Pooled analysis of a single IVIG 5% and 10% product in patients with primary immunodeficiency and immune thrombocytopenic purpura

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BACKGROUND

Intravenous immune globulin (IVIG) infusions are administered across a broad range of infusion rates depending on the brand, labeling, and patient tolerability. Headache and migraine occurring during IVIG infusions are not uncommon and, in some cases, may be related to the rate of infusion.[1,2]

Four individual studies have supported the efficacy, safety, and tolerability of a branded IVIG product in both adults and children.[3-8] To date, data across all four studies have not been pooled.

PURPOSE

This analysis reviewed the rates of headache and migraine reports across all completed clinical studies, demonstrating tolerability with this product utilizing a 15-minute ramp-up protocol.

METHODS

This was an exploratory, retrospective analysis of data pooled from four clinical trials of the 5% or 10% formulations of the IVIG product (Gammaplex®). Infusion and tolerability data from the four trials, investigating both low-dose and high-dose indications in primary immunodeficiency (PI) and immune thrombocytopenic purpura (ITP), respectively, were collected and pooled (where appropriate).[5-8]

All patients received the IVIG product at the doses summarized in Table 1. The majority of subjects in these trials did not receive premedications.

Table 1. Characteristics of the pooled trials

	Moy 2010[5]	Dash 2014[6]	Melamed 2016[7]	Wasserman 2017[8]
	PI	ITP	PI	PI
Design	Open-label noncomparative	Open-label noncomparative	Open-label noncomparative	Open-label crossover bioequivalence
Patient population	Adult and pediatric ≥3 years	Adult and pediatric 6-69 years	Pediatric 2-16 years	Adult and pediatric 2-55 years
Treatment	IVIG (5% formulation)	IVIG (5% formulation)	IVIG (5% formulation)	IVIG (adult: 5% and 10% formulations; pediatric: 10% formulation only)
Dose[a]	300-800 mg/kg/infusion every 21-28 days	2 g/kg (1 g/kg per infusion on 2 consecutive days)	300-800 mg/kg/infusion every 21-28 days	300-800 mg/kg/infusion every 21-28 days

ITP, immune thrombocytopenic purpura; IVIG, intravenous immune globulin; PI, primary immunodeficiency.
[a]For this analysis, 300-800 mg/kg/infusion every 21-28 days is considered low dose; 1 g/kg/infusion on 2 consecutive days is considered high dose.

Statistical analysis: Infusion and adverse event (AE) data were pooled across four studies. Summaries of infusion protocol were generated to identify the proportion of infusions following the 15-minute escalation rate and reaching the maximum infusion rate. Summaries of tolerability were generated to identify the proportion of infusions with associated AEs, defined as occurring within 72 hours of the end of the infusion, specifically headaches and migraines. When assessing infusion protocol and tolerability, 95% confidence intervals (CIs) for the proportion of infusions were calculated using the Clopper-Pearson (exact) method. All *p* values are descriptive. Differences in tolerability across product, dose categories, infusion order, and PI diagnosis were summarized using a 95% CI for difference of proportions. An overall demonstration of efficacy was tabulated across all relevant studies. All analyses were produced using SAS statistical software, version 9.4 (SAS Institute Inc).

METHODS (continued)

Infusion rate: In these studies, a unique infusion rate ramp-up protocol was utilized that increased every 15 minutes to a maximum rate of 0.08 mL/kg/min, using the protocols shown in Table 2.

Table 2. Infusion rate protocols

	IVIG 5% formulation			IVIG 10% formulation		
	mL/kg/min	mg/kg/hour	Elapsed time (min)	mL/kg/min	mg/kg/hour	Elapsed time (min)
Start	0.01	30	0-15	0.005	30	0-15
Increments	0.02	60	16-30	0.01	60	16-30
	0.04	120	31-45	0.02	120	31-45
	0.06	180	46-60	0.04	240	46-60
				0.06	360	61-75
Maximum	0.08	240	61 to end	0.08	480	76 to end

IVIG, intravenous immune globulin; min, minutes.

RESULTS

The analysis included 1576 infusions. As expected from the trial designs, there were substantial differences in the patient populations across trials. Key characteristics are shown in Table 3.

Table 3. Patient demographics and disease characteristics[5-8]

Characteristic	Moy 2010[5]	Dash 2014[6]	Melamed 2016[7]	Wasserman 2017[8]	Pooled data
Patients, n	50	35	25	48	158
Male, n (%)	26 (52.0)	9 (25.7)	19 (76.0)	20 (41.7)	74 (46.5)
Age, years					
Mean ± SD	44.0±19.1	36.3±18.3	10.4±3.8	30.1±17.3	32.8±20.1
Median (range)	44.5 (9-78)	32.0 (6-69)	11.0 (3-16)	30.5 (3-55)	30.5 (3-78)
Age at enrollment, years, n (%)					
2-5	0	0	3 (12.0)	2 (4.2)	5 (3.2)
6-11	2 (4.0)	2 (5.7)	12 (48.0)	7 (14.6)	23 (14.6)
12-15	2 (4.0)	1 (2.9)	7 (28.0)	6 (12.5)	16 (10.1)
16-34	11 (22.0)	15 (42.9)	3 (12.0)	12 (25.0)	41 (25.9)
35-49	15 (30.0)	7 (20.0)	0	12 (25.0)	34 (21.5)
≥50	20 (40.0)	10 (28.6)	0	9 (18.8)	39 (24.7)
Ethnicity, n (%)					
Asian	0	22 (62.9)	0	0	22 (13.9)
Caucasian	46 (92.0)	10 (28.6)	25 (100)	48 (100)	129 (81.6)
African-American	2 (4.0)	0	0	0	2 (1.3)
Hispanic	2 (4.0)	3 (8.6)	0	0	5 (3.2)
Diagnosis, n (%)					
CVID	46 (92.0)	0	22 (88)	38 (79.2)	106 (67.1)
XLA	4 (8.0)	0	3 (12)	8 (16.7)	15 (9.5)
Other PI	0	0	0	2 (4.2)	2 (1.3)
ITP	0	35 (100)	0	0	35 (22.2)

CVID, common variable immunodeficiency; ITP, immune thrombocytopenic purpura; PI, primary immunodeficiency; XLA, X-linked agammaglobulinemia.

Achievement of the Maximum Infusion Rate

Overall, the maximum infusion rate was achieved in 94.7% of infusions, including 94.6% (1402/1482) of infusions for patients with PI and 95.7% (90/94) of infusions for patients with ITP.

RESULTS (continued)

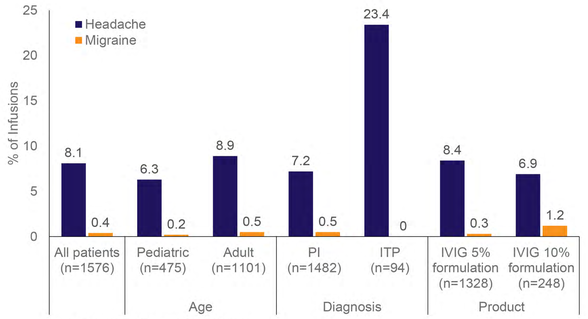
Headache and Migraine

Headache and migraine occurred in 8.1% and 0.4% of infusions, respectively.

Headache rates were significantly different for low-dose (PI) vs high-dose (ITP) infusions (7.2% vs 23.4%, $p<0.0001$, 95%CI -24.9 to -7.59) and first vs subsequent infusions (19.0% vs 6.9%, $p<0.0001$, 95% CI 5.82 to 18.33). There were no significant differences by patient age, whether the maximum infusion rate was reached, or between the 5% vs 10% formulations.

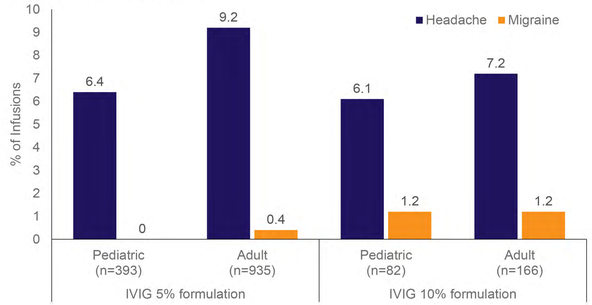
Migraine rates were not significantly different among any of the subgroups assessed, except first vs subsequent infusions (1.9% vs 0.3%, $p=0.026$).

Figure 1: Percentage of Infusions Associated With Headache or Migraine by Subgroup



n values represent the number of infusions.
ITP, immune thrombocytopenic purpura; IVIG, intravenous immune globulin; PI, primary immunodeficiency.

Figure 2: Percentage of Infusions Associated With Headache or Migraine by Patient Age and Product



n values represent the number of infusions.
IVIG, intravenous immune globulin.

Overall Adverse Event Rates

AEs were reported for 25.5% of infusions. AE rates were significantly different for PI (low dose) vs ITP (high dose) (23.5% vs 57.4%, $p<0.0001$, 95% CI -44.2 to -23.7) and first vs subsequent infusions (43.7% vs 23.5%, $p<0.0001$, 95% CI 12.14 to 28.23). There was no significant difference in AE rates between the 5% and 10% IVIG formulations.

AE rates were 24.9% among the 1492 infusions that reached the maximum infusion rate and 35.7% among the 84 infusions that did not reach the maximum infusion rate (95% CI -21.3, -0.30), presumably because rate increases were interrupted if an AE occurred.

DISCUSSION

- AEs such as headache and migraine have been reported with IVIG and in some cases may be related to infusion rate, a key determinant of the overall infusion time for IVIG. If infusion rates are reduced to mitigate AEs such as headaches that occur during an infusion, the overall infusion time is likely to increase. This may, in turn, result in a potential negative impact on patient quality of life as well as healthcare resource utilization.
- This analysis provides a systematic evaluation of headache and migraine in a large population of patients receiving IVIG.
- The maximum infusion rate was achieved in 94.7% of infusions.
- Rates of headache and migraine were low overall and across different diagnoses, infusion rates, and IVIG doses.
  - Rates of headache were ≤8.9% in all subgroups assessed except infusions for ITP (higher doses) and first overall infusions (23.4% and 19.0%, respectively).
  - Rates of migraine were <1.0% in all subgroups assessed except infusions of the IVIG 10% formulation and first overall infusions (1.2% and 1.9%, respectively).
  - IVIG infusions for ITP were associated with higher headache rates than infusions for PI. This could be attributed to a higher IVIG dose for ITP vs PI, enrollment of primarily IVIG-naive patients in the ITP trial, or a combination of both.
- Limitations of this study include the use of a retrospective exploratory analysis, small numbers of patients in some subgroups, and potential bias because of the lack of randomization or blinding.

CONCLUSIONS

- Both the 5% and 10% formulations of this IVIG product were associated with a low rate of headache and migraine across all ages, doses, diagnoses, and other points of comparison when utilizing a 15-minute ramp-up infusion protocol.

References

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