

Observational Study of Intravenous Immunoglobulin 5% for Alleviating Adverse Drug Reactions in Primary Immunodeficiency Disorders

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Abstract

Background: Intravenous immunoglobulin (IVIG) preparations are used to treat individuals with primary immunodeficiency disorders (PIDD) by increasing low immunoglobulin levels. This observational study was designed to assess the change in adverse drug reactions (ADRs) in subjects switching from IVIG 10% to IVIG 5% and explore potential underlying mechanisms.

Methods: The primary endpoint was the change in ADRs between IVIG 10% (various products) and IVIG 5% (Octagam 5%) as assessed by a severity rating scale (1=none, 2=mild, 3=moderate, 4=severe). The recruitment goal was 15 subjects receiving IVIG 10% who had experienced ADRs up to 72 hours post-infusion. Subjects were then switched to IVIG 5% at the next scheduled infusion and continued on this regimen for a total of 6 infusions. Secondary endpoints included changes in C1 esterase inhibitor (C1-INH), SF-36 Quality of Life (QOL) assessments, and measurement of inflammatory biomarkers.

Results: Fifteen subjects were enrolled in the study with a mean age of 51 years. While on IVIG 10%, 15 subjects reported headache, fatigue, generalized pain, and 13 reported joint pain with average severity scores of 3.13, 3.20, 2.87, and 2.20, respectively. After switching to IVIG 5%, the average severity scores for these ADRs significantly decreased: 1.33 ($P<0.0001$), 1.33 ($P<0.0001$), 2.00 ($P=0.0037$), 1.80 ($P=0.2141$). C1-INH decreased significantly and all SF-36 domain scores improved on IVIG 5%.

Conclusion: IVIG 5% may be an alternative to subcutaneous immunoglobulin for subjects who develop ADRs on IVIG 10% preparations. Having multiple therapeutic options for patients with PIDD may improve compliance and continuity of therapy. In our study, there was a lower incidence of ADRs and improvement in QOL with use of IVIG 5%. C1-INH may play a role in the mechanism of ADRs, indicating a potential subset of patients more susceptible to C1-INH down regulation via IVIG 10% who may benefit from switching to IVIG 5%.

Keywords: IVIG 5%; Octagam; Primary immunodeficiency disorders; Adverse reactions; SCIG

Introduction

In the United States (US), it is estimated that approximately 1 in 1,200 people have been diagnosed with primary immunodeficiency disorders (PIDD), yielding a population prevalence between 150,000 and 360,000 [1]. PIDD includes a heterogeneous group of inherited disorders with deficiencies in one or more components of the immune system which increases susceptibility to infections and a predisposition to autoimmune diseases and malignancies [2-5]. There are at least 150 different forms of PIDD [6]. One common form of PIDD is common variable immune deficiency (CVID), which is characterized by infections, gastrointestinal disorders, autoimmune disease, and increased susceptibility to malignancies; another form is hypogammaglobulinemia and/or defective antibody production [3,7,8].

Individuals with PIDD are treated with immunoglobulin G (IgG) preparations which act to replace low or missing antibodies, and reduce infection rates for all forms of PIDD [5-7,9]. The standard of care for more than 20 years has been intravenous immunoglobulin

(IVIG), and it is now the treatment of choice for individuals with PIDD whose humoral immunity is impaired [10-13]. Dosing for IVIG for replacement therapy in patients with PIDD ranges from 300-800 mg/kg body weight with higher doses of 2 g/kg body weight for additional approved conditions such as chronic inflammatory demyelinating polyneuropathy (CIDP), multifocal motor neuropathy (MMN), and immune thrombocytopenic purpura (ITP) [14,15]. High doses have been found to downregulate autoimmune antibodies related to these disorders [14,15].

The mechanisms which result in adverse drug reactions (ADRs) are unclear [8,16-19]. Adverse reactions are more likely to occur in patients who have not previously received IVIG and who have a bacterial infection and/or underlying inflammation [12]. Other factors that may contribute to adverse reactions include higher concentrations and rapid infusion rates [12]. It is not uncommon for patients to experience headaches after IVIG therapy [8,18]. These headaches may vary in intensity from mild to severe, including rare episodes of aseptic meningitis [9]. Additional ADRs may include fatigue, fever, skin rashes, and muscle aches [18]. These ADRs may not be serious, but will likely lead to some patients stopping the infusion and requiring specific treatment [16,20]. Prior pharmacokinetic, safety, and

tolerability studies have shown that patients with PIDD initiated on IVIG 10% can safely switch to a lower concentration IVIG 5% without change in bioequivalence and furthermore, alleviate ADRs [10,17] If patients continue to have moderate to severe ADRs from IVIG preparations, they can then switch to a subcutaneous immunoglobulin (SCIG) preparation [18].

The mechanisms leading to undesirable ADRs with IVIG are unclear but could depend on the differences in manufacturing between products, stabilizers used, etc. In addition, there are certain complement proteins (e.g., C1) and inflammatory biomarkers (e.g., C-reactive protein [CRP], tumor necrosis factor alpha [TNF α], interferon gamma [INF γ]) that are involved in the immune response and inflammatory processes that can be associated with infections or IVIG ADRs [8,21-24]. Recently, in patients with CVID, the C1-esterase inhibitor (C1-INH) has been linked to antibody deficiencies and preliminary research suggests that C1-INH deficiency may be part of immune deficiency [8,25]. C1-INH is a protease inhibitor belonging to the serpin superfamily, and its main function is the inhibition of the complement system to prevent spontaneous activation (i.e., alteration of blood flow, inflammation, and tissue lesions) [8,21]. There is a noted relationship indicating IVIG therapy may downregulate C1-INH or C1-INH function levels, and this downregulation may be associated with increased ADRs, such as headaches and fatigue [8]. Additionally, increased CRP levels were found to be associated with respiratory impairment and more frequent bronchial inflammatory disease [22]. Lastly, TNF α and INF γ , which are both pro-inflammatory biomarkers, may be useful in predicting which patients may be more susceptible to ADRs [23,24].

Although IVIG therapy is generally considered a safe and effective treatment for patients with PIDD, the incidence of reported ADRs varies with the majority being mild and reversible [18,26]. Most reported ADRs are related to the infusion rate, while others may be related to the dosage or selected IVIG product (due to difference in manufacturing processes and final composition) or stabilizer [18,27]. In this study, the main objective was to explore subject responses to the change in IVIG products from IVIG 10% (various preparations) to a specific IVIG 5% preparation (Octagam 5%). The primary endpoint was the change in number of ADRs post-infusion between IVIG 10% and IVIG 5%. Secondary endpoints included changes in total serum concentration of C1-INH, and C1-INH enzymatic function (C1-INHF), up to 30 minutes pre-infusion and 30 minutes post-infusion to assess the percentage of mean normal activity. In addition, changes in inflammatory markers (CRP, TNF α and INF γ levels) and the Short Form- 36 (SF-36) Quality of Life (QOL) survey were also assessed.

Materials and Methods

Study design

This single center, observational study was conducted to explore responses to the change from IVIG 10% to IVIG 5% in patients who were experiencing ADRs (ClinicalTrials.gov: NCT03339778). The protocol for this study was approved by an Independent Review Board (IntegReview), and each participant provided written informed consent to participate in the study. Study staff and subjects were aware of the study treatment (unblinded) and procedures. Study subjects who experienced ADRs during an infusion of IVIG 10%, or within 72 hours post-infusion, who met inclusion criteria, and signed the informed consent, were asked to return to the site for a blood draw prior to the first infusion of IVIG 5%. The detailed procedures of each study visit

are shown in Table 1. The length of study participation after enrollment for the included subjects was 6-7 months depending on infusion cycles. Subjects had an end of study visit after the sixth infusion and completed the study at that time.

Study subjects who had experienced ADRs during IVIG 10% infusions were switched to IVIG 5% per primary investigator guidance on the next scheduled infusion and continued on IVIG 5% for a total of six infusions. If the participant continued to have non-serious ADRs after two infusions with IVIG 5%, they were eligible to switch to SCIG and be withdrawn from the study. If a serious ADR occurred, the principal investigator evaluated whether the subject should continue participation or be withdrawn from the study and pursue alternative treatment options. If the subject experienced an ADR during IVIG 5% treatment or 72 hours post infusion he or she returned to the site for biomarker collection and ADR evaluation.

| Study visit | Schedule of assessments |
|--|--|
| Screening visit | Informed Consent/Assent |
| | Demographics, Medical History, Current Medications |
| | Physical Examination, Vitals, Weight |
| | Screening Labs/Serum Pregnancy Test |
| | SF-36 QOL Questionnaire |
| Visits 1-6 | Distribution/Training for Patient Diary |
| | Physical Examination, Vitals, Weight |
| | Urine Pregnancy Test (WOCBP Only) |
| | SF-36 QOL Questionnaire |
| | Safety Labs |
| | Biomarker Labs (Visit 6 Only) |
| | Pre-Infusion C1-INH |
| | IVIG 5% Infusion |
| | Patient Diary Review/Distribution |
| | Collection/Recording of Adverse Reactions |
| Review of Concomitant Medications/Medication Changes | |
| End of study visit | Post-Infusion C1-INH |
| | Occurred 21-26 Days After Infusion 6 |
| | SF-36 QOL Questionnaire |
| | Final Collection of Patient Diary |
| QOL: Quality of Life; WOCBP: Women of Childbearing Potential; IVIG: Intravenous Immunoglobulin; C1-INH: C1-inhibitor | |

Table 1: Schedule of assessments by study visit.

Study products

Any IVIG 10% product approved by the Food and Drug Administration (FDA) was permitted. Administration rates were determined using each product's Prescribing Information (PI) insert.

IVIg 5% (Octagam 5%) is FDA approved and used for replacement therapy in patients with PIDD.

In this study, subjects who were eligible to switch from IVIg 10% to IVIg 5% received the same equivalent prescribed dose (between 300-800 mg/kg body weight every 21 ± 3 days or 28 ± 3 days).

Subject selection

The recruitment goal was 15 subjects who were eligible to participate if they were diagnosed with CVID and/or hypogammaglobulinemia (according to criteria from International Union of Immunological Societies [IUIS]) [5], between the ages of 10 to 75 years, receiving IVIg 10%, and had experienced moderate to severe ADRs including headaches, fatigue, joint pain, hives, gastrointestinal disorders and cognitive disorders/confusion from the 10% IVIg during or 72 hours post-infusion. Subjects were required to be on 10% IVIg therapy every 21 ± 3 days or 28 ± 3 days at doses ranging from 300 to 800 mg/kg/body weight.

Subjects were excluded if they reported an acute infection requiring antibiotic therapy within seven days prior to Visit 1. Additional exclusions included a history of anaphylactic or severe systemic reactions to human immunoglobulin, IgA deficient subjects with antibodies against IgA and a history of hypersensitivity. Females who were pregnant or lactating were excluded, and subjects who reported exposure to blood or any blood product or plasma derivatives other than IVIg treatment for PIDD within the last month of the ADR on IVIg 10% were also excluded.

Study endpoints

Adverse drug reactions: The primary endpoint was assessed by a rating scale (1=none, 2=mild, 3=moderate, 4=severe) which evaluated the change in number of ADRs post-infusion between IVIg 10% and IVIg 5%. Subject were given a paper diary, or access to an e-diary, to record assessments, symptoms, medication changes, and visits to the hospital/doctor. The paper diary, or equivalent e-diary, was used to capture daily changes in concomitant medications, potential ADRs, and hospital/doctor visits. Diaries were given to subjects at screening and reviewed/collected at each visit.

Subsequently, subjects received a new (paper) diary after the previous one had been collected. A final (paper) diary was distributed at Visit 6 and collected and reviewed at the End of Study (EOS) Visit. The paper diary/e-diary contained a rating scale for any potential symptoms that participants may report. If study staff were alerted through the review of the subject diary/e-diary of an occurrence of an ADR, a follow-up phone call post-infusion by the study staff was completed.

The investigator was responsible for the detection and documentation of events meeting the criteria and definitions of an adverse event, ADR, serious adverse event, or serious suspected adverse reaction as defined in the protocol. All adverse events, whether volunteered, elicited, or noted on physical examination, and regardless of causality or seriousness, were assessed and recorded in the source beginning with informed consent/assent through to the EOS Visit. Only adverse events that, in the opinion of the investigators, constituted an ADR were cause for changing the infusion product to IVIg 5% or drawing biomarkers at screening and study visits 1 through 6.

C1-INH and C1-INH function: Changes in total serum concentration of C1-INH and C1-INH function (C1-INHF) were documented up to 30 minutes pre-infusion and 30 minutes post-infusion to assess percent of mean normal activity between the use of IVIg 10% and IVIg 5%.

To detect changes in C1-INH, nephelometry testing was utilized. In this test, protein in the human serum sample form immune complexes with specific antibodies. The complexes scatter a beam of light passed through the sample. The intensity of the scattered light is proportional to the concentration of the relevant protein in the sample. The result is evaluated by the comparison with a standard of known concentration [28].

The C1-INH Enzyme Immunoassay (EIA) (MicroVue EIA Plus) was utilized to measure functional levels of C1-INH protein present in the samples. The assay is a four-step procedure. Following incubation and wash cycles, in the fourth step a chromogenic enzyme substrate is added. The color intensity of the reaction mixture is proportional to the concentration of functional C1-INH protein present [29,30].

Inflammatory Markers (CRP, TNF α and INF γ levels): Changes in levels of inflammatory markers (CRP, TNF α and INF γ levels) were assessed during therapy with IVIg 10% and IVIg 5%. CRP, TNF α and INF γ levels were all determined using enzyme-linked immunosorbent assay (ELISA), a well-established tool, with an enzyme as the reporter label, for measurements of analytes in samples [30].

SF-36 Quality of Life Survey: The subjects received a paper or link to an e-diary, which was used to capture the SF-36 QOL assessment prior to each visit and also the 24-, 48-, 72-hour post assessments. These assessments were reviewed by the study staff so they could complete the necessary documentation. If the electronic diary malfunctioned, the subject had the opportunity to complete the assessments on a paper document or record events in the paper diary. In this study, we evaluated the difference between IVIg 10% and IVIg 5% at the end of the study. The SF-36 is based on a scale of 0-100 for different quality of life assessments, with 0 being maximum disability.

Statistical analysis

Unadjusted descriptive statistics were conducted to summarize the endpoints for the final subjects to create mean, standard deviation (SD) for continuous variables, and percentages for categorical variables. Differences between subjects were tested using Student's t test for continuous variables and Fisher's exact tests were used for categorical variables. Analyses were conducted using SAS 9.4 software (SAS Institute, Cary, NC). A two-sided P value <0.05 was considered statistically significant.

Results

Study population

Thirty-two subjects were screened between 01/01/2015 to 12/31/2016 and 5 subjects terminated early due to logistical issues not related to study drug. The 15 subjects enrolled in the study included 6 males and nine 9 females with the mean age of 51.47 years (SD 10.91 years). Twelve subjects (80%) were diagnosed with CVID and 3 (20%) were diagnosed with hypogammaglobulinemia (Table 2). The autoimmune diseases were identified as the following: 73% (n=11) of the subjects with gastrointestinal (GI) disease, 93% (n=14) with neuroimmune diseases, 73% (n=11) with joint pain, and 87% (n=13)

subjects with some other autoimmune component such as thyroid or skin problems. Based on the study criteria, all subjects were switched from IVIG 10% to IVIG 5%. The clinical changes noted were collected from clinical interviews during and after infusions and subject diaries.

| Characteristics | Total Patients (N=15) |
|--|-----------------------|
| Age (years), mean SD, range | 51.47 ± 10.91 (35-74) |
| Gender | n (%) |
| Male | 6 (40%) |
| Female | 9 (60%) |
| Diagnosis | n (%) |
| CVID | 12 (80%) |
| Hypogammaglobulinemia | 3 (20%) |
| Biomarker Lab Levels (Pre-Treatment) | |
| IVIG 10% | |
| Serum C1-INH, n (%) | 11 (73%) |
| Serum C1-INH, mean, SD | 26.72 ± 2.57 |
| C1-INH Function, n (%) | 8 (53%) |
| C1-INH Function, mean SD | 90.13 ± 10.19 |
| IVIG 5% | |
| Serum C1-INH, n (%) | 12 (80%) |
| Serum C1-INH, mean SD | 24.42 ± 2.35 |
| C1-INH Function, n (%) | 10 (67%) |
| C1-INH Function, mean SD | 88.70 ± 5.66 |
| SD: Standard Deviation; CVID : Common Variable Immune Deficiency; C1-inhibitor: C1-INH | |

Table 2: Patient baseline characteristics.

Study endpoints

The ADRs noted for the subjects on IVIG 10% were headaches (n=15, 100%), fatigue (n=15, 100%), joint pain (n=13, 87%), generalized pain (n=15, 100%) and other (n=11, 73%). The ADRs in the "other" category (n=11, 73%) included the following: cognitive impairment/confusion (n=3, 20%), GI (n=1, 7%), hives (n=3, 20%), nausea (n=3, 20%), nausea +cognitive impairment/confusion (n=1, 7%). The rating scale was used and collected from subjects while experiencing these ADRs and the mean rating scale score for each of these ADRs are shown in Figure 1. As subjects were switched to IVIG 5%, the mean rating scale score decreased for all ADR categories, and the mean change (Δ) was shown to be statistically significant for headaches (Δ 1.80, $P < 0.0001$), fatigue (Δ 1.87, $P < 0.0001$), and generalized pain (Δ 0.87, $P = 0.0037$). Out of the subjects that had other ADRs (n=11), 9 subjects (82%) had resolution or improvement of their ADRs. There were 2 subjects who did not experience a change in their ADRs (cognitive and GI).

Serum C1-INH protein levels were measured in 11 subjects, and serum C1-INHF levels were measured in 8 subjects during pre-

treatment of IVIG 10% (Table 1). In the pre-treatment phase of IVIG 5%, there were 12 subjects with serum C1-INH levels and 10 subjects with C1-INHF levels measured (Table 1). As seen in Figure 2, the mean change between the pre- and post-treatment IVIG 10% and IVIG 5% for C1-INH and C1-INHF were shown to be statistically significant. The Δ in C1-INH level was 2.9 units less on IVIG 5% (1.8 ± 1.5) versus IVIG 10% (4.7 ± 2.5) and the Δ in C1-INHF was 1.9 units less on IVIG 5% (6.4 ± 2.0) versus IVIG 10% (8.3 ± 5.1) ($P = 0.0221$).

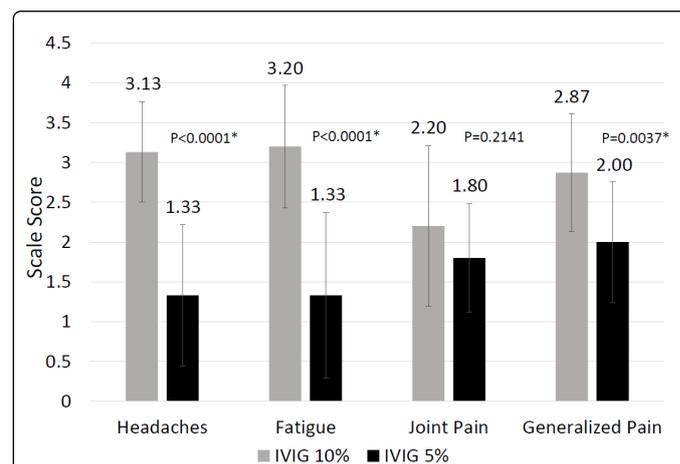


Figure 1: Rate of adverse drug reactions with IVIG 10% and IVIG 5% (N=15). *P value < 0.05 was considered statistically significant; scale 1-4: 1=none, 2=mild, 3=moderate, 4=severe.

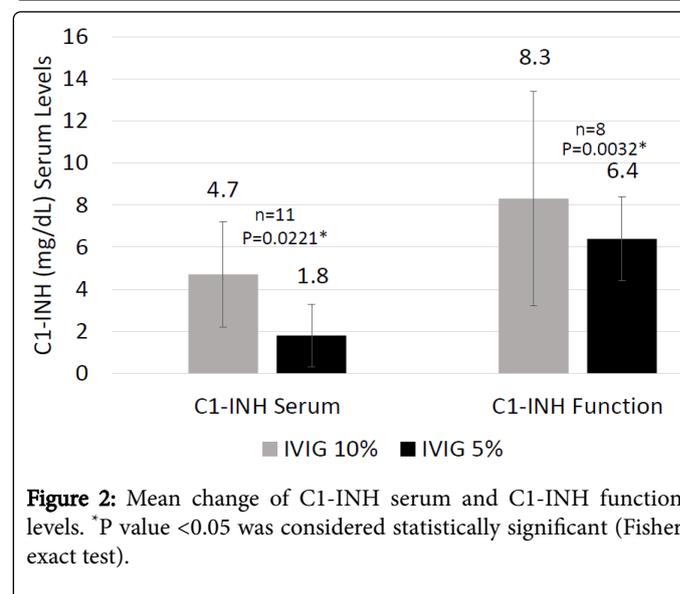
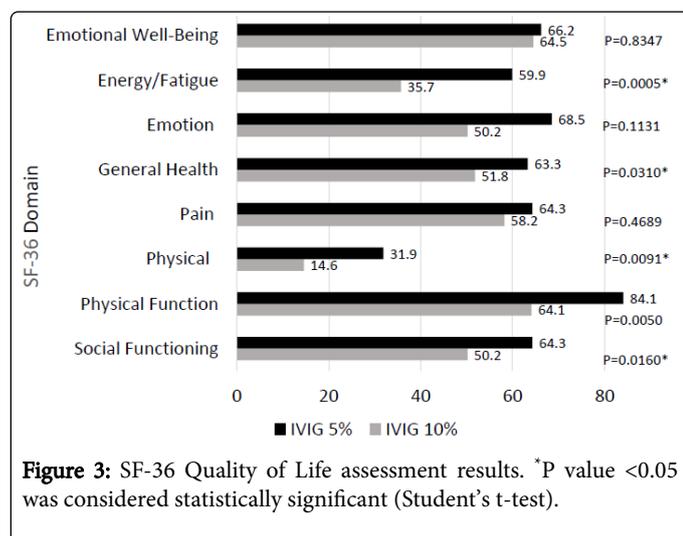


Figure 2: Mean change of C1-INH serum and C1-INH function levels. *P value < 0.05 was considered statistically significant (Fisher exact test).

The number of inflammatory markers (CRP, TNF α , INF γ) collected were very small in number. For example, only 10 subjects had CRP levels, 5 subjects had TNF α levels, and 5 subjects had INF γ levels. There was a consistent decrease in levels for subjects in IVIG 5% compared to IVIG 10%. The mean CRP levels for IVIG 10% were 2.5 ± 1.7 and 1.3 ± 1.0 units for IVIG 5% (Δ 1.2, $P = 0.0201$); 5.2 ± 1.7 and 3.4 ± 0.6 units for TNF α (Δ 1.8, $P \leq 0.001$); and 8.1 ± 1.1 and 5.1 ± 1.7 units for INF γ (Δ 3.0, $P = 0.0011$).

The SF-36 results demonstrated increased QOL measurements with IVIG 5% for all domains assessed (Figure 3). SF-36 domains with statistically significant improvement following the switch to IVIG 5% included general health ($P=0.0310$), energy ($P=0.0005$), physical function ($P=0.0050$), physical role ($P=0.0091$), and social functioning ($P=0.0160$).



Discussion

The mainstay of treatment of PIDD is IgG replacement therapy. Recently, a range of IgG administration options has changed the treatment landscape in PIDD by tailoring treatments to each patient with the goal of preventing infections and minimizing side effects [31]. Most importantly, consistent dosing of IgG is needed, and patient compliance is a key factor. Since the early 1980's, with the introduction of IVIG as the standard treatment approach for PIDD in the US, the primary goal of IgG treatment is to improve patient outcomes by decreasing infections. The availability of different products and modes of administration of IgG can facilitate individualized customization of treatment based on patient outcomes and patient preference. While administration of IVIG is generally well tolerated, some patients will experience moderate to severe side effects including headaches, fever, sinus tenderness, cough, myalgias, and malaise [31,32]. Headache is frequently associated with IVIG administration and premedication with acetaminophen or non-steroidal anti-inflammatory drugs may be suitable for patients with this type of adverse reaction. However, some patients experience severe ADRs that are not ameliorated with premedication [10].

This study was designed to determine if IVIG 5% may be an alternative option for patients who experience ADRs on IVIG 10% preparations, but still prefer IVIG delivery versus SCIG. The specific IVIG 5% preparation used in this study was Octagam 5%. Previously published safety studies for Octagam 5%, including Debes et al. [33] and Frenzel et al. [34], have shown an overall favorable tolerability profile with low frequencies of ADRs. The results of this study reaffirm these findings.

There have been a limited number of studies that have compared IVIG 5% to IVIG 10% [10,17]. Past studies, including our own, have indicated a higher rate of ADRs associated with infusions of IVIG 10% compared to less concentrated formulations [10,16,17,20,27,33]. Moreover, whether frequency of serious but less common ADRs is

higher with concentrated IVIG products remains unclear. Although the number of infusion-associated with ADRs was lower with the 5% product in prior clinical trials, the authors concluded that both products were safe, tolerable, and pharmacokinetically bioequivalent [10,17]. In Alsina et al. [17], the biggest difference between the two concentrations occurred with the ADR of headache (17% on IVIG 10% vs. 0% on IVIG 5%). We previously conducted a retrospective study evaluating patients treated with IVIG 10% who were then switched to an IVIG 5% product [10]. Twelve (12) subjects were included in this study: eight with CVID and four with hypogammaglobulinemia; the rate of ADRs on IVIG 10% was much higher and was reduced when patients were switched to IVIG 5% [10].

There are some key findings from our study related to the studies mentioned above. First, subjects receiving IVIG 10% had higher incidences of ADRs, with all patients experiencing headaches, fatigue, and generalized pain. When the patients were switched to IVIG 5%, there were statistically significant reductions, improvement, and resolution of these ADRs, exhibiting a statistically validated clinical benefit. Another important finding is the correlation of the QOL scores with the improvement in ADRs in patients receiving IVIG 5%. Statistically significant improvements were seen in QOL assessment scores after switching to IVIG 5%. Lastly, the C1-INH and C1-INHF levels decreased demonstrating the impact in reduction of ADRs between the two IVIG preparations.

We have previously evaluated the downregulation of C1-INH, and found that it was associated with the incidence of ADRs and other adverse effects [8]. Our studies demonstrated that there is a subset of CVID patients who phenotypically exhibit an autoimmune presentation, specifically neuroimmune, and experience a higher incidence of IVIG-related adverse effects with IVIG 10% [8,10]. This finding supports a correlation of adverse effects with IVIG 10% with the down-regulation of C1-INH. Thus, there may be a subset of patients more susceptible to C1-INH downregulation as a result of IVIG 10% infusions who may benefit from switching to IVIG 5% and potentially receiving adjunctive C1-INH replacement therapy. We are exploring these interesting findings in further studies.

The findings from this study indicate that patients with PIDD may safely switch to IVIG 5% when adverse effects are experienced with IVIG 10%, providing an alternative to SCIG. A very important component of successful IgG therapy is adherence to treatment at the prescribed intervals, even when the patient feels well [31]. Because SCIG is home-based and not as closely monitored as IV infusions, patients are solely responsible for compliance. Having multiple therapeutic options for patients with PIDD may improve patient compliance and continuity of therapy, especially for those who experience ADRs on IVIG 10%.

There are few prior studies comparing IVIG 10% versus 5% formulations, and even fewer studies comparing different strengths of the same product [10,17]. However, pharmacokinetically, bioequivalence has been demonstrated for differing concentrations of IVIG (10% vs. 5%), and the therapeutic effects are similar [10].

Conclusion

Our results demonstrate that IVIG 5% may be an alternative to SCIG for patients who develop ADRs on IVIG 10% preparations. In our study, there was a lower incidence of ADRs and improvement in QOL with the use of IVIG 5%. Furthermore, C1-INH may play a role in the mechanism of ADRs, indicating a potential subset of patients

more susceptible to C1-INH downregulation via IVIG 10% who may benefit from switching to IVIG 5%.

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