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Assessment of IVIG use in Baqiyatallah Hospital and Efficacy of Standard Protocol

Sina Ebrahimi[1]*, Majid Shohrati[2], Bita Najafian[3]

[1]Student Research Committee, Baqiyatallah University of Medical Sciences, Tehran, Iran.
[2]Department of Clinical Pharmacy, Faculty of Pharmacy, Baqiyatallah University of Medical Sciences, Tehran, Iran.
[3]Department of Pediatrics, Faculty of Medicine, Baqiyatallah University of Medical Sciences, Tehran, Iran.

ABSTRACT

IVIG is a biological product used as an anti-inflammatory and immune regulator agent. The use of IVIG is rising in the world. The imposed drug sanctions have caused the import of this vital drug to be greatly reduced. Therefore, the preparation of a standard protocol that can lead to the improvement of the pattern of use can optimize its use in economic conditions and the existing drug shortage. This cross-sectional, prospective study was conducted in Baqiyatallah Alazam hospital. All patients who received IVIG in hospital wards were included and data were gathered according to the designed form. Finally, all data in similar months of 2019 and 2020 year were compared.
38 patients with a mean age of 42 years old were enrolled in this study. CIDP and ITP were the most causes of IVIG prescription. The total amount of IVIG in 2020 was fallen more than 37% in comparison with 2019 that saved about 1.3 billion Rials. The rate of drug use in third-level indications which is our main goal in reducing irrational IVIG consumption decreased 98.54%. IVIG shortage and the costs associated with taking this drug indicate the importance and value of DUE studies. Designing and conducting DUE studies is not possible without the presence of hospital pharmacists and pharmacotherapists. Pharmacists can prevent possible mistakes by conducting these studies so that the studies can be done in the best possible way.

Keywords: IVIG, Consumption model modification, Standard protocol, Drug use evaluation, Drug utilization review, Medication use evaluation.

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Corresponding author: Sina Ebrahimi
E-mail ✉ sina.ebrahimy@gmail.com
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INTRODUCTION

Since 1986, the American Society of Health-System Pharmacists (ASHP) introduced DUE studies to avoid wasting valuable drugs which would be helpful to evaluate the medical indication [1]. Pharmacists are the key persons for supervising DUE studies because of their surrounding science in kinetic, toxicology, pharmacology, and pharmacotherapy [2]. According to the JCAHO protocol, pharmacists have to evaluate the accuracy of indications before prescribing [3]. DUE research would promote health care level in addition to rationalizing the use of drugs and possibilities which is leading to cost reduction. The cost of drug therapy is about 6-8% of the total health care costs [4].

Highly concentrated immunoglobulin G is found in Intravenous immunoglobulin (IVIG), which is regarded as the main immunoglobulin that exists in human serum [5]. It has been primarily introduced for the treatment of immune deficiencies; however, over the last decades, immunoregulatory and anti-inflammatory properties of IVIG have been considered for

managing several inflammatories and autoimmune disorders [6]. According to the existing evidence, this rapid IVIG indications expansion has lead to the increase in IVIG employment for unapproved indications. Nevertheless, in clinical guidelines, the narrowed indications were approved [7-10]. For instance, for using IVIG, only seven official indications were approved by the US Food and Drug Administration (FDA), including primary immunoglobulin deficiency (PID), multifocal motor neuropathy, Kawasaki disease, chronic lymphocytic leukemia, idiopathic thrombocytopenia purpura, passive immunity, and chronic inflammatory demyelinating polyneuropathy (CIDP) [5].

It should be stated that experts' opinions or strong evidence also support some of the off-label indications for utilizing IVIG, proposing that it is considered to be efficient [5, 8, 11]. Although only restricted data supported some of these indications of IVIG, many academic physicians and consultants still consider these off-labeled indications in practice [12]. It must be remarked that over 150 unlabeled utilization of IVIG exceeds the FDA labeled indications and is attributed to the most IVIG practice with a noticeably high cost [8]. Concerning the rational prescribing of IVIG, Limited accessibility, a diverse range of IVIG off-labeled indications, and economic burden have produced challenges for healthcare providers [13, 14]. Hence, specific rules and regulations have been fixed for checking the treatment of IVIG. The IVIG clinical guidelines from the European Union, Canada, and Australia are among the best instances of these protocols and guidelines [15-20].

Previously, numerous investigations have been carried out to assess the IVIG application's concordance with established protocols and guidelines. Nonetheless, in categorizing the IVIG indications, there is still inconsistency in different protocols and to review the indications and approve a specific protocol for utilizing this highly expensive drug, it is suggested to establish a local clinical committee in each healthcare institute [21, 22].

For all reasons mentioned above, we decided to perform DUE on IVIG to evaluate the correctness of indications in Baqiyatallah Alazam hospital.

MATERIALS AND METHODS

This cross-sectional, prospective study was conducted in Baqiyatallah Alazam hospital from January 2019 to March 2020. All patients who received intravenous immunoglobulin in all hospital wards were included in the study. In the first phase of this study, which lasted for 6 months, a drug use evaluation (DUE) was performed. At this stage, patients' information was obtained through examination of patients' files, as well as questions from the doctor and nurses. The results are then evaluated by a committee of experts including a pharmacist, an internal specialist (gastroenterology, rheumatology, etc.), a specialist care unit, a nursing service, pharmacy management, and the head of the neurology department who is most in need of intravenous immunoglobulin have been studied. During the meetings and study of similar interventional and observational studies in the world and Iran, a standard protocol for the administration of intravenous immunoglobulin was developed and it was announced to the various departments of the hospital. In the second phase of this study, the status of intravenous immunoglobulin in the same ward and the same period, according to the communicative protocol, was reviewed by the regulatory team appointed by the Medicines and Treatment Committee. Then, the amount of intravenous immunoglobulin intake, as well as information related to the indication and dosage, were compared before and after the protocol.

To assess the IVIG indications' concordance with the standard and rational prescription of strategies, we sub-classified the identified indications of IVIG into 3 key groups:

(a) FDA labeled indications, (b) off-labeled with support (strong evidence recommend its effectiveness), and (c) off-labeled with no support (there is no adequate evidence to validate its usage). In our investigation, indications of IVIG in groups A and B were considered as appropriate, whereas category C indications were considered inappropriate.

The protocol of study had the requirement of the Ethical Committee at Baqiyatallah Alazam University of Medical Sciences (Registration number: IR.BMSU.REC.1397.301).

Data analysis

Statistical analysis was carried out using Microsoft excel 2017 for windows release and SPSS 16.

RESULTS AND DISCUSSION

38 patients with a mean age of 42 years old were enrolled in this study. 63.19% (N=24) of patients were male and 36.81% (N=14) were female.

The cases in which intravenous immunoglobulin was prescribed for them include Chronic inflammatory demyelinating polyneuropathy (42.31%), Immune thrombocytopenic purpura (19.63%), Guillain-Barré syndrome (11.8%), Multiple sclerosis (7.52%), Kidney graft rejection (6.1%), Multifocal motor neuropathy (4.06%), Myasthenia gravis (3.05%), Polymyositis and dermatomyositis (2.44%), Kawasaki disease (1.62%), and 1.47% of other diseases. The total amount of IVIG (gr) consumed during the same period in the years 2019 and 2020 were 3367.5 gr and 2457.5 gr respectively. As can be seen, IVIG consumption has decreased by 37.03%.

Most of the prescriptions were for the neurology section, 1355 gr of 2457.5 (55.13%) of drugs were consumed in this segment. Afterward, the Internal and Pediatrics ward took more drugs. **Table 1** shows the IVIG consumption rate by indication category.

Table 1. Comparison of IVIG consumption rate by indication category of the same period in the years 2019 and 2020.

Indication Category	Amount of drug used in 2019 (%)	Amount of drug used in 2020 (%)
(a) FDA labeled indications	42.8	68.26
(b) Off-labeled with support	24.8	31.53
(c) Off-labeled with no support	32.4	0.21

Of the total cases of Off-labeled with support and Off-labeled without support, 46.79% were reported by neurologists, 22.43% by nephrologists, 9.61% by gastroenterologists, 6.41% by urologists, 5.12% by oncologists, 3.84% by rheumatologists, 3.2% by surgical specialists, 1.92% by internal medicine specialists, and 0.71% of pediatricians are prescribed. The utilization of IVIG by indication and evidence category in this study is based on **Table 2**.

Table 2. Indication categories for use of IVIG.

A- FDA labeled
• Chronic inflammatory demyelinating polyneuropathy (CIDP)
• Prevention of bacterial infection in patients with hypogammaglobinemia and/or recurrent bacterial infections with B-cell chronic lymphocytic leukemia (CLL)
• Treatment of immune thrombocytopenia purpura (ITP)
• Treatment of primary humoral immunodeficiency syndromes (PID)
• Kawasaki syndrome
• Multifocal motor neuropathy (MMN)
• Passive immunity
B- Off-labeled with support
• Secondary to malignant acquired hypogammaglobulinemia (CLL, MM, Non Hodgkin Lymphoma) to prevent infection
• Rejection of cardiac and renal transplantation by antibody
• Recurrent dermatomyositis/polymyositis
• Guillain-Barré syndrome
• HIV-related thrombocytopenia
• Myasthenia gravis
• MS relapse
• *Lambert–Eaton myasthenic syndrome*
• Treatment of Clostridium difficile infection
• Prevention of bacterial infection in the association of blood cells with severe hypogammaglobulinemia
• *Stiff person* syndrome
• Neonatal hemochromatosis
• Autoimmune hemolytic anemia
• Systemic necrotizing vasculitis with anti-neutrophil cytoplasmic antibody (ANCA-positive)
• Autoimmune blistering diseases (pemphigus vulgaris, annular pemphigoid, etc.)
• Acute disseminated encephalomyelitis
• Allogeneic hematopoietic cell transplantation for primary immune deficiency diseases
• Fetal and neonatal alloimmune thrombocytopenia
• Hemolytic disease of the fetus and newborn
• Post-transfusion purpura
• Treatment of secondary hemorrhagic immunodeficiency
C- Off-labeled without support
Indications that do not place into any of the above groups.

As can be seen, after the approval of the protocol, the rate of drug use in third-level indications (C-Off-labeled without support), which are our main goal in reducing irrational IVIG consumption, decreased by 98.54%, which shows the significant success of the implemented protocol.

Health providers in the implanting program will be able to prevent unsuitable medication use if they are able to comprehend the factors that influence the medications' misapplication, and medication use evaluation (MUE) is the cornerstone in this manner [23]. Limited worldwide accessibility of IVIG, escalating costs, and increasing the demands for unlicensed utilization, in addition to probable adverse reactions and insufficient information for the

application of IVIG, particularly in the Middle East, has persisted in assessing IVIG misapplication as one of the priorities of MUE for some years [13, 19, 21]. Hence, this investigation was designed to describe IVIG application in one of the largest academic tertiary referral hospitals in a developing country in the Middle East.

In this cross-sectional study, according to the FDA, 99.79% of the IVIG that were prescribed were appropriately indicated for the off-labeled with support indications or approved indications. IVIG prevalence with rational prescribing was described widely from 36% to overwhelmingly appropriate, as >90% in previous investigations.

However, for the unsuitable indications, high cost is a common dilemma in diverse conducted investigations before the intervention, which can be compared with our findings, showing >2000 US dollars spent for each patient for the inappropriate IVIG indication. The guidelines utilized for the IVIG use assessment are the most significant reason clarifying the variation of rational prescribing rate. Using a diverse interpretation of reviewing organizations, more than 150 unlabeled IVIG applications were identified [8].

Furthermore, the assessment setting (academic/tertiary care centers, country, forwards, in which investigations were conducted) and the research type (prospective or retrospective) are different between the investigations that were carried out. For example, in a retrospective study, Foster *et al*. reported that >90% of the applications of IVIG were properly indicated (support in the medical literature or approved indication) in the ICUs based on the classification that was developed in a Canadian Blood Services Consensus Conference [24]. Another investigation in a Pediatric Intensive Care Unit of a tertiary referral pediatric hospital showed that IVIG for indications with the level Ia/Ib evidence was given to 62% of patients received and the other cases received IVIG for indications with level II and III pieces of evidence [13]. Furthermore, this high rate of compliance with the guideline was also signified in the noncritical care situation with a strict system for the approval of IVIG prescription, particularly in the developed countries [9, 25, 26]. Nevertheless, the lower ranges of the proper utilization of IVIG (35%–60%) were reported in other investigations [10, 19, 21]. Also, it should be stated that a few investigations conducted in the Middle East region also revealed an inappropriate use of IVIG [14, 27-29]. Regarding the indications for the prescription of IVIG, almost all the patients with CIDP receive IVIG in this center. Therefore, CIDP serves as the most frequent indication for the administration of IVIG. Moreso, as CIDP is the FDA-label indication, the IVIG administration in the hospital was more suitable than in the other wards. On the other hand, neurological disorders including Guillain-Barré syndrome, Multiple sclerosis, Multifocal motor neuropathy, Myasthenia gravis, and Polymyositis and dermatomyositis were responsible for 28.87% of IVIG indications, which is aligned with most repeated IVIG prescriptions by the neurologists, which is in agreement with that on the literature [22, 25, 30]. Despite the presence of some data regarding the IVIG utilization assessment in the literature review, there was not enough information concerning the variables related to the misuse of that. Even though this study has created a new perspective for the various aspects of using IVIG, it should be noted that some factors may limit these data. First, this study was carried out in a regional hospital in a short time. Second, to represent all groups of patients, our population may not be suitable. On the other hand, the results in refractory patients to conventional therapy and the referral university hospital with rare diseases may be different from those from other hospitals. Because specialists give diverse interpretations of clinical evidence, the adequacy of unlabeled indications of IVIG is inconsistent in several guidelines of healthcare institutions. Nevertheless, the institutional guideline is essential for the delineation that patients benefit from the application of IVIG and limit the IVIG prescription for the unlabeled indications by the implementation of some control tools [5]. IVIG consumption has decreased by 37.03% after the approval of the protocol, the rate of drug use in third-level indications, which are our main goals in reducing irrational IVIG consumption, decreased by 98.54%, which shows the significant success of the implemented protocol.

The implementation of such studies is costly, but in practice and the long run, it will not only decrease part of the hospital's waste costs but also enhance the physical and mental well-being of the patients. A complete and necessary investigation of a DUE will not be probable unless

the hospital pharmacist plays his part in leading and conducting the research. Pharmacists should be able to act in the field of guidance to help the medical staff remedy existing deficiencies.

CONCLUSION

A noteworthy amount of IVIG was prescribed for accepted indications. However, given the cost of IVIG, global shortage, and limited data about its clinical benefits in many conditions, strategies to optimize IVIG utilization should be originated to diminish the unsuitable use of IVIG for low-evidence indications.

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This research was approved by Research Ethics Committees of Baqiyatallah University of Medical Sciences and registered with the code: IR.BMSU.REC.1397.301.
All the participants signed written informed consent forms.

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