AAAAI 2023
Poster #250

Treatment With Intravenous Immune Globulin 10% In A Real-World Outpatient Setting

Richard F. Herrscher, MD, FACAAI[1]; Kevin Rosenbach, MD[2]; Quyen Luu, MD[3]; Dawn N. Kim-Romo, PharmD, PhD, MS[4]; Lucinda J. Van Anglen, PharmD[4]

[1]AIR Care, Dallas, TX; [2]Naples Allergy Center, Naples, FL; [3]Central Georgia Infectious Disease, Macon, GA; [3]Healix Infusion Therapy, LLC, Sugar Land, TX

Introduction

Intravenous immune globulin 10% liquid (IVIG 10%) is FDA-approved for the treatment of primary humoral immunodeficiency (PI).[1] IVIG 10% (BIVIGAM®) was originally introduced to the US market in 2012 but was voluntarily withdrawn in December 2016 by the original manufacturer. Another manufacturer subsequently acquired IVIG 10%, optimized the manufacturing process, and obtained FDA approval for re-introduction to the US market in May 2019.[2-4]

A multicenter, open-label clinical trial was conducted prior to manufacturing changes demonstrating efficacy, safety, and tolerability of IVIG 10% in patients with PI. Although not reported in the clinical trial, intravenous immunoglobulins have been associated with renal dysfunction and hemolysis. IVIG 10% contains polysorbate 80, which has been associated with blood pressure changes, primarily as hypotension and liver function changes in animals.[1]

The objective of this study was to assess the tolerability of IVIG 10% infused in a real-world outpatient setting.

Methods

A multicenter retrospective, observational study was conducted in patients receiving IVIG 10% between July 2021 and November 2022.

A random sample of patients was selected from patients receiving IVIG 10% (BIVIGAM®) within a national network of immunology and infectious disease physician office infusion centers (POICs).

Data were collected through 6 months of therapy and included the following:

- Baseline demographics and disease characteristics
- Prior immune globulin (IG) therapy
- IVIG 10% therapy details
- Pre-medications and pre- and post-hydration
- Blood pressure measurements
- Available laboratory values including liver function, hematology, and renal function tests
- Adverse events (AEs)

Descriptive statistics were provided as means, standard deviations (SD), medians, interquartile ranges [IQR], and minimum and maximum values for continuous variables. For categorical variables, frequencies and percentages were reported.

The overall rate of AEs per infusion was calculated as the total number of AEs reported divided by the total number of IVIG 10% infusions utilized over the study period.

Figure 1. Study Cohort

Results

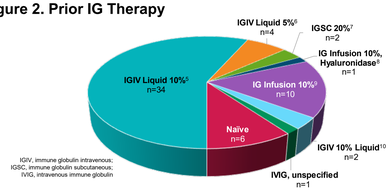
Study Patients

Table 1. Baseline Characteristics

Parameter	IVIG 10% N=60
Age in years, mean ± SD	74 ± 8.2
Female gender, n (%)	49 (82%)
Body mass index in kg/m^2, mean ± SD	27 ± 5.7
Common comorbidities, n (%)	
Hypertension	33 (55%)
Gastroesophageal reflux disease	27 (45%)
Asthma	24 (40%)
Primary Diagnosis, n (%)	
PI Diagnosis	
Common variable immunodeficiency	29 (48%)
Nonfamilial hypogammaglobulinemia	18 (30%)
Selective deficiency of IgG subclasses	11 (18%)
Chronic lymphocytic leukemia	1 (2%)
Dermatomyositis	1 (2%)

- 60 patients initiated IVIG 10%; 48 (80%) completed 6 months of treatment. Twelve discontinued due to the following reasons: AEs (n=5), patient/MD preference (n=4), unrelated death (n=2), and transfer of care (n=1).

Figure 2. Prior IG Therapy



- 6 were naïve to IG replacement therapy prior to starting IVIG 10%.
- 54 patients (51 IVIG, 3 SCIG) had been on IG therapy for a median of 2.4 years (min 0.1, max 8.6).

IVIG 10% Therapy

Table 2. IVIG 10% Dosing and Administration

Parameter	IVIG 10% N=346 infusions
IVIG 10% Dosing	
Number of infusions per patient, mean ± SD	5.8 ± 2.6
Dose in mg/kg, mean ± SD	500 ± 215.2
Dosing interval	
Every 3 weeks, n (%)	47 (14%)
Every 4 weeks, n (%)	293 (85%)
Other, n (%)*	6 (1%)
IVIG 10% Administration	
Maximum infusion rate in mL/hr, mean ± SD	158 ± 28.8
Infusion ramping time in minutes, mean ± SD	80 ± 27.9

*Other includes every 2 weeks (n=5) and every 6 weeks (n=1).

- 1 dermatomyositis patient received IVIG at 2 g/kg divided over 2 days.
- Maximum infusion rates ranged from 100 to 280 mL/hr.
- 78% of infusions were given at a maximum rate of 150 mL/hr, which was per POIC standardized protocol.

Table 3. Medications Prior to IVIG 10% Infusions

Parameter	IVIG 10% N=346 infusions
Infusions with pre-medication, n (%)	265 (77%)
Pre-medications per infusion, mean ± SD	1.7 ± 1.1
Pre-medications	
Acetaminophen, n (%)	194 (56%)
Diphenhydramine, n (%)	207 (60%)
Corticosteroids, n (%)*	145 (42%)
Other, n (%)†	27 (8%)

*Includes IV hydrocortisone (n=68 infusions), IV methylprednisolone (n=52), IV dexamethasone (n=24), PO prednisone (n=1).
†Other includes ondansetron (n=13 infusions), ibuprofen (n=8), famotidine (n=4), loratadine (n=3), cyanocobalamin (n=1), hydrocodone (n=1), levocetirizine (n=1).

- The most common pre-medication utilized by study patients was diphenhydramine (68%, n=41) with 207 infusions.
- 10 patients used no pre-medications during the study period (17%).
- Pre-medications were at the discretion of the prescriber.

IVIG 10% Outcomes

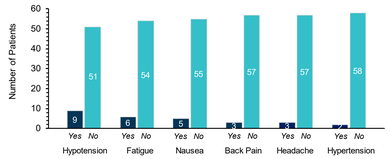
Table 4. Hydration with 0.9% Sodium Chloride

Parameter	IVIG 10% N=346 infusions
Pre-infusion Hydration	
Infusions with 0.9% sodium chloride, n (%)	100 (29%)
Volume in mL, mean ± SD*	383 ± 196.1
Post-infusion Hydration	
Infusions with 0.9% sodium chloride, n (%)	118 (34%)
Volume in mL, mean ± SD†	198 ± 120.5

*Volume statistics based on n=100 patients with pre-infusion hydration.
†Volume statistics based on n=118 patients with post-infusion hydration.

- 17 of 60 patients (28%) received pre-infusion hydration with 250 mL, 500 mL, or 1000 mL of 0.9% sodium chloride.
- 21 of 60 patients (35%) received 100 mL, 250 mL, 500 mL of post-hydration with 0.9% sodium chloride.
- 18% (n=11) received both pre- and post-hydration; 55% (n=33) received no hydration.

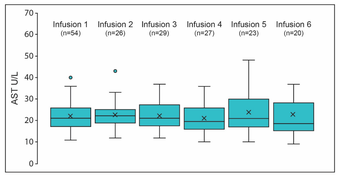
Figure 3. Common Adverse Events



- 46 AEs were reported in 23 patients, equating to an AE per infusion rate of 0.13.
- 2 infusions were interrupted due to AEs (1 hypertension, 1 back pain) and subsequently resumed.
- 5 patients discontinued treatment due to AEs (2 nausea, 1 hypertension, 1 fatigue, 1 headache and aphthous ulcers).

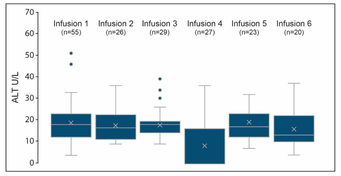
Laboratory Values

Figure 4. Aspartate Aminotransferase (AST)



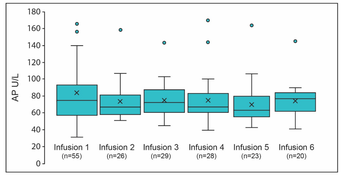
- 45 of 56 patients (80%) maintained normal AST levels through the study period.
- 11 patients had elevated AST levels (3 normalized, 5 fluctuated, and 3 remained elevated over the study period).

Figure 5. Alanine Transaminase (ALT)



- 47 of 56 patients (84%) maintained normal ALT levels.
- 9 patients had elevated levels (2 normalized, 5 fluctuated, 1 had an elevated value at baseline only, and 1 developed elevated levels over time).

Figure 6. Alkaline Phosphatase (AP)



- 46 of 56 patients (82%) maintained normal AP levels.
- 8 patients had elevated values (2 normalized, 2 fluctuated over time, and 4 remained elevated over the study period).
- 2 patients had lower than normal AP levels.

Table 5. Clinical Indices

Laboratory Values	Baseline n=40	Follow-up* n=40	Mean Δ n=40
Hg, g/dL, mean ± SD	12.7 ± 1.3	12.6 ± 1.5	-0.1
Hct, % of RBC, mean ± SD	38.2 ± 3.2	38.1 ± 4.2	-0.1
WBC, 10^3/mm^3, mean ± SD	6.6 ± 2.0	6.8 ± 1.9	0.2
BUN, mg/dL, mean ± SD	18.2 ± 6.0	17.9 ± 5.5	-0.3
SCr, mg/dL, mean ± SD	1.1 ± 1.1	0.9 ± 0.3	-0.2
Blood Pressure	**Pre-infusion n=249**	**Post-infusion n=249**	**Mean Δ n=249**
Systolic in mmHg, median [IQR]	127 [114 - 136]	132 [121 - 143]	6 ± 17.4
Diastolic in mmHg, median [IQR]	69 [62 - 77]	73 [66 - 79]	3 ± 9.8

*Last follow-up laboratory value available from infusion 4, 5, or 6.

- There were no marked changes in laboratory values from baseline through infusions 4 to 6 when follow-up labs were obtained.
- Blood pressure was stable overall with slight increases from pre-infusion to post-infusion for available data.

Discussion

We present outcomes in PI patients who infused IVIG 10% in a physician clinic-based outpatient setting.

- A total of 60 patients received an average of 5.8 infusions. Patients were mostly female, immunoglobulin treatment-experienced, and had a primary diagnosis of PI. Off-label treatment diagnoses included dermatomyositis and chronic lymphocytic leukemia.
- Patients with a diagnosis of PI utilized dosing and treatment intervals consistent with prescribing information.[1]
- Most study patients received infusions at a maximum infusion rate of 150 mL/hr per POIC standardized protocol. This infusion rate was lower than the maximum recommended rate provided in the prescribing information.
- Pre-medications and 0.9% sodium chloride hydration were administered as per the prescriber. Over three-fourths of patients received pre-medications and approximately a third received hydration.
- Overall, the rate of AE per infusion was lower at 0.13 compared to 0.58, which was reported in the clinical trial conducted prior to the manufacturing optimization of IVIG 10%.[1] Five study patients discontinued therapy due to AEs.
- Liver function tests (AST, ALT, ALP) were generally stable throughout with elevations mostly occurring at baseline. No patients required therapy modifications.
- There were no clinically relevant changes in hemolytic or renal function laboratory values over 6 months of therapy.
- No marked changes in blood pressure were observed.

Conclusion

IVIG 10% therapy demonstrated safety and tolerability in patients with PI.

Adverse events were lower than reported in the clinical trial.[1]

Standardized protocols, slower than allowed infusion rates, and an optimized manufacturing process of IVIG 10% may have contributed to the favorable tolerability.

References

1. ADMA Biologics, Inc. Ramsey, NJ. BIVIGAM® (immune globulin intravenous (human) 10% liquid) [prescribing information]. Accessed July 2022.
2. ADMA Biologics, Inc. (2018, July 26) [press release]. Accessed July 2022.
3. Wasserman RL. Expert Rev Clin Immunol. 10(3), 2014.
4. Church JA, et al. J Clin Immunol. 26(4), 2006.
5. Octapharma USA, Inc. Paramus, NJ. Octagam® 10% (immunoglobulin human intravenous) [prescribing information]; March 2022.
6. Octapharma USA, Inc. Paramus, NJ. Octagam® 5% (immunoglobulin human intravenous) [prescribing information]; April 2022.
7. CSL Behring AG. Bern, Switzerland. HIZENTRA® (immunoglobulin human subcutaneous) [prescribing information]; April 2022.
8. Baxalta US Inc. Lexington, MA. HYQVIA® (immunoglobulin human subcutaneous) [prescribing information]; March 2021.
9. Baxalta US Inc. Lexington, MA. GAMMAGARD LIQUID® (immunoglobulin human intravenous) [prescribing information]; March 2021.
10. CSL Behring AG. Bern, Switzerland. PRIVIGEN® (immunoglobulin human intravenous) [prescribing information]; March 2022.

This study was sponsored by ADMA Biologics, Inc. Ramsey, NJ.