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

S. Jolles,† J. S. Orange,‡ A. Gardulf,§ M. R. Stein,† R. Shapiro,⊕ M. Borte,⊕ and M. Berger

†Immunodeficiency Centre for Wales, University Hospital of Wales, Cardiff, UK, ‡Texas Children’s Hospital, Baylor College of Medicine, Houston, TX, ⊥Allergy Associates of the Palm Beaches, North Palm Beach, FL, *Midwest Immunology Clinic, Plymouth, MN, ⊥CSL Behring LLC, King of Prussia, PA, USA, †Unit of Clinical Nursing Research, Immunotherapy and Immunology, Division of Clinical Immunology, Department of Laboratory Medicine, Karolinska Institutet, Karolinska University Hospital, Huddinge, Stockholm, Sweden, and **Department of Pediatrics, Hospital ‘St. Georg’ GmbH Leipzig, Academic Teaching Hospital of the University of Leipzig, Leipzig, Germany

Accepted for publication 10 October 2014
Correspondence: S. Jolles, Department of Immunology, University Hospital of Wales, Heath Park, Cardiff CF14 4XW, UK.
E-mail: jollessr@cardiff.ac.uk

In memory of Dr Jeff S. Baggish

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,
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
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 immunemediated 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 agammaglobulinemia (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.

|Patient, weight| SCIG 0·4 g/kg/month, q2w| SCIG 0·4 g/kg/month, q1w| SCIG 0·5 g/kg/month, ×2 per week| SCIG 0·6 g/kg/month, ×2 per week| IVIG 0·4 g/kg/month, q4w| IVIG 0·5 g/kg/month, q3w| IVIG 0·6 g/kg/month, q3w|
|---------------|--------------------------|------------------------|----------------------------------|----------------------------------|------------------------|------------------------|------------------------|
|Infant, 12 kg  | 12 ml/site                | 6 ml/site              | 3·8 ml/site                      | 4·5 ml/site                      | 48 ml                  | 36 ml                  | 45 ml                  |
|               | 1 site                    | 1 site                 | 1 site                           | 1 site                           | 1 site                 | 1 site                 | 1 site                 |
|               | 0·6 h                     | 0·3 h                  | 0·19 h                           | 0·23 h                           | 0·83 h                 | 0·63 h                 | 0·78 h                 |
|Child, 23 kg   | 11·5 ml/site              | 11·5 ml/site           | 7·2 ml/site                      | 8·6 ml/site                      | 92 ml                  | 69 ml                  | 86 ml                  |
|               | 2 sites                   | 1 site                 | 1 site                           | 1 site                           | 1 site                 | 1 site                 | 1 site                 |
|               | 0·58 h                    | 0·58 h                 | 0·36 h                           | 0·43 h                           | 0·83 h                 | 0·63 h                 | 0·78 h                 |
|Adolescent, 50 kg | 25 ml/site             | 25 ml/site             | 16 ml/site                       | 19 ml/site                       | 200 ml                 | 150 ml                 | 188 ml                 |
|               | 2 sites                   | 1 site                 | 1 site                           | 1 site                           | 1 site                 | 1 site                 | 1 site                 |
|               | 1·25 h                    | 1·25 h                 | 0·78 h                           | 0·94 h                           | 0·83 h                 | 0·63 h                 | 0·78 h                 |
|Adult 1, 60 kg | 15 ml/site                | 15 ml/site             | 19 ml/site                       | 23 ml/site                       | 240 ml                 | 180 ml                 | 225 ml                 |
|               | 4 sites                   | 2 sites                | 1 site                           | 1 site                           | 1 site                 | 1 site                 | 1 site                 |
|               | 0·75 h                    | 0·75 h                 | 0·94 h                           | 1·13 h                           | 0·83 h                 | 0·63 h                 | 0·78 h                 |
|Adult 2, 70 kg | 17·5 ml/site              | 17·5 ml/site           | 22 ml/site                       | 13 ml/site                       | 280 ml                 | 210 ml                 | 263 ml                 |
|               | 4 sites                   | 2 sites                | 1 site                           | 2 sites                          | 1 site                 | 1 site                 | 1 site                 |
|               | 0·88 h                    | 0·88 h                 | 1·09 h                           | 0·66 h                           | 0·83 h                 | 0·63 h                 | 0·78 h                 |
|Adult 3, 90 kg | 22·5 ml/site              | 22·5 ml/site           | 28·2 ml/site                     | 17 ml/site                       | 360 ml                 | 270 ml                 | 338 ml                 |
|               | 4 sites                   | 2 site                 | 1 site                           | 2 sites                          | 1 site                 | 1 site                 | 1 site                 |
|               | 1·13 h                    | 1·13 h                 | 1·41 h                           | 0·84 h                           | 0·83 h                 | 0·63 h                 | 0·78 h                 |

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 solu-
tions allows larger doses to be administered in smaller
volumes. When using SCIG, larger volumes can be accom-
mmodated 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 indi-
vidualizing the SCIG therapy. However, increasing both
variables at the same time may complicate resolving poten-
tial 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 simulta-
neously [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 life-
style 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 ‘loa
ding’ 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 subse-
quint 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-
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 clini-
cal outcomes and minimize lung complications [62,79].
Overall, all studies in pediatric patients indicate that man-
gement 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 evaluat-
ing 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
dependence 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 ¼"×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, tolerability to previous IgG treatment, lifestyle, and in-depth discussion with the patient/parents. Although care must be taken to agree on 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.
Fig. 5. Continued
and 20% concentrations with weekly, bi-weekly, and rapid push regimens as well as FSCIG. 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.

Acknowledgements

The authors thank Dr Alphonse Hubsch for critical review of the manuscript. A. G. reported funding from Karolinska Institutet in Stockholm, Sweden for this study; S. J. is supported by a NISCHR Fellowship. Medical writing support was provided by Emiliana Jelezarova, PhD, Fishawack Communications GmbH, a member of the Fishawack Group of Companies, funded by CSL Behring.

Disclosure

S. J reports consulting, speaker, travel, advisory board and research support from CSL Behring, Baxter, BPL, Biotest and Octapharma; J. S. O. has received consultancy fees from CSL Behring, Grifols, Baxter, Octapharma, BPL, ASD, Atlantic Research Group, research grant from CSL Behring; A. G. has collaborated with CAL, Baxter and Octapharma for advisory boards, but received no direct funding; M. R. S. has received advisory board and speaker fees from CSL Behring, advisory board, speaker and investigator fees from Baxter, investigator support from BPL, Green Cross, Kedrion and ADMa; R. S. serves as clinical investigator and adviser for CSL Behring, Baxter, Viropharma and Kedrion and as speaker for CSL Behring, Baxter and Viropharma; M. B. has received consulting, speaker, travel, advisory board fees and research support from CSL Behring, Baxter and Octapharma; M. B. is a salaried employee of CSL Behring with equity interest and has received a consulting fee from Octapharma; M. B. is a salaried employee of CSL Behring and research support from CSL Behring, Baxter, Viropharma and Kedrion and as speaker for CSL Behring, Baxter and Viropharma; M. B. has received advisory board and speaker fees from CSL Behring, Baxter, Viropharma, and Kedrion and as speaker for CSL Behring, Baxter and Viropharma; M. B. is a salaried employee of CSL Behring with equity interest and has received a consulting fee from America’s Health Insurance Plans.

References

1 Berger M. Principles of and advances in immunoglobulin replacement therapy for primary immunodeficiency. Immunol Allergy Clin North Am 2008; 28:413–37.
2 Park MA, Li JT, Hagan JB, Maddox DE, Abraham RS. Common variable immunodeficiency: a new look at an old disease. Lancet 2008; 372:489–92.
3 American Academy of Allergy Asthma and Immunology. Eight guiding principles for effective use of IVIG for patients with primary immunodeficiency. Milwaukee, WI, USA, 2011.
4 Chapel HM, Spicckett GP, Ericson D, Engl W, Eibl MM, Bjorkander J. The comparison of the efficacy and safety of intravenous versus subcutaneous immunoglobulin replacement therapy. J Clin Immunol 2000; 20:94–100.
5 Fasth A, Nystrom J. Safety and efficacy of subcutaneous human immunoglobulin in children with primary immunodeficiency. Acta Paediatr 2007; 96:1474–8.
6 Abrahamsen TG, Sanderson H, Bustnes A. Home therapy with subcutaneous immunoglobulin infusions in children with congenital immunodeficiencies. Pediatrics 1996; 98:1127–31.
7 Gardulf A, Andersen V, Bjorkander J et al. Subcutaneous immunoglobulin replacement in patients with primary antibody deficiencies: safety and costs. Lancet 1995; 345:365–9.
8 Hansen S, Gustafson R, Smith CI, Gardulf A. Express subcutaneous IgG infusions: decreased time of delivery with maintained safety. Clin Immunol 2002; 104:237–41.
9 Gardulf A, Hammarström L, Smith CI. Home treatment of hypogammaglobulinaemia with subcutaneous gammaglobulin by rapid infusion. Lancet 1991; 338:162–6.
10 Welch MJ, Stiehm ER. Slow subcutaneous immunoglobulin therapy in a patient with reactions to intramuscular immunoglobulin. J Clin Immunol 1983; 3:285–6.
11 Hagan JB, Fasano MB, Spector S et al. Efficacy and safety of a new 20% immunoglobulin preparation for subcutaneous administration, IgPro20, in patients with primary immunodeficiency. J Clin Immunol 2010; 30:734–45.
12 Borte M, Quinti I, Sorensina A et al. Efficacy and safety of subcutaneous Vivaglobin® replacement therapy in previously untreated patients with primary immunodeficiency: a prospective, multicenter study. J Clin Immunol 2011; 31:952–61.
13 International Patient Organisation for Primary Immunodeficiencies. IPOPI PID Patient Needs and Outlooks Survey. Cornwall, UK, 2012.
14 Church JA, Howard V, Seasman JW, Borte M, Berger M. Subcutaneous immunoglobulin replacement therapy in infants and children with primary immunodeficiencies. J Allergy Clin Immunol 2011; 127:AB213.
15 Orange JS, Grossman WI, Navickis RJ, Wilkes MM. Impact of trough IgG on pneumonia incidence in primary immunodeficiency: a meta-analysis of clinical studies. Clin Immunol 2010; 137:21–30.
16 Orange JS, Belohradsky BH, Berger M et al. Evaluation of correlation between dose and clinical outcomes in subcutaneous immunoglobulin replacement therapy. Clin Exp Immunol 2012; 169:172–81.
17 Bonagura VR. Illustrative cases on individualizing immunoglobulin therapy in primary immunodeficiency disease. Ann Allergy Asthma Immunol 2013; 111:S10–S13.
18 Freiberger T, Grodecka L, Ravuckova B et al. Association of FeRn expression with lung abnormalities and IVIG catabolism in patients with common variable immunodeficiency. Clin Immunol 2010; 136:419–25.
19 Lucas M, Lee M, Lortan J, Lopez-Granados E, Misbah S, Chapel H. Infection outcomes in patients with common variable immunodeficiency disorders: relationship to immunoglobulin therapy over 22 years. J Allergy Clin Immunol 2010; 125:1354–60.
20 Bonagura VR, Marchlewski R, Cox A, Rosenthal DW. Biologic IgG level in primary immunodeficiency disease: the IgG level that protects against recurrent infection. J Allergy Clin Immunol 2008; 122:110–2.
21 Gardulf A, Nicolay U, Math D et al. Children and adults with primary antibody deficiencies gain quality of life by subcutaneous IgG self-infusions at home. J Allergy Clin Immunol 2004; 114:936–42.
22 Buckley RH. Pulmonary complications of primary immunodeficiencies. Paediatr Respir Rev 2004; 5 (Suppl. A):S225–33.
23 Gardulf A, Borte M, Ochs HD, Nicolay U. Prognostic factors for health-related quality of life in adults and children with primary antibody deficiencies receiving SCIG home therapy. Clin Immunol 2008; 126:81–8.

24 Nicolay U, Kiessling P, Berger M et al. Health-related quality of life and treatment satisfaction in North American patients with primary immunodeficiency diseases receiving subcutaneous IgG self-infusions at home. J Clin Immunol 2006; 26:65–72.

25 Gardulf A, Nicolay U. Replacement IgG therapy and self-therapy at home improve the health-related quality of life in patients with primary antibody deficiencies. Curr Opin Allergy Clin Immunol 2006; 6:434–42.

26 Gardulf A, Bjorvell H, Gustafson R, Hammarstrom L, Smith CI. The life situations of patients with primary antibody deficiency untreated or treated with subcutaneous gammaglobulin infusions. Clin Exp Immunol 1993; 92:200–4.

27 Lingman-Framme J, Fasth A. Subcutaneous immunoglobulin for primary and secondary immunodeficiencies: an evidence-based review. Drugs 2013; 73:1307–19.

28 Fasth A, Nyström J. Quality of life and health-care resource utilization among children with primary immunodeficiency receiving home treatment with subcutaneous human immunoglobulin. J Clin Immunol 2008; 28:370–8.

29 Haddad E, Barnes D, Kafal A. Home therapy with subcutaneous immunoglobulins for patients with primary immunodeficiency diseases. Transfus Apher Sci 2012; 46:315–21.

30 Gelfand EW, Ochs HD, Shearer WT. Controversies in IgG replacement therapy in patients with antibody deficiency diseases. J Allergy Clin Immunol 2013; 131:1001–5.

31 Orange JS, Ballow M, Steihm ER et al. Use and interpretation of diagnostic vaccination in primary immunodeficiency: a working group report of the Basic and Clinical Immunology Interest Section of the American Academy of Allergy, Asthma & Immunology. J Allergy Clin Immunol 2012; 130:S1–24.

32 Roifman CM, Schroeder H, Berger M et al. Comparison of the efficacy of IGIV-C, 10% (caprylate/chromatography) and IGIV-SD, 10% as replacement therapy in primary immune deficiency. A randomized double-blind trial. Int Immunopharmacol 2003; 3:1325–33.

33 Bezrodnik L, Gomez RA, Belardinelli G et al. Comparative study of subcutaneous versus intravenous IgG replacement therapy in pediatric patients with primary immunodeficiency diseases: a multicenter study in Argentina. J Clin Immunol 2013; 33:1216–22.

34 Empson MB, Tang ML, Pearce LK et al. Efficacy, safety and pharmacokinetics of a novel subcutaneous immunoglobulin, Evogam(R), in primary immunodeficiency. J Clin Immunol 2012; 32:897–906.

35 Hernandez-Trujillo HS, Chapel H, Lo Re V III et al. Comparison of American and European practices in the management of patients with primary immunodeficiencies. Clin Exp Immunol 2012; 169:57–69.

36 Condino-Neto A, Costa-Carvalho BT, Grumach AS et al. Guidelines for the use of human immunoglobulin therapy in patients with primary immunodeficiencies in Latin America. Allergol Immunopathol (Madr) 2014; 42:245–60.

37 Chapel H, Gardulf A. Subcutaneous immunoglobulin replacement therapy: the European experience. Curr Opin Allergy Clin Immunol 2013; 13:623–9.

38 Berger M. Choices in IgG replacement therapy for primary immune deficiency diseases: subcutaneous IgG vs. intravenous IgG and selecting an optimal dose. Curr Opin Allergy Clin Immunol 2011; 11:532–8.

39 Landersdorfer CB, Bexon M, Edelman J et al. Pharmacokinetic modeling and simulation of biweekly subcutaneous immunoglobulin dosing in primary immunodeficiency. Postgrad Med 2013; 125:53–61.

40 Bonilla FA. Pharmacokinetics of immunoglobulin administered via intravenous or subcutaneous routes. Allergy Immunol North Am 2008; 28:803–19. ix.

41 Porter CJ, Charman SA. Lymphatic transport of proteins after subcutaneous administration. J Pharm Sci 2000; 89:297–310.

42 Gustafson R, Gardulf A, Hansen S et al. Rapid subcutaneous immunoglobulin administration every second week results in high and stable serum immunoglobulin G levels in patients with primary antibody deficiencies. Clin Exp Immunol 2008; 152:274–9.

43 Borte M, Pac M, Serban M et al. Efficacy and safety of Hizentra®, a new 20% immunoglobulin preparation for subcutaneous administration, in pediatric patients with primary immunodeficiency. J Clin Immunol 2011; 31:752–61.

44 Gregory R, Malcolmson C, Patel C, Woolley T, Jones A. Experience with a 20% subcutaneous immunoglobulin (Hizentra) in children with primary immunodeficiency diseases – a single-center review. J Allergy Clin Immunol 2013; 131:AB154.

45 Lawo J-P, Hubsch A, Rojaev M. Quantification of the wear-off effect towards the end of the intravenous immunoglobulin infusion interval: pooled data analysis. J Allergy Clin Immunol 2014; 133:AB179.

46 Berger M. Clinical focus on primary immune deficiencies: subcutaneous IgG replacement therapy in immune deficiency diseases. Immune Deficiency Foundation, Towson, MD, USA, 2008:1–12.

47 Jolles S, Sleasman JW. Subcutaneous immunoglobulin replacement therapy with Hizentra®, the first 20% SCIG preparation: a practical approach. Adv Ther 2011; 28:321–33.

48 Jolles S, Stein MR, Longhurst HJ et al. New frontiers in subcuteaneous immunoglobulin treatment. Biol Ther 2011; 1:3–18.

49 Steihm ER. Adverse effects of human immunoglobulin therapy. Transfus Med Rev 2013; 27:171–8.

50 Ballow M, Bullinger A, Murphy E, Berger M. Immunologists’ attitudes on ‘wear-off’ effects of IgG replacement therapy for primary immunodeficiency disease (PIDD) patients. J Allergy Clin Immunol 2013; 131:AB156.

51 Orange JS, Hossny EM, Weiler CR et al. Use of intravenous immunoglobulin in human disease: a review of evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology. J Allergy Clin Immunol 2006; 117:5525–53.

52 Hogy B, Keinecke HO, Borte M. Pharmacoeconomic evaluation of immunoglobulin treatment in patients with antibody deficiencies from the perspective of the German statutory health insurance. Eur J Health Econ 2005; 6:24–9.

53 Gardulf A, Moller G, Jonsson E. A comparison of the patient-borne costs of therapy with gamma globulin given at the hospital or at home. Int J Technol Assess Health Care 1995; 11:345–53.

54 Ducruet T, Levassure MC, Des Roches A, Kafal A, Dicaire R, Haddad E. Pharmacoeconomic advantages of subcutaneous versus intravenous immunoglobulin treatment in a Canadian pediatric center. J Allergy Clin Immunol 2013; 131:585–7.
75 Martin A, Lavoie L, Goetgheuer M, Schellenberg R. Economic benefits of subcutaneous rapid push versus intravenous immunoglobulin infusion therapy in adult patients with primary immune deficiency. Transfus Med 2013; 23:55–60.
76 Immune Deficiency Foundation. Treatment experiences and preferences of patients with primary immune deficiency diseases: first national survey. Townson, MD, USA, 2003.
77 Jolles S. The variable in common variable immunodeficiency: a disease of complex phenotypes. J Allergy Clin Immunol Pract 2013; 1:545–56.
78 Jolles S, Heaps A, Moody M, Jones R. The utility of anti-pneumococcal antibody measurement in patients with primary immunodeficiency receiving immunoglobulin. J Allergy Clin Immunol 2014; 133:AB68.
79 Steinh E R. Human intravenous immunoglobulin in primary and secondary antibody deficiencies. Pediatr Infect Dis J 1997; 16:696–707.
80 Sneller MC, Strober W, Eisenstein E, Jaffe JS, Cunningham Rundles C. New insights into common variable immunodeficiency. Ann Intern Med 1993; 118:720–30.
81 Ballow M, Notarangelo L, Grimbacher B et al. Immunodeficiencies. Clin Exp Immunol 2009; 158 (Suppl. 1):14–22.
82 Quartier P, Dubre M, De Blic J et al. Early and prolonged intravenous immunoglobulin replacement therapy in childhood agammaglobulinemia: a retrospective survey of 31 patients. J Pediatr 1999; 134:589–96.
83 Yong PL, Boyle J, Ballow M et al. Use of intravenous immunoglobulin and adjunctive therapies in the treatment of primary immunodeficiencies: A working group report of and study by the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology. Clin Immunol 2010; 135:255–63.
84 Immune Deficiency Foundation. Primary immunodeficiency diseases in America: 2007 – the third national survey of patients. Townson, MD, USA, 2009.
85 Wanieki J, Gardulf A, Hammarstrom L. Bioavailability of gamma-globulin after subcutaneous infusions in patients with common variable immunodeficiency. J Clin Immunol 1994; 14:90–7.
86 Shaprio R. Subcutaneous immunoglobulin therapy by rapid push is preferred to infusion by pump: a retrospective analysis. J Clin Immunol 2010; 30:301–7.
87 Shapiro RS. Subcutaneous immunoglobulin therapy given by subcutaneous rapid push vs infusion pump: a retrospective analysis. Ann Allergy Asthma Immunol 2013; 111:51–5.
88 Hoffmann F, Grimbacher B, Thiel J, Peter HH, Belohradsky BH. Home-based subcutaneous immunoglobulin G replacement therapy under real-life conditions in children and adults with antibody deficiency. Eur J Med Res 2010; 15:238–45.
89 Gardulf A, Nicolay U, Asensio O et al. Rapid subcutaneous IgG replacement therapy is effective and safe in children and adults with primary immunodeficiencies – a prospective, multi-national study. J Clin Immunol 2006; 26:177–85.
90 Gardulf A, Hansen S, Elnerson K et al. ALPI-studien Att Leva med Primär Immunbrist Vuxenrapport. Rapport 1 [The SweP1D study; to live with a primary immunodeficiency. Report regarding adults. Report 1/2007]. Stockholm: Karolinska Institutet, 2007.
91 Talecris Biotherapeutics, Inc., Research Triangle Park, NC: Grifols, USA.
92 Baxter Healthcare Corporation, Westlake Village, CA, USA.
93 Stein MR, Koterba A, Rodden L, Berger M. Safety and efficacy of home-based subcutaneous immunoglobulin G in elderly patients with primary immunodeficiency diseases. Postgrad Med 2011; 123:186–93.
94 Shapiro R. Subcutaneous immunoglobulin (16 or 20%) therapy in obese patients with primary immunodeficiency: a retrospective analysis of administration by infusion pump or subcutaneous rapid push. Clin Exp Immunol 2013; 173:365–71.
95 Thomas MJ, Brennan VM, Chapel HH. Rapid subcutaneous immunoglobulin infusions in children. Lancet 1993; 342:1432–3.
96 Church JA, Borte M, Taki H et al. Efficacy and safety of Privigen in children and adolescents with primary immunodeficiency. Pediatr Asthma Allerg Immunol 2009; 22:53–62.
97 Skull S, Kemp A. Treatment of hypogammaglobulinemia with intravenous immunoglobulin, 1973–93. Arch Dis Child 1996; 74:527–30.
98 Gardulf A, Hansen S, Elnerson K et al. ALPI-studien Att Leva med Primär Immunbrist Föräldrarapport. Rapport 2 [The SweP1D study; to live with a primary immunodeficiency. Report regarding parents], Stockholm: Karolinska Institutet, 2007.
99 Stein MR, Farnan K, Eufrasio D et al. Use of subcutaneous IgG in patients on concomitant anticoagulant and antiplatelet therapy. Immunoglobulin Nursing Society National Conference, 3–5 August, 2012, Orlando, FL, USA. Conference Proceedings.
100 Gardulf A, Andersson E, Lindqvist M, Hansen S, Gustafson R. Rapid subcutaneous IgG replacement therapy at home for pregnant immunodeficient women. J Clin Immunol 2001; 21:150–4.
101 UK Department of Health. Clinical guidelines for immunoglobulin use: update to second edition. London, UK, 2011.
102 Shapiro RS. Subcutaneous immunoglobulin: rapid push vs infusion pump in pediatrics. Pediatr Allergy Immunol 2013; 24:49–53.
103 Duff C, Ochoa D, Riley P, Murphy E, Zampelli A. Importance of ancillary supplies for subcutaneous immunoglobulin infusion: management of the local infusion site. J Infus Nurs 2013; 36:384–90.
104 American Academy of Allergy Asthma and Immunology. Guidelines for the site of care for administration of IGIV therapy. Milwaukee, WI, 2011.
105 Chapel H, Brennan V, Delson E. Immunoglobulin replacement therapy by self-infusion at home. Clin Exp Immunol 1988; 73:160–2.
106 Gardulf A, Bjorvell H, Andersen V et al. Lifelong treatment with gammaglobulin for primary antibody deficiencies: the patients’ experiences of subcutaneous self-infusions and home therapy. J Adv Nurs 1995; 21:917–27.
90 Frost GI. Recombinant human hyaluronidase (rHuPH20): an enabling platform for subcutaneous drug and fluid administration. Expert Opin Drug Deliv 2007; 4:427–40.
91 Wasserman RL, Melamed I, Stein MR et al. Recombinant human hyaluronidase-facilitated subcutaneous infusion of human immunoglobulins for primary immunodeficiency. J Allergy Clin Immunol 2012; 130:951–7.
92 European Medicines Agency (EMA). HyQvia. Summary of product characteristics, 2014.
93 HY QVIA [Immune Globulin Infusion 10% (Human) with Recombinant Human Hyaluronidase] [package insert]. US License no. 140. Westlake Village, CA, USA: Baxter Healthcare Corporation, 2014.
94 Gardulf A. Immunoglobulin treatment for primary antibody deficiencies: advantages of the subcutaneous route. BioDrugs 2007; 21:105–16.
95 Eijkhout HW, van den Broek PJ, van der Meer JW. Substitution therapy in immunodeficient patients with anti-IgA antibodies or severe adverse reactions to previous immunoglobulin therapy. Neth J Med 2003; 61:213–7.
96 Gustafson R, Gardulf A, Granert C, Hansen S, Hammarstrom L. Prophylactic therapy for selective IgA deficiency. Lancet 1997; 350:865.
97 Sundin U, Nava S, Hammarstrom L. Induction of unresponsiveness against IgA in IgA-deficient patients on subcutaneous immunoglobulin infusion therapy. Clin Exp Immunol 1998; 112:341–6.
98 Lozano-Blasco J, Martin-Mateos MA, Alsina L et al. A 10% liquid immunoglobulin preparation for intravenous use (Privigen®) in paediatric patients with primary immunodeficiencies and hypersensitivity to IVIG. Allergol Immunopathol (Madr) 2012; 42:136–41.
99 Wasserman RL, Church JA, Peter HH et al. Pharmacokinetics of a new 10% intravenous immunoglobulin in patients receiving replacement therapy for primary immunodeficiency. Eur J Pharm Sci 2009; 37:272–8.
100 Wasserman RL, Melamed I, Nelson RP et al. Pharmacokinetics of subcutaneous IgPro20 in patients with primary immunodeficiency. Clin Pharmacokinet 2011; 50:405–14.
101 Koterba A, Farnan K, Sierra C, Eufrasio D, Stein MR. Experience with subcutaneous loading of Vivaglobin® or Hizentra® in primary immunodeficiency patients naive to immunoglobulin replacement therapy. Annual Scientific Meeting of the American College of Allergy, Asthma & Immunology, November 8–13 2012, Anaheim, CA, USA. Conference Proceedings: P221.