Immunotherapy

Tolerability of subcutaneous immunoglobulin 20%, Ig20Gly, in pediatric patients with primary immunodeficiencies

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Aim: To assess Ig20Gly tolerability in pediatric patients with primary immunodeficiencies. **Patients & methods:** Infusion parameters and tolerability were analyzed in pediatric patients (aged 2–5 years [n = 6], 6–11 years [n = 22] and 12–17 years [n = 22]) receiving Ig20Gly in two Phase II/III trials. **Results:** Of 2624 Ig20Gly infusions, >99% did not require any rate reduction, interruption or discontinuation due to adverse events (AEs). Median maximum infusion rates and volumes/site were higher in patients 12–17 years of age (30 ml/h/site; 30 ml/site) versus 6–11 years (20 ml/h/site; 15 ml/site) and 2–5 years (18 ml/h/site; 14 ml/site). Rates of causally related systemic and local AEs (0.009 and 0.063 AEs/infusion) were low. **Conclusion:** Ig20Gly infused at relatively high rates and volumes was well tolerated in children.

Patients with primary immunodeficiency disease (PIDD) associated with antibody defects require replacement therapy with immunoglobulin (IG) administered either intravenously or subcutaneously [1,2]. In pediatric patients, intravenous IG (IVIG) infusions can be especially challenging because it is often difficult to obtain venous access in children [3]. Subcutaneous IG (SCIG) can be self-administered or administered by a caregiver at home, does not require venous access, and results in fewer systemic adverse events (AEs) compared with IVIG [2,4], which makes SCIG especially suitable for children [5]. Conventional SCIG requires frequent administration (i.e., weekly or biweekly) and multiple infusion sites owing to the limited volume that can be infused subcutaneously. This results in multiple needle sticks, which can be difficult for children, especially those with needle phobia [2,4]. However, SCIG formulations containing higher IG protein concentration could allow for the infusion of the same dose in smaller volumes compared with less concentrated products, resulting in reduced infusion duration and number of sites needed [6,7].

Future Medicine

The SCIG 20% product, Cuvitru® (immune globulin subcutaneous [human], 20% solution [Ig20Gly]; Baxalta US Inc., now part of Shire, CA, USA), is a ready-for-use IgG preparation with a manufacturing process similar to IVIG 10% (Gammagard Liquid® [USA]/Kiovig® [EU], immune globulin infusion [human], 10% solution; Baxalta US Inc., now part of Shire) except for an additional step of ultradiafiltration resulting in a final formulation with a protein concentration of 20% w/v [8]. Ig20Gly has a ≥98% IgG purity and a distribution of IgG subclasses similar to those of normal plasma [8]. The safety, tolerability and efficacy of Ig20Gly were demonstrated in adult and pediatric patients with PIDD in two Phase II/III studies conducted in North America and Europe [6,7]. During these studies, Ig20Gly infusion rates of up to 60 ml/h/site were used which is higher than the infusion rates reported previously in clinical trials for PIDD with other conventional SCIG products (up to 35 ml/h/site depending on tolerability) [9–12]. The high infusion rates and volumes (up to 60 ml/h/site and 60 ml/site) used in the Ig20Gly pivotal studies were well tolerated, resulting in short infusion durations (median duration, <1 h) and ∼85% of infusions using ≤2 infusion sites.

The objective of this analysis is to assess the safety and tolerability of relatively high infusion rates and volumes/site in a broad pediatric patient population who were treated with Ig20Gly in the two Phase II/III studies in Europe [7] and North America [6].

Methods

Study design

Data were pooled from patients <18 years of age from two Phase II/III studies conducted in North America (11 sites in the USA and Canada [ClinicalTrials.gov, NCT01218438]) [6] and Europe (ten sites in five countries [NCT01412385]) [7]. Study designs for both trials have been described previously and are summarized below [6,7].

The North American trial consisted of four study periods. During period 1, all patients received IVIG 10% for 13 weeks to determine the area under the curve for IgG after IVIG treatment. Patients received Ig20Gly during periods 2 through 4, and systemic exposure equivalent to previous IVIG 10% treatment was targeted. In period 2, an adjustment factor of 145% was approximated to calculate Ig20Gly dose based on pharmacokinetic (PK) data from other SCIG products [12,13]. PK data were collected from the first 18 patients ≥12 years of age treated with Ig20Gly at 145% of the IVIG 10% dose. The adjusted Ig20Gly dose that would provide IgG exposure equivalent to IVIG 10% was determined to be 145% of the IVIG 10% dose. In period 3, all patients received the adjusted dose (145% of the IVIG 10% dose) for 12 weeks, and individual IgG trough levels were assessed. During period 4, all patients continued to receive Ig20Gly for 40 weeks at an individually adapted dose [6].

The European trial consisted of 2 periods. During period 1, patients received IVIG 10% for 13 weeks or SCIG 16% (Subcuvia®, human normal immunoglobulin 160 g/l solution for injection; Baxalta Innovations GmbH, Vienna, Austria) for 12 weeks to attain a stable baseline serum IgG and to assess IgG trough levels and the PK of IVIG 10% or SCIG 16% before starting Ig20Gly treatment. In period 2, patients were treated with Ig20Gly for 52 weeks during which time IgG trough levels and PK were assessed [7].

This pooled analysis evaluated only the time periods in each trial when patients were receiving Ig20Gly (periods 2–4 in the North American trial and period 2 in the European trial). Both studies were performed in accordance with the Declaration of Helsinki and the international standards of Good Clinical Practice as well as in accordance with the ethical standards of the institutional and/or national research committee. Written informed consent was obtained from all patients or their legally authorized representatives in both studies [6,7].

Patients

The European and North American trials included patients 2–67 and 3–83 years of age, respectively, who were diagnosed with PIDD associated with antibody deficiency, had previously received a stable dose (0.3–1 g/kg body weight every 4 weeks) of replacement IVIG or SCIG for ≥12 weeks before study entry, and had a serum IgG trough level of >5 g/l at screening [6,7]. Patients were excluded if they had an active infection, had a history of hepatitis B or C, had a positive HIV test, had an acute serious bacterial infection within 3 months before screening, or were receiving antibiotics. Additional eligibility criteria have been reported previously [6,7]. This pooled analysis included only patients <18 years of age from both trials.

Immunoglobulin treatment

In periods 2 through 4 of the North American study and period 2 of the European study, patients received Ig20Gly once weekly (doses during periods as described previously) [6,7]. The Ig20Gly infusions were administered using an

electromechanical syringe-driver pump (CME T34L; Caesarea Medical Electronics, Caesarea, Israel) and 24-gauge needles (MarCal Medical, MD, USA, for European study; RMS Medical Products for North American study), with needle sets ranging in length from 6 to 12 mm used at the discretion of the investigator. The infusion rates in both studies were increased incrementally. The first two infusions were initiated at a rate of 10 ml/h/site and could be increased to a maximum of 20 ml/h/site. Subsequent infusions could be infused at a maximum rate of 60 ml/h/site as tolerated. Infusion volumes up to 60 ml/site were permitted in patients with a body weight ≥40 kg as tolerated or according to patient preference and physician discretion. For patients weighing <40 kg, the infusion volume was ≤20 ml/site for the initial 2 infusions and then increased up to 60 ml/site as tolerated.

Safety & tolerability assessments

Safety data were collected throughout the duration of both studies [6,7]. Systemic and local AEs were collected by the investigators at the study site during each infusion. Patients/caregivers received guidance from the investigators on identification and documentation of local and systemic AEs if they occurred at home. A diary or eDiary tablet was used by all patients/caregivers to record home treatments, AEs, concomitant medications, days unable to attend school/work or perform normal daily activities, and health resource utilization (such as acute physician visits). The investigators also contacted the patients within 3 to 5 days of each infusion to ensure appropriate AE documentation. Investigators assessed AEs for seriousness, severity, temporal association to Ig20Gly administration (occurring within 72 h of the infusion), and causality (causal relationship between AE and Ig20Gly) and documented their assessment using comprehensive data collection systems. Investigator assessment of AEs included regular review of the patient diaries.

The number of infusions that required a rate reduction, interruption or discontinuation owing to tolerability concerns or AEs was collected. The proportion of infusions associated with ≥1 local or systemic AE and the proportion of patients reporting ≥1 local or systemic AE were determined.

Statistical analysis

Safety and tolerability data from the two studies were pooled and stratified by age group (2–5, 6–11 and 12–17 years). The median (range) number of infusions that required a rate reduction, interruption or discontinuation because of intolerability or AEs, and infusion parameters (volume/site, maximum rate/site, duration, number of sites/infusion) were summarized by age group for all Ig20Gly infusions. The number of AEs and the rate per infusion of systemic and local AEs were reported by severity and age group.

Results

Study population & Ig20Gly exposure

The pooled analysis comprised 50 patients with PIDD <18 years of age (2–5 years, n = 6; 6–11 years, n = 22; 12–17 years, n = 22) who received Ig20Gly during the Phase II/III studies conducted in North America [6] and Europe [7] (Table 1). The most common PIDD diagnosis was common variable immunodeficiency (38%) followed by X-linked agammaglobulinemia (32%). The total exposure to Ig20Gly in the different age groups is shown in Table 2. The Ig20Gly treatment duration did not vary substantially between age groups (mean treatment duration was 358.7, 371.6 and 375.6 days in patients 2–5, 6–11 and 12–17 years of age, respectively).

Safety

The rates of causally related systemic and local AEs per infusion were low in pediatric patients. Overall causally related local AEs occurred at a rate of 0.063 per infusion; the most common were infusion site pain, erythema, pruritus and swelling (Table 3). Causally related systemic AEs occurred at a rate of 0.009 per infusion; the most common were headache and fatigue (Table 3). All causally related AEs were mild or moderate in severity (no severe cases reported). Of note, one 13-year-old patient incurred 50.0% (12/24) of all causally related systemic AEs and 48.2% (79/164) of all causally related local AEs. When that patient was excluded from the analysis, the rates of AEs were comparable across the different age groups (Table 4).

In addition, no serious AEs (SAEs) related to Ig20Gly infusions were reported. Three SAEs that were not treatment related were reported in three patients (chronic rhinorrhea, acute bacterial pneumonia and acute exacerbation of chronic sinusitis in patients 2–5, 6–11 and 12–17 years of age, respectively); all were moderate in severity and resolved without sequelae.

Table 1. Demographics of pooled patients by age group.

Parameter	Age			Total (N = 50)
	2–5 years (n = 6)	6–11 years (n = 22)	12–17 years (n = 22)	
Sex, n (%)				
– Male	5 (83.3)	19 (86.4)	17 (77.3)	41 (82.0)
– Female	1 (16.7)	3 (13.6)	5 (22.7)	9 (18.0)
Mean (SD) age, y	3.7 (1.5)	8.3 (1.6)	14.5 (1.8)	10.5 (4.3)
Mean (SD) weight, kg	19.6 (9.8)	31.5 (10.8)	61.6 (15.6)	43.3 (21.1)
Race, n (%)				
– White	6 (100.0)	17 (77.3)	19 (86.4)	42 (84.0)
– Black	0 (0)	2 (9.1)	1 (4.5)	3 (6.0)
– Asian	0 (0)	2 (9.1)	1 (4.5)	3 (6.0)
– Multiple	0 (0)	1 (4.5)	1 (4.5)	2 (4.0)
Ethnicity, n (%)				
– Hispanic or Latino	0 (0)	0 (0)	1 (4.5)	1 (2.0)
– Not Hispanic or Latino	6 (100.0)	22 (100.0)	21 (95.5)	49 (98.0)
PIDD diagnosis[†], n (%)				
– Ataxia telangiectasia	0 (0)	1 (4.5)	0 (0)	1 (2.0)
– Autosomal recessive hypogammaglobulinemia	1 (16.7)	0 (0)	0 (0)	1 (2.0)
– Common variable immune deficiency	2 (33.3)	4 (18.2)	13 (59.1)	19 (38.0)
– Hyper IgM	0 (0)	1 (4.5)	0 (0)	1 (2.0)
– X-linked hyper IgM	0 (0)	2 (9.1)	0 (0)	2 (4.0)
– Severe combined immune deficiency	0 (0)	0 (0)	1 (4.5)	1 (2.0)
– Specific antibody deficiency	0 (0)	1 (4.5)	3 (13.6)	4 (8.0)
– Specific antibody deficiency with hypogammaglobulinemia	0 (0)	3 (13.6)	0 (0)	3 (6.0)
– Specific antibody deficiency with IgG subclass deficiency	0 (0)	2 (9.1)	0 (0)	2 (4.0)
– X-linked agammaglobulinemia	3 (50.0)	8 (36.4)	5 (22.7)	16 (32.0)

[†]One patient with 'CD 40 ligand deficiency' is grouped under 'X-linked hyper IgM' and another patient with 'familial TACI mutation C.512>G' is grouped under 'common variable immune deficiency'.
PIDD: Primary immunodeficiency diseases.

Table 2. Total exposure to Ig20Gly by age group.

Parameter	Age			Total (N = 50)
	2–5 years (n = 6)	6–11 years (n = 22)	12–17 years (n = 22)	
Mean (SD) treatment duration, d	358.7 (3.2)	371.6 (48.5)	375.6 (98.9)	371.8 (72.3)
Total number of patient-years on treatment	5.9	22.4	22.6	50.9

Ig20Gly: Subcutaneous immune globulin 20% solution.

Tolerability

A total of 305, 1162 and 1153 Ig20Gly infusions administered to patients 2–5, 6–11 and 12–17 years of age, respectively, were analyzed for tolerability. More than 99% of the infusions administered in each age group (100%, 99.7% and 99.4%) and >86% of patients in each age group (100%, 86.4% and 86.4%) did not require a reduction in infusion rate, interruption, or discontinuation because of tolerability concerns or AEs (Table 5).

Infusion parameters

The median of the maximum infusion rates achieved were slightly higher in the older age group versus the younger patients (18.0, 20.0 and 30.0 ml/h/site in the patients 2–5, 6–11 and 12–17 years of age, respectively; Table 6). The median of the maximum infusion rate of the overall pediatric population was 25.0 ml/h/site. Two patients (9.1%) 6–11 years of age and eight patients (36.4%) 12–17 years of age reached maximum infusion rates of 60 ml/h/site for ≥1 infusion. The median infusion volumes were higher in the older versus younger pediatric patients (14.0, 15.0 and 30.0 ml/site in patients 2–5, 6–11 and 12–17 years of age, respectively; Table 6). The median infusion

Table 3. Causally related local and systemic adverse events, excluding infections.

Parameter	AEs, n	Patients with AEs, [†] n (%) N = 50	AEs/patient[‡] N = 50	AEs/infusion[§] N = 2624	AEs at various time points after infusion,[¶] n		
					1 h	24 h	72 h
Local AEs, n (%)							
Total	164	17 (34.0)	3.280	0.063	156	164	164
– Infusion/injection site pain/discomfort	49	11 (22.0)	0.980	0.019	48	49	49
– Infusion/injection site erythema	34	9 (18.0)	0.680	0.013	30	34	34
– Infusion/injection site pruritus	30	7 (14.0)	0.600	0.011	27	30	30
– Infusion site swelling	44	2 (4.0)	0.880	0.017	44	44	44
– Burning sensation	4	1 (2.0)	0.080	0.002	4	4	4
– Infusion site urticaria	2	1 (2.0)	0.040	<0.001	2	2	2
– Infusion site edema	1	1 (2.0)	0.020	<0.001	1	1	1
Systemic AEs, n (%)							
Total	24	8 (16.0)	0.480	0.009	6	17	23
– Headache	14	2 (4.0)	0.280	0.005	0	9	14
– Fatigue	3	2 (4.0)	0.060	0.001	1	3	3
– Diarrhea	2	1 (2.0)	0.040	<0.001	1	1	2
– Somnolence	2	1 (2.0)	0.040	<0.001	2	2	2
– Abdominal pain	1	1 (2.0)	0.020	<0.001	1	1	1
– Coombs direct test positive	1	1 (2.0)	0.020	<0.001	0	0	0
– Hypotension	1	1 (2.0)	0.020	<0.001	1	1	1

[†]Total number of affected patients divided by the total number of patients under treatment multiplied by 100.
[‡]Total number of AEs divided by the total number of patients under treatment.
[§]Total number of AEs divided by the total number of infusions.
[¶]For AEs in which only the date of the AE was available, the designation of the AE occurring within 1 h and within 24 h used the following assumptions:
  • if the AE happened on the same day as the infusion, it was assumed the AE occurred within 1 h and within 24 h of the infusion.
  • if the AE happened on the next day after the infusion, it was assumed the AE occurred within 24 h, but not within 1 h of the infusion.
AE: Adverse event.

Table 4. Rate of causally related systemic and local adverse events, excluding infections, by age group.

Category	Severity	Age		
		2–5 years (n = 6)	6–11 years (n = 22)	12–17 years[†] (n = 21)
Infusions, n		305	1162	1106
Systemic AEs, n (rate[‡])	All	3 (0.010)	4 (0.003)	5 (0.005)
	Mild	1 (0.003)	3 (0.003)	5 (0.005)
	Moderate	2 (0.007)	1 (<0.001)	0 (0.000)
Local AEs, n (rate[‡])	All	0 (0.000)	45 (0.039)	40 (0.036)
	Mild	0 (0.000)	43 (0.037)	40 (0.036)
	Moderate	0 (0.000)	2 (0.002)	0 (0.000)

[†]Excludes a 13-year-old patient who incurred 50.0% (12/24) of all causally related systemic AEs and 48.2% (79/164) of all causally related local AEs reported throughout the study; all (79) causal local AEs were of mild severity. Inclusion of this patient results in rates of 0.015 for all systemic AEs and 0.103 for all local AEs for this age group.
[‡]Rate = total number of AEs divided by total number of infusions.
AE: Adverse event.

durations were low across the age groups (median, 0.75, 0.78 and 1.05 h). The median number of sites used per infusion was 1 or 2 for all pediatric age groups (Table 6).

Discussion

In children with PIDD, the administration of IG therapy is accompanied by unique challenges. IVIG can be disadvantageous in children because of the need for venous access and increased risk for systemic AEs [3,4,14–16]. Thus, the availability of SCIG products was an initial advancement in IgG therapy, allowing treatment to be completed at home. The development of concentrated SCIG products, such as Ig20Gly, allows the infusion of the same dose in smaller volumes compared with less concentrated products, thus reducing infusion time and the

Table 5. Ig20Gly infusions requiring rate reduction, interruptions or discontinuations by age group

Parameter	Age					
	2–5 years		6–11 years		12–17 years	
	Infusions	Patients	Infusions	Patients	Infusions	Patients
Total, n	305	6	1162	22	1157[†]	22
Infusions with a rate reduction, n (%)	0 (0)	0 (0)	1 (0.1)	1 (4.5)	7 (0.6)	3 (13.6)
Infusions interrupted, n (%)	0 (0)	0 (0)	2 (0.2)	2 (9.1)	0 (0)	0 (0)
Infusions discontinued, n (%)	0 (0)	0 (0)	1 (0.1)	1 (4.5)	0 (0)	0 (0)
Infusions without a rate reduction, interruption, or discontinuation, n (%)	305 (100.0)	6 (100)	1158 (99.7)	19 (86.4)	1146 (99.4)	19 (86.4)

[†] 1153 infusions were included in the analysis.
Ig20Gly: Subcutaneous immune globulin 20% solution.

Table 6. Infusion parameters for patients by age group.

Infusion parameter[†]	Age							
	2–5 years (n = 6)		6–11 years (n = 22)		12–17 years (n = 22)		Total (N = 50)	
	Infusions, n	Median (range)	Infusions, n	Median (range)	Infusions, n	Median (range)	Infusions, n	Median (range)
Infusion volume, ml/site	305	14.0 (6.5–26.0)	1161	15.0 (6.4–43.0)	1153	30.0 (10.0–67.5)	2619	20.0 (6.4–67.5)
Maximum infusion rate, ml/h/site	305	18.0 (2.5–40.0)	1157	20.0 (4.4–80.0)	1145	30.0 (5.0–120.0)	2607	25.0 (2.5–20.0)
Infusion duration, h	303	0.75 (0.4–3.0)	1126	0.78 (0.3–3.5)	1105	1.05 (0.3–3.5)	2534	0.93 (0.3–3.5)
Sites per infusion, n	305	1 (1–2)	1161	2 (1–3)	1153	2 (1–4)	2619	2 (1–4)

[†] Only infusions with complete infusion parameters were considered for each analysis.

number of sites needed for administration, which is especially beneficial in the treatment of children [2,4,5]. In the North American and European Phase II/III studies, Ig20Gly was well tolerated when administered at infusion volumes up to 60 ml/site and infusion rates up to 60 ml/h/site in patients of all ages with PIDD [6,7].

Our analysis of the pediatric patients from the North American and European trials showed that these patients had a safety and tolerability profile similar to the overall populations from the individual trials. In the current analysis, no treatment-related SAEs were observed in the pooled pediatric population, reflecting what was previously reported for the overall population in the North American and European trials [6,7]. The rates of causally related systemic and local AEs per infusion in the pooled pediatric population were low (0.009 and 0.063, respectively) and, again, similar to data previously reported for the total population. In the North American and European trials, the rates for the total population per infusion of causally related systemic AEs were 0.021 and 0.032, respectively, and causally related local AEs were 0.016 and 0.069.

In the pooled pediatric population, the majority of causally related local AEs (162/164) and systemic AEs (21/24) were mild; none were severe. In the 13-year-old patient who incurred 50.0% (12/24) of all causally related systemic AEs and 48.2% (79/164) of all causally related local AEs, the AEs were nonserious and mild in severity. Additionally, this patient, whose parent/caregiver was a healthcare professional, completed the study and expressed a preference to remain on Ig20Gly treatment poststudy. Because this patient was an outlier experiencing a disproportionally large number of AEs, we evaluated the rates of AEs by age group with and without inclusion of this patient. Rates of causally related systemic and local AEs per infusion were low and similar among age groups when excluding the patient (systemic: 0.010, 0.003 and 0.005; local: 0, 0.039 and 0.036 in patients 2–5, 6–11 and 12–17 years of age, respectively). When that patient was included in the analysis, the rate per infusion in the 12- to 17-year-age group was still low at 0.015 and 0.103 for systemic and local AEs, respectively.

Although the study designs of the trials were very similar, infusion rates lower than the allowed limit were used in the European study compared with the North American study because of patient and physician preference rather than tolerability issues (the median [range] of the maximum infusion rate used for the total population was 20 [2.5–60] in the European study [N = 48] vs 60 [4.4–180] ml/h/site in the North American study [N = 74]). Despite the higher infusion rates used in the North American study, the rates of causally related AEs reported for the total population were lower compared with the European study (systemic AEs/infusion, 0.021 vs 0.032; local AEs/infusion, 0.016 vs 0.069). In the European study, 99.8% of infusions were administered without any rate reduction, interruption or discontinuation due to tolerability concerns or AEs, indicating that patients in the study started with the low infusion rates and continued using those rates (vs starting at higher rates and switching to lower rates because of AEs). In addition, there were no increases in the rates of causally related local AEs with increasing infusion rates in the pooled analysis from both studies or for the individual studies indicating tolerability to the high infusion rates.

In the pooled pediatric population, the patients' infusion volumes and infusion rates were observed to be age dependent. The median of the maximum infusion rate in patients 12–17 years of age (30 ml/h/site) were higher compared with patients in the younger age groups (18 and 20 ml/h/site in patients 2–5 and 6–11 years of age, respectively). The lower infusion rates in the younger children corresponded with the lower dose volumes used in these age groups (14.0 ml/site [2–5 years] and 15.0 ml/site [6–11 years]) versus adolescents (30 ml/ site). In the North American study, high median infusion rates and volumes were used in adolescents (12 to <16 years; 50–60 ml/h/site and 42.7 ml/site); these infusion rates were close to the maximum rate. The overall average infusion rates for the pooled population from North American and European study was low because of the lower infusion rates used in the European study (because of patient and physician preference rather than tolerability issues).

Infusion rates of 60 ml/h/site for ≥1 infusion were achieved in 10 patients (12–17 years [n = 8]; 6–11 years [n = 2]); 6 of these patients used this rate for >75% of their infusions. However, the maximum infusion rate was not tried in the majority of pediatric patients presumably because their infusions were already of short duration (<1 h; owing to the small doses required in these patients), rather than because of tolerability concerns. Notably, >99% of infusions were well tolerated without requiring infusion rate reduction or interruption (<1% of infusions had a rate reduction, interruption or discontinuation owing to a tolerability concern or an AE).

For another SCIG 20% product, IgPro20 (Hizentra®, immune globulin subcutaneous [human] 20%; CSL Behring AG, Bern, Switzerland), infusion rates up to 25 ml/h/site were studied in adults and children [9,17,18]. Median weekly infusion durations ranged from 1.6 to 2.0 hours, and the number of infusion sites per treatment ranged from 1 to 12 (73% of infusions required ≤4 sites) [19]. In an analysis of pediatric data from a Phase III study in patients who switched from IVIG to SCIG 20% (IgPro20), the mean of the individual median infusion rates in children (2–11 years, 19.0 ml/h) was lower than those reported for adolescents (12–15 years, 31.2 ml/h) and adults (28.5 ml/h); the median infusion durations were 0.78, 1.0 and 1.42 hours for children, adolescents and adults, respectively [5]. In a Phase III study in adults and children receiving SCIG 16% (Vivaglobin® immune globulin subcutaneous [Human]; CSL Behring GmbH, Marburg, Germany) and SCIG 20% products, the average infusion times were 1.7 and 1.2 h, respectively, and the average number of infusion sites used were 3.3 and 2.2 [10]. It is important to note that these trials employed different study designs and methodology; hence, caution should be used in the interpretation of any data comparisons.

The currently available IVIG and SCIG products have individual formulations and characteristics that make them unique; however, no single product or administration route is ideal for all patients. Providing patients with the choice for their treatment may be a feasible, safe and efficient strategy in terms of improving adherence to treatment as seen in a retrospective analysis of 143 pediatric patients who were given the choice between hospital-based IVIG and home-based SCIG [20]. In a survey conducted through the International Patient Organization for Primary Immunodeficiencies (IPOPI) in patients with PIDD, patients and caregivers preferred self-administration, treatment at home, monthly administrations, shorter duration of administrations and fewer needle sticks [21]. This study also showed that treatment preferences varied by patient and caregiver and highlights the importance of access to different treatment options and administration modes to ensure that individual patient needs are met [21].

Conclusion

This pooled analysis of pediatric patients from the North American and European Phase II/III studies further supports the safety and tolerability of Ig20Gly in children with PIDD that were previously reported for the total

populations. Relatively large infusion volumes up to 60 ml/site and fast infusion rates up to 60 ml/h/site of Ig20Gly were well tolerated in pediatric patients, with low rates of causally related systemic and local AEs. Ig20Gly administration also demonstrated the advantage of few needle sticks and short infusion duration, which may be of particular benefit in children with needle phobia or when infusion duration is a concern. Thus, Ig20Gly provides a well-tolerated IG treatment option for children with PIDD.

Summary points

- Patients with primary immunodeficiency disease (PIDD) often require lifelong immunoglobulin therapy administered either intravenously or subcutaneously.
- The subcutaneous immune globulin 20% product, Ig20Gly, was well tolerated and efficacious in patients with PIDD in two Phase II/III studies in North America and Europe.
- This *post hoc* analysis assessed the tolerability in a broader pediatric patient population treated with Ig20Gly in the two pivotal clinical trials.
- Fifty pediatric patients (aged 2–5 years [n = 6], 6–11 years [n = 22] and 12–17 years [n = 22]) received 2624 Ig20Gly infusions; >99% of infusions did not require any rate reduction, interruption or discontinuation because of adverse events (AEs).
- Median infusion rates and volumes were higher in patients 12–17 years of age (30 ml/h/site; 30 ml/site) versus those 6–11 years of age (20 ml/h/site; 15 ml/site) and 2–5 years (18 ml/h/site; 14 ml/site).
- Low rates of causally related systemic and local AEs (0.009 and 0.063 AEs/infusion) were observed in all pediatric patients; none were serious or severe.
- Ig20Gly infused at relatively high rates and volumes was well tolerated in pediatric patients with PIDD.

Ethical disclosure

The two clinical studies (NCT01218438 and NCT01412385) of which the primary results were reported previously were performed in accordance with the Declaration of Helsinki and the international standards of Good Clinical Practice as well as in accordance with the ethical standards of the institutional and/or national research committee. Written informed consent was obtained from all patients or their legally authorized representatives in both studies.

Author contributions

All authors were involved in the conception and design of the study, data generation, data analysis and interpretation, preparation and writing of the manuscript, critical review of the manuscript and approved the final version of the manuscript. K Paris, E Haddad, I Hussain and A Darter were investigators who enrolled pediatric patients in the North American trial. M Borte, N Brodszki, B Dérfalvi and L Maródi were investigators who enrolled pediatric patients in the European trial. W Engl was the statistician, and H Leibl, B McCoy and L Yel were clinical leads involved in each trial.

Data sharing

The datasets, including redacted study protocol, redacted statistical analysis plan and individual participant data behind the results reported in this article, will be available 3 months after manuscript publication, to researchers who provide a methodologically sound proposal after de-identification, in compliance with applicable privacy laws, data protection and requirements for consent and anonymization. Data requests should follow the process outlined in the Data Sharing section on Shire's website: http://www.shiretrials.com/en/our-commitment-to-transparency/data-sharing-with-researchers and should be directed to clinicaltrialdata@shire.com

ClinicalTrials.gov registry

NCT01218438 and NCT01412385

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References

Papers of special note have been highlighted as: • of interest; •• of considerable interest

1. Bonilla FA, Khan DA, Ballas ZK *et al.* Practice parameter for the diagnosis and management of primary immunodeficiency. *J. Allergy Clin. Immunol.* 136(5), 1186–1205 (2015).

2. Perez EE, Orange JS, Bonilla F *et al.* Update on the use of immunoglobulin in human disease: a review of evidence. *J. Allergy Clin. Immunol.* 139(3S), S1–S46 (2017).

3. Abrahamsen TG, Sandersen H, Bustnes A. Home therapy with subcutaneous immunoglobulin infusions in children with congenital immunodeficiencies. *Pediatrics* 98(6 Pt 1), 1127–1131 (1996).

4. Wasserman RL. Progress in gammaglobulin therapy for immunodeficiency: from subcutaneous to intravenous infusions and back again. *J. Clin. Immunol.* 32(6), 1153–1164 (2012).

• **Reviews the advantages and disadvantages of subcutaneous immunoglobulin (IG) in comparison with intravenous IG as an administration route.**

5. 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.* 31(5), 752–761 (2011).

•• **Reports Phase III data from pediatric patients who received the subcutaneous IG 20% product, Ig20Pro.**

6. Suez D, Stein M, Gupta S *et al.* Efficacy, safety, and pharmacokinetics of a novel human immune globulin subcutaneous, 20% in patients with primary immunodeficiency diseases in North America. *J. Clin. Immunol.* 36(7), 700–712 (2016).

•• **Reports primary results of the Ig20Gly Phase II/III North American pivotal study.**

7. Borte M, Krivan G, Derfalvi B *et al.* Efficacy, safety, tolerability and pharmacokinetics of a novel human immune globulin subcutaneous, 20%: a Phase II/III study in Europe in patients with primary immunodeficiencies. *Clin. Exp. Immunol.* 187(1), 146–159 (2017).

•• **Reports primary results of the Ig20Gly Phase II/III European pivotal study.**

8. Cuvitru (immune globulin subcutaneous [human], 20% solution), prescribing information. Baxalta US Inc., Westlake Village, CA, USA (2016).

9. Jolles S, Bernatowska E, de Gracia J *et al.* Efficacy and safety of Hizentra® in patients with primary immunodeficiency after a dose-equivalent switch from intravenous or subcutaneous replacement therapy. *Clin. Immunol.* 141(1), 90–102 (2011).

10. Niebur HB, Duff CM, Shear GF *et al.* Efficacy and tolerability of 16% subcutaneous immunoglobulin compared with 20% subcutaneous immunoglobulin in primary antibody deficiency. *Clin. Exp. Immunol.* 181(3), 441–450 (2015).

11. 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.* 26(2), 177–185 (2006).

12. 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.* 30(5), 734–745 (2010).

13. Wasserman RL, Melamed I, Kobrynski L *et al.* Efficacy, safety, and pharmacokinetics of a 10% liquid immune globulin preparation (GAMMAGARD LIQUID, 10%) administered subcutaneously in subjects with primary immunodeficiency disease. *J. Clin. Immunol.* 31(3), 323–331 (2011).

14. Shabaninejad H, Asgharzadeh A, Rezaei N, Rezapoor A. A comparative study of intravenous immunoglobulin and subcutaneous immunoglobulin in adult patients with primary immunodeficiency diseases: a systematic review and meta-analysis. *Exp. Rev. Clin. Immunol.* 12(5), 595–602 (2016).

15. Wasserman RL. Overview of recombinant human hyaluronidase-facilitated subcutaneous infusion of IgG in primary immunodeficiencies. *Immunotherapy* 6(5), 553–567 (2014).

16.   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.* 11(6), 532–538 (2011).

17.   Kanegane H, Imai K, Yamada M *et al.* Efficacy and safety of IgPro20, a subcutaneous immunoglobulin, in Japanese patients with primary immunodeficiency diseases. *J. Clin. Immunol.* 34(2), 204–211 (2014).

18.   Jolles S, Borte M, Nelson RP Jr *et al.* Long-term efficacy, safety, and tolerability of Hizentra® for treatment of primary immunodeficiency disease. *Clin. Immunol.* 150(2), 161–169 (2014).

19.   Hizentra® (immune globulin subcutaneous [human], 20% liquid), prescribing information. CSL Behring AG, Bern, Switzerland (2018).

20.   Samaan K, Levasseur MC, Decaluwe H *et al.* SCIg vs. IVIg: let's give patients the choice! *J. Clin. Immunol.* 34(6), 611–614 (2014).

••   **Describes the impact of patient choice in determining the appropriate IG administration route for individual patients.**

21.   Espanol T, Prevot J, Drabwell J, Sondhi S, Olding L. Improving current immunoglobulin therapy for patients with primary immunodeficiency: quality of life and views on treatment. *Patient Prefer. Adherence* 8, 621–629 (2014).