were administered during 5–20 min at an average frequency of two to three times per week [66]. More than 80% of patients using the rapid push infusion used only one infusion site per session, with 20 ml as the most common total volume infused (67.3% of patients). An additional 18.6% of patients infused 10–14 ml per infusion. The frequent push technique is considered much more convenient by some patients [66]. A more recent analysis of administration techniques in a larger cohort (173 patients) confirmed these results: the mean (±standard deviation) infusion volume was 15.0 ml (±7.3 ml) and the time needed for each infusion was substantially lower than that for pump administration [67]. Similar results were obtained in pediatric patients [85]. As the push technique requires no pump or tubing, the cost for equipment and its maintenance is reduced [47].

Regardless of whether using pump or ‘push’, the choice of needle length and gauge can have a marked effect on tolerability [86]. Sufficiently long needles (9–15 mm in adults) are essential for delivering the drug into the subcutaneous tissue rather than the dermis, but needles which are too long may deliver the IgG into muscle [86]. Erring on either side of the subcutaneous tissue has the potential for causing pain and discomfort. A ¾” × 23–25-gauge butterfly needle is usually used for syringe administration in adults [9,47]. For infants, a 24–27-gauge, 4–6-mm needle is appropriate [14]. Equipment for measuring the thickness of the subcutaneous tissue is now available, making it easier to choose the correct needle length. The needle tip can also contribute to better tolerability, with the tricuspid type being usually better tolerated than the lancet type [86]. Not surprisingly, patients with a lower BMI experience infusion-site reactions more frequently [7]. Local itching experienced after infusions by some patients may be due to mechanical and/or chemical local mechanisms affecting superficial, dermal sensory nerve fibres [7].

Crono PCA-50 or Super-PID infusion pumps (Cane S.R.L., Turin, Italy) are used predominantly in Europe, while the FREEDOM60 syringe infusion system (Repro-Med Systems, Inc., Chester, NY, USA) is preferred in the
United States [47]. The tubing size for FREEDOM60 is used to adjust the infusion rate, and thus has to be chosen according to the rate tolerated by the patient [86].

In a Swedish survey comprising 841 adults with PAD receiving IgG therapy, 20% of those receiving IVIG at the hospital reported that inserting the intravenous needle was often a problem. The needle was often placed in the antecubital vein (44%), followed by the radial side of the wrist (20%), the back of the hand (18%) or in an already-established port-a-cath (17%). However, the use of long-term indwelling catheters should generally be avoided in immunodeficient patients due to the risk of infection. Of those on IVIG self-infusions at home, a clear majority (71%) placed the needle on the back of the hand. Most of the adults on SCIG therapy used sites on the abdomen (74% of those at home; 63% of those at the hospital). A 23–25-gauge butterfly needle was used by a majority of the patients on SCIG (87% home; 70% hospital) [73]. In the United States, butterfly needles are infrequently used for SCIG, as most patients receive commercially available SCIG needles such as Clear-Vue® (Best, the Netherlands).

Site of care

IgG replacement therapy may be administered in a hospital, clinic or infusion center setting, at the doctor’s office, at home or, in some cases, even as self-infusions at work. The AAAAI site of care guidelines recommend highest level of physician supervision in a hospital or practice, so that any AEs can be handled appropriately [87]. In stable patients who are tolerating therapy well, the site of care can be changed to a lower level of supervision and a less controlled environment. Home-based IVIG self-administration is preferred by some patients after appropriate education and evaluated to be safe [88]. At the University Hospital of Wales (Cardiff, UK) and in Sweden, approximately 80% of the newly diagnosed adult patients commence home SCIG therapy after appropriate education and assessment. A recent survey by IPOPI showed that among 300 patients in 10 countries, 14% of patients on IVIG and 94% for those on SCIG received therapy at home [13].

Administration personnel and training programs

Patients usually prefer self-administration at home, as it increases flexibility, HRQoL and self-perceived health [9,23,24,26,28,29,69,73,81,89]. Self-administration is more practical with SCIG than IVIG, but IVIG self-infusions are possible at home [13,73,88] or administered by a nurse for patients anxious about needles or self-infusions. Self-administration requires patients or caregivers to undergo education and training until they feel comfortable to perform infusions on their own and demonstrate their competence to the trainer. In most cases this is accomplished within three to six infusions, but training programs may differ by country [47]. In many cases, instruction in SCIG involves newly diagnosed patients or those taking increased responsibility for their own care. Therefore, it is important that the education and training program includes education about PAD, aims and importance of IgG therapy, infections, systemic adverse reactions including management of any severe reactions, self-care and infection prevention, behavior changes (e.g. the IgG therapy itself being a change in life, smoking cessation, maintaining play time and activities), and self-infusion technique, including safety measures before starting the infusion [37]. Some providers have concerns about higher rates of systemic AEs accompanying self-administration of IVIG at home as opposed to SCIG. Therefore, a reliable system of reporting AEs associated with home-based infusions has to be developed. Support for pediatric patients may include the use of ‘play therapy’ to improve adherence to treatment regimens.

Use of hyaluronidase to facilitate SCIG administration

The use of hyaluronidase to facilitate dispersion of larger volumes of liquid into the subcutaneous space has been suggested to help absorption of a number of drugs, including IgG [90]. In an open-label multi-center Phase III study of administration of hyaluronidase followed by subcutaneous immunoglobulin (IGHy), a mean volume of 292.2 ml of 10% Ig was administered using one site every 3 or 4 weeks and serum IgG trough levels were similar with IGHy and IVIG [91]. The area under the serum IgG concentration–time curve suggested a bioavailability of 86% for IGHy compared with approximately 67% for SCIG without hyaluronidase [71]. The overall rate of infection was 2.97 days per patient-year for IGHy compared with 4.51 for previous IVIG. IGHy may be practical for patients who prefer infrequent (e.g. 2–4-weekly) dosing, although ‘wear-off’ effects towards the end of the longer cycle may be an issue, as with IVIG. Recombinant human hyaluronidase has been well tolerated in occasional use; however, only relatively small numbers of PID patients, mostly in studies, have been treated repeatedly with limited long-term follow-up. IGHy is approved in Europe and the United States for use in adults; in Europe, it is not approved in women who are pregnant or planning to become pregnant [92,93]. The extent to which IGHy will be used in future will depend on longer-term experience and follow-up and cost–benefit analysis.

Special situations

SCIG administration has been reported to be more compatible with an active lifestyle, including sports and schooling, and more convenient during business trips or holiday [13,21,24,26–28,68,69]. Ninety per cent of patients receiving IVIG report having skipped a dose compared with 18%
of those receiving SCIG therapy, and 45% of patients with SCIG self-administered doses with delay by 3 or more days at least once in the last 6 months [8,13]. The choice between SCIG and IVIG for patients who travel frequently depends upon the time spent away from home and whether traveling with equipment is needed.

For surgery, the recommendation is to ensure that a dose is given close to and preceding the surgery date.

Patients with anti-IgA antibodies require careful assessment, as high-titre anti-IgA antibodies have been associated with severe anaphylactic reactions, and in some countries they are not treated with IVIG. Patients with high titres of anti-IgA antibodies have been treated successfully with SCIG in Sweden [9,94–97].

Management of AEs

Available products differ substantially and, as a result, some patients tolerate different products differently. In patients with adverse reactions, a switch from one product to another may be needed [98]. Once a patient is stabilized on a specific product, that same product should be continued to ensure good tolerability and stable therapy [3]. Products should not be changed without consent and oversight of the physician.

Different types of AEs are observed with IVIG and SCIG therapy: the former is associated with a higher rate of systemic AEs such as headache, nausea, and fatigue, while the latter is accompanied mainly by local infusion-site reactions. Although initial local tissue reactions are to be expected with SCIG, they are usually considered only ‘mild’ or ‘moderate’ and their frequency decreases with prolonged therapy (Fig. 4) [47,69].

The infusion technique and materials used are important for good tolerability of SCIG infusions; the change from a 6- to a 9-mm needle reduced local AEs in some patients [86]. It is also important to individualize the choice of infusion sites: some adult patients will prefer to use the thighs, others the abdomen and others the combination of both or the backs of the arms. Some patients prefer to alternate between several sites, while others find that the use of new sites results in an increased rate of local reactions. In either case, long-term changes at infusion sites such as tissue scarring or atrophy have not been reported. There are limited long-term data concerning the regular use of hyaluronidase in the same site.

Alleviation of AEs

Most systemic AEs typical of IVIG treatment (headache, nausea and fatigue) occur during the infusion or within 2 days after it, when the serum IgG level is at its peak. Reduction of the infusion rate is often sufficient to alleviate AEs. Premedication with anti-pyretics, anti-histamines and/or short-term corticosteroids can be used with IVIG to ameliorate systemic AEs [1]. In some patients, the switch to SCIG and a more steady-state serum IgG level has alleviated recurrent problems such as severe post-IVIG headaches, which are presumably related to the pharmacokinetics of the intravenous route.

Selection of the appropriate therapy regimen

Confirming the diagnosis necessitating IgG therapy is the first step in the proposed algorithm for selecting the right therapy for each patient (Fig. 5). Determining whether IVIG or SCIG will be used requires information about personal preferences, venous access, dose required, tolerance to previous IgG treatment, lifestyle, and in-depth discussion with the patient/parents. Although care must be taken to agree to an initial treatment plan at the outset, subsequent support, especially for home therapy, is essential. As the patient becomes familiar with his/her disease and its treatment, the regimen should be reviewed and adjusted as needed, and changes in living circumstances and/or exposure to infectious diseases should be considered. With current products, routes of administration, and pumps/devices, there should always be the flexibility to modify the regimen to fit changing requirements or preferences.

Conclusions

It is now possible to adjust individually the IgG administration route, infusion technique, frequency of infusion, number of infusion sites, and volumes to suit patients of any age or circumstance (pregnancy, infants and elderly people) with IVIG or SCIG regimens. Measures that increase the flexibility and convenience of therapy are important, and choices may be different for pediatric and elderly patients. The range of options now includes IVIG with 5 and 10% products, SCIG products at 10, 16, 16.5,
Fig. 5. Graphic algorithm for selection of treatment regimen. The proposed algorithm is based on individual clinical outcomes and patient-related factors and relates to immunoglobulin (Ig)G therapy only. Adjunct antibiotic prophylaxis is not included, but can be considered as concomitant treatment.
and 20% concentrations with weekly, biweekly, and rapid push regimens as well as iSCIG. These allow the tailoring of an optimal IgG regimen to enhance compliance, strengthen patient and provider confidence, improve HRQoL, and achieve the best possible clinical and patient outcomes.

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