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REVIEW

Subcutaneous Immunoglobulin Replacement Therapy with Hizentra®, the First 20% SCIG Preparation: a Practical Approach

S. Jolles · J. W. Sleasman

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ABSTRACT

To reduce the risk of infection in adults and children with primary immunodeficiencies, replacement therapy with IgG, which can be administered to patients intravenously or subcutaneously, is required. Although intravenous administration of IgG (IVIG) has been the therapy of choice in the US and widely used in Europe for many years, subcutaneous administration of IgG (SCIG) has recently gained considerable acceptance among patients and doctors. SCIG therapy achieves high and stable serum IgG levels, is well tolerated, and can be self-administered. Hizentra® (IgPro20; CSL Behring, Berne, Switzerland) is the first, ready-to-use 20% liquid preparation of human IgG specifically formulated for subcutaneous infusions. The high concentration (20%) might allow shorter infusion times due to smaller infusion volumes, with potential improvement in the convenience of SCIG therapy. Hizentra is well tolerated and has been shown to protect adult and pediatric primary immunodeficiency patients against serious bacterial infections. In addition, it is easy to handle and can be stored at a temperature up to 25°C. In summary, Hizentra is an advance in the field of immunoglobulin replacement therapy, which might offer benefits for home therapy patients.

Keywords: Hizentra; subcutaneous IgG treatment; IgG; replacement therapy; primary immunodeficiency

INTRODUCTION

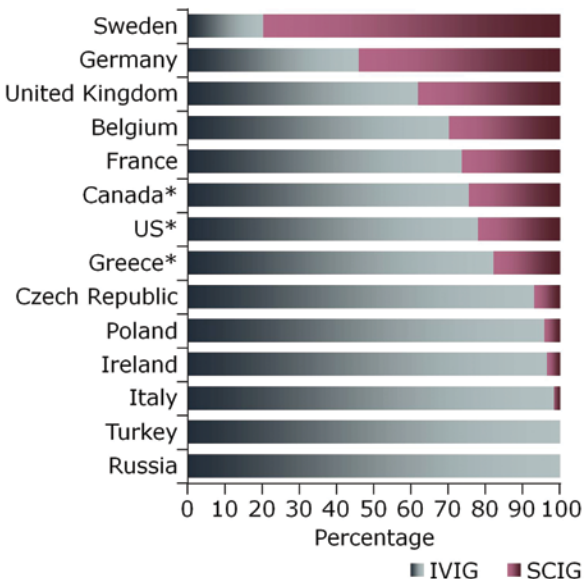
Patients with primary immunodeficiency (PI) disorders, such as common variable immunodeficiency (CVID), X-linked agammaglobulinemia (XLA), and autosomal recessive agammaglobulinemia (ARAG) that are caused by B-cell dysfunction are prone to recurrent bacterial infections.[1,2] Lifelong immunoglobulin (Ig) replacement therapy is the only effective treatment for these patients, and is thus the gold standard in the management of primary antibody deficiency.[3]

S. Jolles
Department of Medical Biochemistry and Immunology, University Hospital of Wales, Cardiff, UK

J. W. Sleasman (✉)
Department of Pediatrics, University of South Florida, St. Petersburg, FL, USA. Email: jsleasma@healthsc.usf.edu

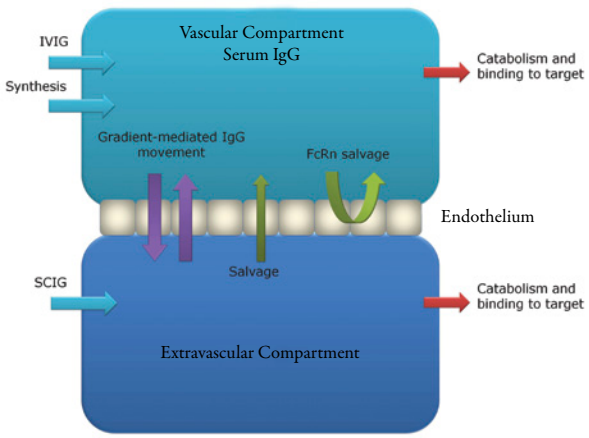
IgG can be administered subcutaneously (SCIG) or intravenously (IVIG) and was first used by Bruton in a child with agammaglobulinemia in 1952.[3] SCIG preparations were introduced in the 1980s in the US and Europe. However, the slow infusion technique and the low concentration of the preparations available at the time made SCIG impractical and less attractive to patients and healthcare professionals. Therefore, IVIG, which allowed infusions of higher monthly doses, became the preferred route of administration. Despite its success, IVIG may not be suited to all patients, especially those with poor venous access. IVIG may be associated with systemic adverse events (AEs) and IVIG self-administration is technically more demanding and requires more training than SCIG self-administration. With recent technical advances in IgG formulation, pure and highly concentrated SCIG preparations that have relatively low viscosity, and can therefore be infused relatively rapidly, have been developed and are increasingly used worldwide.[4-6] Usage of SCIG therapy varies greatly across countries and is predominant in Sweden, Germany, and the UK (Figure 1).

Figure 1. Estimated market usage of intravenous administration of IgG (IVIG) versus subcutaneous administration of IgG (SCIG) for the treatment of primary immunodeficiencies. Estimated market usage of IVIG and SCIG is shown for selected European and North American countries (CSL Behring, unpublished results). *Local marketing affiliates estimate.



While IVIG is infused every 3-4 weeks, SCIG is typically administered once a week, with the total IVIG monthly dose divided in smaller portions. The distribution of IgG between the vascular and extravascular compartments after subcutaneous administration can be described by a two-compartment model, which accurately describes the distribution of serum IgG in healthy individuals and PI patients (Figure 2).[7] In this model, IgG enters the vascular compartment (blood) from the extravascular compartment (subcutaneous space) via the lymphatics at a defined rate, which integrates IgG catabolism and total IgG distribution. This model predicts a progressive release of IgG into the circulation that contributes to the more stable serum IgG levels achieved with SCIG.

Figure 2. IgG distribution model. The serum IgG concentration depends on the rates of bidirectional movement across the endothelium, catabolism, and binding to targets. The IgG catabolism is mediated by the neonatal Fc receptor (FcRn), with FcRn-bound IgG molecules being salvaged from degradation and returned to the circulation. IVIG=intravenous administration of IgG; SCIG=subcutaneous administration of IgG.



In comparison to IVIG, SCIG results in more sustained serum IgG levels, avoiding the peaks and troughs associated with IVIG.[6,8] SCIG is associated with fewer systemic AEs than IVIG and requires no venous access.[4,6,8] Finally, SCIG is easy to use and is easier to self-administer, providing patients with flexibility and improved quality of life.[9] Patients treated with SCIG do not need to go to the hospital or infusion centers, avoiding unnecessary travel and their potential concerns for acquiring nosocomial infections. Patients require less assistance from healthcare professionals, reducing the cost associated with Ig replacement therapy, and can take greater control over their therapy. This review summarizes the available data on and practical considerations regarding the use of the subcutaneous 20% IgG preparation, IgPro20 (CSL Behring, Berne, Switzerland), currently marketed in the US under the brand name of Hizentra®. Hizentra has a good safety profile and has been shown to effectively protect PI patients from serious and non-serious bacterial infections.[10,11]

INTRODUCING HIZENTRA

Hizentra is a 20% (200 g/L) ready-to-use liquid preparation of polyvalent human IgG for subcutaneous administration that is well tolerated.[10,11] Currently, it is the only 20% SCIG therapy approved by the US Food and Drug Administration (FDA) for the treatment of PIs. The safety, tolerability, and efficacy of Hizentra have been tested in phase 1 and 3 clinical trials involving a total of 48 healthy subjects[10,12] and 100 patients.[10,11]

Formulation

Hizentra has high purity (≥98% IgG and only trace amounts of IgA; Table 1) and is formulated without preservatives.[13] In contrast to other subcutaneous IgG preparations, it is stabilized with L-proline (250 mmol/L), a nonessential natural amino acid found at high level in human plasma. The amphiphilic property of L-proline prevents the dimerization and/or aggregation of IgG molecules in the concentrated solution during storage. In addition, the presence of L-proline enables the final formulation to have a low viscosity (14.7±1.2 mPa/second), which is comparable to that of other SCIG formulations (eg, the 16% SCIG Vivaglobin®; CSL Behring, Marburg, Germany; 14.4 mPa/second) and compatible with the infusion pumps in current use.[13,14]

Table 1. Hizentra characteristics.

Characteristic	Parameter
Protein concentration	200 g/L
IgG content	≥98%
IgA content	≤50 μg/mL
L-proline	210-290 mmol/L
Polysorbate 80	10-30 mg/L
Sodium	Trace
Carbohydrate	None
Preservatives	None
Stability	Stable at room temperature (up to 25°C) for up to 24 months
Number of recommended sites/infusion	Maximum of 4
Recommended maximal volume/site	15 mL for the first four infusions; maximum 25 mL for following infusions
Recommended maximal infusion rate	15 mL/hour/site for the first infusion; maximum 25 mL/hour/site for following infusions

IgA=immunoglobulin A; IgG=immunoglobulin G.

Manufacture

Hizentra is manufactured from human plasma derived from usually more than 6000 donors by a multistep process identical to that of IgPro10

production (Privigen®; CSL Behring, Berne, Switzerland). The process includes cold ethanol fractionation, octanoic acid precipitation, and anion-exchange chromatography.[15] In order to minimize potential inadvertent transmission of blood-transmitted viruses, collected plasma donations are screened for hepatitis B, hepatitis C, human immunodeficiency virus, and B19 virus. Only donations with negative test results are used for production.[15] The manufacturing process includes steps that are specifically designed to remove/inactivate viruses over and above viral screening undertaken on all donated plasma. These steps are virus inactivation by incubation at pH 4, virus reduction by partitioning mechanisms, and virus (nano)filtration.[15] The process has been shown to have the potential for an overall reduction in known viruses ranging from $>10^7$ to $>10^{24}$, depending on the model virus tested.[15] By combining thorough virus screening of donations with rigorous manufacturing processes, the likelihood of blood-borne virus transmission is reduced to a minimum. Similarly, the manufacturing process has been shown to have a very high potential for reduction of prions, the transmissible spongiform encephalopathy agents, ranging from $>10^{10}$ to $>10^{14}$.[15] Taken together, this results in a state-of-the-art product with respect to pathogen safety.[15]

Profiling of product-related and process-related impurities includes the procoagulatory factors, factor IX and factor XIa. Testing has shown that these factors are present in the starting material, but are depleted below assay detection levels by octanoic acid fractionation. As a consequence, these factors are undetectable in the final product, minimizing their potential contribution to the risk of thromboembolic events. Current post-marketing safety data for Privigen indicate a very low incidence of thromboembolic events (CSL Behring, unpublished results). Identical post-marketing safety monitoring is in place for Hizentra. Currently, testing of procoagulatory factors or activities in IVIG/SCIG products is not a regulatory requirement for product release. However, discussions are ongoing between industry and regulatory authorities (FDA, European Medicines Agency) on the possible use of functional assays for routine measurement of thrombogenic (procoagulant) activity in IVIG/SCIG products. Such assays test the ability of a given entity to activate the intrinsic or extrinsic pathways of coagulation.

Stability

The stability of Hizentra has been tested after 24 months of storage in the dark at 5°C, 25°C, and 30°C, with regards to protein integrity, antigen-specific antibody titers, and Fc function, according to International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines.[16] Storage at up to 25°C for 24 months showed values within predefined specifications.[13] In highly concentrated IgG solutions, proteins tend to aggregate and fragment, which may result in reduced efficacy and poor tolerability. After 24 months of storage at up to 25°C, the content of aggregates in Hizentra increased from approximately <0.1% to ≤0.5% (specification: ≤4%) and the content of monomers/dimers changed from approximately 98% to approximately 95% (specification: ≥90%).[13] The content of fragments was ≤4%, which is below the specified limits of ≤10%.[13] Furthermore, long-term storage did not significantly affect antigen-specific antibody titers (eg, anti-hepatitis B, anti-streptolysin O, anti-measles, anti-polio type 1, anti-parvovirus B19, and diphtheria antitoxin), which remained

above or significantly exceeded specified levels.[13] Finally, after 24 months of storage at up to 25°C, the Fc function changed from approximately 100% to between 79% and 101% in Fc-receptor-mediated leukocyte activation assays, including assays of complement and neutrophil activation. The Fc function was therefore maintained above the specified limit of 60% upon long-term storage at up to 25°C. An extension of Hizentra shelf life to 30 months at up to 25°C was recently approved by the FDA.[17] These long-term storage qualities simplify product storage in pharmacies, at home, or during travel. In addition, as delivery can take place less frequently and a dedicated fridge is no longer needed, the cost of home delivery packages may decrease.

Indications and Additional Treatment Options for Patients

Hizentra is registered in the US, and pending approval in Europe and other countries, for treatment of PIs, which include but are not limited to congenital agammaglobulinemia, CVID, XLA, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.[18] It is also labeled for secondary immunodeficiencies in countries outside the US. SCIG is often administered only during the maintenance phase of immunoglobulin replacement therapy, while IVIG is administered during both the initiation and the maintenance phase. A recent study of Vivaglobin showed that initiation of immunoglobulin replacement treatment with SCIG therapy successfully achieved sufficiently high IgG trough levels (≥5 g/L) and was well tolerated (Borte et al., unpublished results). Although practice varies across countries, the usage of SCIG from the very beginning of replacement therapy, including the loading phase, is increasingly being used in Europe. Beside immunodeficiencies, IVIG therapy shows efficacy in the treatment of myopathies and autoimmune neurological conditions, especially multifocal motor neuropathy, chronic inflammatory demyelinating polyneuropathy, and Guillain-Barré syndrome.[19] Although there are limited data on the use of SCIG for immune modulation, SCIG was recently successfully used in maintenance therapy of multifocal motor neuropathy [20-23] and in the treatment of polymyositis and dermatomyositis.[24] The range of therapeutic areas in which SCIG could be applied successfully during the maintenance phase is therefore expanding beyond immune replacement therapy for primary antibody deficiency into immunomodulation. However, it remains to be elucidated whether the high peaks of IgG levels following IVIG infusions are required to achieve remission in these diseases.

Efficacy

Two prospective, open-label, multicenter, single-arm, phase 3 clinical trials, one performed in the US and one in Europe, evaluated the efficacy and safety of Hizentra in patients with PI over 60 and 40 weeks, respectively.

In the US clinical trial, 49 CVID or XLA patients, who were previously successfully treated with monthly IVIG infusions, were switched to weekly SCIG self-infusions.[10] The trial consisted of a 12-week wash-in/wash-out period, followed by a 48-week efficacy period. At the beginning of the efficacy period, doses were adjusted individually to 1.53 times the IVIG dose to achieve areas under the concentration-time curves (AUCs) for serum IgG that were comparable to the AUCs obtained with previous IVIG treatment, in line with FDA requirements. The dose adjustment coefficient of 1.53 had been specifically determined

for Hizentra in a pharmacokinetic substudy included in this trial.[25]

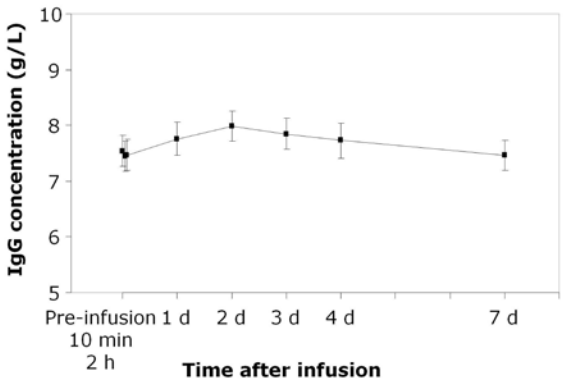
In the European trial, 51 PI patients previously on stable IVIG or SCIG therapy switched to weekly self-administration of Hizentra at monthly doses equivalent to their previous treatment. A 12-week wash-in/wash-out period was followed by a 28-week efficacy period completed by 43 patients, including 16 patients below the age of 12 years. A pharmacokinetic substudy was conducted in 18 patients to determine the variation in steady-state serum IgG concentrations between infusions.

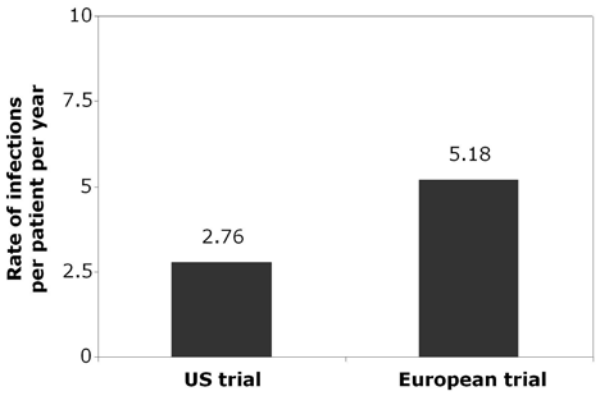
Weekly subcutaneous administration of Hizentra to PI patients resulted in serum IgG levels within the normal range. The mean IgG trough levels during the efficacy period of the two clinical trials were within the range found in healthy individuals (mean level: 12.5 g/L in the US study and 8.1 g/L in the European study).[10,11,26,27] In addition, the pharmacokinetic substudy of the European trial showed that serum IgG levels remained stable between SCIG infusions (Figure 3).[11]

Figure 3. Serum IgG concentrations during one Hizentra dosing interval in the European trial. Mean and standard error of the serum IgG concentrations measured during 1 week are shown. Samples were collected up to 30 minutes before the start of the infusion (preinfusion), 10 minutes prior to the end of the infusion (10 minutes), 2 hours after the end of the infusion (2 hours), and after 1, 2, 3, 4, and 7 days.[11]

In keeping with the high and sustained serum IgG levels, no serious bacterial infections (SBIs) occurred during the efficacy period of the two studies.[10,11] One pediatric patient in the European study experienced pneumonia, qualified as an SBI, during the wash-in/wash-out period, on a background of historical recurrent pulmonary infections.[11] The rate of any infections was 2.76 events/patient/year in the US trial and 5.18 events/patient/year in the European trial (Figure 4).[10,11] Consistent with the low incidence of infections, the rate of days missed from work/school was 2.06 days/patient/year and 8.00 days/patient/year in the US and European trials, respectively, and the rate of days spent in hospital was 0.2 days/patient/year and 3.48 days/patient/year, respectively.[10,11] Direct comparison of these results is not possible because the studies were not powered to determine dose-related differences in clinical outcomes. Moreover, a number of factors, such as country-specific medical practices for diagnosing infections, cultural differences relating to absence from work/school, and the higher number of children in the European

Figure 4. Rates of infections in primary immunodeficiency patients treated with Hizentra. The rates of any infections reported in the US trial[10] and in the European trial[11] are shown. No serious bacterial infections occurred during the efficacy period of either trial.





study may have contributed to the differences in efficacy results obtained. Despite differences in the two clinical trials, both studies demonstrated that Hizentra achieved clinical efficacy in patients with PI, with stable and physiologically relevant serum IgG levels.

Safety

Hizentra is well tolerated by PI patients.[10,11] Most AEs reported in both phase 3 clinical trials were of mild or moderate intensity.[10,11] As expected with subcutaneous infusions, the most common AEs were local injection site reactions, with rates of 0.580 events/infusion and 0.060 events/infusion in the US and European trials, respectively.[10,11] Patients' tolerability to local reactions improved over time. Systemic AEs, such as headache, fatigue, and nausea were relatively rare. For example, the rate of headache was 0.018 events/infusion in the US trial and 0.029 events/infusion in the European trial. No serious AEs were considered related to Hizentra treatment.

CONSIDERATIONS FOR USING HIZENTRA

Hizentra introduces a number of important potential benefits to IgG replacement therapy. Several of these are described below.

Convenient Storage at Room Temperature

Hizentra can be stored at up to 25°C for up to 30 months without compromising its safety and biological activity, bringing a number of benefits to patients and healthcare professionals.[13] First, the need to maintain refrigeration facilities at hospitals or doctor's offices is obviated for many countries, and storage at home is easier for patients, especially when several months worth of immunoglobulin is delivered at once. Second, patients may not need to wait for the solution to warm up before infusion, reducing the overall duration of an infusion. Finally, with its high stability at 25°C, Hizentra could easily be transported, increasing flexibility for patients when they travel.

Reduced Infusion Duration

The high IgG content (200 g/L) and relatively low viscosity influence the volume and duration of infusion.[13] Currently, 16% IgG preparations, such as Vivaglobin, are infused at 10-20 mL per hour.[6,8] Hizentra was infused at a median infusion rate of 25.3 mL/hour in the recent European study, and rates as high as 35.0 mL/hour were used in 34.8% of patients.[11] In the US study, the median infusion rate was 39.1 mL/hour, with a maximum infusion rate of 50 mL/hour for all simultaneously used sites.[10] The high infusion rates, as well as the small volume required, led to a short duration of weekly infusions, with median values ranging from 1.14 to 1.27 hours[11] and from 1.6 to 2 hours.[10]

Benefits for Pediatric Patients

SCIG therapy is particularly attractive for pediatric patients because it does not require venous access and because it is relatively free of systemic AEs. It was previously shown that a young infant with XLA was successfully switched from IVIG to SCIG with no SCIG-related AEs reported.[28] Pediatric patients have been treated successfully with SCIG in several studies.[29-32] Hizentra may be especially well suited to pediatric patients because the 20% concentration allows the delivery of the required dose in a smaller volume. The efficacy and safety of Hizentra in 23 pediatric patients was assessed in the European phase 3 clinical trial (Borte et al., unpublished results). A total of 21 pediatric patients, including 16 children

(age, 2-11 years) and five adolescents (age, 12-15 years), completed the efficacy period of this trial. As four out of five adolescents were previously treated with SCIG, the mean serum IgG trough level achieved in adolescents was comparable to that at study start (from 7.99 g/L to 7.91 g/L) (Borte et al., unpublished results). In contrast, with two-thirds of the children previously treated with IVIG, the mean IgG trough level increased by 13.3% (from 6.94 g/L to 7.86 g/L) in children (Borte et al., unpublished results). No SBI occurred during the efficacy period.

Low rates of local injection site reactions were observed in children (0.040 events/infusion) and adolescents (0.035 events/infusion) (Borte et al., unpublished results). In addition, excluding local reactions, the rate of AEs was lower in children (0.158 events/infusion) and adolescents (0.206 events/infusion) than in adults (0.282 events/infusion). Treatment of pediatric patients with Hizentra was well tolerated and effective in protecting them from infections without any specific dose adjustment of the previous IVIG dose (Borte et al., unpublished results).

Health-Related Quality of Life (HRQL) and Self-administration

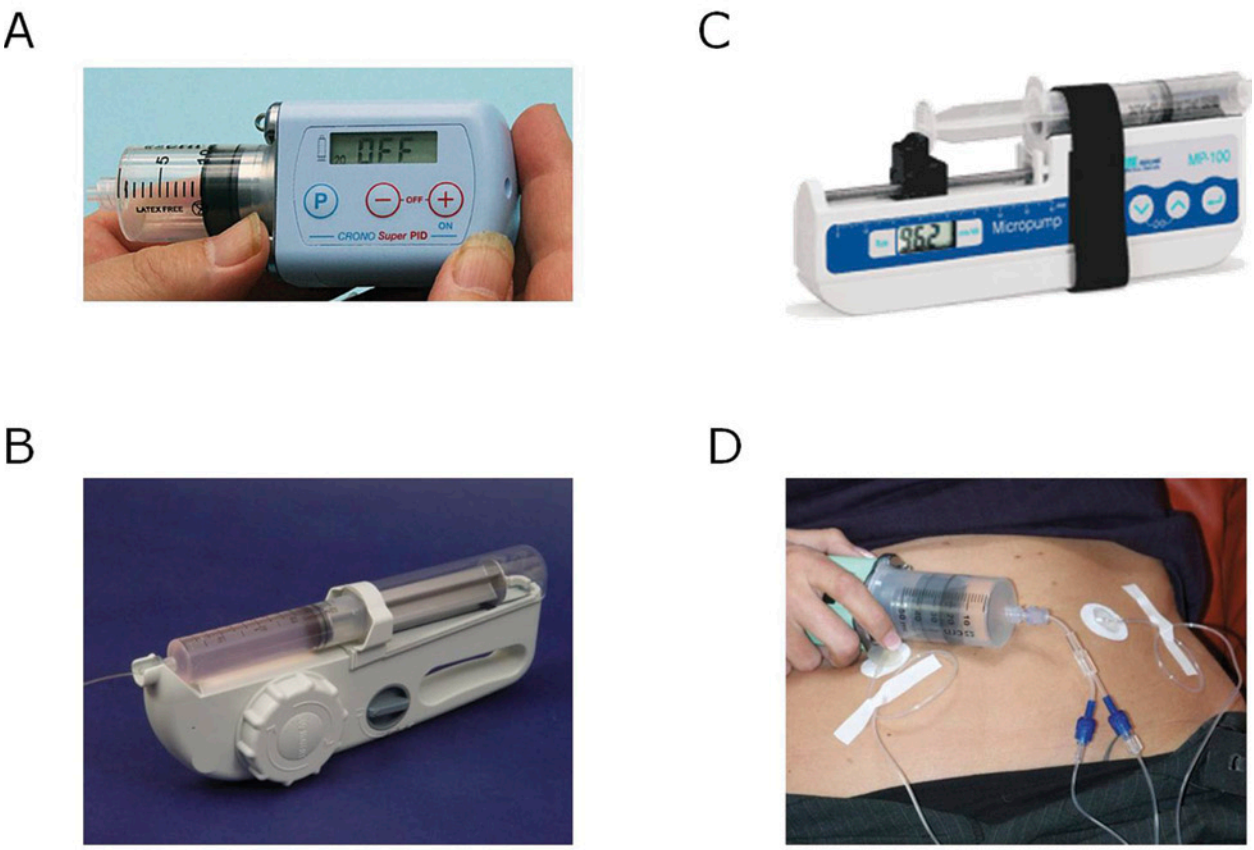
The poor HRQL of untreated patients with PI was markedly improved by SCIG therapy,[33] and further improved by home therapy with SCIG.[4,9] Home therapy allows patients to have more control over their treatment, giving them a sense of responsibility and independence. In addition, patients have the choice to schedule their infusions at a time that is most convenient for them, limiting the disruption of their daily activities.

The impact of Hizentra on HRQL of PI patients was investigated in the European phase 3 clinical trial.[11] The patients enrolled in this trial had been previously treated with either IVIG (29 patients) or SCIG (19 patients) and switched to weekly doses of Hizentra. At baseline, the HRQL, as assessed by the Life Quality Index and Treatment Satisfactory Questionnaire for Medication, was better in patients previously on SCIG than in those previously on IVIG. After switching to Hizentra, the HRQL remained stable for the former and improved for the latter, with a statistically significant change in median Treatment Satisfactory Questionnaire for Medication domain score for "convenience" (from 55.6 at baseline to 83.3 at study end; 95% CI: 22.2, 38.9). These results support previous data on the positive impact of SCIG therapy on HRQL in PI patients, when compared to IVIG therapy.[34-37] This is also reflected in the clinical practice in Cardiff, UK, where more than 80% of new PI patients choose SCIG over IVIG (unpublished data). The impact of Hizentra on HRQL compared to other SCIG therapies is currently being investigated in greater detail in patients treated with SCIG and transitioning to Hizentra.

Equipment Required for Hizentra Infusion

SCIG preparations can be infused with conventional infusion pumps, such as Crono Super-PID infusion, FREEDOM60 Syringe Infusion System (Repro-Med Systems, Inc., NY, USA), Micrel Micropump MP™ (Micrel Medical Devices S.A., Athens, Greece), or Cane Crono PCA-50 (Figure 5). In the European trial, Cane Crono PCA-50 or Super-PID infusion pumps (Cane S.R.L., Turin, Italy) were used to infuse Hizentra, while, in the US trial, Cane Crono PCA-50 pumps were used. In the clinical practice at Cardiff, UK, Crono pumps have become the standard for new patients commencing SCIG infusions, and are specified with the home care packages provided. In the US, the FREEDOM60 Syringe Infusion System is most often used. This system is simple, reliable, and does not depend

Figure 5. Pumps for subcutaneous administration of IgG (SCIG) infusions and SCIG infusion. (**A**) Crono Super-PID infusion. (**B**) FREEDOM60 Syringe Infusion System. (**C**) Micrel Micropump MP. (**D**) Photo of subcutaneous infusion with a Cane Crono PCA-50 pump. *Reproduced with the kind permission of OMT GmbH & Co. KG.*



on batteries or electrical outlets. Infusions are given through a 91.4-cm (36-inch) bifurcated tubing system with a 27-gauge needle that is 6, 9, or 12 mm in length. A common cause of site-associated AEs with SCIG is using shorter, 6 mm needles in adults leading to intradermal rather than subcutaneous infusion.

An emerging alternative to conventional pump-assisted SCIG infusion is the frequent push technique with one to seven infusions per week. This technique consists of the more frequent manual infusion of small portions of the weekly dose using a syringe and a 23-25-gauge butterfly needle. A recent retrospective analysis in PI patients treated with Vivaglobin showed that, if the same weekly dose is used, both techniques are equivalent in terms of serum IgG levels and safety.[38] As no pump or tubing is required with the frequent push technique, the cost and time for equipment maintenance are considerably reduced, making this approach attractive to patients and insurance companies.

Training for Self-administration of Hizentra

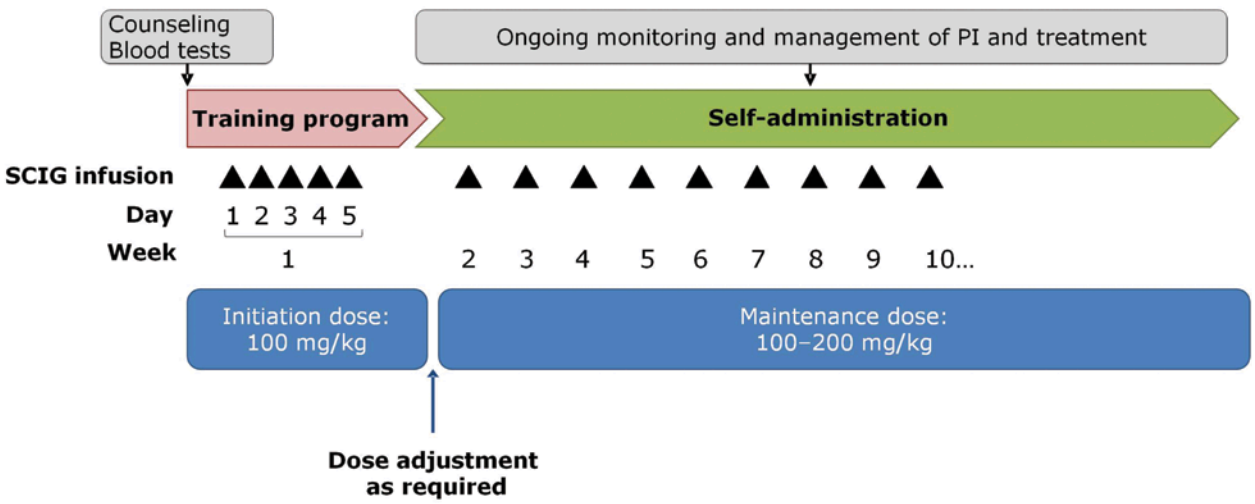
At the beginning of the two phase 3 clinical trials, training sessions were conducted at the study sites to teach patients how to self-infuse and to teach parents of pediatric patients how to perform SCIG infusions on their child.

Self-infusion was not reported as being difficult and no patients were discontinued from either trial because of technical difficulties.[10,11] As with other SCIG products, self-infusion with Hizentra was shown to be easy to learn. In clinical practice, the duration and modalities of training programs for SCIG self-infusion may vary from country to country. In Cardiff, UK, the training, supervised by healthcare personnel, consists of six infusions at the day care unit of the University Hospital of Wales, with the procedures being increasingly managed by the patient. The nursing team then visits the patient at home for their first independent home infusion and ensures that the patient is confident with the procedure. In the US, the training takes place at the doctor's office or at the patient's home with the help of nurses skilled in SCIG administration. During the training sessions, the selection of proper subcutaneous needle gauge and length, the selection of infusion sites, the management of local adverse reactions, and the use of the infusion equipment including aseptic infusion skills and proper disposal of infusion materials are reviewed. Generally, patients can independently self-infuse SCIG doses after three to four training sessions, and a protocol to initiate and monitor patients with Hizentra is proposed (Figure 6). For previously untreated patients, the initial loading phase of five daily subcutaneous infusions of 100 mg/kg affords the opportunity to rapidly train patients for subsequent home therapy. During the maintenance phase, patients self-administer their SCIG dose at home each week. Monitoring and management of the disease and treatment would occur at a frequency appropriate for each patient (Figure 6).

Doses

For the treatment of PIs, dose adjustment when switching from IVIG to SCIG therapy is still a matter of debate. In the European Hizentra study, doses equivalent to previous IVIG doses were administered according to the clinical practice in Europe.[11] In contrast, the US Hizentra study aimed to achieve AUCs similar to that of previous IVIG treatment.[10] Therefore,

Figure 6. Proposed model for treatment of primary immunodeficiency patients with Hizentra. Infusions occur daily during the initiation phase and weekly during the maintenance phase. The training program may vary in length from country to country and will include training on pump use.



in this trial, Hizentra doses were adjusted at the beginning of the efficacy period either individually or using a mean dose adjustment coefficient of 1.53, and thus the resulting doses were 1.49 times higher than the doses during previous IVIG therapy.[25]

The European study showed that using doses equivalent to previous IVIG doses resulted in a 17.7% increase in serum IgG levels in patients switching from IVIG to SCIG, and protected patients from SBIs, suggesting that a dose adjustment coefficient of 1.53 is not required.[11]

While stable serum IgG levels, in the physiological range of immunocompetent individuals, were achieved in both studies, these studies alone were not powered to answer the independent question regarding the level of serum IgG required to provide optimal protection from infections overall.[10,11] However, published data on immunoglobulin replacement therapy, including the two Hizentra clinical trials, support a linear correlation between serum IgG trough level and infection rate, with higher trough levels associated with fewer infections.[6,8,10,11,25,39,40]

While there is increasing evidence for improvements in outcomes associated with increasing trough levels up to a level of 10 g/L, it is important to base the optimization of dose on the overall clinical assessment of individual patients rather than the steady state IgG level alone.[10,11,40] Clinical indicators of efficacy include the frequency of sinopulmonary infections, the frequency and duration of antibiotic therapy, and the overall well-being of the patient.

Prevalence and Management of AEs Associated with SCIG

In comparison to IVIG therapy, a major advantage of SCIG therapy is the very low frequency of systemic AEs, such as headaches, nausea, and fatigue.[6,8,10,41] Most systemic AEs following IVIG occur during the infusion or within 48 hours post infusion, when the serum IgG level is increasing or near its peak. With less variable serum IgG levels, SCIG therapy is relatively free of systemic AEs. All systemic AEs related to Hizentra administration were mild or moderate in intensity.[10,11]

Local injection site reactions, typically associated with SCIG therapy, may include edema, erythema, and itching, which, if treatment is required, can usually be managed easily with antihistamines and analgesics. These local AEs are generally mild and transient, and mainly require no intervention. In addition, the proportion of patients experiencing AEs tends to decline over time, as patients become accustomed to the product and procedure.[6,10,41] Most local reactions after Hizentra administration were also mild and showed a decreasing frequency over time.[10]

Overall, Hizentra is well tolerated by patients, with regards to both local and systemic reactions, making this product ideal for self-administration.

CONCLUSION

Clinical research and clinical practice have shown that SCIG therapy is effective and well tolerated in patients with PI. With its short infusion duration and stability at up to 25°C, Hizentra, a new 20% SCIG preparation, represents a further advance in the field of SCIG therapy for patients with PI, including pediatric patients and frequent travelers.

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