

Tolerability of Human Immunoglobulin 10% (IgG) Administered Subcutaneously (SC) or Facilitated with Recombinant Human Hyaluronidase (rHuPH20) in Patients with Primary Immunodeficiency Disease (PID)

I. Melamed,¹ R. L. Wasserman,² M. Stein,³ A. Rubinstein,⁴ B. McCoy,⁵ W. Engl,⁵ H. Leibl,⁵ D. Gelmont,⁶ R. I. Schiff,⁵ and The rHuPH20-facilitated IGSC Study Group

1. IMMUNOe International Research Center, Centennial, CO; 2. DallasAllergyImmunology, Dallas, TX; 3. Allergy Associates of the Palm Beaches, North Palm Beach, FL; 4. Albert Einstein College of Medicine and Montefiore Hospital, Bronx, NY; 5. Baxter BioScience, Vienna, AUSTRIA; 6. Baxter BioScience, Westlake Village, CA

Abstract

Rationale: IV and SC routes of IgG administration have both advantages and disadvantages. One disadvantage of IGSC therapy is decreased bioavailability compared to IGIV. rHuPH20 is a permeation enhancer that increases systemic absorption of fluids infused subcutaneously. A phase III trial comparing the efficacy, tolerability, and PK of IGIV and facilitated-subcutaneous infusion of IgG 10% and rHuPH20 (IGHy) in patients with PID is now completed (NCT00814320). This is an interim analysis of that study evaluating the tolerability of IGHy at rates and frequencies equivalent to IGIV administration in PID patients.

Methods: The study included 2 arms. Patients enrolled in Arm 1 had been treated with IgG administered IV and SC in a previous clinical study (study number 160601). In Arm 1, patients immediately began treatment with IGHy administration using the same IgG 10% product administered SC. Arm 2 included patients not treated in the previous clinical study. These patients were first treated with IGIV and then switched to IGHy. For IGHy, 75 U of rHuPH20/g IgG was administered subcutaneously, followed by IgG 10% infusion at the same site at a dose of 108% of the previous IV dose. rHuPH20 and IgG were injected through the same needle using an infusion set. Subsequent IgG dosing was adjusted based on IgG trough levels. In this interim analysis, tolerability of IGHy was evaluated in patients enrolled in Arm 1.

Results: Twenty-nine patients were included in the interim analysis. Median age was 28 years (≥12 years, n = 23; <12 years, n = 6), and median weight was 64 kg (range: 20–136 kg). IGHy was started at a 1-week dose and interval and ramped up to 3- or 4-week intervals at 3- or 4-week doses. Twenty-eight patients achieved their previous IV dosing interval. In total, 563 IGHy infusions were administered, all without interruption (data not available for 86 infusions). Infusion rate was reduced for 1% (n = 6). The majority of the infusions after ramp-up were administered using a single site and 97% (463/475) were administered in 1 or 2 sites every 3 or 4 weeks. Mean volume and dose per 4 weeks was 300 mL (30.0 g). Mean duration of infusion was 2.2 h. Mean time to infuse (including rHuPH20) was 2.4 h. The mean maximum infusion rate per site was 245 mL/h. Most treatment-related adverse events (AEs) were mild and localized to the infusion site. Local AEs occurred in 14% of infusions and the rate of all treatment-related systemic AEs was 9% of the infusions. The most frequent AEs were infusion site pain (N=35), headache (N=16), and infusion site erythema (N=15).

Conclusion: IGHy was well tolerated, at infusion volumes, intervals, and rates equivalent to patients' previous IV administration. Most patients were able to infuse in 1 or 2 sites every 3 or 4 weeks.

Introduction

- Lifelong immune globulin (IgG) replacement therapy is required by patients with primary immunodeficiency disease (PID).
- IgG administered either intravenously (IGIV) or subcutaneously (IGSC) is considered safe, effective, and generally well tolerated.
- Choice of administration may be based on the advantages or disadvantages specific to administration route (Table 1).

Table 1. Advantages and Disadvantages of IgG Administration Route

	IGIV	IGSC
Advantages	<ul style="list-style-type: none"> • Higher bioavailability than IGSC • Usually 1 infusion every 3 to 4 weeks 	<ul style="list-style-type: none"> • Associated with a lower incidence of systemic AEs compared with IGIV • Does not require venous access • Can be self-administered providing more freedom and flexibility
Disadvantages	<ul style="list-style-type: none"> • May be associated with systemic AEs, including headache, fatigue, and myalgia • Requires venous access • Usually requires healthcare professional to begin infusions 	<ul style="list-style-type: none"> • Associated with reduced bioavailability compared with IGIV • Requires weekly infusions using multiple infusion sites

- Facilitated subcutaneous infusion of IgG 10% and recombinant human hyaluronidase (IGHy) represents a novel approach to IgG replacement therapy that may overcome the barriers associated with traditional SCIG infusions.
 - For SC administered fluids, hyaluronan (HA) forms a barrier to entry into the vascular compartment.¹⁻³ The recombinant human hyaluronidase (rHuPH20) component of IGHy is a genetically engineered, soluble version of naturally occurring human hyaluronidase that transiently degrades HA (integrity restored in 24 to 48 h) thereby reducing the barrier to diffusion in the interstitium.^{3,4}
 - Therefore, IGHy may 1) enable improved bioavailability compared with IGSC decreasing the requirement for dose adjustments, and 2) minimize the need for multiple administration sites.

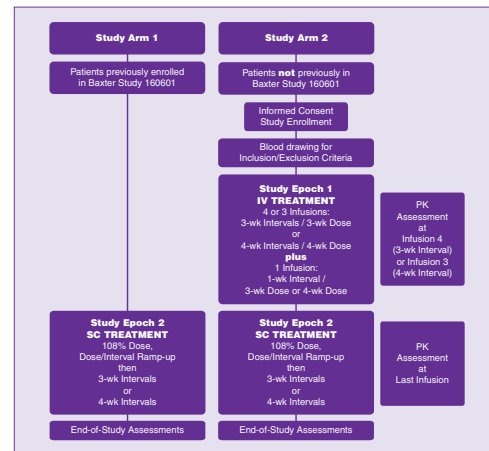
- In a phase I/II study of patients with PID, IGHy enabled administration of IgG at volumes equivalent to a full monthly IGIV dose at a single site.⁵
- We report data from an interim analysis evaluating tolerability in patients (n=29) enrolled in Study Arm 1 of a phase III trial (NCT00814320).

Methodology

Pilot Study

- Prospective, open-label, non-controlled, multicenter phase III trial
- A total of 89 patients were enrolled; 29 patients were included in the interim analysis.
- Two study arms with 2 epochs (Figure 1):
 - Study Arm 1
 - Patients were treated with IgG 10% (GAMMAGARD LIQUID[®]) administered IV and SC in a previous clinical study (study number 160601).
 - Patients began treatment with IGHy (Epoch 2 only).
 - Study Arm 2
 - Patients were not previously treated in study 160601.
 - Patients were first treated with IGIV 10% (Epoch 1) for a period of 3 months and then switched to IGHy (Epoch 2).
- Primary endpoint: rate of acute serious bacterial infections
- Secondary endpoints include: pharmacokinetics (AUC and trough levels); annual rates of infections (all and bacterial) per subject; specific antibody titers; acute physician visits and the number of days off school/work, on antibiotics, and in hospital.

Figure 1. Study Design



Treatment

- Epoch 1: IGIV for 12 weeks at same dose and frequency as prior to the study (minimum of 300 mg/kg by weight/4 weeks), followed by 1 IV infusion of a 3 or 4 week dose administered 1 week prior to initiation of Epoch 2
- Epoch 2: IGHy
 - IgG 10%: 108% of IV dose with the aim to reach 3- or 4-week intervals (as for pre-study) if tolerated; dose and treatment interval gradually increased from 1 week to 3 or 4 weeks
 - rHuPH20: 75 U/g IgG, administered before infusion of IgG 10%
 - rHuPH20 and IgG 10% were injected through the same needle using a SC infusion set.

Results

- All patients included in the interim analysis were from Study Arm 1 (n = 29); median age was 28 years (≥12 years, n = 23; <12 years, n = 6); median weight was 64 kg (range: 20–136 kg).
- IGHy was started at a 1-week dose and interval and ramped up to 3- or 4-week intervals at 3- or 4-week doses.
- All but one patient (28/29) reached their previous IV dosing interval (Table 2).

Table 2. Summary of Dose Administered After Ramp-up

IV Dose Interval Achieved?	Treatment Interval Category	Number of Patients (%)
Yes	3 weeks	6 (20.7%)
	4 weeks	22 (75.9%)
	Total	28 (96.6%)
No	4 to 3 weeks	0 (0.0%)
	4 to 2 weeks	1 (3.4%)
	3 to 2 weeks	0 (0.0%)
Total	1 (3.4%)	

- In total, 563 infusions were administered. Among the 475 infusions after the ramp-up, the majority were administered using a single site and 97% were administered in 1 or 2 sites every 3 or 4 weeks (Table 3).

Table 3. Summary of SC Treatment Intervals and Infusion Sites After Ramp-up

Treatment Interval	Number of Infusions	Percentage of Infusions Given at		
		1 Site	2 Sites	>2 Sites
2 weeks	12	8.3%	91.7%	0.0%
3 weeks	127	56.7%	43.3%	0.0%
4 weeks	336	79.2%	20.8%	0.0%

- Three- or 4-week targets were determined by pre-study intervals.
- All evaluable infusions were administered without interruption (data not available for 86 infusions). The infusion rate was reduced for 1% of infusions (Table 4).

Table 4. Infusions for Which the Infusion Rate Was Reduced and/or the Infusion Was Interrupted or Stopped for Tolerability Concerns or for AEs

	Total Number of Infusions	Completed Without Change n (rate)	Reduced n (rate)	Interrupted n (rate)	Stopped n (rate)
IGIV ^a	124	116 (9.9%)	4 (0.03%)	4 (0.03%)	0 (0.00%)
IGSC ^b	477 ^c	471 (9.9%)	6 (0.01%)	0 (0.00%)	0 (0.00%)

^aData on IGIV were from study 160601.

^bFor this analysis, data was not available for 86 of the 563 infusions.

- Mean volume and dose per 4 weeks was 300 mL (30.0 g), as shown in Table 5.

Table 5. Summary of Volume per Site After Ramp-up

Treatment Interval	Volume (mL)		
	Mean	Min	Max
2 weeks (n = 1)	160	144	287
3 weeks (n = 6)	212	100	397
4 weeks (n = 22)	300	60	716
Overall (n = 29)	269	60	716

- Mean duration of infusion was 2.2 h. Mean time to infuse (including rHuPH20) was 2.4 h. The mean of maximum infusion rates for one site was 245 mL/h (Table 6).

Table 6. Summary of Other Infusion Parameters After Ramp-up

Parameter	Mean	Min	Max
Duration of IgG infusion [h]	2.2	0.8	4.7
Infusion Rate of IgG [mL/h]	163.2	61.9	370.3
Maximum IgG Infusion Rate per Infusion Site (mL/h)	245.0	80.9	300.0
Time to Infuse [hours] ^a	2.4	1.0	5.0

^aDefined as the time interval between start of rHuPH20 infusion and stop of IgG infusion

- Most treatment-related AEs, such as pain and erythema, were mild and localized to the infusion site (Table 7).

Table 7. Summary: Tolerability—Number of AEs by Severity

AE	Local/Systemic	Mild	Moderate	Severe	Total
All AEs	Local	60	18	0	78 ^a
Related AEs	Systemic	183	123	4	310 ^b
	Local	58	18	0	76 ^c
	Systemic	26	22	0	48 ^d

^aSeverity not available in 2 AEs; ^bSeverity not available in 4 AEs; ^cSeverity/relationship not available in 8 AEs

- Local AEs occurred in 14% of infusions, and the rate of all treatment-related (IGSC/rHuPH20) systemic AEs was 9% of all infusions (Table 8).

Table 8. Relationship of AEs to Study Products

Relationship	Local AEs			Systemic AEs		
	Total Number of AEs	Rate of AEs per Infusion	Rate of AEs per Subject	Total Number of AEs	Rate of AEs per Infusion	Rate of AEs per Subject
Unrelated	2	0.00	0.07	258	0.46	8.90
Related to IGSC	19	0.03	0.66	26	0.05	0.90
Related to rHuPH20	10	0.02	0.34	0	0.00	0.00
Related to IGSC and rHuPH20	47	0.08	1.62	22	0.09	0.76
Data pending	2	0.00	0.07	8	0.01	0.28
Total	80	0.14	2.76	314	0.56	10.80

- The most frequently occurring product-related AEs are shown in Table 9.

Table 9. Summary of the Most Frequently Occurring Product-Related AEs

MedDRA Preferred Term	Total Number of AEs	Rate of AEs per Infusion
Infusion site pain	35	0.06
Headache	16	0.03
Infusion site erythema	15	0.03
Pyrexia	5	0.01
Infusion site hematoma	4	0.01
Vomiting	4	0.01
Nausea	4	0.01
Infusion site discomfort	3	0.03
Infusion site edema	3	0.01
Infusion site reaction – swelling and soreness at sites	3	0.01
Infusion site swelling	3	0.01
Abdominal pain upper	3	0.01

Conclusions

- Based on the interim results from the phase III trial reported here, IGHy was well tolerated at infusion volumes, intervals, and rates equivalent to the patients' previous IV administration.
- The majority of patients were able to receive a 3- to 4-week dose into a single site, with good local tolerability (local AEs in 14% of infusions) and a low systemic AE rate (9% of infusions).
- Most local side effects were mild and did not result in slowing or interruption of infusions.
- Data from the final analysis to confirm these results are forthcoming.

References

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