ORIGINAL ARTICLE

Adverse Reactions of Prophylactic Intravenous Immunoglobulin; A 13-Year Experience With 3004 Infusions in Iranian Patients With Primary Immunodeficiency Diseases

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Abstract

Intravenous immunoglobulin (IVIG) replacement therapy improves health-related quality of life in patients with a primary immunodeficiency disease, although there have been reports of adverse reactions associated with its regular administration.
The study population was composed of 99 patients with primary antibody deficiencies. All the patients were diagnosed with a primary immunodeficiency disease and received at least 4 infusions of IVIG at the Children's Medical Center Hospital, Tehran, Iran over a 13-year period (1995-2007).
A total of 3004 infusions were recorded, and 216 (7.2%) of these were associated with adverse reactions in 66 patients. Adverse reactions were classified as mild (172 reactions), moderate (41 reactions), and severe (3 reactions). The rate of adverse reaction varied by diagnosis from 3.35% in patients with X-linked agammaglobulinemia to 17.4% in IgG subclass deficiency. There were no age-related differences in the rates of adverse reactions.
Adverse reactions to IVIG infusions are occasionally encountered; therefore, physicians and nurses should be aware of these reactions in order to manage and prevent them.

Key words: Adverse reactions. Infusion. Intravenous immunoglobulin. Primary antibody deficiencies. Primary immunodeficiency diseases.

Resumen

La terapia de sustitución con inmunoglobulina intravenosa (IGIV) mejora la calidad de vida asociada a la salud en pacientes con inmunodeficiencias primarias, aunque se han comunicado reacciones adversas asociadas con su administración regular.
La población de estudio se compuso de 99 pacientes con deficiencia primaria de anticuerpos. Todos los pacientes fueron diagnosticados de inmunodeficiencia primaria y recibieron al menos 4 infusiones de IGIV en el Children's Medical Center Hospital, Teherán, Irán durante período de 13 años (1995-2007).
Se documentaron un total de 3004 infusiones, y 216 (7,2%) de estas se asociaron con reacciones adversas en 66 pacientes. Las reacciones

adversas se clasificaron en leves (172 reacciones), moderadas (41 reacciones), y graves (3 reacciones). El índice de reacciones adversas varió con el diagnóstico de 3,35% en pacientes con agammaglobulinemia ligada al X al 17,4% en la deficiencia de subclases de IgG. No había diferencias relacionadas con la edad en el índice de reacciones adversas.
Las reacciones adversas a la infusión de IGIV se producen ocasionalmente; por tanto, los médicos y enfermeras deberían estar alerta frente a estas reacciones para manejarlas y prevenirlas.

Palabras clave: Reacciones adversas. Infusión. Inmunoglobulina intravenosa. Deficiencias primarias de anticuerpos. Inmunodeficiencias primarias.

Introduction

During the past 2 decades, intravenous immunoglobulin (IVIG) infusions have become the mainstay of therapy for a group of primary immunodeficiency diseases in which the antibody-mediated immune system is disrupted [1,2]. The effectiveness of immunoglobulin in reducing serious bacterial infections in X-linked agammaglobulinemia (XLA) [3,4] and common variable immunodeficiency (CVID) [5-7] is well documented.

Administering IVIG reduces the incidence and severity of infection, improves health-related quality of life [3-10], and significantly reduces morbidity and mortality in patients with primary immunodeficiency disease [6].

Since IVIG is a biological product derived from blood products [11,12], there are some adverse reactions associated with its regular administration. Studies evaluating adverse reactions to IVIG have revealed incidence rates varying from 1% to as high as 40% [13-17]. Therefore, a significant gap still exists in our understanding of its adverse effects.

The most common adverse events are immediate-type reactions, occurring within 72 hours after initiation of the infusion. These reactions can be mild, moderate, or even severe [18]. The purpose of the present study was to evaluate immediate-type adverse reactions to IVIG in patients with primary immunodeficiency disease.

Patients and Methods

Patients and Referral Center

Our hospital serves as a referral center for both adult and pediatric patients with primary immunodeficiency diseases [19,20]. Patients with primary antibody deficiency diagnosed at this center receive prophylactic IVIG under the supervision of trained nurses.

Diagnosis was based on the criteria of the European Society for Immunodeficiency (ESID) and the Pan-American Group for Immunodeficiency (PAGID) [21]. The diagnosis of CVID in patients older than 2 years was made by standard criteria, including decreases in serum IgG, IgA, and/or IgM levels by 2 or more standard deviations from the mean and absence of other well-defined antibody deficiencies [22]. The diagnosis of XLA, hyper IgM syndromes (HIGM), ataxia-telangiectasia (AT), and Wiskott-Aldrich syndrome (WAS) was confirmed by mutation analysis [23]. Patients on stable IVIG treatment and who had received at least 4 infusions were included in the study.

Infusions

We designed a 2-page questionnaire to record the results of physical examinations before starting IVIG, vital signs, and signs of infusion-related immediate-type adverse reactions. All patients receiving IVIG were observed by a clinical immunologist and a nurse trained in IVIG therapy. Adverse reactions were recorded in the questionnaire. The patients received doses of 300-600 mg/kg every 3 to 4 weeks [24], and IVIG was administered at the rate of infusion recommended by the manufacturer.

The 10 types of IVIG preparation administered to the patients were Gamimune (Bayer Pharmaceuticals Corp, West Haven, Connecticut, USA), Nordimmun (Hemasure, Gentofte, Denmark), Sandoglobulin (Sandoz Pharmaceutical Corp, Hanover, New Jersey, USA), Vigam (Bio Products Laboratory Hertfordshire, UK), Intraglobulin (Biotest Pharma, Dreieich, Germany), Endobulin (Baxter AG, Vienna, Austria), Ig VENA NIV (Petrone, Naples, Italy), Venoglobulin-S (Alpha Therapeutic Corp, Los Angeles, California, USA), Octagam (Octapharma, Langenfeld, Germany), and Gammonative (Pharmacia and Upjohn, Stockholm, Sweden).

Classification of Reactions

Immediate-type adverse reactions (within 72 hours of the infusion) were categorized as mild, moderate, and severe. Mild reactions included light headache, flushing, chills, anxiety, fever, itching, malaise, and fatigue, and required the infusion to be slowed and antihistamines and nonsteroidal anti-inflammatory drugs (NSAIDs) to be administered [24]. Moderate reactions included chest pain, wheezing, vomiting, myalgia, arthralgia, back pain, nausea, dizziness, and severe headache, and required the infusion to be discontinued and antihistamines and NSAIDs to be administered. Severe reactions included altered mental status, hypotension, bronchospasm, and anaphylaxis, and required the infusions to be discontinued, adrenaline to be administered, and medical attention [24]. The severity grade for all reactions was confirmed by independent review.

Statistical Analysis

Data were analyzed using Epi Info version 2.5.1 (Centers for Disease Control and Prevention, www.cdc.gov/epiinfo). The frequency of adverse reactions was categorized according

to severity. The number of reactions was calculated according to the different diseases and per patient. Adverse reactions were compared between the 2 time periods using the chi-square test. A *P* value of less than .05 was considered significant.

Results

Patient Characteristics

The study population was composed of 99 patients with diagnosed antibody deficiency and who had received at least 4 infusions of IVIG in our hospital during a 13-year period (1995-2007). There were 69 males and 30 females aged 2 to 57 years. Fifty-four patients had CVID, 28 patients XLA, 8 patients ataxia-telangiectasia, 5 IgG subclass deficiency (IgGSd), 3 patients HIGM, and 1 patient WAS.

Adverse Reactions Caused by IVIG

During the study period, a total of 3004 infusions were administered: 2270 (75.6%) infusions were administered to patients under 18 years old and 734 (24.4%) were administered to patients older than 18.

A total of 216 (7.2%) infusions were associated with adverse reactions in 66 patients: 169 out of 2270 (7.4%) infusions in children and adolescents, and 47 out of 734 (6.4%) infusions in adults. There was no significant association between the rate of adverse reactions and age. The adverse reaction rate was 7.1 in adults, 6.97 in adolescents (10-17 years), and 7.88 in children (< 10 years).

A comparison of the adverse reactions between the periods 1995-2002 and 2003-2007 revealed a significant decrease in the rate of these reactions (12.35% vs. 3.6%, $P < .0001$; odds ratio 0.27; 95% confidence interval, 0.19-0.36).

Infusion and adverse reaction data are shown in Table 1. Of 216 recorded adverse reactions, 172 (79.6%) were mild, 41 (18.9%) were moderate, and only 3 (1.3%) were severe.

Severity of Reactions

Mild. One hundred and seventy-two reactions were classified as mild. The most common feature was chills (102 cases), followed by fever (46 cases), feeling of cold (44 cases), backache (40 cases), and headache (32 cases) (Figure). Symptoms subsided when the IVIG infusion rate was slowed and resolved without the need for further interventions.

Of these 172 mild reactions, 132 were in 55 children and 40 were in 12 patients (adolescents and adults). One patient experienced 12 mild reactions when she was younger than 18, despite premedication, and 2 adult patients each had 11 mild reactions (one had recurrent episodes of idiopathic thrombocytopenic purpura and hemolytic anemia, in addition to her underlying CVID).

Moderate. Moderate adverse reactions occurred in 41 of the 3004 infusions. These included vomiting, chest pain, and wheezing, in 20, 10, and 3 infusions, respectively (Figure).

Sixteen infusions were stopped and antihistamines and corticosteroids were administered. In 14 patients, the signs and symptoms disappeared when the infusion rate was reduced and anti-inflammatory agents administered. Of 41 moderate reactions, 6 occurred in 6 adults and the other 35 were in 18 patients under 18 years old. One patient aged less than 18 years had 3 moderate reactions and 5 patients under 18 years experienced 2 moderate reactions while receiving IVIG. Of these 5 patients, 3 had CVID (1 patient also had irritable bowel disease and another had idiopathic thrombocytopenic purpura).

Severe. Severe adverse reactions occurred in 3 out of 216 reactions, and included severe chest pain, severe wheezing, and severe headache. Two severe adverse reactions occurred in 2 CVID patients under 18 years old and included hypotension, bronchospasm, chest pain, and anaphylaxis.

Adverse Reaction in Different Diseases

The patients were grouped by diagnosis (Tables 1 and 2).

Table 1. Adverse Reactions by Diagnosis

Diagnosis	Total No. of Patients	Total No. of Infusions	Patients With Adverse Reactions	Infusions With Adverse Reactions (%)
Common variable immunodeficiency	54	1866	44	159 (8.52%)
X-linked agammaglobulinemia	28	864	11	29 (3.35%)
IgG subclass deficiency	5	63	3	11 (17.4%)
Hyper-IgM symdrome	3	77	3	12 (15.5%)
Ataxia-telangiectasia	8	129	5	5 (3.8%)
Wiskott-Aldrich syndrome	1	5	0	0 (0%)
Total	99	3004	66	216 (7.1%)

Abbreviation: Ig, immunoglobulin.

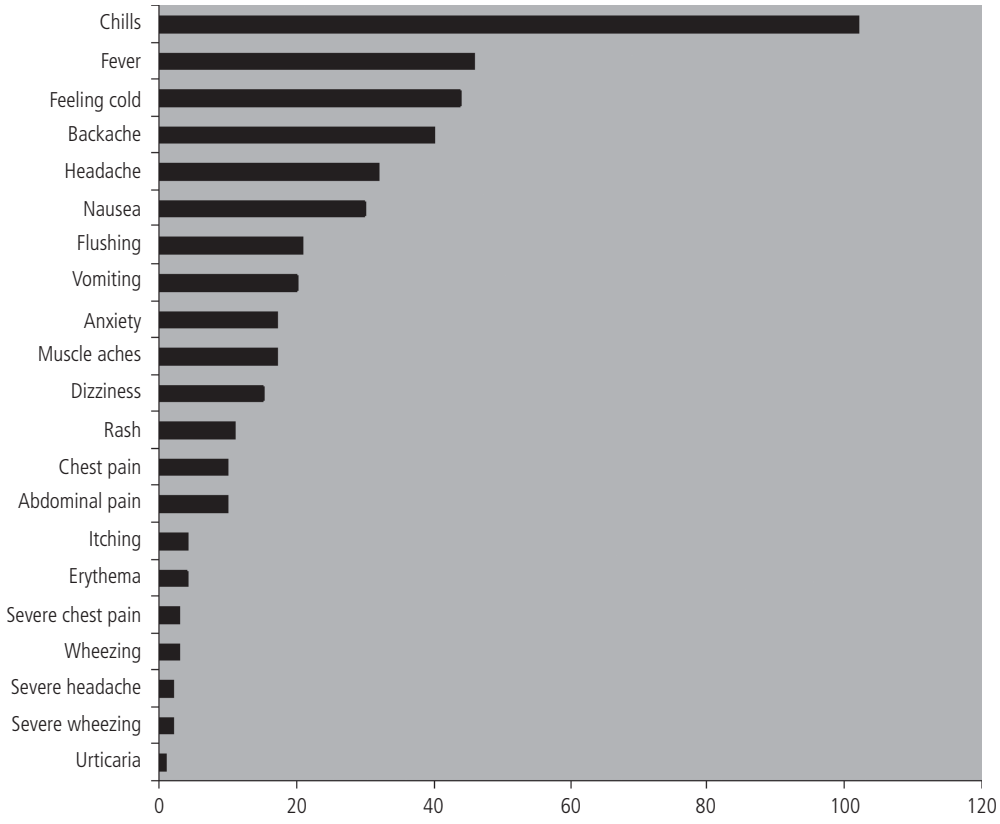

Figure. Adverse Reactions.

Table 2. Adverse Reactions by Patients' Ages and Diagnosis

Diagnosis	Age Group	<18 Years				>18 Years		Total	
		0-9 Years		10-17 Years					
	Number of patients	Total infusions	Number of adverse reactions (%)	Total infusions	Number of adverse reactions (%)	Total infusions	Number of adverse reactions (%)	Total infusions	Number of adverse reactions (%)
CVID	54	487	46 (9.44%)	852	67 (7.86%)	526	46 (8.74%)	1866	159 (8.52%)
XLA	28	372	12 (3.22%)	298	16 (5.36%)	194	1 (0.51%)	864	29 (3.35%)
IgGSd	5	34	10 (29.41%)	16	0	13	1 (7.69%)	63	11 (17.46%)
HIGM	3	77	12 (15.58%)	0	0	0	0	77	12 (15.6%)
AT	8	77	3 (3.89%)	52	2 (3.84%)	0	0	129	5 (3.87)
WAS	1	5	0	0	0	0	0	5	0
Total	99	1053	83 (7.88%)	1218	85 (6.97%)	733	48 (6.54%)	3004	216 (7.19%)

Abbreviation: AT, ataxia-telangiectasia; CVID, common variable immunodeficiency; HIGM, hyper-IgM syndrome; IgGSd, IgG subclass deficiency; WAS, Wiskott-Aldrich syndrome; XLA, X-linked agammaglobulinemia.

The rate of adverse reactions varied between 3.35% and 17.4% in patients with XLA and IgGSd respectively (Table 2).

Reactions per Patient

Thirty-three patients receiving IVIG did not have any reactions. Sixty-six patients experienced mild, moderate, or severe reactions.

Fifty-five patients under 18 years of age had 169 reactions of which 132, 55, and 2 adverse reactions were mild, moderate, and severe, respectively. In this group, the number of adverse reactions per patient varied from 1 to 15.

Thirteen adult patients experienced 47 reactions (40 mild and 7 moderate, no severe reactions), of which 31 occurred in 3 patients, whereas the remaining 16 reactions occurred in the remaining 10 patients.

Associated Factors

Infection. Out of 216 adverse reactions, 18 were associated with infection; 12 present at the time of infusion and 6 that were intercurrent.

Infusion-related reactions occurred in 8% of infected patients. There were 40 adverse reactions (18/240 with infection [7.5%] and 22/2754 with no infection [0.79%]).

Rate of infusion. The most common cause of the 216 adverse reactions was faster administration than recommended (52 rapid infusions). Mild infusion-related adverse reactions subsided when the rate of infusion was reduced.

Change in preparations. Ten types of IVIG preparations were administrated to our patients and 34 out of 216 adverse reactions were caused by a change in the IVIG product.

First administration. Of the 216 adverse reactions, 16 were first administrations. The proportion of adverse reaction to infusion during the first and subsequent infusions were 16.2% (16 reactions among 99 infusions) and 6.9% (200 reactions among 2905 infusions), respectively ($P = .0009$).

Delay since the last infusion. In 11 reactions there was a delay in administering the infusion. Because delay is often due to an untreated infection, such a reaction may also be due to an intercurrent infection.

Anti-IgA antibodies. In our study, 3 patients with CVID who were taking IVIG therapy had anti-IgA antibodies in serum. The ratio of serum IgG/anti-IgA antibody levels to total antibody levels in these patients was significantly higher than in patients who received IVIG.

Discussion

IVIG is the standard treatment for patients with primary immunodeficiency disease [1]. In the present study, a total of 3004 infusions of IVIG were administered to 99 patients with antibody deficiency over a period of 13 years. The overall reaction rate was 7.2% (216/3004).

The reported incidence of adverse reactions varies widely, from 1% to 40% depending on the study and immunoglobulin used [13,14,25-31]. Brennan et al [28] observed adverse reactions in 13 508 infusions in 459 patients over a period of 2 years. No severe reactions occurred and the reaction rate was low (0.8%). In contrast, Galli et al [31] reported around 40% of adverse events in children treated for immunodeficiency. This study was performed prior to the introduction of low-pH IgG aggregate formulations of IVIG.

Skull et al [13] compared the rate of adverse reactions in patients with hypogammaglobulinemia who received IVIG between 1973 and 1993, and showed that the rate of adverse reactions to immunoglobulin infusions fell from 9.1% to 0.8% after the introduction of low-pH IgG aggregate IVIG in 1986.

A comparison between the results of the present study and our previous results [29] shows that the rate of adverse reactions decreased from 12% to 3.6%. We think these differences are due to better monitoring of patients while they are receiving IVIG. These data also point toward an improvement in the manufacturing of IVIG and suggest that expert monitoring by doctors and trained nurses can reduce the rate of adverse reactions.

Our data show that there were no significant differences in adverse reaction rates between children and adults. Furthermore, a previous study observed a reaction rate of 0.8% in adults and 0.7% in children under the age of 10 years [28]. Therefore, there seems to be no difference between adults and children with primary antibody deficiency receiving IVIG treatment.

In our study, 172 (79%) reactions were considered mild. None required the infusion to be stopped, and symptoms subsided when the infusion rate was reduced.

Data from previous studies have shown no severe reactions in a total of 16 223 infusions [14,28]. In our study, severe adverse reactions occurred in 3 infusions in which 2 patients with CVID were under 18 years. Therefore, although severe adverse reactions are rare, awareness that they exist and training to treat them are essential.

In our study, the highest proportion of adverse reactions occurred in 44 of 54 CVID patients. Two of these were severe, suggesting that CVID patients could be more susceptible to severe adverse reactions, which could be due to the development of autoantibodies [32-34] and IgG/anti-IgA antibodies [35].

Chills and fever were the most common symptoms we observed. Postinfusion fever and chills pose a diagnostic dilemma in patients with primary immunodeficiency, because they could be indicative of infection. Patients with these symptoms require a prompt and thorough evaluation to rule out infection, but physicians should be aware of the possibility that they are infusion-related. The mechanism behind the development of fevers and chills in patients with primary immunodeficiency receiving IVIG is unknown, but an immune complex–mediated reaction seems likely, considering that circulating immune complexes are identifiable in patients immediately after IVIG administration [36].

Of the 216 adverse reactions reported in our study, 52 (24%) were due to infusions administered faster than recommended, 18 (8%) were associated with infection, and 34 (16%) were caused by a change in IVIG products.

Sudden adverse reactions during treatment are almost always the result of an extremely rapid infusion rate [37];

therefore, regulating the infusion rate plays a significant role in preventing adverse reactions. It is strongly recommended that the infusion rate be no faster than 1 mg/kg/min for the first 30 minutes, gradually increasing to a maximum rate of 7 mg/kg/min only if well tolerated [37]. Nearly a quarter of the reactions we observed could have been prevented if the infusion rate had been slower.

Awareness of intercurrent infection during the administration of IVIG can help prevent adverse reactions. In infected hypogammaglobulinemic patients, the antigenic load must be decreased by previous appropriate antibiotic treatment for 2 to 7 days before IVIG.

Severe reactions can occur in previously untreated agammaglobulinemic patients with chronic infections. In these cases, IVIG may lead to acute complement activation with the production of anaphylatoxins C3a and C5a [15].

Adverse reactions are particularly likely in a patient who has not received IVIG previously. A survey by the Immune Deficiency Foundation showed that as many as 34% of reactions occurred during the first infusion of an IVIG product [38]. In our study, 7% of reactions were associated with the first IVIG infusion. Therefore, the first infusion of a hypogammaglobulinemic patient should be administered slowly as a 3% or 5% solution, starting at 0.5-1.0 mg/kg/min [39]. This strategy could probably decrease the incidence of adverse reactions.

It is unusual for an entire population of immunodeficient patients to receive the same preparation of IVIG. Patients started on one preparation may be changed to another for reasons of cost or availability [40]. A recent study advised caution when one IVIG preparation is switched to another, as there may be an increased risk of adverse reactions [41].

The data we present indicate that adverse reactions to IVIG infusions are occasionally encountered. Physicians and nurses should be aware of these reactions in order to manage and prevent them.

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