

Intravenous immunoglobulin therapy in immunodeficiency states

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ABSTRACT

The i.v. immunoglobulin (IVIG) therapy is one of the mainstays of treatment for humoral immunodeficiencies, but there is limited knowledge of the adverse reactions associated with this therapy, especially reactions occurring in the postinfusion period. The purpose of this prospective, observational, multicenter study was to identify and quantify the adverse reactions that can occur both during and after IVIG infusions (Gamimune N) in patients with humoral immunodeficiency. Patients with primary immunodeficiencies requiring IVIG therapy were followed over a 6-month period, and data regarding adverse events, particularly the time of onset, duration, and type of reaction associated with IVIG infusions was collected via direct observation and patient interviews. Data were obtained during and up to 72 hours after the completion of infusions. Sixty-five patients were recruited and received a total of 447 infusions over a 6-month period. Four hundred fifty-one adverse reactions were noted, with 17% of infusions associated with an intrainfusion reaction and 41% associated with a postinfusion reaction. Most postinfusion reactions occurred within 24 hours of the infusion and consisted mainly of headaches, fatigue, and nausea. Adverse reactions to Gamimune N infusions are common and occur primarily in the postinfusion period. Estimates of the rate of adverse reactions to Gamimune N infusions currently are underestimated because they do not account for postinfusion reactions. In addition, once recognized, effective treatment of postinfusion reactions may improve patient compliance and quality of life.

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Regular infusions of i.v. immunoglobulin (IVIG) are one of the mainstays of therapy for primary immunodeficiencies affecting the humoral immune system. This therapy not only decreases the incidence of infectious diseases contracted by patients with primary immunodeficiencies,¹ but also improves their health-related quality of life.^{2,3} Despite the widespread, regular use of IVIG in these disorders, there is a significant gap in our understanding of its adverse effects. Adverse events occurring at the time of infusion have been reported previously and generally have been found to be infrequent and of mild severity,^{4–6} but there is limited data on adverse events that persist or begin after the infusion has ended.

The purpose of this study was to determine the number and type of adverse events occurring both during and after IVIG infusions received as therapy for

humoral primary immunodeficiency. We focus primarily on events occurring in the postinfusion period. It is not entirely intuitive that symptoms starting after completion of an IVIG infusion may be related to the infusion itself; therefore, it is necessary to identify and quantify adverse reactions if physicians are to appropriately identify and treat these patients.

MATERIALS AND METHODS

Participants

Sixty-five participants were recruited from five office-based infusion centers located in Cleveland, OH; Omaha, NE; Lincoln, NE; Dallas, TX; and Tacoma, WA. Inclusion criteria included the diagnosis of a primary immunodeficiency state⁷ requiring IVIG therapy and the receipt of at least two previous IVIG infusions, the last of which was required to be Gamimune N (Bayer Pharmaceuticals Corp., West Haven, CT). All eligible patients from the study sites were invited to participate. Patients of all ages were recruited, and there were no exclusion criteria. Informed consent was obtained from each participant or from a legal guardian in the case of pediatric patients.

Study Design

This was a prospective, observational, multicentered study. Participants were recruited beginning in Octo-

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ber 1998 and were followed for 6 months after recruitment. Data collection ended in September 1999. All patients received Gamimune N. A single IVIG brand was chosen to avoid confounding effects from different formulations, and Gamimune N was chosen because of its high rate of utilization in the participating clinics. Patients received IVIG at the same dosage and schedule as before entrance in the study, which was generally 200–600 mg/kg administered every 3–4 weeks. The rate of infusion was determined at the discretion of the treating physician based on rates previously tolerated by the patient.

Interviews were conducted by trained researchers at the time of recruitment to collect demographic data and medical history. Patients were subsequently interviewed and observed at each infusion encounter and contacted by telephone ~72 hours after each infusion.

Data collected during these times included the process of obtaining i.v. access (number of attempts to obtain access, pain or bruising at i.v. insertion site, and functioning of i.v. catheter after placement); the use of premedications; the onset, type, and duration of adverse reactions; and interventions used to address adverse reactions. Adverse reactions were categorized as intrainfusion reactions (events occurring during the infusion) or postinfusion reactions (events occurring after the infusion ended). Institutional Review Board approval was obtained from the university affiliated with each infusion center.

RESULTS

Participants

Sixty-five patients were recruited and received a total of 447 IVIG infusions. No patients withdrew from the study, but one pediatric patient died from an unrelated cause. Baseline demographic and medical data are detailed in Table 1. The age distribution was bimodal with the first mode occurring in the pediatric age group between the ages of 5 and 7 years and the second occurring in the adult age group between the ages of 40 and 49 years.

IVIG Administration

Four hundred eleven (92%) of the infusions were administered *via* a peripheral i.v. catheter, and the majority of these (89%) were without complications. Complications that occurred included multiple attempts at i.v. catheter placement; pain, erythema, or bruising at the catheter site; poor i.v. flow; or infiltration. Seven percent of infusions were administered *via* an implanted port or central line, and the remaining 1% was administered subcutaneously because of inability to obtain i.v. access.

Premedication was used by 48 (74%) patients before IVIG administration based on a history of previous

Table 1 Demographics and medical characteristics of the 65 participants

Characteristic	Number (%), Mean (Median; Range)
Age (yr)	
Total population mean (median; range)	33 (38; 2–75)
Pediatric population mean (median; range)	9 (9.5; 2–17)
Adult population mean (median): range	51 (52; 24–75)
Sex	
Female	35 (54)
Male	30 (46)
Race	
White	61 (94)
African American	4 (6)
Diagnosis*	
CVID	33 (51)
Selective antibody deficiency	20 (31)
IgG subclass deficiency	14 (22)
X-linked agammaglobulinemia	2 (3)
Other	6 (9)
Length of PID diagnosis (yr)	
Mean (median; range)	3.9 (3; 0.25–16)
Time from PID diagnosis to IVIG initiation (yr)	
Mean**; range	0.95; 0–9
Duration of IVIG therapy***	
<3 months	3 (5)
3–6 months	4 (6)
6–12 months	9 (14)
>12 months	48 (75)
Distribution of patients by location	
Cleveland	22 (34)
Tacoma	18 (28)
Dallas	10 (15)
Lincoln	8 (12)
Omaha	7 (11)

*Discrepancy in values is caused by dual diagnosis in certain patients.

**Median of <6 months.

***Data unavailable for one patient.

CVID = common variable immunodeficiency; PID = primary immunodeficiency.

reactions to infusions. The most commonly used medications included antihistamines (29%), nonsteroidal anti-inflammatory drugs (24%), acetaminophen (24%), or corticosteroids (19%).

All infusion rates were below the maximum rate specified by the manufacturer (8 mg of IgG per kilogram per minute; Micromedex Healthcare Series. Drugdex evalua-

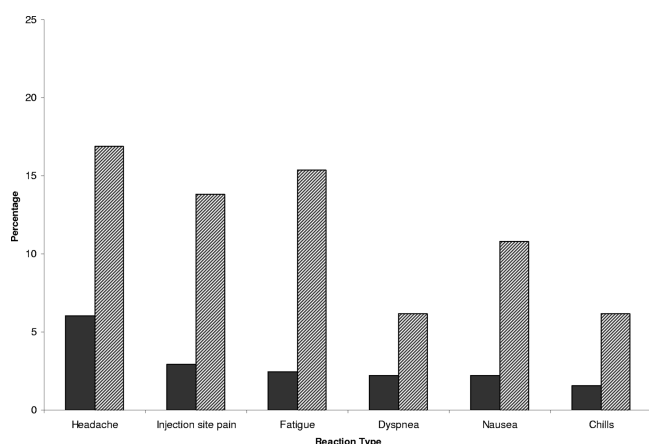


Figure 1. Intrainfusion adverse reactions. Solid bars represent percentage of infusions affected. Lined bars represent percentage of patients affected ($n = 447$ infusions).

tions. Immune globulin: www.thomsonhc.com/hcs/librarian/ND_PR/Main/SBK/2/PFPUI/Zu4dN5G165-pHXX/ND_PG/PRIH/CS/F696F7/ND_T/HCS/ND_P/Main/DUPLICATIONSHIELDSYNC/3A3976/ND_B/HCS/PFAActionId/hcs.common.RetrieveDocument-Common/DocId/0693/ContentSet_Id/31; December 22, 2005) with an average rate of infusion of 3.6 mg of IgG per kilogram per minute).

Adverse Reactions

Seventy-five (17%) infusions were associated with 101 intrainfusion reactions (Fig. 1). The interventions for these reactions included slowing the rate of six infusions, discontinuation of two infusions, and symptomatic therapy with medications (*e.g.*, analgesics, bronchodilators) or comfort measures (*e.g.*, blankets, heating pads) in the remainder of the infusions.

One hundred eighty-three (41%) infusions were associated with one or more postinfusion reactions, with a total of 350 reactions occurring in 55 (85%) patients (Table 2 and Fig. 2). The average number of postinfusion reactions per infusion was 0.8. The median number of postinfusion reactions per infusion was zero because >50% of infusions were not associated with reactions. Data regarding the time of onset was available for 301 of these reactions, and although there were no associations identified between the occurrence of intrainfusion reactions and the subsequent development of postinfusion reactions, 38 (13%) of the postinfusion reactions began during the infusions and, therefore, were categorized as both intra- and postinfusion reactions.

Data regarding the onset of all postinfusion reactions combined, plus the five most common, are detailed in Fig. 3. Overall, 73% of postinfusion reactions started within 24 hours of the infusion. Fewer reactions occurred as time elapsed from the time of infusion for all

Table 2 Postinfusion reactions

Reaction Type	Number (%) of Infusions	Number (%) of Subjects
Headache	95 (21.3)	25 (38.5)
Fatigue	67 (15.0)	25 (38.5)
Nausea	38 (8.5)	17 (26.2)
Fever	29 (6.5)	15 (23.1)
Chills	24 (5.4)	13 (20.0)
Dyspnea or wheezing	14 (3.1)	8 (12.3)
Emesis	13 (2.9)	9 (13.8)
Light-headedness	13 (2.9)	8 (12.3)
Infusion site erythema	11 (2.5)	5 (7.7)
Diarrhea	8 (1.8)	4 (6.2)
Arthralgias	7 (1.6)	6 (9.2)
Myalgias	5 (1.1)	4 (6.2)
Diaphoresis	5 (1.1)	4 (6.2)
Irritability	5 (1.1)	3 (4.6)
Abdominal pain or cramping	4 (0.9)	3 (4.6)
Chest tightness	3 (0.7)	1 (1.5)
Anorexia	2 (0.4)	2 (3.1)
Somnolence	2 (0.4)	1 (1.5)
Urticaria	1 (0.2)	1 (1.5)
Diarrhea	1 (0.2)	1 (1.5)
Rhinitis	1 (0.2)	1 (1.5)
Numbness of extremities	1 (0.2)	1 (1.5)
Memory difficulties	1 (0.2)	1 (1.5)

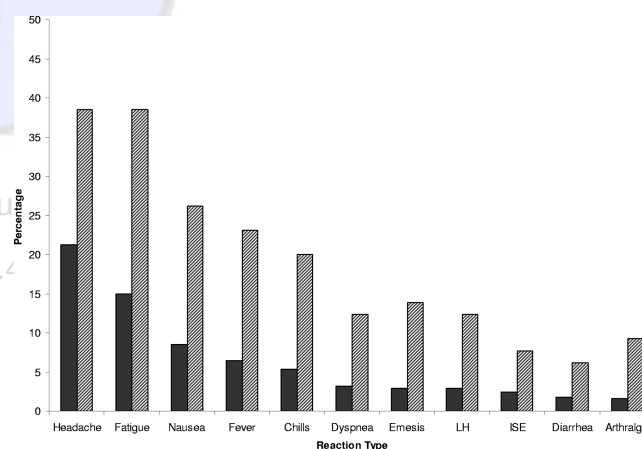


Figure 2. Postinfusion adverse reactions. Solid bars represent percentage of infusions affected. Lined bars represent percentage of patients affected. LH = lightheadedness; ISE = injection site erythema ($n = 447$ infusions).

postinfusion reactions except for nausea and emesis (data not shown) where there was a decrease in the occurrence of reactions from 24 to 48 hours postinfusion but no decrease in incidence after that time. Infusion site erythema was the only reaction for which there was no onset of reactions after the first 24 hours.

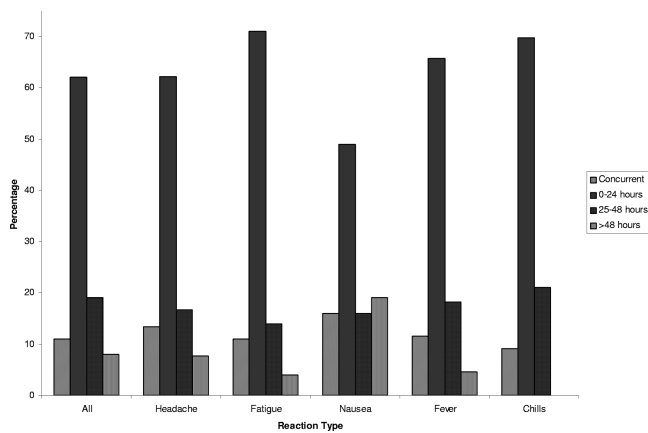


Figure 3. Time of onset of postinfusion adverse reactions after infusion ($n = 270$ reactions).

For reactions that occurred in <2% of infusions, there were too few data points to obtain meaningful results. Most postinfusion reactions were self-managed with over-the-counter analgesics (72%) or antihistamines (4%), and the remainder required prescription medications, such as β_2 -agonists, corticosteroids, or analgesics. Data regarding the duration of adverse reactions are available for 153 of the 183 infusions associated with postinfusion reactions. The reactions resolved within 24 hours (35%), 48 hours (41%), or >48 hours (24%).

DISCUSSION

This study reveals that although only a small number of IVIG infusions are complicated by an intrainfusion reaction, nearly one-half of all infusions are associated with a postinfusion reaction. A vast majority of patients experienced a postinfusion reaction at some point during the 6-month study period. Of reactions that began during the IVIG infusion, 38% ($n = 38$) persisted after the infusion ended. It is notable that 58% of all adverse reactions had an onset after the completion of the infusion (excluding those postinfusion reactions for which the time of onset is unknown), and only 12% were limited to the infusion period itself. It is possible that the postinfusion reactions reported as starting >48 hours after the end of an infusion may not be truly associated with the infusion, but these are only 8% of the total, and removing them from the analysis does not affect the large skewing toward postinfusion reactions. In addition to having a late onset, most postinfusion reactions were long-lived, lasting >24 hours after the discontinuation of the IVIG infusion. These results indicate that not only are adverse reactions to IVIG infusions common, but treating physicians are unlikely to be aware of the majority of them, which may make attempts at treatment or prevention difficult.

The previously reported frequency of intrainfusion reactions in patients receiving IVIG for primary immune deficiency has been inconsistent. Aghamohammadi *et al.*⁶ recently reported a rate of 12%, whereas Brennan *et al.*^{4,5} previously reported rates of <1%. The relatively high rate of 17% found in this study may be because a large number of our patients had already experienced previous reactions, as evidenced by the use of premedications in 74% of patients, which indicates a predisposition to recurrence. This is consistent with previous reports that patients who have one intrainfusion reaction are prone to recurrence.⁵ Furthermore, patients who have had previous adverse reactions to IVIG infusions may have an increased awareness of these reactions and therefore may be more likely to recognize and report them during future infusions. In addition, patients with common variable immunodeficiency have been shown to have higher rates of intrainfusion reactions, and 50% of our study population had this type of immunodeficiency.⁶ It is also important to note that patients with primary humoral immunodeficiencies may be at higher risk for the development of allergic disorders than the general population; therefore, these patients may have a relatively high baseline risk for the development of adverse reactions during IVIG infusions.^{8,9}

In addition to factors intrinsic to the patients that may have affected the findings of this study, it is possible that selection bias may have existed that skewed toward the recruitment of patients prone to adverse reactions; although data to this effect was not collected as part of this study, patients that had been tolerating infusions may have been shifted from office- to home-based infusions and therefore may not have been recruited for the study. Also, the purpose of this study was to quantify all adverse reactions, regardless of severity or time of onset; therefore, it is possible that reactions that were deemed too mild to be included in previous studies may have been included in this study, which would increase the reported rate of adverse events. Although a single brand of IVIG was used in this study to avoid the confounding effect of using multiple different IVIG formulations, it is possible that this formulation of IVIG was more likely to cause adverse reactions than other brands, leading to the increased incidence of observed adverse reactions. It also is possible that the specific types of adverse reactions seen with this formulation of IVIG occur at a different frequency than with other IVIG formulations because different IVIG formulations can have different adverse event profiles.¹⁰

The most common adverse reaction reported for both intra- and postinfusion reactions was headache. Headaches associated with a high rate of infusion have been previously reported,¹¹ but the etiology of headaches beginning after the infusion period is unclear. None-

theless, the frequency of this problem indicates that physicians should ascertain proactively whether their patients are developing headaches in association with their IVIG infusions. For patients with persistent or severe postinfusion headaches, consideration should be given to scheduled analgesia during and after infusions, although this treatment should be approached with caution because the effects of this therapy have not been investigated. Prophylactic treatment also should be considered for the large number of patients experiencing postinfusion nausea. The optimal approach for the high incidence of postinfusion fatigue is not apparent, but physicians and patients should be aware of this effect and consider patient-specific approaches, such as scheduling infusions around particularly taxing patient schedules.

The incidence of postinfusion fevers and chills in 4–5% of infusions poses a diagnostic dilemma in patients who have primary immunodeficiency because these can be presenting signs of infection. Patients with these symptoms require prompt and thorough evaluation to exclude infection, but physicians should be aware of the possibility that they are caused by the infusion. The mechanism behind the development of fevers and chills in patients with primary immunodeficiency receiving IVIG is unknown, but an immune-complex-mediated reaction is a likely possibility considering that circulating immune complexes are identifiable in patients immediately after IVIG administration.¹² Additional studies are required to determine the best approach to differentiating infection-related and infusion-related symptoms.

This study reveals that adverse reactions to Gamimune N brand IVIG infusions used as therapy for primary immunodeficiency are quite common and most often occur in the postinfusion period. Previous reports underestimate the incidence of these adverse reactions because they do not fully account for postin-

fusion reactions. Physicians and patients must be aware of adverse reactions to appropriately identify them and intervene when they occur.

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