RBFHSS
Revista Brasileira de Farmácia Hospitalar e Serviços de Saúde

Original Paper

Open Access

Intravenous Human Immunoglobulin usage profile in a university hospital in Rio de Janeiro

Bárbara da Silva FERNANDES[1], Cesar Augusto TEIXEIRA[2]

[1]Programa de Residência Integrada Multiprofissional em Saúde com ênfase em Clínica Médica no Hospital Universitário Clementino Fraga Filho, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brasil; [2]Serviço de Farmácia do Hospital Universitário Clementino Fraga Filho, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brasil

Corresponding author: Fernandes BS, barbara.fern16@gmail.com

Submitted: 14-01-2022 Resubmitted: 06-04-2022 Accepted: 11-04-2022

Peer review: blind reviewer and Maely Peçanha Favero Retto

Abstract

Objective: Identify the IVIg indication profile, the rational use according to the indications contemplated by the CEAF/MS and data available in literature. **Methods**: a retrospective descriptive study was carried out at a University Hospital in Rio de Janeiro through the analysis of prescriptions of IVIg. Electronic medical records of inpatients were evaluated between January 2014 and June 2019. Data collected included age, sex, ICD-10 indication, number of cicles, predictability of use (situation in which the hospitalization is scheduled predicting the use of IVIg) and the financial resources mobilized**. Results**: The sample consisted of 199 cycles of use referring to 138 patients, the ICD-10 group with the highest number of indications was G00-G99 (diseases of the nervous system) (66 cycles; 33.2%) and M00-M99 (diseases of the musculoskeletal system and tissue connective tissue) (57 cycles; 28.6%), followed by D50-D89 (diseases of the blood and hematopoietic organs and some immune disorders) (43 cycles; 21.6%). Overall, 36.2% (72 cycles) of the indications were for diseases that are covered by CEAF/MS and there was an occurrence of 30.2% (60 cycles) of predictability of use at the time of hospitalization. About the historical series, there is some consistency in the frequency of almost all indications, except for expressive growth in the frequency of treatments for rheumatological and dermatological conditions. During the evaluated period, only one cycle was provided by CEAF/MS, in the other cases, the hospital paid for the cost of all treatments using its own resources, which represented an annual average of 7.3% of all the institution's expenditure on medicines. **Conclusion**: the study showed a high percentage of use in indications not covered by national protocols. Indications related to skin and subcutaneous tissue diseases, followed by diseases of the musculoskeletal system and connective tissue, were the groups that had the highest percentage of indication without CEAF/MS coverage. More robust studies are needed to support the use of IVIg in these situations, especially given its high cost and potential budgetary impact. It is important that institutions mobilize themselves to develop strategies to promote rational use, especially through the Pharmacy and Therapeutics Commission and Clinical Pharmacy services.

Key words: Immunoglobulins; Drug Utilization; Pharmaceutical Services; Pharmacy Service; Healthcare Financing

Perfil de uso de Imunoglobulina Humana Intravenosa em um hospital universitário no Rio de Janeiro

Resumo

Objetivo: Traçar o perfil de utilização de Imunoglobulina Humana Intravenosa e avaliar seu uso racional comparando com as indicações contempladas pelo CEAF/MS e dados disponíveis na literatura. **Métodos:** estudo descritivo retrospectivo realizado em um hospital universitário do Rio de Janeiro através de análise de prescrições de pacientes internados em uso de IgIV no período de janeiro de 2014 a junho de 2019. Os dados coletados incluíram idade, sexo, indicação pelo CID-10, número de ciclos, previsibilidade do uso (situação na qual a internação é agendada prevendo o uso de IgIV) e recurso financeiro mobilizado no período. **Resultados:** A amostra consistiu em 199 ciclos de utilização referentes a 138 pacientes, o grupo de CID-10 com maior número de indicações foi G00-G99 (doenças do sistema nervoso) (66 ciclos; 33.2%) e M00-M99 (doenças do sistema osteomuscular e tecido conjuntivo) (57 ciclos; 28,6%), seguido por D50-D89 (doenças do sangue e órgãos hematopoéticos e alguns transtornos imunitários) (43 ciclos; 21.6%). No geral, 36,2% (72 ciclos) das indicações foram para doenças que são contemplados para atendimento pelo CEAF/MS e houve uma ocorrência de 30,2% (60 ciclos) de previsibilidade de uso. Quanto à série histórica, há certa constância na frequência de quase todas as indicações, salvo um crescimento expressivo da frequência de tratamentos para indicações clínicas reumatológicas e dermatológicas a partir de 2016. Neste período, apenas um ciclo foi fornecido pelo CEAF/MS, os demais foram financiados pelo hospital com recursos próprios, o que representou uma média anual de 7,3% em relação aos gastos da instituição com medicamentos. **Conclusão:** o estudo revelou um alto percentual de uso em indicações não contempladas pelos protocolos nacionais, as indicações relativas a doenças de pele e tecido subcutâneo, seguido pelas doenças do sistema osteomuscular e tecido conjuntivo, foram os grupos que apresentaram maior percentual de indicação sem cobertura do CEAF/MS. Estudos mais robustos são necessários para fundamentar o uso de IgIV nessas situações, especialmente devido a seu alto custo e potencial impacto orçamentário. É importante que as instituições se mobilizem para desenvolver estratégias de promoção do uso racional, em especial através da Comissão de Farmácia e Terapêutica e serviços de Farmácia Clínica.

Palavras-chave: Imunoglobulinas Intravenosas; Uso de Medicamentos; Assistência Farmacêutica; Serviço de Farmácia Hospitalar; Financiamento da Assistência à Saúde.

Introduction

Human Intravenous Immunoglobulin (IVIg) is a medication that has been presenting a worrying trend of increased use at the global level due to scarcity of raw material, high product added value and off-label applications.[1-3] Its clinical use started in 1939, when at Harvard University, Cohn et al. developed an ethanol plasma fractionation method capable of separating plasma proteins into stable fractions, of which one is rich in antibodies with a protective effect against some infectious diseases and very useful in the treatment of primary immunodeficiencies.[4] In 1981, Imbach et al. noticed that the IVIg infusion in high doses increased platelet titrations in patients with autoimmune thrombocytopenic purpura.[5] After this finding, IVIg use has been expanded and applied to a variety of inflammatory and autoimmune conditions worldwide since then, despite having formal therapeutic indications for a limited number of diseases.[6]

Currently, IVIg represents the main class of therapeutic antibodies in use volume. It is a pool of non-specific antibodies produced from thousands of donors, consisting of a minimum of 90% Immunoglobulin G (IgG).[7-8] The IgG content in these formulations comprises antibodies targeting exogenous antigens to which donors were exposed throughout their lives, in addition to natural anti-idiotypic antibodies capable of neutralizing autoantibodies.[8-9] Its mechanism of action is complex, with the possibility of having both a repository character, especially in primary immunodeficiencies, and an immunomodulator nature. This latter encompasses regulation of the expression and function of Fc receptors, interference with the complementary system activation and with the cytokine network, modulation of the activation and differentiation and effector functions of T and B cells, as well as other probable mechanisms.[3,6] Due to the heterogeneity of clinical conditions that respond to IVIg, such as Thrombocytopenic purpura, Myasthenia gravis, and Guillain-Barré syndrome, different pathways specific to each disease are likely to mediate clinical efficacy of this agent.[8]

In the context of the Brazilian Unified Health System (*Sistema Único de Saúde*, SUS), IVIg is included in the Specialized Pharmaceutical Assistance Component (*Componente Especializado da Assistência Farmacêutica*, CEAF), which was developed to assist in the treatment of chronic and/or rare diseases and was regulated by Ordinance No. 1,554 of July 30th, 2013, consisting of an access strategy whose care lines are defined in Clinical Protocol and Therapeutic Guidelines (CPTGs) published by the Brazilian Ministry of Health (*Ministério da Saúde*, MS).[10] Overall, treatment with IVIg via CEAF is covered for 51 International Classification of Diseases (ICD) codes belonging to different groups (Appendix 1 - Supplementary Material).[11]

Through the Superintendence of Pharmaceutical Assistance and Strategic Supplies (*Superintendência de Assistência Farmacêutica e Insumos Estratégicos*, SAFIE), which manages distribution of the CEAF medications at the state level, it was settled that IVIg should be offered to hospitalized SUS users who comply with the criteria established in the CPTGs, in order to ensure access and budgetary balance between the entities.[12]

In this sense, the current study aims at understanding the IVIg indication profile at a university hospital located in the city of Rio de Janeiro, Brazil, raising discussions on rational use according to the indications covered by the CEAF/MS and data available in the literature.

Methods

This is a descriptive and retrospective study conducted in a university hospital located in the city of Rio de Janeiro. It is a large-size tertiary-level general hospital focused of providing medium- and high-complexity assistance. This hospital has nearly 280 beds and is a recognized center of excellence in teaching, research and extension, with several specialties such as Neurology, Rheumatology, Hematology, Cardiology and Medical Clinic, among others.

Data collection involved the analysis of medical charts from patients hospitalized from January 1st, 2014 to June 30th, 2019, who used IVIg in 5.0 g (100 mg/mL) and 2.5 g (50 mg/mL) vials.

Data regarding the following were collected from the institution's own medical charts: age, gender, indication by ICD-10, number of cycles, and use predictability. These data were grouped by year and also by ICD-10 group in an Excel spreadsheet for analysis purposes. The mean and standard deviation corresponding to the data collected were used. No other statistical treatments were conducted due to the exploratory nature of the study.

Beforehand information on the need of IVIg treatment exerts important operational impacts on streamlining the requests to CEAF/MS, which demands a number of requirements, relieving institutions from mobilizing their resources in situations where the burden is not imposed on them. For a set of clinical conditions, especially Primary Immunodeficiencies, whose IVIg treatment plays a primarily replacement role, it is predicted to be used on a regular basis, whereas other conditions, such as Myasthenia gravis and Guillain-Barré syndrome, require this treatment only in acute circumstances or in exacerbation crises and thus have an unpredictable demand.[4,13] To assess the frequency of this type of situation, treatment predictability at the time of hospitalization was estimated by reading the first note at hospital admission recorded on patient's medical chart. Such notes often include a topic describing "reason for hospitalization", whose reading enabled identifying whether it was explicitly described that the hospitalization purpose was specifically IVIg pharmacotherapy.

Furthermore, data referring to the total expenses on medications, total expenses on IVIg, and items that were in the first positions in the ABC consumption curve for each year studied were obtained from the institution's stock management system, in order to assess representativeness of the institution's expenses on IVIg.

The patients excluded from the analysis were those whose electronic medical charts did not include the clear use indication and/or the ICD code referring to the diagnosis.

As a single patient might have used IVIg more than once and thus could eventually distort the frequency of each ICD, 2 different units of analysis were worked on: a group consisting of the number of patients counted only once, regardless whether they underwent more than one use cycle; and another group called "cycles", which could include repeated use by the same patient during the study period. By "cycle", we considered use of the full therapeutic scheme, where administration of the doses was distributed between 2 and 5 days, depending on the clinical indication.

The current study was approved by the Research Ethics Committee (CAAE 16312419.2.0000.5257).

Results

The initial sample consisted of 229 IVIg use cycles from January 2014 to June 2019. Of this total, 30 (13.1%) were excluded due to absence of a clear record of the use indication and/or the ICD code referring to the diagnosis in the medical chart. Consequently, 199 cycles remained, belonging to 138 patients **(Table 1)**. Among all the patients, 30 underwent more than one IVIg treatment cycle, with the number of repetitions varying from 2 to a maximum of 9. The total population consisted of 63% of female users with mean age of 41 years old (±17), and 37% of male users with a mean age of 47 years old (±18), revealing heterogeneous distribution of users.

Table 1 allows noticing a trend of increased use over the years, with a slight reduction in 2018, but which shortly thereafter, in only 6 months during 2019, already corresponded to 95% of the previous year, with the same number of cycles. These data corroborate those described in the literature, which point to an increasing consumption trend at the global level.[1-3] Interestingly, the number of cycles has presented a more significant increase in relation to the number of patients, indicating a repetitive use profile by the same patients. Except for 2014, IVIg occupied the leading position in the institution's ABC curve, representing a mean of 7.3% of the overall hospital expenses on medications, whose list of medications selected in October 2021 consisted of 472 items. In this period, only one patient received treatment via SAFIE for the equivalent to one cycle, with indication of the Guillain-Barré syndrome (ICD 61.0); in the rest of the cases, the hospital paid for the cost of all treatments using its own resources.

Table 1. Annual characteristics regarding IVIg consumption from January 2014 to June 2019.

Year	No. of patients	No. of cycles	IVIg amount(g)	Representativeness in relation to the Institution's total expenses on medications (%)	Position in the ABC curve
2014	20	25	3,467.5	6	2nd
2015	19	28	3,387.5	5.7	1st
2016	32	38	4,285	6.6	1st
2017	28	38	4,765	7.2	1st
2018	16	35	4,640	7.4	1st
2019	23	35	4,397.5	10.9	1st
Total	138	199	24,942.5	7.3	-

It can be seen that the IVIg use indications by ICD-10 are concentrated in 3 main groups **(Table 2)**: G00-G99 (Diseases of the nervous system), M00-M99 (Diseases of the musculoskeletal system and connective tissue), and D50-D89 (Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism). In combination, these three groups account for more than 90% of the consumption during the period analyzed.

There was also high repetition of patients within certain groups, i.e., the same patient was readmitted several times for repeated IVIg therapy cycles, indicating a continuous use pattern for the treatment of chronic conditions. This phenomenon was mostly observed in the group of skin diseases, in which only 4 patients were responsible for 25 cycles (12.6%), meaning that the mean use per patient for this group of indications was 6.2 cycles in the period, reaching the maximum of 9 cycles (4.5%) in a single patient for the indication of Acquired Bullous Epidermolysis (L12.3). As an aggravating factor, none of the indications belonging to this group were covered by CEAF/MS, which, as reinforced by the data described in the next paragraph, indicates planned off-label use in this scenario. This cycle/patient ratio was 1.4 for the groups of neurological and hematological diseases, 1.2 for the rheumatological diseases, and remained at 1 (one) for the other indications.

Table 2. General and scheduled distribution of indications for IVIg treatment from January 2014 to June 2019 by ICD-10 group

ICD-10 group	Title	No. of patients	No. of cycles	Cycles scheduled
G00-G99	Diseases of the nervous system	48 (34.8%)	66 (33.2%)	27 (40.9%)
M00-M99	Diseases of the musculoskeletal system and connective tissue	48 (34.8%)	57 (28.6%)	2 (3.5%)
D50-D89	Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	30 (21.7%)	43 (21.6%)	10 (23.3%)
L00-L99	Diseases of the skin and subcutaneous tissue	4 (2.9%)	25 (12.6%)	20 (80%)
A00-B99	Infectious and parasitic diseases	4 (2.9%)	4 (2%)	0 (0%)
C00-D48	Neoplasms	1 (0.7%)	1 (0.5%)	0 (0%)
J00-J99	Diseases of the respiratory system	1 (0.7%)	1 (0.5%)	0 (0%)
O00-O99	Pregnancy, delivery and puerperium	1 (0.7%)	1 (0.5%)	0 (0%)
Z00-Z99	Factors that influence health status and contact with health services	1 (0.7%)	1 (0.5%)	1 (100%)
Total		138	199	60 (30.2%)

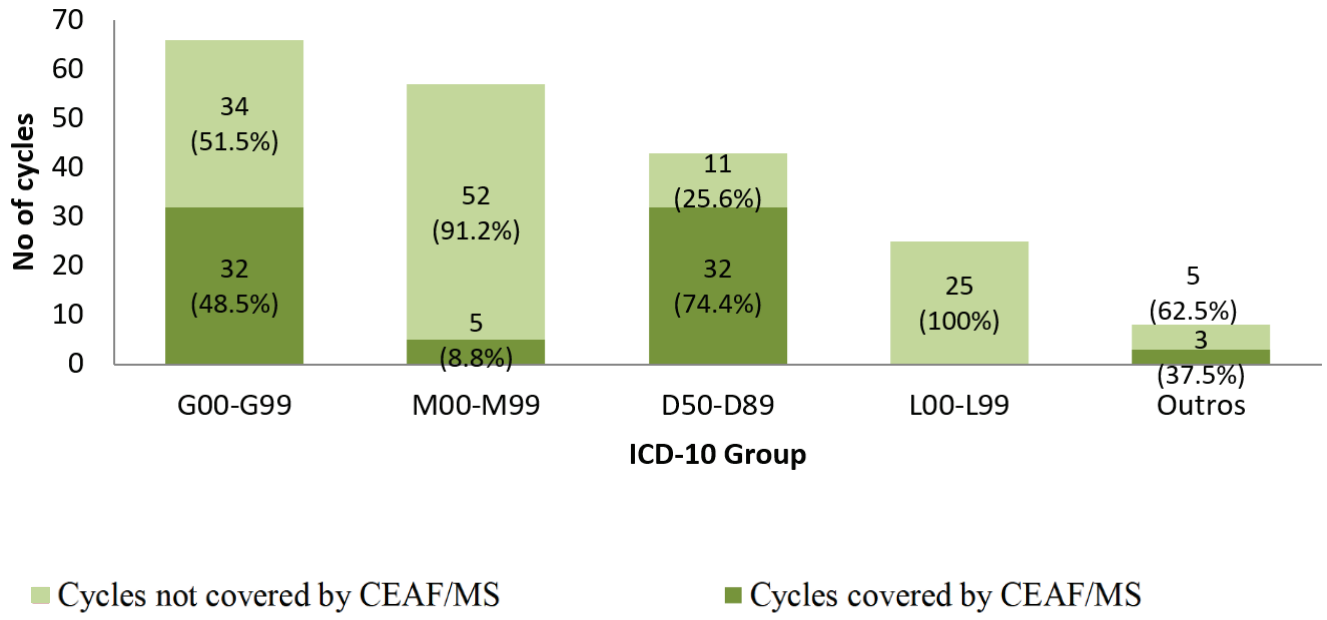
Furthermore, there was a considerable percentage of scheduled use (30.2%), i.e., clinically stable patients with a defined therapeutic plan who were admitted on a scheduled date for IVIg use. The highest schedule percentage was for the dermatological indications (80%), reinforcing the scenario already described, followed by neurological (40.9%) and hematological (23.3%) diseases.

When considering the specific diseases contemplated for assistance via CEAF/MS, it was evidenced that 74.4% of the indications within the group of blood diseases are covered; in turn in the group of diseases of the nervous system, this proportion drops to nearly half (48.5%), whereas it drops to 8.8% in the group of diseases of the musculoskeletal system and connective tissue, reaching zero for the group of skin diseases (**Figure 1**). Overall, 36.2% of the indications in the period were for diseases that could be treated through CEAF/MS. The three most frequent ICD codes in the study period were Systemic lupus erythematosus with impairment of other organs or systems (ICD M32.1; 32 cycles; 16,1%- *not covered by CEAF/MS*), Idiopathic thrombocytopenic purpura (ICD D69.3; 24 cycles; 12.1%) and Myasthenia gravis (G70.0; 22 cycles; 11.1%), the latter two foreseen in CTPGs and covered by CEAF/MS. The full presentation of these data by specific ICD-10 codes can be seen in **Table 3**.

In order to evaluate if the profile of the indications underwent changes throughout the years, the time distribution of the main ICD-10 groups was analyzed through an annual historical series (**Figure 2**). It was observed that the profile of neurological indications (G00-G99) did not oscillate considerably, as they had a slight decrease in 2018 and returned to being closer to their mean values in 2019, thus maintaining a continuous pattern. The hematological indications (D50-D89) presented an increase in 2016, but ended up showing an isolated peak without significant repercussions. In turn, the rheumatological indications (M00-M99) had an increasing curve from 2014 to 2017, presenting a decrease in 2018 and rising again in 2019. The dermatological indications (L00-L99) stood out again, which had very discreet participation until 2018 but then gained prominence and accounted for most of the prescriptions in that year. As previously observed, this finding is not justified by an increased demand related to a greater number of patients treated, but rather by the continuous use by some specific patients.

It is noted that the 2019 numbers only refer to 6 months, from January to June, corroborating again the increasing consumption trend, which evidences the imminent need for a discussion on the subject matter. This year (2019) could not be entirely assessed because, immediately thereafter, the institution experienced a long shortage period that reached a global scale due to difficulties obtaining raw material and to increased prices.[14]

Figure 1. Distribution of IVIg cycles per ICD-10 group segregated by diagnoses covered by CEAF/MS from January 1st, 2014 to June 30th, 2019.



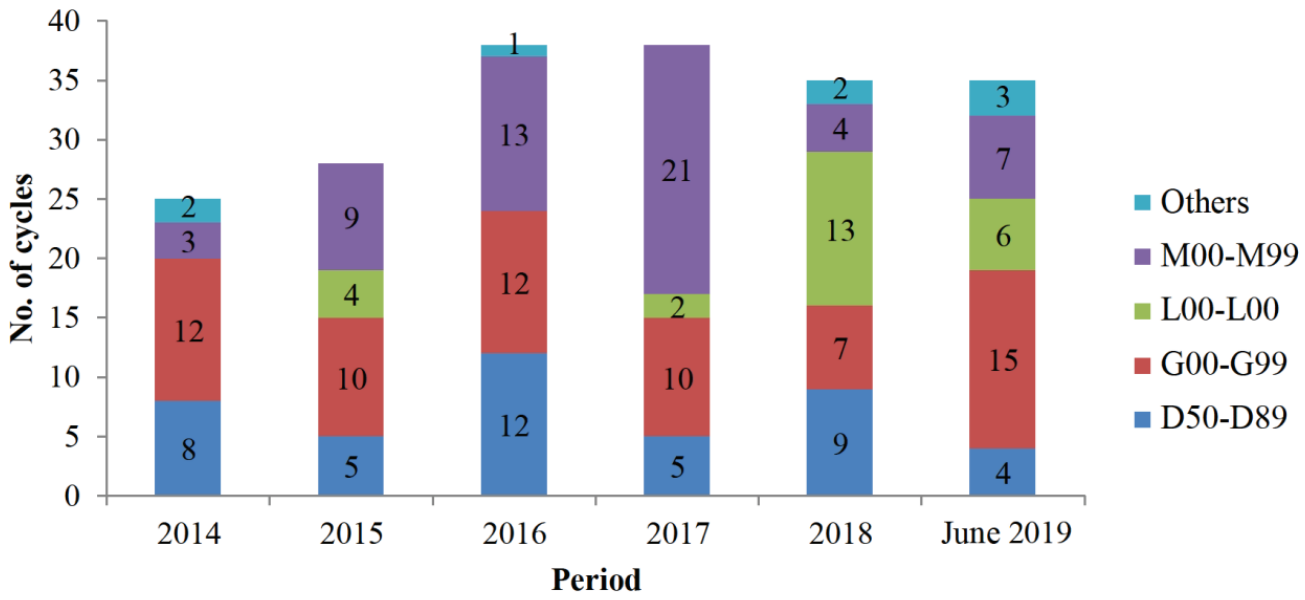
Key: G00-G99- Diseases of the nervous system; M00-M99- Diseases of the musculoskeletal system and connective tissue; D50-D89- Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism; L00-L99- Diseases of the skin and subcutaneous tissue.

Table 3. Distribution of the IVIg treatment indications detailed by ICD-10 category or subcategory between January 2014 and June 2019.

Category or Subcategory (ICD-10)[1]	Patients	Cycles	Disease
A83	1 (0.7%)	1 (0.5%)	Mosquito-borne viral encephalitis
B00	1 (0.7%)	1 (0.5%)	Infections by herpes virus (herpes simplex)
B24[2]	2 (1.4%)	2 (1%)	Unspecified Human Immunodeficiency Virus [HIV] disease
C91.1	1 (0.7%)	1 (0.5%)	Chronic lymphocytic leukemia
D57.0	2 (1.4%)	3 (1.5%)	Sickle cell anemia with crisis
D59.1[2]	2 (1.4%)	4 (2%)	Other autoimmune haemolytic anaemias
D69.0	1 (0.7%)	1 (0.5%)	Henoch-Schönlein purpura
D69.3[2]	16 (11.6%)	24 (12.1%)	Idiopathic thrombocytopenic purpura
D69.5	1 (0.7%)	1 (0.5%)	Secondary thrombocytopenia
D69.6	3 (2.2%)	3 (1.5%)	Unspecified thrombocytopenia
D76.2	2 (1.4%)	2 (1%)	Infection-associated hemophagocytic syndrome
D80.8[2]	2 (1.4%)	4 (2%)	Other immunodeficiencies with predominantly antibody defects
D89.1	1 (0.7%)	1 (0.5%)	Cryoglobulinemia
G04.8	1 (0.7%)	1 (0.5%)	Other types of encephalitis, myelitis and encephalomyelitis
G04.9	1 (0.7%)	2 (1%)	Unspecified encephalitis, myelitis and encephalomyelitis
G05.8	1 (0.7%)	1 (0.5%)	Encephalitis, myelitis and encephalomyelitis and other diseases elsewhere classified
G11	1 (0.7%)	1 (0.5%)	Hereditary ataxia
G11.2	3 (2.2%)	4 (2%)	Late-onset brain ataxia
G13.0	1 (0.7%)	1 (0.5%)	Paraneoplastic neuromiopaty and neuropathy
G25.8	2 (1.4%)	5 (2.5%)	Other extrapyramidal diseases and movement-related disorders, specified
G35	1 (0.7%)	1 (0.5%)	Multiple sclerosis
G40.3	1 (0.7%)	1 (0.5%)	Generalized idiopathic epilepsy and epileptic syndromes
G58.7	1 (0.7%)	1 (0.5%)	Multiple mononeuritis
G61	1 (0.7%)	1 (0.5%)	Inflammatory polyneuropathy
G61.0[2]	9 (6.2%)	10 (5%)	Guillain-Barré syndrome
G61.8	5 (3.6%)	7 (3.5%)	Other inflammatory polyneuropathies
G61.9	3 (2.2%)	3 (1.5%)	Unspecified inflammatory polyneuropathy
G62.8	1 (0.7%)	2 (1%)	Other specified polyneuropathies
G62.9	2 (1.4%)	2 (1%)	Unspecified polyneuropathy
G70.0[2]	13 (9.4%)	22 (11.1%)	Myasthenia gravis
G71.1	1 (0.7%)	1 (0.5%)	Myotonic disorders
J99.1	1 (0.7%)	1 (0.5%)	Respiratory disorders in Systemic lupus erythematosus
L10.0	1 (0.7%)	8 (4%)	Common pemphigus
L10.2	2 (1.4%)	8 (4%)	Foliaceus pemphigus
L12.3	1 (0.7%)	9 (4.5%)	Acquired bullous epidermolysis
M06.1	1 (0.7%)	2 (1%)	Adult-onset Still's disease
M31	1 (0.7%)	1 (0.5%)	Other necrotizing vasculopathies
M32	6 (4.3%)	6 (3%)	Disseminated (systemic) lupus erythematosus
M32.0	1 (0.7%)	1 (0.5%)	Drug-induced Systemic lupus erythematosus
M32.1	25 (18.1)	32 (16.1%)	Systemic lupus erythematosus with impairment of other organs and systems
M32.9	2 (1.4%)	2 (1%)	Unspecified Systemic lupus erythematosus
M33	2 (1.4%)	2 (1%)	Dermatopolymyositis
M33.0[2]	2 (1.4%)	2 (1%)	Juvenile dermatomyositis
M33.2[2]	2 (1.4%)	3 (1.5%)	Polymyositis
M35.0	2 (1.4%)	2 (1%)	Sjögren syndrome
M35.1	1 (0.7%)	1 (0.5%)	Other overlapping syndromes
M35.2	2 (1.4%)	2 (1%)	Behçet's disease
M79.3	1 (0.7%)	1 (0.5%)	Panniculitis, unspecified
O99.1	1 (0.7%)	1 (0.5%)	Other diseases of blood and blood-forming organs and some disorders that impair the immune system, complicating pregnancy, delivery and puerperium
Z94.0[2]	1 (0.7%)	1 (0.5%)	Transplanted kidney
Total	138 (100%)	199 (100%)	

[1]The highest detail level available in the medical chart was used
[2]ICD codes treated by CEAF/MS.

Figure 2. Annual distribution of the main ICD groups that received IVIg treatment.



Key: D50-D89 - Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism; G00-G99 - Diseases of the nervous system; L00-L99 - Diseases of the skin and subcutaneous tissue; M00-M99 - Diseases of the musculoskeletal system and connective tissue.

Discussion

In a scenario where the right to health had been interpreted as the obligation of meeting any existing demand, without considering therapeutic rationality and system sustainability, Law No. 12,401 was promulgated, altering Law No. 8,080/1990, the normative basis for the SUS, and providing for therapeutic assistance and for the incorporation of health technologies in the SUS scope.[15-16] This law instituted the National Commission for the Incorporation of Technologies in the SUS (*Comissão Nacional de Incorporação de Tecnologias no SUS*, CONITEC), which started to advise the MS in developing and altering CPTGs, among other competences.[17-19]

Caution is necessary when assuming that non-protocoled use means irrational use, as not all conditions are covered by a corresponding CPTG and there can be a time frame for updates, in addition to the influence of the funding agreements. In the current study, this situation may be illustrated by chronic demyelinating inflammatory polyneuropathies, which accounted for 3.5% of the cycles performed in the hospital during the period under study. IVIg is considered as a well-established treatment for this type of pathoology[20-23] and is included in the indications approved by the American[24] and European regulatory agencies.[25] In 2019, the National Health Surveillance Agency (*Agência Nacional de Vigilância Sanitária*, ANVISA) approved inclusion of this indication in the package inserts.[26] This situation may represent a still unfinished agenda of the CONITEC with regard to the elaboration of CPTGs, given the amount of available evidence.

Systemic lupus erythematosus with impairment of other organs and systems (ICD M32.1) was the most frequent indication in the period under study, representing 16.1% of the cycles performed. For this indication, there is still no strong evidence and consensus on the efficacy of IVIg treatment, as the available data that point to this use are from non-controlled studies with a reduced number of participants.[2,9,27-28]

As the institution has a teaching and research approach, is a reference for rare cases of countless diseases, and has a clinical staff of specialists with up-to-date knowledge, some use situations not addressed in CPTGs could be expected. However, the results revealed a considerably high use percentage (63.8%) for indications not covered by the national protocols.

A Brazilian study on IVIg use indicated that less than 25% of the prescriptions of the institution where the study was conducted, in Porto Alegre, Brazil, were for indications covered by national protocols. International utilization studies found that, when based on local guidelines, the approved indications accounted for 31% to 75%.[29] In the current study, the value of 36.2% is close to the lower limit of the statistics described, with the particularity of a significant demand for rheumatological and dermatological indications.

Studies from other countries reported that the most frequent indications are neurological, hematological and primary immunodeficiencies, a significantly percentage of which consists of indications lacking appropriate scientific support.[30-34] In the current paper, the neurological indications ranked first, and the hematological ones, third. There were no cases of primary immunodeficiencies, probably due to the outpatient dispensation flow established by the State Pharmacy of Special Medications (*Farmácia Estadual de Medicamentos Especiais*, RIOFARMES), which covers such conditions and prevents the need for hospitalization of the patients.[18]

The fact that the second and fourth positions were respectively occupied by the indications related to the diseases of the musculoskeletal system and connective tissue and to skin and subcutaneous tissue diseases differ from the literature findings; moreover, these are the precisely two groups with the highest percentage of indications not covered by CEAF/MS (91.2% and 100%).

When analyzing the historical series of the cycles in the period under study to better understand this profile, it was noticed that there was certain constancy in the frequency of almost all the use indications. However, from 2016 and reaching a peak in 2017, it is possible to see an expressive increase in the frequency of IVIg treatments for these rheumatological and dermatological indications, especially for those belonging to the Disseminated (systemic) lupus erythematosus category (M32; 41 cumulative cycles; 20.6%).

This profile might be explained by differences in the prescriptive standard, by the possibility that some finding, not identified in our research, may have been disclosed in this period and encouraged IVIg use; or there may have been an atypical increase in the number of cases of patients with refractory lupus during the period, thus distorting the mean. The exploratory scope of this study did not include an exhaustive analysis of these subpopulations of patients; therefore, the methodology employed does not allow establishing these correlations accurately.

The same situation cannot be hypothesized for the dermatological indications, as a peculiar characteristic was observed in this group in which a reduced number of 4 patients (3.5%) underwent 25 cycles (12,6%), which represents a mean of 6.2 cycles per patient, with a single patient even undergoing 9 cycles for Acquired bullous epidermolysis (ICD L12.3) (maximum number of cycles recorded per patient). This means that there is a profile of chronic use, which is ratified by the fact that 80% of cycles in this groups were previously scheduled, revealing the imperative need for debate and alignment with the clinical staff.

An important percentage of the cycles fitted this situation, where hospital admissions for IVIg use took place in a scheduled manner (60 cycles; 30.2%). Differently from clinical urgency situations, these findings are extremely relevant to perform, with all due caution, the assessment of reasonableness of the indication and to schedule the applicable purchases. This is especially valid when considering that, during the period evaluated, the hospital only received provision via SAFIE for one patient, for the equivalent to one cycle with the Guillain-Barré syndrome (CID G61.0) indication. For all the other situations, the hospital provided all treatments using its own resources, regardless whether the indication was covered by CEAF/MS or not, as the flow for provision via SAFIE were still not well-established or agreed upon between the teams.

Such provision represented an annual mean of 7.3% of the total institutional expenses on medications, leading expenditures from 2015 to 2019. Obtaining IVIg treatment for indications covered by CTPGs requires the submission of a number of personal documents and medical examinations that confirm the diagnosis, as well as requirements for assistance via CEAF/MS, which performs a technical assessment and issues an opinion authorizing provision or not.[12] Consequently, agile efficient articulation between the health care teams involved is crucial for timely completion of the procedures and care of the hospitalized patients, in addition to making resources available for other relevant purposes, thus optimizing the health outcomes.

Aggravating this situation, it is worth noting that the increased global demand for IVIg is even more important because its production is limited by the very nature of the raw material, which leads to periods of shortage and market oscillations. One of these periods was evidenced during conduction of the current study when, in 2019, Brazil experienced shortage due to a reduction in global production followed by a significant increase in prices. The solution found was that ANVISA authorized import of the product from manufacturers that were not registered in the country, in order to mitigate supply shortages and minimize the impacts.[14] Such episodes reinforce the need to implement a stricter control over use of this medication.

In this context, the importance of the Pharmacy and Therapeutics Committee (*Comissão de Farmácia e Terapêutica*, CFT) stands out, a collegiate entity of an advisory and deliberative nature that has the purpose of both selecting medications and developing therapeutic protocols with criteria for drug prescription and use in health institutions, continuously promoting rational use.[35] Therefore, it is crucial that the CFT gets involved in the issues pertinent to IVIg use, especially in those with cloudy scientific evidence.

Conclusion

The current study revealed a high use percentage in indications not covered by the national protocols, mainly those related to skin and subcutaneous tissue diseases, followed by diseases of the musculoskeletal system and connective tissue. More robust studies are necessary to support IVIg use in these situations, particularly due to its potential budgetary impact to the institutions that respond to these demands.

It is important that institutions are internally mobilized to develop strategies to promote rational use, especially through the CFT and Clinical Pharmacy services. Knowledge on the usage profile in the health unit is also useful to delineate an agreement for an efficient purchase flow via CEAF/MS by promoting awareness and collaboration among the teams in relation to acquisition and availability of the necessary requirements.

More detailed studies of the subpopulations treated with IVIg may raise discussions on the evidence bases for rational use in each subpopulation, or even produce this evidence through retrospective studies of the clinical outcomes in patients subjected to off-label use.

Funding sources

The research did not receive funding for its conduction.

Collaborators

CAT conceived the project and delineated the study design. BSF conducted the data collection procedure. BSF and CAT analyzed the data and prepared and reviewed the content of the article. The authors assume responsibility for the data published and guarantee accuracy and integrity of the article.

Acknowledgments

The authors wish to thank the institution for allowing conduction of the research.

Conflict of interest statement

The authors declare no conflicts of interest regarding this article.

References

1. Lünemann JD, Quast I, Dalakas MC. Efficacy of Intravenous Immunoglobulin in Neurological Diseases. Neurotherapeutics. 2016; 13(1):34–46. DOI: 10.1007/s13311-015-0391-5.
2. Mulhearn B, Bruce IN. Indications for IVIG in rheumatic diseases. Rheumatology. 2014; 54(3):383-391. DOI: 10.1093/rheumatology/keu429.
3. Ephrem A, Misra N, Hassan G *et al*. Immunomodulation of autoimmune and inflammatory diseases with intravenous immunoglobulin. Clin Exp Med. 2005; 5(4):135-140. DOI: 10.1007/s10238-005-0079-y.
4. Ballow MC. Immunoglobulin Therapy: Replacement and Immunomodulation. In: Rich RR, Fleisher TA, Shearer WT et al. Clinical Immunology, 5ed. Elsevier, 2018: 1143-1153.
5. Imbach P, d' Apuzzo V, Hirt A *et al*. High-dose intravenous gammaglobulin for idiopathic throbocytopenic purpura in childhood. The Lancet. 1981;317(8232), 1228–1231. DOI: 10.1016/s0140-6736(81)92400-4.
6. Chaigne B, Mouthon L. Mechanisms of action of intravenous immunoglobulin. Transfus Apher Sci. 2017; 56(1):45-49. DOI: 10.1016/j.transci.2016.12.017.
7. Radosevich M, Burnouf T. Intravenous immunoglobulin G: trends in production methods, quality control and quality assurance. Vox Sanguinis. 2010; 98:12–28. DOI: 10.1111/j.1423-0410.2009.01226.x
8. Sibéril S, Elluru S, Graff-Dubois S *et al.* Intravenous Immunoglobulins in Autoimmune and Inflammatory Diseases: A Mechanistic Perspective. Ann. N.Y. Acad. Sci. 2007; 1110: 497–506. DOI: 10.1196/annals.1423.052
9. Martínez T, Garcia-Robledo JE, Plata I *et al*. Mechanisms of action and historical facts on the use of intravenous immunoglobulins in systemic lupus erythematosus. Autoimmun Rev. 2019; 18(3):279-286. DOI: 10.1016/j.autrev.2018.10.002
10. BRASIL. Ministério da Saúde. Gabinete do Ministro. Portaria nº 1554 de 30 de julho de 2013. Diário Oficial da União, Brasília (DF), n° 146 de 31 de julho de 2013, Seção I, página 69.
11. Ministério da Saúde. Tabela de Procedimentos, Medicamentos, Órteses, Próteses e Materiais Especiais do SUS - Medicamentos x CID. Available in: http://sigtap.datasus.gov.br/tabela-unificada/app/sec/procedimento/exibir/0604310056/02/2020. Accessed on: 15th Aug. 2021.
12. Secretaria de Saúde do Governo do Estado do Rio de Janeiro. Superintendência de Assistência Farmacêutica e Insumos Estratégicos. Available in: https://www.saude.rj.gov.br/medicamentos/conheca-a-safie. Accessed on: 15th Aug. 2021.
13. Goudouris ES, Silva AMR, Ouricuri AL *et al*. II Brazilian Consensus on the use of human immunoglobulin in patients with primary immunodeficiencies. Einstein (São Paulo) [online]. 2017; 15(1):1-16. DOI:10.1590/S1679-45082017AE3844
14. O Globo. Anvisa autoriza importação de imunoglobulina, que está com estoques em baixa. Available in: https://oglobo.globo.com/brasil/anvisa-autoriza-importacao-de-imunoglobulina-que-esta-com-estoques-em-baixa-24283536. Accessed on: 13th Jul. 2021.
15. Ronsoni RM, Pereira CCA, Stein AT *et al*. Avaliação de oito Protocolos Clínicos e Diretrizes Terapêuticas (PCDT) do Ministério da Saúde por meio do instrumento AGREE II: um estudo piloto. Cad. Saúde Pública. 2015; 31(6):1157-1162. DOI: 10.1590/0102-311X00118814.
16. Mega TP, Lopes ACF, Santos CC *et al*. Protocolos clínicos e diretrizes terapêuticas no SUS: histórico, desafios e perspectivas. Revista Eletrônica Gestão & Saúde. 2015; 6(4):3275-85. https://periodicos.unb.br/index.php/rgs/article/view/3333.
17. Laranjeira FO, Petramale CA. A avaliação econômica em saúde na tomada de decisão: a experiência da CONITEC. Avaliação de Tecnologias de Saúde. 2013; 14(2):165-170.
18. Brasil. Ministério da Saúde. Secretaria de Ciência, Tecnologia e Insumos Estratégicos. Departamento de Gestão e Incorporação de Tecnologias em Saúde. Diretrizes metodológicas: elaboração de diretrizes clínicas / Ministério da Saúde, Secretaria de Ciência, Tecnologia e Insumos Estratégicos, Gestão e Incorporação de Tecnologias em Saúde. Brasília: Ministério da Saúde, 2016. 96 p.
19. Comissão Nacional de Incorporação de Tecnologias no Sistema Único de Saúde. A Comissão. Available in: http://conitec.gov.br/entenda-a-conitec-2. Accessed on: 1st Oct. 2021.
20. Elovaara I, Apostolskib S, van Doorn P *et al*. EFNS guidelines for the use of intravenous immunoglobulin in treatment of neurological diseases. Euro J Neurol. 2008; 15(9):893–908. DOI: 10.1111/j.1468-1331.2008.02246.x
21. Van den Bergh PY, Hadden RD, Bouche P *et al.* European Federation of Neurological Societies/Peripheral Nerve Society guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy: report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society - first revision. Eur J Neurol. 2010; 17(3):356–363. DOI: 10.1111/j.1468-1331.2009.02930.x
22. Patwa HS, Chaudhry V, Katzberg H e*t al*. Evidence-based guideline: Intravenous immunoglobulin in the treatment of neuromuscular disorders. Neurology. 2012; 78(13): 1009-1015. DOI: 10.1212/WNL.0b013e31824de293
23. Oaklander AL, Lunn MPT, Hughes RAC *et al*. Treatments for chronic inflammatory demyelinating polyradiculoneuropathy (CIDP): an overview of systematic reviews. Cochrane Database of Systematic Reviews. 2017; 1(CD010369).
24. Food and Drug Administration. Immune Globulin Intravenous (IGIV) Indications. Available in: https://www.fda.gov/vaccines-blood-biologics/approved-blood-products/immune-globulin-intravenous-igiv-indications. Accessed on: 1st Oct. 2021.
25. European Medicines Agency.Core summary of product characteristics for human normal immunoglobulin for intravenous administration (IVIg). Available in: https://www.ema.europa.eu/en/core-summary-product-characteristics-human-normal-immunoglobulin-intravenous-administration-ivig. Accessed on: 1st Oct. 2021.
26. Portal do Governo Brasileiro. Agência Nacional de Vigilância Sanitária. Informações técnicas/Hizentra (imunoglobulina humana): Nova indicação. Available in: http://antigo.anvisa.gov.br/en_US/informacoes-tecnicas13?p_p_id=101_IN-

STANCE_WvKKx2fhdjM2&p_p_col_id=column-2&p_p_col_pos=1&p_p_col_count=2&_101_INSTANCE_WvKKx2fhdjM2_groupId=219201&_101_INSTANCE_WvKKx2fhdjM2_urlTitle=hizentra-imunoglobulina-humana-nova-indicacao&_101_INSTANCE_WvKKx2fhdjM2_struts_action=%2Fasset_publisher%2Fview_content&_101_INSTANCE_WvKKx2fhdjM2_assetEntryId=5591066&_101_INSTANCE_WvKKx2fhdjM2_type=content. Accessed on: 1st Oct. 2021.

27. Bayry J, Negi VS, Kaveri SV. Intravenous immunoglobulin therapy in rheumatic diseases. Nat Rev Rheumatol. 2011; 7(6):349–359. DOI: 10.1038/nrrheum.2011.61.

28. Watad A, Amital H, Shoenfeld Y. Intravenous immunoglobulin: a biological corticosteroid-sparing agent in some autoimmune conditions. Lupus. 2017 Sep;26(10):1015-1022. doi: 10.1177/0961203317696589. Epub 2017 Mar 9. PMID: 28420062. DOI: 10.1177/0961203317696589.

29. Spacil CR, Bueno D. Análise de prescrições de imunoglobulina humana endovenosa para situações clínicas não referendadas nos protocolos clínicos nacionais. Braz J Allergy Immunol. 2017;1(3):293-298. DOI: 10.5935/2526-5393.20170041.

30. Lin MW, Kirkpatrick PE, Riminton DS. How intravenous immunoglobulin is used in clinical practice: audits of two Sydney teaching hospitals. Intern Med J. 2007; 37(5):308–314. DOI: 10.1111/j.1445-5994.2007.01336.x

31. Constantine MM, Thomas W, Whitman L *et al.* Intravenous immunoglobulin utilization in the Canadian Atlantic provinces: a report of the Atlantic Collaborative Intravenous Immune Globulin Utilization Working Group. Transfusion. 2007; 47(11):2072–2080. DOI: 10.1111/j.1537-2995.2007.01400.x.

32. Ruiz-Antorán B, Agustí Escasany A, Vallano Ferraz A *et al*. Use of non-specific intravenous human immunoglobulins in Spanish hospitals: need for a hospital protocol. Eur J Clin Pharmacol. 2010; 66(6):633-64. DOI: 10.1007/s00228-010-0800-y**.**

33. Frauger E, Grassi J, Pradel V *et al*. Use of intravenous immunoglobulins in clinical practice: data from three French university hospitals. Fundam Clin Pharmacol. 2011; 25(6):753–76. DOI: 10.1111/j.1472-8206.2010.00908.x.

34. Shemer A, Kivity S, Shoenfeld Y. Clinical indications for intravenous immunoglobulin utilization in a tertiary medical center: a 9-year retrospective study. Transfusion. 2017; 58(2): 430–4. DOI: 10.1111/trf.14427.

35. Cipriano SL, Moreira RPP, Da Cunha GWB, *et al*. Comissão de Farmácia e Terapêutica. Pharmacia brasileira. 2011; 83:1-20.