

# Immune Globulin Subcutaneous (Human) 20%

## In Primary Immunodeficiency Disorders

Paul L. McCormack

Adis, Auckland, New Zealand

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### Abstract

Immune globulin subcutaneous 20% is a new high-concentration (200 g/L) solution of highly purified human IgG ( $\geq 98\%$ ) indicated in the EU and the US for antibody replacement therapy in patients with primary immunodeficiency with antibody deficiency, and in the EU for replacement therapy in humoral immunodeficiency secondary to myeloma or chronic lymphocytic leukaemia.

Immune globulin subcutaneous 20% is formulated with L-proline, which imparts long-term stability at room temperature and a relatively low viscosity.

In two pivotal phase III trials in stably treated patients with primary immunodeficiency, immune globulin subcutaneous 20% at weekly subcutaneous dosages either equivalent to each patient's previous intravenous or subcutaneous replacement therapy, or providing equivalent systemic exposure to previous intravenous therapy, produced mean serum IgG trough levels equal to or greater than pre-study levels. In each trial, there were no serious bacterial infections during treatment throughout the 28-week or 12-month efficacy periods. The rates of infectious episodes, days missed from work/school, days hospitalized or days with antibiotics were low.

Immune globulin subcutaneous 20% was generally well tolerated. A high proportion of patients experienced local infusion-site reactions, but infusion-related systemic adverse events were relatively infrequent. Most adverse events were of mild or moderate intensity and did not interfere with therapy.

#### Features and properties of immune globulin subcutaneous (human) 20% (Hizentra<sup>®</sup>)

Features and properties of immune globulin subcutaneous (human) 20% (Hizentra <sup>®</sup> )	
<b>Indication</b>	
Primary immunodeficiency with antibody deficiency, and secondary humoral immunodeficiency	
<b>Mechanism of action</b>	
Antibody replacement therapy	
<b>Dosage and administration</b>	
Dose	Individualized (cumulative monthly dose of $\approx 0.4$ – $0.8$ g/kg at steady state, adjusted for clinical response)
Route of administration	Subcutaneous infusion
Frequency of administration	Initially weekly, but flexible
<b>Mean steady-state pharmacokinetic properties of immune globulin subcutaneous 20% in patients (n = 23) of mean age 20.6 (range 6–49) y with primary immunodeficiency receiving a mean weekly subcutaneous dose of 118.7 mg/kg bodyweight; conducted as a sub-study of a phase III European clinical trial</b>	
Peak serum IgG concentration (C <sub>max</sub> )	8.26 g/L
Time to C <sub>max</sub>	2.06 days
Trough serum IgG concentration	7.5 g/L
Area under the serum IgG concentration-time curve from time zero to 7 d	53.7 g • d/L
<b>Most common (&gt;5% of patients) causally related adverse events</b>	
Local infusion-site reactions, headache, injection site bruising, pruritus, vomiting, pain, fatigue, pyrexia	

Primary immunodeficiency disorders with antibody deficiency, such as X-linked agammaglobulinaemia, common variable immunodeficiency and severe combined immunodeficiency, are caused by genetic mutations that result in B-cell dysfunction (or combined T- and B-cell dysfunction) and inadequate antibody production.<sup>[1]</sup> Humoral immunodeficiency may also be secondary to immunosuppressive drug therapy or diseases, such as myeloma and lymphocytic leukaemia, that severely impair antibody production by B cells.<sup>[1]</sup> Primary immunodeficiency may manifest in childhood or adulthood, and those with antibody deficiency are prone to recurrent bacterial infections, particularly sinusitis and other respiratory tract infections.<sup>[1]</sup> While avoidance of exposure to infection and the use of antibiotics are useful in limiting morbidity, lifelong routine immunoglobulin (antibody) replacement therapy is the only effective treatment for patients with primary immunodeficiency with antibody deficiency.<sup>[2]</sup>

Intravenous administration of gammaglobulin (IgG) has been the gold standard therapy and allows the administration of high doses of IgG.<sup>[3]</sup> However, subcutaneous administration has become widely accepted, with the development of more concentrated, lower viscosity solutions that allow relatively rapid subcutaneous administration of high concentrations of IgG.<sup>[2]</sup> Intravenous administration requires venous access, is technically more difficult and is associated with more systemic adverse events than subcutaneous administration as a result of the more rapid introduction of IgG into the circulation.<sup>[2,4]</sup> Weekly subcutaneous administration provides relatively stable serum IgG levels across the dose interval and avoids the widely different peak and trough levels associated with intravenous administration once every 3–4 weeks.<sup>[2]</sup>

IgG replacement therapy has been shown to improve patients' health-related quality of life (HR-QOL) to a level similar to that of healthy subjects, while subcutaneous IgG therapy has been reported to provide better HR-QOL than previous intravenous or intramuscular therapy.<sup>[5]</sup> The convenience of self-infusion at home makes subcutaneous IgG therapy the preferred option for many patients.<sup>[5]</sup>

Immune globulin subcutaneous 20% (Hizentra®) is a new, stable 20% solution (200 g/L) of highly purified human IgG designed for rapid subcutaneous infusion. It is indicated in the EU and US for antibody replacement therapy in patients with primary immunodeficiency with antibody deficiency, and in the EU for patients with immunodeficiency secondary to myeloma or chronic lymphocytic leukaemia. Until now, existing subcutaneous preparations have been 16% solutions.

This article reviews the efficacy and tolerability of immune globulin subcutaneous 20% in the treatment of patients with immunodeficiency disorders involving antibody deficiency and overviews its pharmacological properties. Medical literature (including published and unpublished data) on the use of immune globulin subcutaneous 20% in primary or secondary immunodeficiency disorders with antibody deficiency was identified by searching databases for studies published since 1996 (including MEDLINE and EMBASE), bibliographies from published literature, clinical trial registries/databases and websites (including those of regional regulatory agencies and the manufacturer). Additional information (including contributory unpublished data) was also requested from the company developing the drug. Searches were last updated 4 May 2012.

## 1. Pharmacodynamic Profile

- Immune globulin subcutaneous 20% is a high-concentration (200 g/L) liquid preparation of polyvalent human IgG ( $\geq 98\%$  purity) designed for subcutaneous administration.<sup>[2,6]</sup> It is free of preservative and is formulated with L-proline (250 mmol/L) for stability; L-proline's amphiphilic properties minimize IgG aggregation and degradation, as well as lower the viscosity of this high-concentration IgG solution. Immune globulin subcutaneous 20% also contains low amounts of Polysorbate 80 (20  $\mu\text{g}/\text{mL}$ ) to improve the visual appearance.<sup>[2,6,7]</sup> It was shown to be stable during storage in the dark at 25°C for  $\geq 24$  months; the proportion of monomers/dimers remained above 95% and the proportion of polymers/aggregates remained below 1% at 24 months.<sup>[7]</sup> The licensed shelf life is 30 months at room temperature.<sup>[8]</sup>

- Immune globulin subcutaneous 20% is usually prepared from pooled plasma from  $\geq 1000$  donors and contains a broad range of IgG antibodies found in the normal population.<sup>[8]</sup> The distribution of IgG subclasses is very similar to that of normal plasma: 68% IgG1, 28% IgG2, 2% IgG3 and 1% IgG4.<sup>[6]</sup> IgA is only present in trace amounts ( $\leq 50 \mu\text{g/mL}$ ).<sup>[2]</sup>

- All donor plasma is routinely screened for known transmissible viral pathogens and rejected if positive.<sup>[9]</sup> Virus inactivation and filtration steps in the production of immune globulin subcutaneous 20% result in 18–24  $\log_{10}$  reductions in enveloped viruses and  $>7-9 \log_{10}$  reductions in nonenveloped viruses, thereby effectively inactivating or removing known and emerging pathogens.<sup>[6,10]</sup> The production process was also shown to have a very high reduction potential for prions ranging from  $>10$  to  $>14 \log_{10}$  reduction.<sup>[11]</sup>

- A pooled analysis of seven studies using four different subcutaneous immunoglobulin preparations was not able to show a correlation between mean steady-state serum IgG trough levels achieved during therapy (8–12.5 g/L) and the annualized rate of serious bacterial infections (SBIs), since the number of episodes was very low (0–0.067 episodes/patient/year).<sup>[12]</sup> However, mean steady-state serum IgG trough levels were shown to correlate inversely with the annual number of infections other than SBIs (2.8–5.2 episodes/patient/year; correlation coefficient  $r = -0.812$ ,  $p = 0.027$ ).<sup>[12]</sup> In contrast, a meta-analysis of studies in patients with primary immunodeficiency administered intravenous immunoglobulin demonstrated an inverse correlation between serum IgG trough levels up to at least 10 g/L and the incidence of pneumonia.<sup>[13]</sup> The incidence of pneumonia decreased by 27% for each 1 g/L increase in trough IgG levels.

## 2. Pharmacokinetic Profile

Information on the pharmacokinetic properties of immune globulin subcutaneous 20% derive primarily from pharmacokinetic sub-studies<sup>[3,14]</sup> of the pivotal phase III efficacy trials conducted in Europe and the US (see section 3 for trial design details).

- Unlike intravenous immunoglobulin therapy administered every 3–4 weeks, which typically produces widely different peak ( $>10 \text{ g/L}$  for a 200–600 mg/kg dose) and trough ( $\geq 5 \text{ g/L}$ ) serum IgG levels during each dose interval,<sup>[15]</sup> weekly subcutaneous administration produces relatively stable mean serum IgG levels throughout the dose interval.<sup>[3]</sup> Therefore, serum IgG trough levels with subcutaneous therapy are higher than with intravenous therapy at the same effective dosage. This was demonstrated in a study of 65 patients with primary hypogammaglobulinaemia on stable intravenous immunoglobulin replacement therapy who were switched to subcutaneous therapy (three different 16–16.5% formulations); mean serum IgG trough levels were increased from baseline by 5.4% (8.82 vs 8.37 g/L) after 12 months of subcutaneous therapy despite a 28.3% reduction in mean weekly IgG dosage (108 vs 151 mg/kg/wk).<sup>[16]</sup>

- In a 1-week pharmacokinetic sub-study ( $n = 23$ ) of immune globulin subcutaneous 20% conducted at week 28 of the European phase III trial, the mean peak serum IgG level (8.26 g/L) was achieved at 2.06 days and then declined slightly to 7.5 g/L at 7 days, just prior to the next dose.<sup>[3]</sup> The area under the serum concentration-time curve (AUC) from time zero to 7 days was 53.7 g  $\cdot$  d/L.<sup>[3]</sup>

- In a pharmacokinetic sub-study ( $n = 19$ ) of the US phase III trial of immune globulin subcutaneous 20%, it was determined that the dose of immune globulin subcutaneous 20% equivalent to the weekly dose of previous intravenous therapy (156.1 mg/kg/wk) would need to be multiplied by 1.53 (i.e. 234 mg/kg/wk) to attain the same 7-day AUC (103.2 g  $\cdot$  d/L) as that of the previous intravenous immunoglobulin therapy (as required by the US FDA).<sup>[14]</sup>

- In this study, serum IgG levels reached steady state by weeks 9–12 of subcutaneous therapy and, after adjusting the dosage using the dosage adjustment coefficient of 1.53, the geometric ratio of AUCs for immune globulin subcutaneous 20% versus the previous intravenous immunoglobulin therapy was 1.002 (lower one-sided 95% confidence limit [CL] 0.951) which met the prespecified criteria for noninferiority (lower 95% CL  $\geq 0.8$ ) and indicated a bioavailability of 65.5% for subcutaneous relative to intravenous administration.<sup>[4,14]</sup>

- Immune globulin subcutaneous 20% attained peak serum levels at a mean time of 2.933 days and maintained a relatively stable serum IgG level with mean peak and trough values of 16.2 and 13.7 g/L compared with mean peak and trough levels of 25.6 and 11.2 g/L with previous intravenous therapy.<sup>[14]</sup> The mean 7-day AUC was 105.6 g • d/L.
- Subcutaneously administered IgG is catabolized at a rate similar to that of intravenously administered IgG, which has been shown to have a mean half-life of  $\approx$ 43 days.<sup>[6]</sup> Hence, only a small proportion of an administered dose is catabolized during a 7-day dosage interval, as noted with the relatively stable serum levels observed over 7 days following an infusion.<sup>[3]</sup>
- In both the European and the US trials, the levels of specific antibodies tested at the end of the dosing interval remained well above the levels considered protective for anti-measles antibodies, anti-*Haemophilus influenzae* type B antibodies and anti-tetanus antibodies.<sup>[3,14]</sup> Anti-*Streptococcus pneumoniae* antibodies were likewise well above the recommended protective level in the US trial,<sup>[14]</sup> but were only just within the protective range in the European trial.<sup>[3]</sup>
- In both the European and the US trials, the elevated L-proline serum levels observed immediately after the infusions were rapidly cleared, returning to pre-infusion levels within  $\approx$ 1 day, and did not accumulate in the circulation.<sup>[3,14]</sup>

### 3. Therapeutic Efficacy

The efficacy of immune globulin subcutaneous 20% in the treatment of primary immunodeficiency disorders involving B-cell dysfunction has been assessed in two phase III, noncomparative, multicentre trials conducted in Europe<sup>[3]</sup> and the US;<sup>[17]</sup> these were the pivotal studies supporting the respective licensing applications for immune globulin subcutaneous 20% in the EU and the US. In each trial, after the first three supervised infusions, patients self-administered immune globulin subcutaneous 20% at home using infusion pumps (e.g. 15–25 mL/infusion using multiple sites and at a rate of  $\leq$ 25 mL/h per site [US] or a total body rate of  $\leq$ 35 mL/h [Europe]), although, at least initially, every fourth infusion was per-

formed under supervision during a clinic visit. The trials differed in several respects according to the specific requirements of the respective regulatory agencies. For example, with respect to dosage of immune globulin subcutaneous 20%, the European Medicines Agency (EMA) simply required that serum IgG trough levels obtained with immune globulin subcutaneous 20% were noninferior to those observed with the patients' existing licensed immune globulin products, while the US FDA required that dosages be increased to compensate for the lower bioavailability of subcutaneous immunoglobulin preparations compared with previous intravenous immunoglobulin therapy.<sup>[4]</sup>

Efficacy endpoints in both trials included the annualized rate of SBIs, number of infection episodes, number of days missed from work/school (including kindergarten/daycare or being unable to perform normal activities) as a result of infection, number of days of hospitalization due to infection and days of antibiotic use for the treatment or prophylaxis of infection, and serum IgG trough levels compared with pre-study levels.<sup>[3,17]</sup> SBIs were defined as bacterial pneumonia, bacteraemia/septicaemia, osteomyelitis/septic arthritis, bacterial meningitis and visceral abscess.<sup>[3,17]</sup>

In addition, 21 patients who completed the phase III US trial entered an extension study and received open-label treatment with immune globulin subcutaneous 20% for an additional median duration of 87 (range 11–104) weeks.<sup>[18,19]</sup>

#### European Clinical Trial

The trial conducted in Europe consisted of a 12-week run-in period followed by a 28-week efficacy assessment period.<sup>[3]</sup> Enrolled patients had common variable immunodeficiency or X-linked agammaglobulinaemia as defined by the Pan-American Group for Immunodeficiency (PAGID) and the European Society for Immunodeficiencies (ESID),<sup>[20]</sup> or autosomal recessive agammaglobulinaemia. Patients were required to be on stable intravenous (administered every 3–4 weeks) or subcutaneous (weekly) immunoglobulin therapy at a dosage of 200–800 mg/kg/month during the previous 6 months and with  $\geq$ 3 documented serum

IgG trough levels of  $\geq 5$  g/L.<sup>[3]</sup> Self-administered treatment with immune globulin subcutaneous 20% was initiated at a once-weekly dose equivalent to the patients' previous immunoglobulin therapy dosage, with dose adjustment permitted during the run-in period if serum IgG trough levels were  $< 5$  g/L; further dosage adjustment was not permitted during the efficacy assessment period. Fifty-one patients were enrolled, 46 patients completed the run-in period (intent-to-treat [ITT] population) and 37 patients received all 40 planned infusions.<sup>[3]</sup> The ITT population consisted of 17 children (aged 2–11 years), 5 adolescents (aged 12–15 years) and 24 adults (aged 16–64 years); the mean age was 21.5 years. Previous therapy was intravenous immunoglobulin in 27 patients and subcutaneous immunoglobulin in 19 patients.<sup>[3]</sup> The mean weekly dosage in the ITT population was 118.7 mg/kg of bodyweight (range 117–121 mg/kg). The primary efficacy endpoint was a descriptive comparison of serum IgG trough levels at weeks 12–17 of the study in the ITT population compared with three serum IgG trough levels measured while on previous therapy in the 3–6 months prior to the study.<sup>[3]</sup>

- The mean IgG level measured prior to infusions 12–17 of immune globulin subcutaneous 20% in the ITT population was 8.10 g/L compared with 7.49 g/L prior to the study (table I),

thereby meeting the primary study objective of achieving similar serum IgG trough levels.<sup>[3]</sup> The mean serum IgG trough level across the whole efficacy period (infusions 12–41) was also 8.10 g/L. The mean serum IgG trough level was maintained or increased from pre-study levels for children (7.86 vs 6.94 g/L pre-study), adolescents (7.91 vs 7.99 g/L) and adults (8.31 vs 7.81 g/L).<sup>[21]</sup>

- In the subset of patients previously receiving subcutaneous immunoglobulin, the mean serum IgG trough level for infusions 12–17 of immune globulin subcutaneous 20% was similar to the pre-study level (8.27 vs 8.43 g/L).<sup>[3]</sup> However, in patients previously receiving intravenous immunoglobulin, the mean serum IgG trough level across infusions 12–17 of immune globulin subcutaneous 20% therapy was 17.7% higher than the pre-study level (7.98 vs 6.78 g/L).<sup>[3]</sup>

- There were no SBIs during the 28-week efficacy period.<sup>[3]</sup> Thirty-six patients experienced an infectious episode, giving an infection rate of 5.18 infections/patient/year (table I). The rates for days missed from school/work, days hospitalized due to infection and days on antibiotics were also low, although higher than seen in the US trial. One child experienced three serious adverse events and as a result missed 71 days of school and spent 63 days in hospital; a secondary analysis omitting this patient was also performed (table I).<sup>[3]</sup>

**Table I.** Efficacy of immune globulin subcutaneous 20% in patients with primary humoral immunodeficiency. Results of two phase III, noncomparative, multicentre trials conducted in Europe<sup>[3]</sup> and the US<sup>[17]</sup>

Parameter	European study (n = 46) <sup>a</sup>	US study (n = 38) <sup>a</sup>
Duration of efficacy assessment period	28 wk	12 mo
Mean weekly dose of immune globulin subcutaneous 20% (mg/kg)	118.7	180–224
Mean serum IgG trough level [pre-study level] (g/L)	8.10 <sup>b</sup> [7.49]	12.53 [10.1]
Rate of SBIs (per pt/y)	0	0 <sup>b</sup>
Rate of infection episodes (per pt/y)	5.18 (5.16) <sup>c</sup>	2.76
Rate of days missed from work/school due to infection (per pt/y)	8.00 (5.25) <sup>c</sup>	2.06
Rate of days hospitalized due to infection (per pt/y)	3.48 (0.95) <sup>c</sup>	0.2
Rate of days with antibiotics for treatment or prophylaxis (per pt/y)	72.75 (66.62) <sup>c</sup>	48.5

a ITT (European study) or modified ITT (US study) population; see text for definitions.

b Primary efficacy endpoint.

c n = 45 after excluding the data for one child who experienced recurrent pneumonias.

ITT = intent to treat; pt = patient; SBIs = serious bacterial infections.

## US Clinical Trial

The US study consisted of a 12-week run-in period, followed by a 12-month efficacy assessment period in patients, aged 5–72 years, with common variable immunodeficiency as defined by PAGID and ESID,<sup>[20]</sup> or X-linked agammaglobulinaemia.<sup>[17]</sup> Patients were required to have been previously treated with intravenous immunoglobulin therapy at 3- to 4-week intervals for  $\geq 3$  months and to have had  $\geq 1$ –3 documented serum IgG trough levels of  $\geq 5$  g/L in the previous 6 months. Immune globulin subcutaneous 20% was initially administered once weekly at a dose equivalent to the average weekly dose of intravenous immunoglobulin adjusted to compensate for the lower bioavailability of subcutaneous immunoglobulin (initially multiplied by 1.3 based on AUC values with a subcutaneous 16% formulation, but later adjusted to multiplying by 1.53 following the results of a pharmacokinetic substudy in 19 patients during the run-in period [see section 2]).<sup>[17]</sup> Of 49 patients enrolled (ITT population), 38 patients of mean age 36.3 years (3 children, 3 adolescents, 28 adults and 4 elderly) completed the run-in period (modified ITT [mITT] population). The primary efficacy endpoint was the annual rate of SBIs per patient in the mITT population (FDA target of  $\leq 1.0$  SBI/patient/year).

- The primary objective of the study was achieved in that there were no SBIs during the 12-month efficacy period in the mITT or ITT populations (table I).<sup>[17]</sup>
- The mean of the individual median serum IgG trough levels during the efficacy period in the mITT population was 12.53 g/L (compared with a median of 10.1 g/L in the 3 months prior to the study), with mean trough levels ranging from 12.1 to 12.9 g/L.<sup>[17]</sup> The rates of infection, days missed from work/school, days hospitalized and days on antibiotics were numerically lower than those observed in the European study (table I) and were generally less than previously observed in pivotal studies with intravenous immunoglobulin preparations.<sup>[17]</sup>

### Longer-Term Extension Study

- Preliminary efficacy results of the extension study (published as an abstract) indicated an

annualized rate of SBIs of 0.06 per patient and an annualized rate of infections of 2.4 per patient.<sup>[18]</sup> Infections were most commonly respiratory tract infections, such as sinusitis, bronchitis and nasopharyngitis. In each of the two patients experiencing SBIs (both pneumonia), serum IgG trough levels ranged from 6.81 to 9.63 g/L throughout therapy. The mean serum IgG trough levels for all patients ranged from 11.71 to 12.76 g/L between weeks 1 and 96. The rates for days missed from work/school, days hospitalized or days with antibiotics due to infections were 4.3, 0.55 and 84 per patient per year, respectively.<sup>[18]</sup>

### Health-Related Quality of Life and Treatment Satisfaction

HR-QOL and patients' satisfaction with treatment were assessed in 16 evaluable patients, aged  $\geq 14$  years, from the long-term extension of the phase III US trial,<sup>[19]</sup> as well as in 29 patients from the phase III European trial who were switched from previous intravenous immunoglobulin therapy to treatment with self-administered immune globulin subcutaneous 20% using an equivalent weekly dose for 40 weeks (published as an abstract).<sup>[22]</sup>

- In the US extension study, HR-QOL remained relatively stable over 72 weeks according to scores for the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) [administered every 24 weeks], the EuroQol 5D (EQ-5D) [administered every 12 weeks] and the Life Quality Index (LQI) [administered at weeks 1 and 60].<sup>[19]</sup> SF-36 domain mean scores and the EQ-5D mean score were close to (usually just below) the US population norms, except for the SF-36 domain of general health, which was consistently below US norms (mean of 56.1 at week 72 vs 70.85). Scores in both scales generally either remained stable over 72 weeks or showed slight worsening.<sup>[19]</sup> LQI domain mean scores were high at week 1 (77.3–89.2), indicating high quality of life; they generally improved slightly by week 60 (82.1–92.3).

- Patient satisfaction with treatment in the extension study was high according to both the Treatment Satisfaction Questionnaire Medication (TSQM) [mean domain scores of 68.4–87.1 at

week 1] and the IgG Therapy-specific Questionnaire [question 1 and 3 mean scores of 82.2 and 88.9 at week 1].<sup>[19]</sup> Mean scores at week 60 for both the TSQM (79.8–93.8) and the IgG Therapy-specific Questionnaire (83.3 and 86.9) indicated continued high levels of satisfaction with self-administered therapy.<sup>[19]</sup>

- At 40 weeks in the European switch study (n=29), all indices of HR-QOL were maintained or improved over the levels seen during the previous intravenous immunoglobulin therapy. Scores for the SF-36 in adults and the Child Health Questionnaire Parental-Form-50 in children showed no major changes from baseline at 40 weeks; patient numbers completing the questionnaires were too low for statistical analysis.<sup>[22]</sup>
- Improvements (increases) from baseline in the switch study were observed for scores in the LQI domains of treatment interference (92 vs 58;  $p < 0.0001$ ), therapy-related problems (83 vs 63;  $p < 0.05$ ), therapy settings (94 vs 56;  $p < 0.0001$ ) and total score (89 vs 70;  $p < 0.05$ ).<sup>[22]</sup> In addition, significant improvement from baseline was seen in the score for the TSQM domain of convenience (83 vs 56;  $p < 0.05$ ).<sup>[3,22]</sup> The scores for the domains of effectiveness (78 vs 67 at baseline) and overall satisfaction (79 vs 71) were not significantly different from baseline. In a separate group of 19 patients previously treated with subcutaneous immunoglobulin who were also treated with immune globulin subcutaneous 20% for 40 weeks in parallel, there were no major changes in any of the HR-QOL indices.<sup>[22]</sup>

#### 4. Tolerability

Tolerability data for immune globulin subcutaneous 20% derive from a phase I study in healthy males (n=28)<sup>[17]</sup> (reported together with the phase III, US trial) and the pivotal European (n=51)<sup>[3]</sup> and US (n=49)<sup>[17]</sup> phase III trials, as well as the extension to the US trial, discussed in section 3, supplemented with information from the US prescribing information.<sup>[9]</sup>

The phase I study in healthy male volunteers was a randomized, single-blind, crossover study of local tolerability until 72 hours from end of infusion after a single subcutaneous infusion of

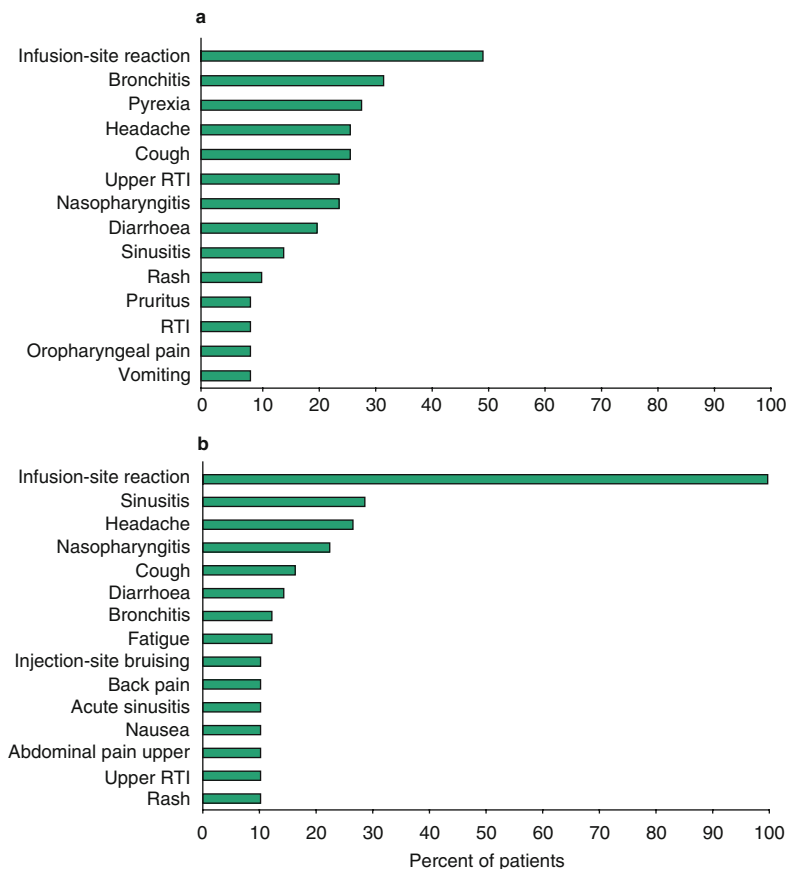
12 mL (2.4 g) of immune globulin subcutaneous 20%, 15 mL (3.0 g) of immune globulin subcutaneous 20% and 15 mL (2.4 g) of two different 16% liquid formulations (stabilized with L-proline or glycine, respectively), each infused at a rate of 25 mL/h.<sup>[17]</sup>

- In the phase I study, maximum and mean pain scores were very low (mean scores of 2.24–3.78 for all formulations on a 100 mm visual analogue scale) and similar between each dose of immune globulin subcutaneous 20% and the 16% liquid formulated with L-proline.<sup>[17]</sup> Pain scores were numerically lower with immune globulin subcutaneous 20% than the 16% liquid formulated with glycine, and the difference reached statistical significance for mean pain with the immune globulin subcutaneous 20% 12 mL infusion (treatment difference  $-1.54$ , 95% CI  $-2.62$ ,  $-0.46$ ;  $p = 0.0205$ ).<sup>[17]</sup>

- There were no major differences between formulations for other local reactions.<sup>[17]</sup> Over 90% of immune globulin subcutaneous 20% recipients experienced erythema (mostly severity 1 or 2 on a 0–4 scale) and all subjects experienced severe (5 on a 0–5 scale) oedema/induration, 71% of which had resolved by day 4. Itching (mostly mild [severity 1 on a 0–3 scale]) was experienced by 39–50% of immune globulin subcutaneous 20% recipients and mild local heat was experienced by 4–18%.<sup>[17]</sup>

- In the phase III efficacy trials, infusion site reactions were the most common adverse events. The rate of local reactions assessed by patients (24 h post-infusion) and investigators (15–45 min post-infusion) in the US trial was 0.592 events per infusion.<sup>[17]</sup> The rate of local reactions as assessed by patients (24–72 h post-infusion) in the European trial was 0.06 events per infusion.<sup>[3]</sup> Local reactions were mostly mild and decreased markedly over time in the European study (from 20% of recipients after the first infusion to <5% at study end),<sup>[3]</sup> but remained constant (investigator assessment) or declined slightly (patient assessment) over time in the US trial.<sup>[17]</sup>

- The most common adverse events, other than local reactions, in the pivotal European trial were infections of the respiratory tract, pyrexia and headache (figure 1), while the most common causally related events were headache (11.8% of



**Fig. 1.** Tolerability of immune globulin subcutaneous 20% in patients with primary humoral immunodeficiency. Treatment-emergent adverse events occurring in  $\geq 4$  (European trial) or  $\geq 5$  patients (US trial) treated with immune globulin subcutaneous 20% for 40 or 64 wk, respectively, in pivotal phase III trials conducted in (a) Europe ( $n=51$ )<sup>[3]</sup> or (b) the US ( $n=49$ )<sup>[17]</sup> RTI=respiratory tract infection.

patients), pruritus (7.8%) and fatigue (5.9%).<sup>[3]</sup> Other causally related events experienced by  $\geq 2$  patients were pyrexia (5.9%), erythema (3.9%), abdominal discomfort (3.9%), rash (3.9%), bronchitis (3.9%), respiratory tract infection (3.9%) and hypothermia (3.9%).

- In the European study, causally related and temporally associated (within 72 hours) adverse events other than local reactions were less frequent in children (39% of patients) and adolescents (40%) than in adults (71%).<sup>[21]</sup>

- After excluding local reactions, the most common adverse events in the US trial were sinusitis, headache and nasopharyngitis (figure 1), while the most common causally related events were

headache (22.4%), injection site bruising (10.2%), vomiting (6.1%), pain (6.1%) and fatigue (6.1%).<sup>[17]</sup>

- Most adverse events ( $\approx 99\%$  in both trials) were of mild or moderate intensity. Serious adverse events occurred in five patients in the European study and seven patients in the US study; none of which were considered related to the study medication. Six patients in the European trial and two in the US trial discontinued treatment as a result of adverse events, consisting mostly of local reactions for those considered at least possibly infusion related, but also including hypersensitivity, myositis, fatigue and feeling cold.<sup>[3,17]</sup>

- There were no signs of haemolysis in either pivotal clinical trial, although five patients in the



US study recorded decreases in haemoglobin levels of  $\geq 2$  g/dL in the absence of a positive direct Coombs' test or other signs.<sup>[3,17]</sup> One patient in the European study and five in the US study developed positive direct Coombs' tests during therapy, but without any reductions in haemoglobin levels.<sup>[3,17]</sup>

- During long-term treatment for up to 104 weeks in the extension to the US trial, there were no treatment discontinuations as a result of adverse events and no treatment-related serious adverse events.<sup>[18]</sup> The most frequent treatment-related adverse events were local reactions, headache and fatigue. The majority (87%) of adverse events were of mild intensity. The incidences of systemic adverse events and local reactions were not related to infusion rates, which varied from low ( $< 35$  mL/h) to high ( $> 50$ – $70$  mL/h).<sup>[18]</sup>
- There have been isolated post-marketing surveillance reports of allergic/anaphylactic reactions, thromboembolic events, chest discomfort (including chest pain) and dyspnoea.<sup>[9]</sup>

## 5. Dosage and Administration

Immune globulin subcutaneous 20% is approved in the EU for antibody replacement therapy in adults and children with primary immunodeficiency disorders, such as common variable immunodeficiency, severe combined immunodeficiency, congenital agammaglobulinaemia and hypogammaglobulinaemia, and IgG subclass deficiencies with recurrent infections.<sup>[8]</sup> It is also approved for antibody-replacement therapy in patients with myeloma or chronic lymphocytic leukaemia with severe secondary hypogammaglobulinaemia and recurrent infections.<sup>[8]</sup> In the US, immune globulin subcutaneous 20% is approved as replacement therapy in adults and children aged  $\geq 2$  years with primary immunodeficiency, including, but not limited to, congenital agammaglobulinaemia, common variable immunodeficiency, X-linked agammaglobulinaemia, Wiskott-Aldrich syndrome and severe combined immunodeficiency.<sup>[9]</sup>

There is no finite recommended dosage of immune globulin subcutaneous 20% in the treatment of humoral immunodeficiency. The dosage should be individualized depending on the serum

IgG trough levels, clinical response (infection rate and severity) and pharmacokinetics for each patient.<sup>[8]</sup> When switching from previous intravenous therapy, two approaches have been used: either using an initial weekly subcutaneous dose equivalent to the weekly dose of the previous therapy in order to achieve serum IgG trough levels noninferior to those achieved on previous therapy (EMA requirement); or using a subcutaneous dose designed to produce a systemic exposure (i.e. standardized AUC) noninferior to that of the previous intravenous therapy (FDA requirement).<sup>[15]</sup> For the latter approach, the previous weekly dose equivalent is multiplied by a dosage adjustment factor of 1.53 to give the initial dose; the steady-state serum IgG trough level should be  $\approx 2.9$  g/L higher than the trough level during the previous intravenous therapy.<sup>[9]</sup>

The European guidelines suggest using an initial loading dose of at least 0.2–0.5 g/kg body-weight, which may be divided over several days.<sup>[8]</sup> Once steady-state serum IgG trough levels have been attained, it is suggested that the monthly equivalent dosage be  $\approx 0.4$ – $0.8$  g/kg. Depending on the clinical response, the dosage and/or dose interval may be adjusted to produce higher serum IgG trough levels, if necessary.

Immune globulin subcutaneous 20% is usually administered with infusion pumps, commonly alternating the infusion site (e.g. abdomen, thigh, lateral hip and upper arm) for each dose.<sup>[8,9]</sup> Large doses ( $> 25$  mL) can be split and administered at up to four separate sites ( $\geq 5$  cm apart) simultaneously, provided the total volume infused over all sites is  $\leq 50$  mL. The recommended initial infusion rate is  $\leq 15$  mL/h/site. This may be increased gradually to 25 mL/h/site, if well tolerated.<sup>[8,9]</sup>

Local prescribing information should be consulted for details related to dosages, administration, contraindications, warnings and precautions.

## 6. Immune Globulin Subcutaneous (Human) 20%: Current Status

Immune globulin subcutaneous 20% is indicated for antibody replacement therapy in adults and children with primary immunodeficiency disorders

involving antibody deficiency in the EU and US, and as replacement therapy for secondary humoral immunodeficiency in patients with myeloma or chronic lymphocytic leukaemia in the EU.<sup>[8,9]</sup> Subcutaneous administration of antibody-replacement therapy does not require venous access and has the additional reported advantages over intravenous administration of being associated with fewer systemic adverse events and being more convenient for many patients.<sup>[2,4-6,17]</sup> More highly concentrated subcutaneous preparations potentially result in lower infusion volumes being required and higher target serum IgG trough levels being achievable.

In pivotal phase III trials in stably treated patients with primary immunodeficiency, immune globulin subcutaneous 20% at weekly subcutaneous dosages either equivalent to each patient's previous intravenous or subcutaneous replacement therapy, or providing equivalent systemic exposure to previous intravenous therapy, produced mean serum IgG trough levels equal to or greater than pre-study levels. In each trial, there were no SBIs during treatment throughout the 28-week or 12-month efficacy periods. The rates of infectious episodes, days missed from work/school, days hospitalized or days with antibiotics were low. Immune globulin subcutaneous 20% was generally well tolerated. A high proportion of patients experienced local infusion-site reactions, but infusion-related systemic adverse events were relatively infrequent. Most adverse events were of mild or moderate intensity and did not interfere with therapy.

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- Correspondence: *Paul L. McCormack*, Adis, 41 Centorian Drive, Private Bag 65901, Mairangi Bay, North Shore 0754, Auckland, New Zealand.  
E-mail: [demail@adis.com](mailto:demail@adis.com)