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Real-World Utilization of Immune Globulin Intravenous 10% at Physician Office Infusion Centers

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Abstract

Introduction: Immune Globulin Intravenous (human) 10% liquid (IGIV 10%) was FDA-approved in 2012, voluntarily withdrawn in 2016, and reintroduced in 2019 by a new manufacturer with an optimized manufacturing process. Given the manufacturing process changes and utilization of the product in the US, the assessment of post-marketing clinical experience is warranted. The objective of this study is to evaluate post-marketing tolerability of IGIV 10% in a real-world setting.

Methods: We conducted a retrospective observational review of a random sample of patients who received IGIV 10% from 8/2021-5/2022 at physician office infusion centers (OICs) throughout the US. Study data from electronic medical records included demographics, therapy details, and infusion-related adverse events (AEs).

Results: Twenty-three of 96 IGIV 10% patients were randomly-selected from 9 OICs. The mean age was 74±5.3 years with 78% female. Common comorbidities included hypertension (74%) and gastroesophageal reflux disease (61%). One patient was immune globulin (IG) naïve, and 22 patients (96%) were IG-treatment experienced. Most (91%) had primary immunodeficiencies, with one chronic lymphocytic leukemia and one dermatomyositis. The mean IGIV 10% dose was 432±129.2 infused every three or four weeks. IGIV 10% infusions were titrated over an average of 78±28.8 minutes with an average maximum infusion rate of 154±18.8 mL/hr. During the study, patients received a mean of 7±2 infusions. Of 155 infusions, five AEs were reported (fatigue, headache, nausea, dizziness) during 4 infusions (17%) for an overall AE rate per infusion of 3%.

Conclusions: IGIV 10% was successfully administered to patients in OICs and was well-tolerated over multiple infusions.

Introduction

Immune globulin intravenous 10% liquid (IGIV 10%) is FDA-approved for the treatment of primary humoral immunodeficiency (PID) [1]. IGIV 10% (BIVIGAM®) was originally introduced to the US market in 2012 but was voluntarily withdrawn in December 2016 by the original manufacturer.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 IGIV 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 formulation changes demonstrating efficacy, safety, and tolerability of IGIV 10% in patients with PID. Although not reported in the study, intravenous immunoglobulins have been associated with renal dysfunction and hemolysis. IGIV 10% contains polysorbate 80, which has been associated with blood pressure changes, primarily hypotension and liver function changes only in large amounts in animals [1].

The objective of this study is to evaluate post-marketing tolerability of IGIV 10% in a real-world setting.

Methods

A multicenter retrospective, observational review was conducted of PID patients receiving IGIV 10% between July 2021 and May 2022.

A random sample of patients was selected from 96 patients receiving IGIV 10% (BIVIGAM®) within a national network of physician office infusion centers (POICs).

Data was collected for all available infusions and included the following:

- Baseline demographics
- Disease characteristics
- IGIV 10% therapy details
- Pre-medications and pre- and post-hydration
- Vital signs prior, during, and after infusion
- Laboratory values through 6 infusions, including liver function tests, hematology, and renal function
- Infusion-related adverse events (AEs)

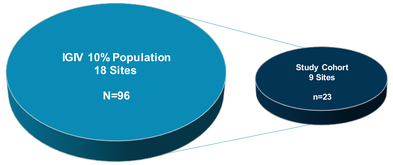
Descriptive statistics are provided as means, standard deviations (SD), medians, and interquartile ranges (IQRs) for continuous variables. For categorical variables, frequencies and percentages are reported.

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

Results

Study Cohort

Figure 1. Study Population



- Study patients were randomly selected from a total of 96 receiving IGIV 10%

Table 1. Baseline Demographics and Disease Characteristics

Parameter	IGIV 10% N=23
Age in years, mean ± SD	74 ± 5.3
Female gender, n (%)	18 (78%)
Body mass index in kg/m^2, mean±SD	29 ± 4.1
Common comorbidities, n (%)	
Hypertension	17 (74%)
Gastroesophageal reflux disease	14 (61%)
Primary Diagnosis, n (%)	
PID-related	
Common variable immunodeficiency	8 (35%)
Selective deficiency of IgG subclasses	7 (31%)
Nonfamiliial hypogammaglobulinemia	6 (27%)
Chronic lymphocytic leukemia	1 (4%)
Dermatomyositis	1 (4%)

- The majority of patients (91%, n=21) had PID; 1 had chronic lymphocytic leukemia and 1 dermatomyositis
- 21 patients (91%) received IGIV 10% following treatment with another intravenous immunoglobulin (IG) product; 1 patient used subcutaneous IG and 1 was naïve to IG therapy
- Pre-medications were continued from prior immunoglobulin therapy in 11 patients (48%), with minor changes in the remainder

IGIV 10% Treatment

Table 2. IGIV 10% Dosing and Administration

Parameter	IGIV 10% N=23
IVIG 10% Dosing	
Number of infusions, mean±SD	6.7 ± 2.0
Dose in mg/kg, mean±SD	432 ± 129.2
Dosing interval	
Every 3 weeks, n (%)	4 (17%)
Every 4 weeks, n (%)	19 (83%)
IVIG 10% Administration	
Maximum infusion rate in mL/hr, mean±SD	154 ± 18.8
Infusion ramping time in minutes, mean±SD	78 ± 28.8

- Patients received a range of 1 to 11 infusions over the study period
- 1 dermatomyositis patient received IGIV at 2 g/kg divided over 2 days
- Maximum infusion rates ranged from 112 to 240 mL/hr
- Most patients infused at a maximum rate of 150 mL/hr, which was protocol-driven

Pre-medications

Table 3. Medications Prior to IGIV 10% Infusions

Parameter	IGIV 10% N=155 Infusions
Pre-medications	
Infusions with premedication, n (%)	114 (74%)
Pre-medications per infusion, mean±SD	2 ± 1.1
Medications	
Acetaminophen, n (%)	108 (70%)
Diphenhydramine, n (%)	93 (60%)
Corticosteroids, n (%)	
Methylprednisolone	39 (25%)
Hydrocortisone	31 (20)
Dexamethasone	4 (3%)

- Pre-medications were provided to 19 patients (83%) in 114 of 155 infusions (74%)
- Acetaminophen was the most utilized pre-medication in 108 of 155 infusions (70%) and in 18/23 patients (78%)

Pre- and Post-hydration

Table 4. Hydration with 0.9% Sodium Chloride

Parameter	IGIV 10% N=155 Infusions
Pre-infusion Hydration	
Infusions with 0.9% sodium chloride	53 (34%)
Volume (mL), mean±SD	92 ± 133.7
Post-infusion Hydration	
Infusions with 0.9% sodium chloride	96 (62%)
Volume (mL), mean±SD	108 ± 103.8

- 8 of 23 patients (35%) received pre-infusion hydration in 53 of 155 infusions with 250 or 500 mL of 0.9% sodium chloride
- 13 of 23 patients (57%) received 100 or 250 mL of post-hydration with 96 of 155 infusions
- Less than a third (30%, n=7) received both pre- and post-hydration therapy; 9 patients received no hydration
- Hydration therapy remained consistent over the patient visits

Vital Signs

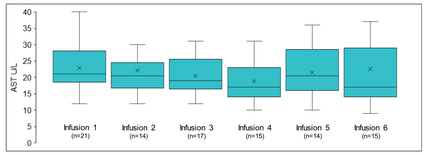
Table 5. Blood Pressure

Parameter	IGIV 10% Infusions
Pre-infusion, n=151	**median [IQR]**
Systolic blood pressure in mmHg	131 [122-137]
Diastolic blood pressure in mmHg	72 [66-79]
Mid-infusion, n=102	**median [IQR]**
Systolic blood pressure in mmHg	136 [124-149]
Diastolic blood pressure in mmHg	75 [69-80]
Post-infusion, n=102	**median [IQR]**
Systolic blood pressure in mmHg	131 [119-148]
Diastolic blood pressure in mmHg	74 [66-79]
Pre- and Post- Difference, n=102	**mean±SD**
Change in systolic blood pressure in mmHg	9 ± 19.1
Change in diastolic blood pressure in mmHg	3 ± 10.3

- Minimal changes were observed in blood pressure from pre- to post-infusion
- Midpoint blood pressure measurements were comparable to pre- and post-measurements

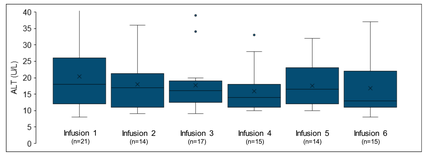
Laboratory Values

Figure 2. Aspartate Aminotransferase (AST)



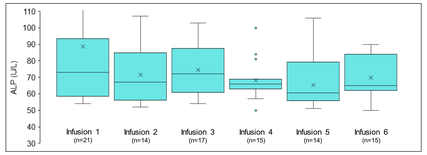
- 15 of 21 patients (71%) had normal AST levels during the study period
- 2 patients had elevated AST levels at baseline, which remained elevated during the study period

Figure 3. Alanine Transaminase (ALT)



- 19 of 21 patients (90%) had normal ALT levels during the study period
- 1 patient had elevated ALT at baseline decreasing to WNL at infusion 3
- 1 patient developed slightly elevated values throughout the study period

Figure 4. Alkaline Phosphatase (ALP)



- 15 of 21 patients (71%) had normal AST levels during the study period
- 3 patients had elevated values, with 2 normalizing and 1 fluctuating over time

Table 6. Laboratory Values

Parameter	Baseline Mean±SD n=22*	Infusion 6 Mean±SD n=17†	Mean Δ n=17
Hg, g/dL	12.8 ± 1.4	13.0 ± 1.6	0.1
Hct, % of RBC	38.5 ± 3.5	39.3 ± 4.6	0.7
WBC, 10^3/mm^3	6.3 ± 1.9	6.6 ± 1.8	0.2
BUN, mg/dL	16.3 ± 4.0	17.2 ± 6.0	1.1
SCr, mg/dL	0.8 ± 0.2	0.9 ± 0.3	0.0

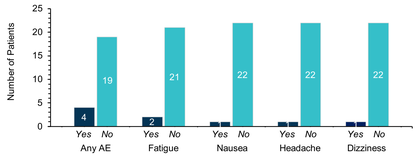
Δ = change, Hg = hemoglobin, g/dL = grams per deciliter, Hct = hematocrit, RBC = red blood cell, WBC = white blood cell, 10^3/mm^3 = thousand cells per cubic millimeter, BUN = blood urea nitrogen, mg/dL = milligrams per deciliter, SCr = serum creatinine

*Labs within 1 month of baseline unavailable (n=1)
†Labs not available due to discontinuation (n=2), not drawn (n=10), infusion 6 not yet reached (n=3)

- There were no clinically relevant changes in lab values from baseline
- Renal function, hemoglobin, and hematocrit remained stable from baseline to infusion 6

IGIV 10% Tolerability

Figure 5. Adverse Events



- 5 AEs occurred in 4 patients during 4 infusions: fatigue and nausea (n=1), fatigue only (n=1), headache (n=1), dizziness (n=1)
- No patients discontinued IGIV 10% due to AEs; 1 discontinued for patient preference and 1 expired unrelated to IGIV 10%
- The overall rate of AEs per infusion was 3.2 for 155 infusions

Discussion / Conclusion

We present utilization and tolerability of IGIV 10% in the physician OIC setting.

- A total of 23 patients received an average of 6.7 infusions, with dosing and treatment intervals consistent with prescribing information [1].
- Patients were primarily female, immunoglobulin treatment-experienced, with a primary diagnosis of PID. Off-label treatment diagnoses included dermatomyositis and chronic lymphocytic leukemia.
- Pre-medications and pre- and/or post-infusion hydration therapy were commonly administered according to standard practice in each OIC.
- The maximum infusion rate was 150 mL/hr for the majority of patients. This conservative infusion rate is lower than the maximum recommended in the prescribing information and along with administration of pre-medications and hydration may have had a beneficial impact on tolerability [1].
- There were no marked changes in blood pressure observed during the infusions and no evidence of hypotension.
- Liver function tests (AST, ALT, ALP) were generally stable throughout with elevations in 11 patients (most of which were at baseline). No patients required therapy modifications.
- There were no clinically relevant changes in renal function and no evidence of hemolysis.
- Overall AE rate was low with very mild occurrences, none of which required discontinuation. This is also less than that reported in the clinical trial of IGIV 10% [1].

In conclusion, IGIV 10% treatment at physician office infusion centers demonstrated good safety and tolerability in patients with PID over multiple infusions.

References

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