HEMATOLOGY, TRANSFUSION AND CELL THERAPY

Original article

Immediate adverse events to intravenous immunoglobulin in pediatric patients with inborn errors of immunity: A longitudinal study with a pre-infusion protocol

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Introduction: Immunoglobulin represents the main therapy for patients with inborn errors of immunity (IEI) and it is a safe procedure, but adverse events (AEs) can occur with variable frequencies.

Objective: To evaluate the frequency of immediate AEs to intravenous immunoglobulin (IVIG) regular therapy in a pediatric cohort with IEI after a pre-IVIG infusion protocol.

Methods: This was a longitudinal study from 2011 to 2019 at a tertiary pediatric hospital in Brazil.

Results: A total of 1736 infusions were studied in 70 patients with IEI, 46 (65.7%) of whom were males and whose median age was 5.8 years old (range: 6 mo − 18 yo). Seven different brands of IVIG were used with the median loading dose of 0.57g/kg (range: 0.23 - 0.88g/Kg). According to the protocol, pre-medication and step-up infusion rate, were performed in 1305 (75.2%) infusions. Immediate AEs were noted in 10 children (14.3%) and in 22 (1.2%) infusions. Skin reactions (rash or urticaria) were the most common AE with 14 episodes (0.8% of all infusions). Almost all AEs were mild (19/86.4%), with no severe ones being observed. The majority of the AEs (81.8%) was identified at a 0.04ml/kg/min infusion rate. Gender, age at first infusion, presence of infection on the infusion day and change of the IVIG brand were evaluated and none of them were associated with AEs.

Conclusion: The low frequency of immediate AEs in children with IEI highlights the safety and tolerability of intravenous immunoglobulin replacement with the procedures established at our center.

Introduction

Intravenous immunoglobulin (IVIG) is a well-known therapeutic approach for patients with inborn errors of immunity (IEI) with impaired antibody production or function, as well as

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Results

Patients and infusion characteristics

In total, 70 patients with IEI in IVIG therapy, median age 5.8 years old (range: 6 months - 18 years old) were included, with a predominance of males, 46 (65.7%). No difference was noted when patients were stratified by age group: infants and toddlers (24.3%), preschool (24.3%), school (25.7%) and adolescents (25.7%). According to the IEI group,[23] patients were classified as: predominantly antibody deficiencies (PAD) (n = 62, 88.6%), combined immunodeficiencies with associated or syndromic features (n = 7, 10.0%) and Immunodeficiencies affecting cellular and humoral immunity (n = 1, 1.4%).

During the study period, a total of 1736 infusions were administered (median: 18.5/patient, range: 1 - 58/patient), distributed according to the IEI group as follows: "PAD" 1509 (86.9%), "combined immunodeficiencies with associated or syndromic features", 208 (12%), and "Immunodeficiencies affecting cellular and humoral immunity", 19 (1.1%).

The mean loading dose of IVIG was 0.57g/kg (range: 0.23 - 0.88g/Kg). The pre-medication and step-up infusion rate were observed in two-thirds of the infusions (n = 1305, 75.2%). Each patient received different brands of IVIG according to the availability of the Brazilian government supply. The preparations used were as follows: Immunoglobulin® (1101, 63.4%), Octagam ® (326 /18.8%), Sandoglobulina® (89, 5.1%), Tegeline® (72, 4.1%), Privigen® (66, 3.8%), Flebogamma® (62, 3.6%), Endobulin Kiovig® (20, 1.2%).

Adverse events to immunoglobulin

In total, immediate AEs were observed in 22 (1.2%) infusions in 10 children (14.3%). The median age of patients who presented AEs was three years old (range: 10 months - 17 years old) and five (50.0%) were males. The predominant diagnosis was specific antibody deficiency (SAD) (5/50%), followed by Transient Hypogammaglobulinemia of Infancy (THI) and unclassified hypogammaglobulinemia (UH), two cases each and one patient with ataxia-telangiectasia (AT).

Among the patients who had AEs, most of them had associated comorbidities previous to the IVIG therapy: autoimmune cytopenia (n = 2), cardiac disease (n = 2), asthma (n = 1) and glucose-6-phosphate dehydrogenase (G6PD) deficiency (n = 1). The patient with AT developed an ovarian cancer during the follow-up. Her past history of drug adverse reaction or allergic disease were negative.

The distribution of brands of IVIG and AEs is shown in Table 1. The brand Immunoglobulin® was used in more than half of the infusions (63.4%). No AEs were observed with the brands Tegeline®, Privigen® and Endobulin Kiovig®, used in 158 (9.1%) infusions.

Skin reactions (rash or urticaria) were the most common AEs, with 14 episodes (63.6%); interestingly, 12 out 14 of these episodes occurred in two patients. Almost all AEs were mild (19, 86.4%), three moderate (13.6%) and no severe were observed (Figure 1). The mean loading dose in the 22 infusions with AEs was 0.56g/Kg (range: 0.23 - 0.78g/kg).

Table 1 – Distribution of infusions and adverse events according to IVIG brands in 70 patients with inborn errors of immunity (2011 - 2019).

IVIG brand	All infusions n = 1736 (%)	Infusions with AEs (%) n = 22 (%)
Immunoglobulin®	1101 (63.4)	7 (0.6)
Octagam®	326 (18.8)	6 (1.8)
Sandoglobulina®	89 (5.1)	2 (2.2)
Tegeline®	72 (4.1)	0 (0.0)
Privigen®	66 (3.8)	0 (0.0)
Flebogamma®	62 (3.6)	7 (11.3)
Endobulin Kiovig®	20 (1.2)	0 (0.0)

IVIG: intravenous immunoglobulin, AEs: adverse events.

It is worth noting that all moderate immediate AEs were observed in the same patient, a 2-year-old boy, with UH (baseline IgG serum level < 200 mg/dL), with recurrent respiratory and gastrointestinal infections in association with a positive history of IEI (his older brother had died due to sepsis at 1 yo). This patient also had a G6PD deficiency, but no clinical feature of allergic or other chronic/autoimmune disease. He received Flebogamma® in all three infusions, however, as no other patient had a moderate AE with this brand, there is not enough data to establish a correlation. In this particular case, after recurrent episodes of skin rash/chills, 6 out of 8 infusions, the intravenous route was changed to subcutaneous with the resolution of reactions.

No significant association was observed in the distribution of latency by severity of the AE, p > 0.05 (Figure 2). However, most AEs occurred at 0.04ml/kg/min rate, n = 18 (81.8%) and three (13.7%) at 0.02ml/Kg/min. In 10 reactions, the infusion was completely interrupted. It is worth noting that in 20 infusions with AE, the patients had already received pre-medication (Supplementary Table).

The age, changing brands, active infection and first three infusions were studied as potential independent risk factors for AEs in our patients. Logistic regression analysis was performed and no statistical association was found (Table 2).

Complete (36.4%) or temporary (66.6%) interruption of IVIG infusion and administration of symptomatic medications
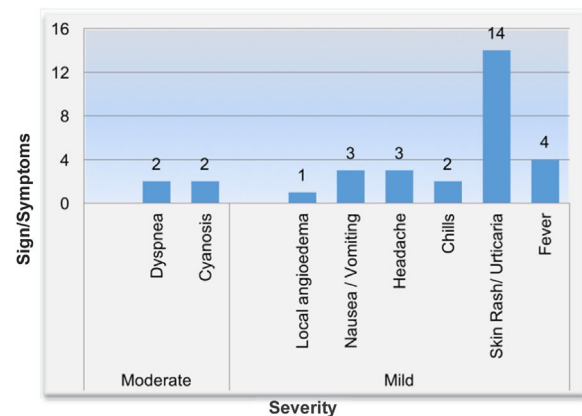

Figure 1 – Sign and symptoms of adverse events in 70 pediatric patients with inborn errors of immunity under intravenous immunoglobulin therapy (n = 1736 infusions).
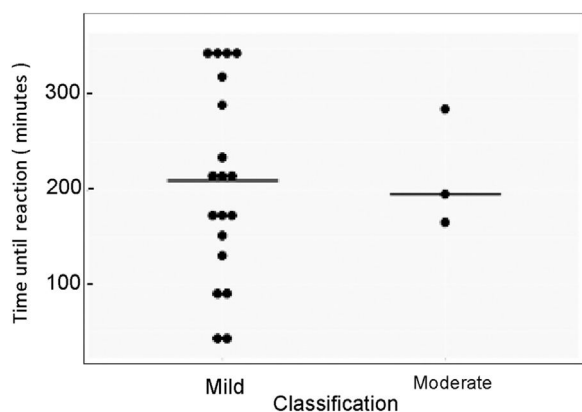
Figure 2 – Time until reaction (minutes) in comparison with severity of 22 immediate adverse effects related to IVIG. Median time of mild and moderate reactions occurred at 210 and 195 minutes after starting IVIG infusions, respectively.

reverted all reactions. In cases of temporary interruption, the infusion restarted with the maximum loading dose of 0.03ml/kg/min.

Discussion

Immunoglobulin represents the main therapy for patients with impaired antibody production or function, with great impact on the quality of life for many patients.[4,5,8,10] It also has benefits in several diseases that manifest with hypogammaglobulinemia, including graft-versus-host disease, multiple myeloma and chronic leukemia.[3] or in patients with immune dysregulation.[1] It is considered a safe procedure, but adverse events are not uncommon and these reactions can be local (at the infusion site) or systemic and immediate (within 6 hours of the infusion) or delayed (6 hours to one week after the infusion).[3,12,13,19] The main strategies described to prevent adverse reactions triggered by immunoglobulin infusion are: controlling triggering factors, hydrating the patient before infusion, infusing the product at room temperature, monitoring vital signs during infusion, infusing at a slower infusion rate in the first administrations and keeping the patient under observation for one hour after the end of the infusion.[3,12,24] Even with the knowledge of triggering factors, the percentages of AEs related to the IVIG can be up to 40% of infusions at replacement doses.[14,15] The present study describes the frequency of immediate AEs in patients with antibody deficiency under regular IGIV replacement therapy,

Table 2 – Potential risk factor associated for adverse effects related to IVIG at replacement dose.			
Independent risk factor	Odds ratio	CI 95%	*p*-value
Age	1.00	0.89 - 1.11	0.994
Changing brands	0.52	0.19 - 1.42	0.200
Active infection	0.41	0.07 - 2.54	0.338
First three infusions	3.71	0.85 - 14.70	0.074

IVIG: Intravenous immunoglobulin, CI: confidence interval of 95%.

using a pre-infusion protocol and, as far as we know, it is the first report on a pediatric cohort with IEI.

A total of 1736 infusions in 70 patients were evaluated and the incidence of AEs was very low, being 1.2 % (*n* = 22) of infusions. This finding was lower than most studies enrolling a pediatric population with IEI.[13,15,18-20] This discrepancy can be related to the protocol described here, or in other words, the use of pre-medications in the first three infusions or in case of switching the IVIG brand. We are quite sure that it had a great impact on our results, as this medical strategy was adopted in 75.2% of all infusions, it also reflects the high frequency in brand switching and, without pre-infusion strategies, the proportion of AEs perhaps could be higher.[25] The IVIG preparations have several differences in formulation and are not equally tolerated;[4,24,26] thus, it has been recommended that changing in brands should be done with caution[4,25] and indicated by the physician,[4] while unfortunately, as described herein, our patients rarely receive the same IVIG in two infusions in a row.

Most of the reactions were mild (86.4%) as expected, three, moderated (cyanosis and dyspnea) in a single patient and no severe reactions. Mild symptoms are predominant in patients with IEI, especially chills, fever and headache and usually have resolution with temporary infusion and symptomatic medication.[12-14,18,27] Severe AEs are more frequent in patients with autoimmunity and neurological disorders and hematological diseases treated with higher IVIG dose.[3,12,24] However, it also can happen in antibody-deficient patients; Bichuetti-Silva and colleagues observed a relevant rate of 7.9% infusions with severe reactions[18] and Esmaeilzadeh et al. described 10% of severe symptoms, especially in patients with Hyper IgM syndrome.[15] Temporary or complete interruption of the infusion is recommended, according to the severity of the reaction.[3,4] The safety of the IVIG infusion at our center, with a very low incidence of AEs and no severe reactions, resulted in only 10 (0.6%) complete interruptions during the eight-year follow-up and this may have had a positive impact on the treatment itself, with more stable IgG serum levels, less use of additional drugs to control adverse reactions and, perhaps, a social and economic impact.

Urticaria was the most common reaction, 14 (63.6%) of the infusions having AEs, with almost all (12 out 14) episodes in two patients and complete resolution after changing to the subcutaneous route. The IVIG- related urticaria is not very common, as we observed, and it is usually resultant of IgG aggregates, with resolution after temporary interruption.[20,24] Fever has been described as the most common AE in some studies[14,20] and, in this study, it was the second most prevalent reaction, followed by headache and nausea/vomiting. Headache is often described in up to 24% of the patients, independent of the age, usually conventional analgesics are effective in controlling symptoms and most cases have resolution in the first 24 hours after stopping the infusion, although some rare patients need to be hospitalized.[12,19,24] Headache was seen in three patients and cyproheptadin or acetaminophen was used, as recommended,[3,24] to prevent new episodes and, fortunately, none of the patients needed hospital admission.

Several factors have been associated with AEs to IVIG, such as a prior history of infusion reaction, large dose, first

infusions and active infection.[4,5,7] No significant correlation was observed with age, active infection or first infusions, nor with changing in IVIG preparations in this study, in contrast to previous data.[14,15,18-20] The IVIG brand as a factor for AEs has controversial results and, in some studies no association has been found, while, on the other hand, some authors have mentioned a significant incidence of AEs with lyophilized products and preparations with high amounts of sucrose are more related to renal impairment.[18,24] In our study, no correlation with IVIG brands was seen, maybe because of the small number of reactions.

It is also important to keep in mind that, in particular cases, as observed in some of our patients, the subcutaneous immunoglobulin (SCIG) should be considered to avoid IG infusion- related AEs.[7] In terms of efficacy, the IVIG and SCIG are similar for patients with IEI.[1] Potential advantages of SCIG therapy over IVIG include a shorter infusion time, almost no wear-off effects and more stable IG concentrations.[1,2,4] Several studies have also demonstrated an overall improvement in the quality of life in patients receiving the SCIG, in comparison to the IVIG administration.[1,2,4,7] On the other hand, because of the smaller SCIG doses frequently given, some patients prefer the IVIG administration[4] and some authors claim that the SCIG therapy may not be optimal in patients who have poor adherence to treatment.[1] Regarding the AEs, the SCIG has significantly lower systemic adverse reactions, which occur in less than 1% of infusions;[4] thus, switching from the IVIG to the SCIG seems to be an effective strategy that reduces immunoglobulin-induced AEs, especially for patients who have previously experienced severe AEs or are at high risk of developing adverse effects.[2,3] Hydrating the patient before infusions (with careful attention to the volume in patients with comorbidities, such as kidney or heart disease),[4] infusing the product at room temperature, monitoring vital signs during infusion, a slower infusion rate in the first administrations and keeping the patient under observation for one hour after the end of the infusion are well-known strategies to reduce AEs related to the IVIG.[4,24] Pre-medications are not usually administrated before the IVIG[19,24] and some authors claim that it does not influence the frequency of the AEs.[3] However, according to data from the Immune Deficiency Foundation (IDF), in a survey of 1500 patients under IVIG treatment, almost half of the patients (45%) stated that they were usually receiving premedication before infusion and, in a retrospective study assessing the safety profile of the IVIG in 424 patients, premedication was provided to 276 patients (65.7%) and the incidence of adverse reactions to the IVIG was significantly lower in patients who received premedication, compared to the non-premedicated patients (18.4% *vs.* 27.1%, p = 0.04), cited by Cherin et al.[24] Our results suggest that premedication has influenced the low rates of AE to IVIG in pediatric patients with IEI, although only a comparative study with and without premedication could give us more convincing data.

Conclusion

This study has some limitations, such as the absence of data on previous reactions to other blood products, detailed data on the use of prophylactic antibiotics, chronic use of steroids to treat comorbidities, or the use of immunosuppressive drugs. Nevertheless, we described a protocol for the IVIG infusion in pediatric patients with IEI who commonly received different brands during their treatment and the low frequency of immediate AEs highlights the safety and tolerability of intravenous immunoglobulin replacement with the procedures established at our center.

Conflicts of interest

The authors declare no conflicts of interest

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.htct.2022.06.009.

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