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One-year consumption pattern of intravenous immunoglobulin at a teaching hospital in Sari

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ABSTRACT

Background: There is an increasing trend to use intravenous immunoglobulin (IVIG) for new indications, mainly off-labeled conditions for numerous diseases. IVIG is an expensive drug and is occasionally not available, so it is recommended that medical centers evaluate how to use it permanently. This study aimed to assess the pattern of IVIG use in an educational hospital.

Methods: All patients who received IVIG for any condition for a year were enrolled in this cross-sectional observational study. A predesigned checklist form was used to gather demographic, clinical, and biochemical data. The collected data were compared to the FDA recommendations for IVIG use.

Results: Overall, in 62.8% of the patients, IVIG was administrated for FDA-approved indications, 21.2% for off-label uses, and the remaining 16% for investigational conditions. The most common cause of IVIG use was for primary immunodeficiency disease (PID) in 22 patients (19.5%). The highest prevalence of primary diagnoses in patients receiving IVIG was immune thrombocytopenic purpura (ITP). In addition, Chronic inflammatory demyelinating polyneuropathy (CIDP) (28.4%) and final diagnoses were ITP and Guillain-Barré syndrome (GBS) in 30% of patients. 26.5% of patients experienced side effects, and headache, fever and chills, and inflammation of the injection site were the most common adverse drug reactions.

Conclusion: National or local drug protocols are needed to prescribe more rational IVIG utilization and assist physicians in using IVIG for approved or high evidence-based indications.

Introduction

Human Intravenous immunoglobulin (IVIG) is a replacement therapy for immunodeficiency states but is also prescribed for various autoimmune and inflammatory disorders (1). IVIG is a sterile biologic product that contains concentrated antibodies that should be extracted from a pool of at least 1000 individual donors based on minimum standards for manufacturing IVIG preparations published by the World Health Organization (2). The donor population has a different environment. IVIG from pooled plasma reflects a collective exposure to numerous antigens and contains multiple specific antibodies with a broad spectrum to treat various infectious and autoimmune diseases (3). Many donors can increase the individual antibody activities in the pool preparation. IVIG products usually consist of more than 95% whole IgG, as little IgA as possible, and traces of other Igs (4).

Although IVIG was initially used to treat immune thrombocytopenia (ITP) in 1981. It is widely administered nowadays for hematologic, neurologic, rheumatologic, dermatologic, and nephrological diseases (5). The US Food and Drug Administration (FDA) has approved the administration of IVIG for primary immunodeficiency (PI), immune thrombocytopenia (ITP), Kawasaki disease (KD), bone marrow transplantation, B-cell chronic lymphocytic leukemia (B-cell CLL), pediatric HIV, chronic inflammatory demyelinating polyneuropathy (CIDP), and multifocal motor neuropathy (MMN) (6). Many off-label indications of IVIG have been mentioned in articles with more robust evidence. For instance: autoimmune diseases, ocular diseases, ophthalmopathy neurologic diseases, Guillain-Barre syndrome, hemolytic disease of the newborn, and myasthenia gravis (6-8). Although it has been approved for selected indications, the list of its clinical indications, particularly off-labels, has grown considerably. Unfortunately, most of these indications do not have enough clinical evidence for efficacy, and IVIG is prescribed irrationally. Studying IVIG's drug use pattern is considered an important research topic due to its significant role in treating and controlling many diseases, high cost, and limited access to it (9). Although the clinical benefit of IVIG has been proved in specific cases, it is not an entirely safe therapeutic drug. Adverse reactions of IVIG can be categorized as immediate or delayed with different intensities, mild, moderate, or even severe, occurring within the first hour of starting the drug infusion. (10). Drug use evaluation (DUE) is a structured, ongoing, criteria-based review of medical evaluations that help ensure appropriate medication use. These studies assess the appropriate drug usage according to predetermined standards and guidelines (11). Although IVIG has limited the FDA-approved indications, consumption of this drug for off-labeled indications is increasing (12-15).

Regarding cost, IVIG ranked ninth and eighth among drugs consumed in Iran in 2017 and 2020, respectively (16). The Ministry of Health and Medical Education of Iran insists that drugs, costly and less available items such as IVIG, should be used rationally. This study aimed to investigate the pattern of prescription and utilization of IVIG in a referral teaching hospital.

Method

This cross-sectional observational study was performed at Bu-Ali Sina Hospital in Sari, affiliated with Mazandaran University of Medical Sciences, in northern Iran. All patients receiving IVIG for any reason during a year were included in the study. The Research Committee approved this study of the Mazandaran University of Medical Sciences, Sari, Iran (Protocol no. IR.MAZUMS.REC.1396.10237).

A predesigned checklist form was used for data gathering. It included patient's demographics (i.e., age, sex), primary and final diagnoses, admission ward, physician specialty, the reason for admission and IVIG prescription, as well as drug-related data (i.e., dose, duration of use, rate of infusion, side effects), and other parameters (i.e., length of hospitalization, the outcome of treatment and mortality rate). We also recorded any related laboratory tests; Including:

Red blood cell (RBC), white blood cell (WBC), hematocrit (Hct), hemoglobin (Hgb), platelet (Plt), bilirubin (Bil), serum creatinine (Cr), blood urea nitrogen (BUN), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP)), interacting drugs, and premedication (if a patient received any). Finally, the collected data were compared to the FDA-approved criteria for IVIG use patterns regarding indications and their dosages. The Statistical Package analyzed data for the Social Sciences software, version 21. The independent sample T-test and Chi-square test were used to compare quantitative and qualitative variables. Qualitative and quantitative variables were reported as numbers or percentages and mean ± standard deviation (SD). A P-value less than 0.05 was considered a statistically significant difference.

Findings

One hundred thirteen patients receiving IVIG (Intratect® manufactured by Biotest company,

each ml containing 50 mg human normal immunoglobulin) were evaluated. Among them, 69 (61.1%) and 44 (38.9%) cases were male and female, respectively. The means age and weight of the patients were 18.9±22.9 years (range from 3 days to 83) and 35.1±23.4 Kg (range from 1 to 98), respectively. The mean hospital stay duration of the patients in different wards was 11.8±7.9 days (range from 2 to 46). The pediatric ward (48.7%), neurosurgery ward (28.3%), and then pediatric intensive care unit (PICU) (16.8%) had the highest amounts of IVIG consumption. Also, the rate of IVIG use in other wards was as follows: neonatal ICU (3.5%) and pediatric oncology ward (2.7%). Most of the prescriptions containing IVIG were written by pediatricians (70.8%).

Although the most common primary diagnosis in patients receiving IVIG was ITP and CIDP, the final diagnosis was ITP and Guillain-Barré syndrome (GBS) (Table 1). Overall, IVIG was prescribed for 16 different indications, as reported in table 3. In 71 patients (62.8%), IVIG was ordered based on FDA-approved indications, whereas 21.2% of mentioned indications were used for off-labeled with robust evidence and the remaining 16% for investigational indications. The indication means the dose of IVIG was FDA-approved in 67% of patients. The average infusion rate was 70.9±60.2 mg/kg/hr (range from 15.4 to 416.7). In 21% of cases, the infusion rate exceeded the manufacturer's maximum recommended rate (95 mg/kg/hr).

In 83 patients (73.5%), no side effects were reported. Thirty cases (23.1%) experienced adverse drug reactions to IVIG administration, including headaches (twelve), fever and chills (nine), and inflammation of the injection site (nine). Ninety-eight patients (86.7%) receiving IVIG were administered oral or parenteral corticosteroids as premeditation, followed by acetaminophen for 27 patients (23.9%) and antihistamines for 16 patients (14.15%). The mean duration of use of IVIG was 2.8±1.9 days (range from 1 to 9). A total of 5959.5 grams of IVIG was consumed, and the average dose of the IVIG for a treatment period in patients was 53.3±58.8 grams (2-240). So 3992 grams were administered for the FDA-approved indications, and the rest, 1967.5 grams, for the cases without approval. During this study, 74 patients (65.5%) underwent just one treatment cycle, and 39 (34.5%) underwent more than one treatment cycle. Of the total patients, 20 (17.7%) patients recovered completely, 88 (77.9%) patients had partial recovery, and 5 (4.4%) patients died.

Biochemical markers, including RBC, WBC, Hct, Hgb, Plt, Bili, Cr, BUN, AST, ALT, and ALP, were also monitored in this study before and after a course of treatment with IVIG. There was an increase in mean serum Cr (from 0.77±0.18 to 0.94±0.21 mg/dl) and BUN (from 14.32±2.16 to 15.28±2.45 mg/dl) after IVIG administration in 111 (98.2%) patients ($p<0.001$ and $p<0.001$). Liver parameters including AST, ALT, and ALP in 64.6% of patients showed a significant increase between before and after IVIG administration ($p<0.001$). Among all of the patients, only the mean value of Hct after receiving IVIG did not show a significant difference compared to baseline ($p=0.055$). While WBC, Plt counts, and Hgb revealed statistically significant increases before and after IVIG administration ($p=0.017$, $p<0.001$, and $p<0.001$, respectively). Total and conjugated bilirubin levels were also measured only in three patients and revealed a statistically significant increase between Pre- and post-intervention ($p<0.001$ and $p=0.02$, respectively) (Table 2).

Discussion

Due to the limited availability, high cost, possible side effects, and lack of sufficient clinical evidence for some indications of IVIG, the rational use evaluation of this pivotal product in all hospitals should be considered. The primary purpose of this study was to review the pattern of IVIG consumption in our hospital. Overall, 62.8% of the patients received IVIG consistent with FDA-approved indications, 21.2% for evidence-based off-label uses, and 16% for non-authorized and non-accepted indications. Similarly, a study in Spain showed that IVIG was used in 60% of patients with authorized indications, 16% of cases with non-authorized indications with scientific evidentiary support, and 24% with non-authorized and non-accepted indications (12). A retrospective, an evidence-based study assessed the use of IVIG in pediatric patients. The authors mentioned that 77.3% of total prescriptions were FDA-labeled indications (17). Fakhari et al. reported that the appropriate indication (FDA-labeled and off-labeled ones with solid evidence) represented 72% of the total IVIG indications (18). The results of our study resembled a study that examined the indication for prescribing IVIG, which was 73% for FDA-approved diagnoses, 24% for evidence-supported off-label diagnoses, and 3% for other off-label diagnoses, respectively (19). A study that determined the amount of IVIG prescribed by Canadian medical specialties revealed that the majority of overall IVIG use

(89% in both adult and pediatric populations) was considered appropriate by guideline definition (20). Contrary to our and some other studies conducted in Iran, more than half of patients received IVIG based on the FDA-labeled indications (21, 22); the results of many other studies showed this index was significantly lower (23, 24).

In the current study, the most common causes of IVIG use were PID (19.5%), CIDP (19.5%), GBS (15%), and ITP (15%). Most studies use IVIG as a replacement therapy for immunodeficiency conditions. The CVID was the most diagnosed of patients (23%) in the study by Lin et al. (25).

Furthermore, the results of a study in Spanish hospitals showed that the most common authorized indications of IVIG were primary (30.5% of patients) and secondary immunodeficiencies (16.8% of patients) (12). In contrast with the current study, several studies in Iran reported different results. For example, ITP (38.8%) was the most frequent diagnosis in a cross-sectional study in Zabol, east of Iran (21). Also, the most prevalent cause of IVIG administration at “Shahid Sadoughi” hospital in Yazd during four months was ITP (37.3%) (13). Moreover, the most common indication of IVIG consumption was ITP (31.3%) in a study performed at “Amir Kola” Hospital in Babol, northern Iran (26).

The frequency of off-labeled use of IVIG, including dermatomyositis, Guillain-Barre syndrome, and myasthenia gravis, was 21.2% in the present study. It resembles the results of the Dashti-Khavidaki et al. study (22). In our hospital, neurologists (54.9%) and hematologists (20.4%) were the most common prescribers of IVIG use homogenous to the reports by several studies (20, 22, 27). In the current study, the mean dose of IVIG was FDA-approved in 67% of patients. Similarly, Dashti-Khavidaki et al. reported a higher dose of IVIG administered for a labeled indication (mean 19.8 g) compared to the dose administered for off-label (mean 14.9 g) or investigational uses (mean 9.2 g) (22). In another study, 83.7% of the patients received an appropriate dose of IVIG according to FDA-approved indications (21). Contrary to these studies, Kargar et al. (2019) reported that the mean dose of IVIG for FDA-labeled indications was appropriate in 43.6% of patients (24).

The manufacturer recommends Intratect® 5% should be infused intravenously at an initial rate of fewer than 0.3 ml/kg/h (15 mg/kg/hr) for 30 minutes. If the patient is well tolerated, the rate of administration may gradually be increased to a maximum of 1.9 ml/kg/h (95 mg/kg/hr). In the present study, the mean IVIG infusion rate was 70.9±60.2 mg/kg/hr (15.4 to 416.7), and 21% of patients had an infusion rate more than the manufacturer's maximum recommended rate (95 mg/kg/hr). At the beginning of IVIG administration, none of the patients had an infusion rate of less than 15 mg/kg/hr. In other words, all patients had more infusion rates than the manufacturer's minimum recommended value. Although the average consumption rate was lower than 95 mg/kg/hr, 21% of patients received IVIG more than the maximum recommended value.

Most IVIG side effects are mild and diminished after reducing infusion rate or withdrawal. However, some rare adverse reactions are profound, including renal impairment, aseptic meningitis, hemolytic anemia, and thrombosis (28). The incidence of side effects in the current study was 26.5%, which is consistent with the reported 20%–50% in the previous studies (13, 29). Furthermore, our results are similar to the finding of a study in which IVIG had a good safety profile and was well tolerated in pediatric patients (30). Although potentially dangerous adverse effects of IVIG occur in limited cases, paying attention to reducing them is crucial (31). Less than one-third of patients (26.5%) in our study experienced mild reactions, including injection site reactions, headache, fever, and chills that occurred during infusion in some patients due to high infusion rates. Of these, 12 patients (40%) experienced headaches, nine patients (30%) had fever and chill, and nine patients (30%) had redness and itching at the injection site. They are primarily self-limited and were eliminated by reducing the injection speed in pediatric patients (32).

Many factors affect the incidence of side effects, including dose, concomitant medications,

premedication, and hydration status. In our study, a premedication protocol containing corticosteroids (86.7%), acetaminophen (23.9%), and antihistamines (14.15%) were nearly appropriate. Hydration before receiving IVIG is an essential factor involved in adverse effects, especially in patients with a history of diabetes mellitus, renal dysfunction, cardiovascular patients, and adults over 65 years (33).

Safety concerns and adverse reactions occurrence, concomitant with the high cost of treatment, are essential topics in most medical centers. Establishing and adhering to evidence-based guidelines can lead to an increase in rational IVIG consumption. (11,13,15,17,27).

Limitations

There were some limitations to the current study. This study was conducted in one hospital. Due

to a shortage of IVIG, the pharmacy could not supply sufficient drugs, and some patients did not receive IVIG despite the physicians' orders.

Conclusion

Due to high cost, limited drug production, clinical significance, and occasional shortage, IVIG should be used as rationally as possible. National or local drug protocols can help to optimize consumption and minimize the prescription of IVIG for less evidence-based conditions.

Ethical Considerations

Compliance with ethical guidelines

The Research Committee approved this study of the Mazandaran University of Medical Sciences, Sari, Iran (Protocol no. IR.MAZUMS.REC.1396.10237).

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Conflicting interests

The authors claim no conflict of interest.

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Authors contributions

Conceptualization, Mohammadreza Rafati, Kaveh Jafari; Methodology, Mohammadreza Rafati, Ebrahim Salehifar; Investigation, Kaveh Jafari, Sima Sahraee, Amirmohammad Rafati, Razieh Avan; Writing – Original Draft, Kaveh Jafari, Amirmohammad Rafati, Razieh Avan; Writing – Review & Editing, Mohammadreza Rafati, Ebrahim Salehifar; Funding Acquisition, Mohammadreza Rafati; Supervision, Mohammadreza Rafati, Razieh Avan; All authors contributed to obtain final approval.

Tables

Table 1. Frequency of IVIG prescribing based on primary and final diagnosis

Indication	Labeled indication	Off labeled with strong evidence support	Off labeled with no evidence to support	Frequency	Percentage
PID	√	-	-	22	**19.5**
CIDP	√	-	-	18	**15.9**
GBS	-	√	-	17	**15**
ITP	√	-	-	17	**15**
KD	√	-	-	7	**6.2**
MND	-	-	√	6	**5.3**
DRE	-	-	√	6	**5.3**
B-cell Chronic Lymphocytic Leukemia	√	-	-	5	**4.4**
Dermatomyositis	-	√	-	4	**3.5**
Myasthenia gravis	-	√	-	3	**2.7**
SJS	-	-	√	2	**1.8**
Neonatal jaundice (ICTER)	-	-	√	2	**1.8**
HIV	√	-	-	1	**0.9**
Varicella	√	-	-	1	**0.9**
Hemolytic Anemia	-	-	√	1	**0.9**
Juvenile Rheumatoid Arthritis	-	-	√	1	**0.9**
Total				113	**100**

Abbreviations:CIDP: Chronic Inflammatory Demyelinating Polyneuropathy; CVA: Cerebrovascular accident; DRE: Drug Resistant Epilepsy; GBS: Guillain-Barré syndrome; HIV: Human Immunodeficiency Virus; KD: Kawasaki Disease; IT: Immune Thrombocytopenia; MND: Motor Neuron Disease; PID: Primary Immunodeficiency Disease; SJS: Stevens-Johnson Syndrome

Table 2. Biochemical markers before and after administration of IVIG

Biochemical markers (Mean±SD)	Before	After	P value
BUN	14.3±2.2	15.3±2.4	<0.001
Cr	0.8±0.2	0.9±0.2	<0.001
AST	67.1±60.6	110±80.7	<0.001
ALT	33.8±19.1	89.5±63.1	<0.001
ALP	121.6±83	150.7±87.9	<0.001
WBC	9±4.9	9.4±4.49	0.017
RBC	4.2±0.5	4.3±0.4	<0.001
HCT	37.2±4.3	37±4.1	0.055
Hgb	11.1±1.3	11.4±1.2	<0.001
Plt	228.2±130.1	272.5±102.1	<0.001
Total bilirubin	14.3±0.6	11.3±0.6	<0.001
Conjugated bilirubin	0.7±0.1	0.5±0.1	0.02

ALP: Alkaline phosphatase; ALT: Alanine transaminase; AST: Aspartate transaminase; BUN: Blood Urea Nitrogen; Cr: Creatinine; HCT: hematocrit; Hgb: Hemoglobin; Plt: Platelet; RBC: Red Blood Cell; WBC: White Blood Cell

Table 3. Classification of indications of IVIG use in patients based on FDA approval

Diagnosis	Primary		Final	
	Frequency	Percentage	Frequency	Percentage
ITP	16	14.2	17	**15**
CIDP	16	14.2	16	**14.2**
GBS	15	13.3	17	**15**
Cerebral encephalitis	10	8.8	10	**8.8**
PID	8	7.1	9	**8**
Influenza	7	6.2	0	**0**
DRE	6	5.3	7	**6.2**
KD	6	5.3	7	**6.2**
Hypersensitivity reaction	4	3.5	3	**2.7**
CVA	4	3.5	2	**1.8**
MND	4	3.5	6	**5.3**
Dermatomyositis	3	2.7	3	**2.7**
Meningitis	2	1.8	2	**1.8**
Myasthenia gravis	2	1.8	3	**2.7**
SJS	2	1.8	2	**1.8**
Neonatal jaundice (ICTER)	2	1.8	2	**1.8**
Ataxia	2	1.8	2	**1.8**
Chronic neuropathy	2	1.8	0	**0**
Varicella	1	0.9	1	**0.9**
HIV	1	0.9	1	**0.9**
Acute Disseminated Encephalomyelitis	0	0	1	**0.9**
Hemolytic Anemia	0	0	1	**0.9**
Juvenile Rheumatoid Arthritis	0	0	1	**0.9**

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