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Original Article

Immediate adverse reactions to intravenous immunoglobulin in primary immune deficiencies: a single center experience

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ABSTRACT

Background and objective. Adverse reactions related to intravenous immunoglobulin (IVIG) infusions vary from 1 to 81%, with an average of 20%. They may be classified as immediate; occurring during the infusion itself or delayed; occurring after the infusion has been ceased. In the present study, we aimed to evaluate the frequency of immediate adverse reactions due to IVIG infusions in primary immune deficiency (PID) patients.

Methods. The study population was composed of 109 patients. A total of 763 infusions were recorded for demographic data and adverse reactions.

Results. The participants included 32 girls (29%) and 77 boys (71%). The mean age was 11.8 ± 5.7 years (0.6-33.5 years). Early adverse events (AE) were recorded in 34 (4.5%) among 763 IVIG infusions including 30 mild (88.2%), 3 moderate (8.8%) and 1 severe (2.9%). The most common immediate adverse reactions were fever (29.4%) and headache (29.4%). The risk of AE was higher among primary antibody deficiency (PAD), compared to combined immunodeficiency (OR 2.61, 95%CI 1.061-6.475; p = 0.037).

Conclusions. Use of various intravenous immunoglobulin treatments should be considered with regard to side effect profiles observed. In our cohort, PID patient experienced mostly mild AE; PAD was associated with an increased risk of AE.

Key words: IVIG, adverse reaction, primary immunodeficiencies.

Intravenous immunoglobulin (IVIG) has been used for primary immune deficiencies (PID) since the 1980's.[1] It has been shown that IVIG treatment decrease the morbidity, mortality and the frequency of severe bacterial infections in X-linked agammaglobulinemia and common variable immune deficiency (CVID) patients.[2-6]

The frequency of adverse events seen in IVIG treatment varies between 1-81% with a mean value of 20%.[7-10] These are classified as early or late according to the time of occurrence of the reaction.[11] The most common early adverse events (AE) are fever, chills, headache, nausea, hypotension, myalgia, wheezing, back pain and rash.[11] Adverse reactions are reported to be related to product, patient or infusion characteristics. During the production process, ethanol precipitation or stabilizer addition may generate immunoglobulin aggregates resulting in AE.[7,8] Primary antibody deficient patients with very low levels of IgA are predisposed for reactions during IVIG treatment due to anti IgA antibodies which could be managed by the use of products containing trace amount of IgA.[12] Moreover, rapid rate especially at the initial phase of the infusion, presence of an acute infection, osmolality of the product, sodium

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and sugar contents and pH value may also be related to adverse reactions.[13] Since there are several concentrations and ingredients of IVIG products such as 5%, 10%.[14,15] To minimize rate-related adverse effects, infusions should be started slowly, at rates not above 0.01 ml/kg/minute. Infusion rate may be increased to 0.08 ml/kg/minute in the absence of any reactions.[15] In addition, the minimum duration of the infusion should be at least three hours.[12]

We hereby evaluated the early adverse events in our PID patient cohort during hospital-based IVIG administration and aimed to define risk factors associated with AE.

Material and Methods

A total of 109 PID patients receiving 763 IVIG infusions between the years of 2014-2016 were enrolled in the study. Diagnosis of PID was based on criteria of European Society for Immunodeficiency (ESID) and Pan-American Group for Immunodeficiency (PAGID) and classified by using the charts in International Union of Immunodeficiency Societies.[16-18] The study protocol was approved by the local Ethics Committee of Marmara University (IRB number: 09.2015.136) and a written informed consent for patients was obtained from either adult patients and parents of the children.

Demographic data and infusion details including current age, age at diagnosis, final diagnosis and age at first IVIG treatment, IVIG dose, the number of previous IVIG treatments, use of premedication, duration of infusion, serum IgG levels (mg/dl) prior to and after IVIG were recorded. Documentation of a patient's baseline and bi-annual virologic status, complete blood cell count, hepatic and renal function tests, and urinalysis were documented during IVIG therapy. A complete physical examination was performed before each infusion. Patients self-infusing IVIG as home therapy were excluded. Patients who had severe infection requiring hospital admission and had concomitant IVIG infusion were not enrolled into the study as well. The concentrations of the products were 5% and 10%. Patients received IVIG with a dose of 300-800 mg/kg (median: 500 mg/kg) every 3-4 weeks and the infusion rate was started at 0.01 ml/kg/minute (equaling 0.5 mg/kg/minute of 5% solution or 1 mg/kg/minute of 10% solution) and increased to 0.08 ml/kg/minute (4 or 8 mg/kg/ minute of 5% or 10% solution, respectively) in the absence of any reactions. All infusions were performed under the supervision of physician and nurse. Adverse reactions were recorded by the same physician (EN). The early AE of IVIG infusion were defined as mild including fever, chills, headache, rash, pruritus, urticaria, abdominal pain, myalgia, back pain, moderate as hypertension, wheezing, chest pain and severe as hypotension, anaphylaxis and impairment of consciousness.[11]

The infusion was suspended if any mild AE occurred and patients were treated accordingly. In case any moderate or severe AE developed, IVIG infusion was ceased, symptoms were treated accordingly and IVIG brand was switched to another one. Premedication was only given to patients who developed previous moderate to severe adverse reactions. Prophylaxis involved the use of single or several agents including: methylprednisolone (IV, 1 mg/kg/dose, maximum 40 mg given immediately prior to the infusion), antihistamine (IV or per oral, pheniramine maleate, 1 mg/kg/dose), paracetamol (per oral, 10 mg/kg/dose) given up to 1 h prior to the infusion.

Statistical analyses

Data was described as frequencies and medians with minimum-maximum values unless otherwise indicated. Continuous variables were analyzed by Independent Student's t-test and Mann-Whitney U tests as appropriate. Differences between the groups were assessed by chi-square analysis for categorical variables. All analyses were performed by the Statistical Package for the Social Sciences (SPSS) program (Version 16.0; SPSS Inc., Chicago, IL, USA) using default settings. Statistical significance level was set as $p<0.05$.

Results

A total of 109 patients (32 girls, 29.4%; 77 boys, 70.6%) with 763 IVIG infusions were included. The mean age was 11.8 ± 5.7 years (0.6-33.5 years). Distribution of age groups was as follows: <18 years (n = 829 75.2% and ≥18 years (n = 27) 24.8%. Demographic, clinical and laboratory features of patients is shown in Table I. PID cohort consisted of 65 (59.6%) combined immune deficiency (CID) and 44 (40.4%) primary antibody deficient (PAD) patients. The CID cohort consisted of CID with pending molecular diagnosis (n = 29, 26.6%), ataxia telangiectasia (n = 9, 8.2%), hyper IgE syndrome (n = 7, 6.4%), CD4 lymphopenia (n = 7, 6.4%), immunodeficiency / centromeric region instability / facial anomalies syndrome (ICF; n = 3, 2.7%), hyper IgM syndrome (n =2, 1.8%), DiGeorge syndrome (n = 2, 1.8%), Bloom syndrome (n = 2, 1.8%), MHC Class II deficiency (n = 1, 0.9%), Cernunnos syndrome (n = 1, 0.9%), Nijmegen breakage syndrome (n = 1, 0.9%), and Wiskott-Aldrich syndrome (WAS; n = 1, 0.9%). The PAD cohort consisted of CVID (n = 16, 14.6%), unclassified antibody deficiency (n = 16, 14.6%), Bruton disease (n = 4, 3.6%), IgG2 subclasses deficiency (n = 2, 1.8%), IgG2 subclasses deficiency with IgA deficiency (n = 1, 0.9%) , activation induced cytidine deaminase (AID) mutation (n = 1, 0.9%), CD55 deficiency (n = 1, 0.9%), CD21 deficiency (n = 1, 0.9%), CD19 deficiency (n = 1, 0.9%), phosphatidylinositol 3- kinase, catalytic, delta (PIK3CD), and p110 mutation (n = 1, (0.9%).

The early AE of IVIG infusion were defined as mild including fever, chills, headache, rash, pruritus, urticaria, abdominal pain, myalgia, back pain; moderate as hypertension, wheezing, chest pain; and severe as hypotension, anaphylaxis and impairment of consciousness.[11] The early AE were recorded in 34 (4.5%) infusions among 763 IVIG infusions including 30 mild (88.2%), 3 moderate (8.8%) and 1 severe (2.9%). The distribution of the AE is given in Figure 1. The recorded AE were 18 (6.3%) in 65 PAD patients with 290 infusions, while 16 (3.3%) in 44 combined immune deficiency patients among 473 infusions; having a PAD among PIDs was found to increase the AE risk with an OR of 2.61 (95%CI 1.061-6.475; p = 0.037). The distribution of AEs between two groups is presented at Table II.

The most common AE were fever (10/34, 29.4%) and headache (10/34, 29.4%). Mild AE were managed by antipyretics, antihistaminics and

Table I. Demographic, clinical and laboratory characteristics of patients (N = 109).

Features	Results
Age, year*	12 (0.6-33.5)
Gender (female/male), n (%)	32 (29.4%) / 77 (70.6%)
Age at onset, year*	1 (0.1-18)
Age at diagnosis, year *	1 (0.2-21)
Duration of follow-up, year*	2.5 (0.1-15)
Age at first IVIG administration, year*	6 (0.1-20)
IVIG dose, g/kg/dose*	0.5 (0.3-0.8)
Duration of infusion, hour*	4.5 (3-6.3)
Serum IgG level at diagnosis, mg/dl*	576 (6-1430)
Serum through IgG levels, mg/dl*	956 (464-2390)
Respiratory infections within the last month, n/N (%)	28/763 (3.7%)
Antibiotic use within the last month, n/N (%)	16/763 (2.1%)
Hospitalization within the last month, n/N (%)	1/763 (0.13%)
Time between IVIG infusion and infection occurrence, day*	20 (1-49)

*: results are presented as median (minimum-maximum)

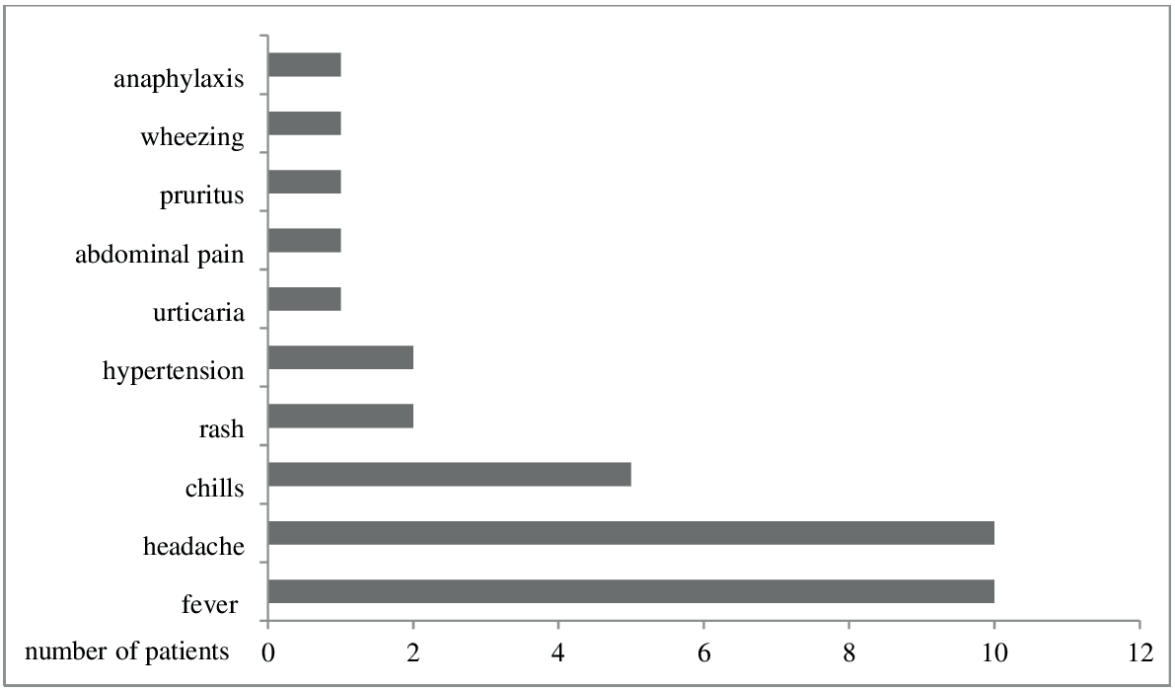

Fig. 1. Distribution of early adverse reactions to IVIG infusion.

Table II. Distribution of adverse events according to primary immune deficiency phenotype.

Adverse events	Primary antibody deficiency (N = 290 infusions in 65 patients)	Combined immune deficiency (N = 473 infusions in 44 patients)	p value
Mild	15 (5.2)	15 (3.2)	0.039
Fever, n (%)	3 (1.0)	7 (1.5)	>0.05
Headache, n (%)	10 (3.4)	-	<0.001
Chills, n (%)	1 (0.3)	4 (0.8)	>0.05
Urticaria, n (%)	1 (0.3)	-	>0.05
Pruritus, n (%)	-	1 (0.2)	>0.05
Abdominal pain, n (%)	-	1 (0.2)	>0.05
Rash, n (%)	-	2 (0.4)	>0.05
Moderate	3 (1.0)	-	>0.05
Wheezing, n (%)	1 (0.3)	-	>0.05
Hypertension, n (%)	2 (0.7)	-	>0.05
Severe	-	1 (0.2)	>0.05
Anaphylaxis, n (%)	-	1 (0.2)	>0.05
Total, n (%)	18 (6.2)	16 (3.4)	0.037

by decreasing the infusion rate. Moderate AE were documented in 3 patients and included increase in blood pressure (n = 2) and wheezing (n = 1); in these cases IVIG treatment was ceased; antihypertensive, short acting beta agonists and steroids were given. Only one patient experienced anaphylaxis and was treated with intramuscular epinephrine, antihistaminic and steroids.

Premedication was administered in 77 (10.1%) infusions in patients who developed adverse reactions during their previous infusions;

mild AE during the study period occurred in 6 (7.8%) of these infusions although they were receiving premedication. There was no significant difference between groups according to premedication use in the context of mild AE frequency, age at diagnosis, IVIG dose and infusion duration (Table III). The percentage of patients who received 5% IVIG among patients who required premedication was higher, compared to that of patients who did not require premedication (71/77, 92.2% vs. 531/686, 77.4%; OR 3.57, 95%CI 1.52-8.36; p = 0.002). Regarding various IVIG brands, number of adverse reactions for each brand were insufficient for accurate statistical analyses (Table IV).

The majority of patients (78.9%) were on IVIG products of 5% concentration. Nine AE were recorded in 161 infusions with IVIG products of 10% concentration (5.6%); 25 AE were recorded in 602 infusions with IVIG products of 5% concentration (4.2%; p>0.05).

Discussion

In this study, we evaluated 763 infusions in 109 patients with PID. The overall frequency of AE was 4.5% in which majority was mild reactions with a higher AE frequency in PAD group. Adverse reaction frequency was not found to be related to IVIG dose, duration and concentration. IVIG infusions with 5%

Table III. Comparison of patients according to use of premedication.

Features	Premedication		p value
	Yes (N = 77)	No (N = 686)	
Adverse events, n (%)	6 (7.8)	28 (4.1)	>0.05
Age at diagnosis, year	2 (0.08- 18)	0.66 (0.08-18)	>0.05
IVIG dose, g/kg/dose	0.57 ± 0.94	0.50 ± 0.84	>0.05
IVIG infusion duration, hours	5.2 ± 0.5	4.9 ± 0.6	>0.05
10% IVIG concentration, n (%)	6 (7.8)	155 (22.6)	0.002
5% IVIG concentration, n (%)	71 (92.2)	531 (77.4)	

IVIG: intravenous immunoglobulin
Premedication was administered in 77 infusions in patients who developed adverse reactions during their previous infusions.

Table IV. Adverse events associated with various IVIG brands and concentrations.

Adverse events	Brands (concentration)							Total
	Ig vena (5%)	Tegeline (5%)	Nanogam (5%)	Octagam (5%)	Phlebogamma (5%)	Kiovig (10%)	Gamunex-c (10%)	
Number of infusions, n	116	161	88	150	87	115	46	763
Fever, n (%)	1 (0.86)	1 (0.62)	3 (3.41)	1 (0.66)	2 (2.30)	2 (1.74)	-	10 (1.31)
Headache, n (%)	-	-	-	4 (2.66)	2 (2.30)	4 (3.48)	-	10 (1.31)
Chills, n (%)	-	1 (0.62)	1 (1.14)	3 (2.00)	-	-	-	5 (0.65)
Rash, n (%)	-	-	-	1 (0.66)	-	1 (0.87)	-	2 (0.26)
Hypertension, n (%)	-	-	-	1 (0.66)	1 (1.15)	-	-	2 (0.26)
Abdominal pain	-	-	-	-	-	1 (0.87)	-	1 (0.13)
Wheezing, n (%)	-	-	-	1 (0.66)	-	-	-	1 (0.13)
Itching, n (%)	-	-	-	1 (0.66)	-	-	-	1 (0.13)
Urticaria, n (%)	-	1 (0.62)	-	-	-	-	-	1 (0.13)
Anaphylaxis	-	-	-	-	-	1 (0.87)	-	1 (0.13)
Total events, n (%)	1 (0.86)	3 (1.86)	4 (4.55)	12 (8.00)	5 (5.75)	9 (7.83)	-	34 (4.46)

concentration was found to be frequent among infusions with premedication use.

The mean frequency of AE seen during IVIG treatment was reported to be 20% changing from 1 to 81%.[7-10] Galli et al.[19] reported 40% of AE seen in PID children. In addition, Dashti-Khavidaki et al.[20] documented 216 AE (7.2%) in 3,004 infusions for 13 years. In our cohort, the overall frequency of AE was 4.5% in which the majority was mild reactions with a higher AE frequency in PAD group. This data was compatible with the higher rate of AE reported for CVID group by Dashti-Khavidaki et al.[20] This entity was reported to be related to the generation of anti IgG and anti IgA antibodies in this group of patients.[21,22]

The recorded mild AE in our cohort consisted of mostly fever, headache and chills which were similar to data reported at previous studies.[20,23] The symptoms were managed with a decrease in infusion rate, antihistaminics, low dose steroids and antipyretics. Although not well clarified, the most reasonable cause of the fever was postulated to be an immune complex driven reaction.[24] The headache seen during IVIG infusion was asserted to be related to aseptic meningitis which can be controlled with antihistaminics, anti-inflammatory drugs and with decreased infusion rates.[25] It was also reported that higher doses and concentrations may increase headache ratios.[25,26] In our cohort, headache was not found to be related to infusion rate, dose or concentration.

In a study showing that frequency of infusions associated with AE was lower with the 5% concentration; the type, seriousness, and severity of AE detected were similar for both 5% and 10% concentrations of same brand.[27] Headache and fever were reported as most common AE in 10% concentrations of IVIG.[27,28] In our study we observed that headache and fever were most common AE for 10% concentration, whereas no differences were detected between IVIG concentrations. In another cohort, Souayah et al.[29] showed that premedication decreased AE seen in the home infusion of IVIG in patients with neuroimmunologic disorders. In our cohort, 77 infusions were given with premedication in patients who had a history of adverse events; adverse events was not observed in 71 of them (92.2%).

Kaba et al.[23] compared the rate of adverse events between various IVIG solutions which showed no difference. Our patients received 7 different brands of IVIG with various rates of adverse reactions. These data agree with a prior study data finding that preparations are not equally tolerated even with similar concentration.[30] If patients persistently develop adverse events following administration with a particular IVIG product, switching to another immunoglobulin product may result with fewer AE and safer infusions.[30]

Expression of a mutation of novel gain-of-function splice variant of the FcRIIa receptor in patients with CVID is reported to be associated with pro-inflammatory signaling toward IgG, which then induces recurrent anaphylactic reactions to IVIG.[31] We documented severe AE as anaphylaxis in only one patient. Among previous reports, no severe AE were recorded in 16,223 applications,[32,33] whereas one study reported severe AE in 3 patients with 2 of them evaluated as anaphylaxis.[20]

Adverse events are particularly likely in a patient who has not been given IVIG previously. A survey by the Immune Deficiency Foundation (IDF) displayed that as many as 34% of adverse reactions occurred during the first infusion of an IVIG product[34] with another study noting 7%.[20] It was also reported that switching among different brands increase the risk of AE.[35] Similar to the IDF's report, AE detected were noted in earlier infusions but not at first infusion among our cohort (data not shown). The main reasons for initial high reaction rates that reduce with subsequent doses of the same product are unknown. Therefore, the first infusion recommended to be given slowly at a dose of 0.5 to 1.0 mg/kg/min.[36] In addition, in infected patients, high rates of adverse reactions are related to the pattern of antigen–antibody

complexes, and rates can be reduced if the patient is apyrexial or receiving antibiotics.[37,38]

Our study has shown that adverse events during hospital based IVIG infusions are infrequent and that IVIG preparations and concentrations are equally tolerated. Use of various intravenous immunoglobulin treatments should be considered with regard to side effect profiles observed. In our cohort, PID patient experienced mild AE in the presence of PAD disorder and demanded antihistaminic premedication for 5% IVIG infusions. Therefore, identification of risk factors, use of adjunctive therapies for adverse events and trained medical supervision are measures to provide safe use of this medication.

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