Intravenous immunoglobulin G use and pharmacovigilance in a tertiary care children's hospital

Silvana Yori, M.D.^a, Florencia Belleri, Pharmacist^a, Juliana Testard, Pharmacist^a,
Ángeles Fierro Vidal, M.D.^a and Marcela Rousseau, Magister^a

Collaborator: Roxana Rivero

a. Hospital de
Pediatria "Prof. Dr.
Juan P. Garrahan",
Autonomous City
of Buenos Aires.
Argentina.

E-mail address:
Silvana Yori, M.D.:
silvanayori@gmail.com

Funding:
Silvana Yori received
a scholarship from
the Blood Products
Laboratory of
Universidad Nacional
de Córdoba.

Conflict of interest:
• Silvana Yori
received a scholarship
from the Blood
Products Laboratory of
Universidad Nacional
de Córdoba for this
research, which was
executed through an
agreement between
Hospital de Pediatría
"Juan P. Garrahan"
and said institute
once the Research
and Teaching Board
of Hospital Garrahan
and the Research
Protocol Ethics Review
Committee had
reviewed the research
protocol (protocol
no. 1045).

• Roxana Rivero
works for the Blood
Products Laboratory
of Universidad
Nacional de Córdoba,
Department of
Pharmacoepidemiology
and Scientific
Information.
• Magister Marcela
Rousseau was Silvana
Yori's research
scholarship supervisor,
but received no
compensation for such
role.

Received: 6-2-2020
Accepted: 12-1-2020

ABSTRACT

Introduction. Intravenous immunoglobulin G (IVIG) is a blood product from polyvalent and polyclonal immunoglobulin G. It covers a broad range of indications as immunomodulator or replacement therapy. In addition, although it is considered a safe therapy, the incidence of adverse reactions reported in the bibliography ranges from 1% to 81%. The objective of this study was to assess IVIG use and describe related adverse events in a tertiary care children's hospital.

Population and methods. This was a pharmacoepidemiological, observational, and prospective study. Patients receiving IVIG for 7 months in 6 areas of a tertiary care children's hospital in the Autonomous City of Buenos Aires were assessed. The analysis unit was each IVIG infusion, and the main variable was the presence of adverse reactions.

Results. A total of 305 infusions in 111 patients were analyzed. In 81.6% of cases, the indication was for replacement. The maximum dose was 1 g/kg. In 99.6% of infusions, some type of premedication was indicated; diphenhydramine was the most common drug, with varying dosages. A total of 12 adverse reactions (3.9% of infusions) were recorded; 3 were severe: aseptic meningitis (2 cases) and seizures (1 case). All resolved to normal.

Conclusions. The rate of IVIG adverse reactions in our setting was low; most reactions were mild and immediate and resolved favorably in all patients.

Key words: intravenous immunoglobulin, drug-related side effects and adverse reactions, therapeutic use, pediatrics.

<http://dx.doi.org/10.5546/aap.2021.eng.192>

To cite: Yori S, Belleri F, Testard J, Fierro Vidal A, Rousseau M. Intravenous immunoglobulin G use and pharmacovigilance in a tertiary care children's hospital. *Arch Argent Pediatr* 2021;119(3):192-197

INTRODUCTION

Intravenous immunoglobulin G (IVIG) is a purified, sterile blood product from polyvalent and polyclonal immunoglobulin G (IgG). It can be used for multiple indications, including replacement therapy in primary or secondary immunodeficiency diseases with humoral immunity involvement¹⁻³ and as an immunomodulator in a large variety of generalized, inflammatory autoimmune diseases^{4,5} and acute infections.^{1,6}

IVIG is commonly used in Hospital de Pediatría "Prof. Dr. Juan P. Garrahan," with over 2000 annual infusions, and has accounted for the leading drug expenditure for the past 8 years.⁷ At the hospital, IVIG is mainly acquired at a differential price through an agreement with the Blood Products Laboratory of Universidad Nacional de Córdoba, which receives the plasma from the hospital's donors. This trademark of IVIG is distributed into IgG subclasses similar to normal serum IgG, with an immunoglobulin A (IgA) content that may range from 0 to 30 mg/dL, and sorbitol and glycine are used as stabilizers.⁸

Although IVIG is considered a safe therapy, the incidence of adverse reactions reported in the bibliography ranges from 1% to 81% of infusions. Most reactions are mild, immediate, and reversible.⁹⁻¹³ Immediate reactions include fever, chills, headache, rash, myalgia, back pain, dyspnea, chest tightness, nausea, vomiting, diarrhea, hypo- or hypertension, tachycardia, and anaphylactic reactions, especially among patients with IgA deficiency. Delayed adverse

reactions are uncommon and include acute renal failure, thromboembolic events, aseptic meningitis, hemolytic anemia, neutropenia, pseudohyponatremia, arthritis, and skin reactions.^{9,10,13}

A slow IVIG drip rate, especially in the first infusions, and premedication with acetaminophen, antihistamines or corticosteroids may be related to a reduction in immediate adverse reactions.⁹ The objective of this study was to assess IVIG use and describe adverse drug events in a tertiary care children's hospital.

POPULATION AND METHODS

This was a pharmacoepidemiological, observational, and prospective study^{14,15} conducted between August 2018 and February 2019 at Hospital de Pediatría "J. P. Garrahan" in patients receiving IVIG. It was approved by the hospital's Research Ethics Review Committee; and a verbal informed consent was obtained from the patients or their caregivers for IVIG infusion data collection.

Inclusion criteria were patients receiving IVIG in the following hospital areas: Multipurpose Day Hospital, Cancer Day Hospital, Bone Marrow Transplant Unit, and three hospitalization wards. The former three areas administered IVIG infusions on a daily basis; however, the hospitalization wards administered IVIG less frequently and with varying indication profiles.

A registration card was developed for each infusion. Data were collected by the Department of Nursing, responsible for administering IVIG. Patients who had received IVIG and whose infusion was not fully documented were excluded.

The analysis unit was each IVIG infusion, which may be multiple in 1 patient. All data were loaded into the REDCAP base and analyzed using the IBM SPSS 18 software.

STUDY VARIABLES AND OUTCOME MEASUREMENT

Variables related to intravenous immunoglobulin G

In relation to IVIG, the following data were recorded: product (lot, expiry date), trademark used, and dosage (infusion number, dose, infusion rate). Prescribed dose, premedication, and administration mode, which were decided by each area's treating physician, were also recorded.

Variables related to patient's characteristics and therapy

In relation to patient's characteristics and treatment, the following data were collected: age, sex, geographic origin, underlying diagnosis, IVIG indication, comorbidities considered a risk for IVIG adverse reactions (anemia, malnutrition, renal failure, liver failure or prior drug allergic reaction).^{9,13} In addition, in relation to other medications administered to patients during hospitalization, drugs exclusively administered during their stay were recorded, without considering their standard medication.

Variables related to safety

Adverse drug events (ADEs)¹⁶ were defined as those causing an alteration or harm in the patient, and encompassed the following:

- *Adverse drug reaction (ADR)*: a harmful and involuntary drug response that occurred with normally used doses.
- *Medication errors (MEs)*: a preventable incident that may harm the patient or result in an inadequate drug use while being used under the supervision of a health care provider or by the patient. These incidents may be related to failures in prescription, communication, labeling, packaging, naming, preparation, dispensing, distribution, administration, education, follow-up, and use.¹⁷

In relation to ADE monitoring duration, it was performed during administration and for the 5 following days of hospital stay. If patients were discharged before that time, they were given warning signs, and those who made a new consultation for potential ADEs within 5 days after infusion were included.

All ADEs were recorded in the pharmacovigilance card of the National Drug, Food and Technology Administration of Argentina (*Administración Nacional de Medicamentos, Alimentos y Tecnología Médica*, ANMAT).¹⁸ For MEs, the hospital's Patient Safety Committee and Drug, Medication, and Pharmacovigilance Committee made an effort to prevent them using different strategies, such as Hospital Garrahan's Pharmacotherapeutic Form,¹⁹ Medication tables for critical situations,²⁰ periodic reports, etc.

Adverse reactions were imputed based on Naranjo's algorithm categories: definite, probable, possible, and doubtful.²¹ Severity was established based on the classification by the World Health Organization (WHO): mild, moderate, severe or lethal.²²

RESULTS

A total of 305 infusions in 111 patients were reviewed; they accounted for 28 % (1090) of all infusions administered in the areas included in the research during the study period. The infusions excluded from the study were due to poor documentation by the responsible staff. More than 1 infusion was done to 70 % of patients. Most cases corresponded to patients receiving monthly IVIG infusions as replacement therapy (Table 1).

Out of the 111 patients, 67 (60.3 %) were males. Patients' average age was 8.27 years, with a standard deviation of 5.16 and an age range of 3 months to 19 years. In relation to patient's origin, 65 patients (58.55 %) were from the Province of Buenos Aires; 27 (24.32 %), from other provinces; 18 (16.21 %), from the Autonomous City of Buenos Aires; and 1 from abroad.

Indication for intravenous immunoglobulin G

Out of all infusions, 249 (81.6 %) were done as replacement therapy. This is because 67.2 % of all infusions corresponded to primary immunodeficiency disease. The second leading indication was bone marrow transplant (Table 2).

Trademarks of intravenous immunoglobulin G

Out of all IVIG infusions, 94.54 % were done with the drug provided by the Blood Products Laboratory of Universidad Nacional de Córdoba. This was followed by the IVIG from CSL Behring (Privigen®), with 4.6 %. A single IVIG infusion (0.3 %) with each of the following trademarks was recorded: CSL Behring (Sandoglobulina®), Baxter (Kiovig®), and Tuteur (Cieldom®).

Dosage

The maximum dose indicated was 1 g/kg and corresponded mainly to cytopenias (immune thrombocytopenic purpura, hemolytic anemia) and neurological disorders (Guillain-Barré

syndrome, Miller-Fisher syndrome, autoimmune encephalitis, opsoclonus-myoclonus syndrome, Rasmussen's encephalitis, etc.). The 0.5 g/kg replacement dose was indicated more frequently to patients with neoplasms and bone marrow transplant, whereas the IVIG dose for replacement therapy in primary immunodeficiency disease was 0.6-0.8 g/kg.

Premedication

Out of 305 infusions, premedication was not performed in only 1 case. Diphenhydramine was the most common drug; it was given in 297 (90.5 %) of infusions, either orally or intravenously, alone or in combination. The intravenous diphenhydramine-hydrocortisone combination was recorded only in 38 (12.4 %) cases. Other less common drugs (less than 3 %) included acetaminophen, dipyron, and metoclopramide.

Infusion rate

All infusions were started at a slow rate (0.01-0.02 mL/kg/min) and increased progressively, to a maximum of 0.06 mL/kg/min. Out of 305 infusions, the drip rate was not recorded in 43 (14 %) given at the Bone Marrow Transplant Unit.

TABLE 1. Number of infusions per patient

No. of infusions	No. of patients
1	34
2	34
3	13
4	11
5	6
6	10
7	3

TABLE 2. Diagnosis for indication

Diagnosis	Frequency	Percentage (%)
Primary immunodeficiency disease	205	67.3
BMT with chronic GVHD	17	5.5
BMT with hypogammaglobulinemia	16	5.2
Autoimmune encephalitis	11	3.6
Parvovirus in BMT	11	3.6
Cytopenia	9	3
Neoplasms	6	2
Opsoclonus-myoclonus syndrome	6	2
Hypogammaglobulinemia due to rituximab	5	1.6
Transplant desensitization	4	1.3
CIDP	4	1.3
Guillain-Barré/Miller-Fisher syndrome	3	1
Rasmussen syndrome	2	0.65
Cytomegalovirus in BMT	2	0.65
BK virus in BMT	2	0.65
Other*	2	0.65
Total	305	100

BMT: bone marrow transplant; GVHD: graft versus host disease; CIDP: chronic inflammatory demyelinating polyneuropathy.

* Other: longitudinal myelitis, radiculitis in juvenile dermatomyositis.

Safety

IVIG demonstrated an excellent tolerance in 96.1 % of cases, which corresponded to 293 infusions without adverse reactions. Twelve ADEs were recorded in 10 patients (2 developed an ADE twice), which accounted for 3.9 % of all infusions. These are detailed in *Table 3*. Eleven of the 12 ADEs were ADRs, and 1 was a prescription ME due to a fast initial infusion rate (0.05 mL/kg/min).

The diagnoses of patients with ADEs are shown in *Table 4*. No ADEs were observed in the Bone Marrow Transplant Unit, where the infusion rate was not recorded.

Among reported ADEs, 8 of 10 patients had received prior IVIG infusions and only 2 developed an ADE during their first infusion. On the contrary, only 2 patients who experienced an ADE developed it again with the following infusions. In relation to the IVIG dose, among infusions related to an ADE, 6/12 corresponded to the maximum dose of 1 g/kg of IVIG; 4/12, 0.8 g/kg; and the rest (2/12), 0.5 g/kg.

Out of the 10 patients who developed an ADE, 3 had comorbidities associated with a higher risk for IVIG adverse reactions: anemia and renal failure, allergic reaction to diphenylhydantoin, and malnutrition. In relation to ADE severity, 7 were considered mild; 2, moderate; and 3, severe. The infusion was interrupted for all mild ADEs recorded; ibuprofen (10 mg/kg) was administered in the case of fever/headache or hydrocortisone (1 mg/kg) in the case of rash; the infusion was restarted at a slower rate and completed without complications. An expectant management was adopted in the patient with tachycardia and hypertension, and no other events were recorded.

The severe ADEs corresponded to 2 cases of aseptic meningitis and 1 case of seizures. In relation to the time between the IVIG infusion

and early symptom onset, seizures occurred during the infusion (1 hour after initiation) and, in the 2 cases of aseptic meningitis, early symptoms (headache, photophobia, and vomiting) developed at 24 hours and 4 days, respectively. All events resolved to normal and without sequelae; however, ancillary studies were required and hospitalization was prolonged 11 days, considering the 3 patients together.

In relation to the attribution of reported ADEs to IVIG, causality was probable in 9/12; possible in 2/12; and definite in 1/12. The latter corresponded to the ME.

DISCUSSION

In our study, most IVIG indications were for replacement therapy and adverse reactions were reported in a small percentage, with a favorable course in all patients. Unlike what has been reported in the bibliography, most patients in our study who experienced an ADE had received prior IVIG infusions.¹³ Such discrepancy may be because a significant percentage of our sample received IVIG as replacement therapy, so it corresponded to chronic IVIG administration. This underscores the importance of ongoing monitoring during IVIG infusion in all patients, both treatment-naïve and previously treated.

In relation to dose/kg, most ADEs occurred with high IVIG doses (0.8-1 g/kg), as described in the bibliography, and this is considered to be associated with the rapid increase in serum IgG levels.⁹ In addition, in agreement with the bibliography, most ADEs were mild and immediate.⁹⁻¹³ These symptoms generally occur in the first 30 minutes of administration, and it has been proposed that they are hypersensitivity reactions due to immunoglobulin molecule

TABLE 3. Adverse reactions

Symptom	Frequency
Rash	3
Fever	2
Headache	2
Aseptic meningitis	2
Fever and chills	1
Tachycardia and hypertension	1
Seizures	1

TABLE 4. Diagnoses of patients who developed adverse reactions

Diagnosis	Frequency
Primary immunodeficiency disease	3
Autoimmune encephalitis	2*
Guillain-Barré syndrome	1
Miller-Fisher syndrome	1
Neuromyelitis optica	2*
Kidney transplant rejection	1
Longitudinal myelitis under study	1
Thrombocytopenia under study	1

* The same patient developed adverse reactions with 2 different IVIG infusions.

aggregation causing complement activation or antigen-antibody reactions.^{9,10,13} This type of adverse reactions are usually managed by reducing the infusion rate and administering medications, such as antihistamines, acetaminophen, and corticosteroids, which corresponded to the management of our patients, who showed a good response.⁹

In relation to severe adverse reactions, two cases of aseptic meningitis were reported. Both patients had received a high IVIG dose (1 g/kg for 2 days in a row) and had a diagnosis of Guillain-Barré syndrome and Miller-Fisher syndrome. These findings are consistent with bibliography reports that indicate that aseptic meningitis is a complication associated with high-dose IVIG infusions in patients with nervous system autoimmune conditions.^{10,13,23,24} It is believed that the pathophysiological mechanism of meningeal irritation may be caused by IgG itself or, more likely, by the immune complexes formed between therapeutic and endogenous IgG in cerebrospinal fluid. A delayed symptom onset may be due to the time necessary for IgG to cross the blood-brain barrier.¹³

Limitations and future perspectives

One of the limitations of our study was that a large number of IVIG infusions were excluded from the research because they were not correctly documented in the study registration cards. This is especially due to the high demand on the hospital, which, many times, results in providers being unable to adequately comply with activities not related to health care. For this reason, it is critical to carry out similar investigations so that this problem is addressed and strategies aimed at improving patient safety are developed.

In addition, the large number of patients receiving IVIG as replacement therapy resulted in a selection bias because most studied infusions were done in patients who had received prior IVIG infusions. This may have resulted in a smaller incidence of ADEs due to a fact reported in the bibliography that a first infusion or a change in IVIG trademark were considered risk factors for ADEs.¹³ Future studies should include a larger number of patients receiving IVIG for the first time.

The emergence of subcutaneous IgG in recent years, especially for replacement therapy, opens up new lines of research about its use and safety. This route of administration is already in use in many locations worldwide²⁵ and our hospital is starting

its implementation. Costs are reduced and quality of life improves because it is associated with a lower incidence of systemic adverse effects, higher and stable serum IgG levels, and the possibility of not using a peripheral venous access and, instead, performing an outpatient treatment that may be carried out at home.

CONCLUSION

The rate of IVIG adverse reactions in our setting was low; most reactions were mild and immediate and resolved favorably in all patients.

REFERENCES

1. IVIG Guideline Development Group of the IVIG Expert Group. Clinical guidelines for immunoglobulin use: update to second edition. London: Department of Health; 2011.
2. Comité Nacional de Infectología, Grupo de Trabajo de Inmunología. Consenso sobre actualización en inmunizaciones en pacientes con inmunodeficiencias primarias. *Arch Argent Pediatr*. 2018; 116(Supl 2):S20-33.
3. Ballow M. Optimizing immunoglobulin treatment for patients with primary immunodeficiency disease to prevent pneumonia and infection incidence: review of the current data. *Ann Allergy Asthma Immunol*. 2013; 111(6 Suppl):S2-5.
4. Ballow M. The IgG molecule as a biological immune response modifier: mechanisms of action of intravenous immune serum globulin in autoimmune and inflammatory disorders. *J Allergy Clin Immunol*. 2011; 127(2):315-23.
5. Perez EE, Orange JS, Bonilla F, Chinen J, et al. Update on the use of immunoglobulin in human disease: A review of evidence. *J Allergy Clin Immunol*. 2017; 139(3S):S1-46.
6. Rezaei N, Abolhassani H, Aghamohammadi A, Ochs HD. Indications and safety of intravenous and subcutaneous immunoglobulin therapy. *Expert Rev Clin Immunol*. 2011; 7(3):301-16.
7. Sberna N. Informes Comité de Farmacia y Terapéutica. Buenos Aires: Hospital Garrahan, 2012-2019.
8. Prospecto de Inmunoglobulina G Endovenosa UNC, Inmunoglobulina Humana Normal. Laboratorio de Hemoderivados □Presidente Illia□. Universidad Nacional de Córdoba. Most recent review: Marzo de 2007. [Accessed on: April 1st, 2020]. <https://unc-hemoderivados.com.ar/prodHemoderivados.php>.
9. Cherin P, Marie I, Michallet M, Pelus E, et al. Management of adverse events in the treatment of patients with immunoglobulin therapy: A review of evidence. *Autoimmun Rev*. 2016; 15(1):71-81.
10. Guo Y, Tian X, Wang X, Xiao Z. Adverse Effects of Immunoglobulin Therapy. *Front Immunol*. 2018; 9:1299.
11. Bichuetti-Silva DC, Furlan FP, Nobre FA, Pereira CT, et al. Immediate infusion-related adverse reactions to intravenous immunoglobulin in a prospective cohort of 1765 infusions. *Int Immunopharmacol*. 2014; 23(2):442-6.
12. Frenzel W, Wietek S, Svae TE, Debes A, et al. Tolerability and safety of Octagam® (IVIG): a post-authorization safety analysis of four non-interventional phase IV trials. *Int J Clin Pharmacol Ther*. 2016; 54(11):847-55.
13. Berger M. Adverse Effects of IgG Therapy. *J Allergy Clin Immunol Pract*. 2013; 1(6):558-66.
14. Capellà D, Laporte JR. Métodos aplicados en estudios descriptivos de utilización de medicamentos. In: Laporte JR, Tognoni G (eds.). *Principios de epidemiología del medicamento*. 2.^a ed. Barcelona: Masson-Salvat; 1993. Pages.67-93.

15. Figueras A, Vallano A, Narváez E. Estudios de utilización de medicamentos. Manual práctico. Managua: Ministerio de Salud, Dirección de recursos de salud; 2003.
16. Ortega MJ, Domínguez-Gil A. Acontecimientos adversos por medicamentos: una patología emergente. *Farm Hosp.* 2000; 24(4):258-66.
17. NCC MERP Taxonomy of Medication Errors. National Coordinating Council on Medication Error Reporting and Prevention. 2001. [Accessed on: April 1st, 2020]. Available at: <https://www.nccmerp.org/sites/default/files/taxonomy2001-07-31.pdf>.
18. Administración Nacional de Medicamentos, Alimentos y Tecnología Médica (ANMAT). Sistema Nacional de Farmacovigilancia comunicación de efectos adversos. [Accessed on: April 1st, 2020]. Available at: <http://www.anmat.gov.ar/farmacovigilancia/notificaciones/FichaFVG.pdf>.
19. Rousseau M, Sberna N, Calle G, Rodríguez M. Formulario Farmacoterapéutico del Hospital de Pediatría Garrahan. 3.^a ed. Buenos Aires: Fundación Garrahan; 2016.
20. Lorenzini L, Boto A, Rino P. Comité de Medicamentos de Alto Riesgo. Tablas de medicación para situaciones críticas. Hospital de Pediatría Garrahan. Enero de 2018. [Accessed on: April 1st, 2020]. Available at: http://garrahan.gob.ar/images/Tablas_de_medizacion_para_situaciones_criticas.pdf.
21. Naranjo CA, Busto U, Sellers EM, Sandor P, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther.* 1981; 30(2):239-45.
22. WHO Meeting on the Role of the Hospital in International Drug Monitoring (1968: Geneva, Switzerland) & World Health Organization. (1969). International drug monitoring: the role of the hospital, report of a WHO meeting [held in Geneva from 18 to 23 November 1968]. [Accessed on: April 1st, 2020]. Available at: <https://apps.who.int/iris/handle/10665/40747>.
23. Sekul EA, Cupler EJ, Dalakas MC. Aseptic meningitis associated with high-dose intravenous immunoglobulin therapy: frequency and risk factors. *Ann Intern Med.* 1994; 121(4):259-62.
24. Bharath V, Eckert K, Kang M, Chin-Yee IH, et al. Incidence and natural history of intravenous immunoglobulin-induced aseptic meningitis: a retrospective review at a single tertiary care center. *Transfusion.* 2015; 55(11):2597-605.
25. Paris K, Haddad E, Borte M, Brodski N, et al. Tolerability of subcutaneous immunoglobulin 20 %, Ig20Gly, in pediatric patients with primary immunodeficiencies. *Immunotherapy.* 2019; 11(5):397-406.