Intravenous immunoglobulin utilization in a tertiary care teaching hospital in Saudi Arabia

Abdullah A. Alangari, MBBS, FAAAAI, *Mohammad H. Abutaleb,* MSc,
Ahmad A. Albarraq, Pharm.D, *Abdullatif A. Al-Dhowailie,* PhD.

ABSTRACT

الأهداف: تقييم الانتفاع بالإميونوقلوبيولين الوريدي (IVIG) خلال 3 سنوات في مستشفى الملك خالد الجامعي.

الطريقة: تم التعرف بطريقة استرجاعية على المرضى الذين اعطوا IVIG في الفترة مابين يناير 2003م وحتى ديسمبر 2005م. في مستشفى الملك خالد الجامعي – الرياض – المملكة العربية السعودية، باستخدام نظام الكومبيوتر في المستشفى. ومن ثم تمت مراجعة ملفات المرضى. تم جمع معلومات عن المرضى تشمل معلومات مسحية عامة، أسباب إعطاء IVIG، الجرعة المعطاة، وتخصص الطبيب المعالج. كما تم تقسيم أسباب إعطاء IVIG إلى 4 أصناف: المقرة من FDA، غير مقرة ولكن يوصى بها كخيار أول، غير مقرة ولكن يوصى بها كخيار ثاني، غير مقرة.

النتائج: كان هناك 305 مريضاً ممن تم إعطائهم IVIG في فترة الدراسة. أعطي IVIG لمئة وتسعة مرضى (35.7%) لأسباب مقرة من الـ FDA. تسعة وعشرون مريض (9.5%) لأسباب غير مقرة ولكن يوصى بها كخيار اول، 97 مريض (31.8%) لأسباب غير مقرة ولكن يوصى بها كخيار ثاني، و 70 مريض (23%) لأسباب غير مقرة. كانت كمية IVIG المستهلكة خلال فترة الدراسة 43.65Kgs وتقدر تكلفتها بـ 1.75 مليون دولار أمريكي، 24.4% منها أعطيت لاسباب غير صحيحة. كان أخصائيوا الدم والأعصاب هم أكثر الفئات التي وصفت IVIG.

خاتمة: تم وصف كمية كبيرة من IVIG لأسباب غير صحيحة. وهذا يسبب ضغط مالي كبير على ميزانية المستشفى المحدودة.

Objectives: To evaluate the effect of intravenous immunoglobulin (IVIG) utilization at King Khalid University Hospital, an 850 bed tertiary care academic center, over a-3-year period.

Methods: Patients who received IVIG in the period from January 2003 to December 2005 at King Khalid University Hospital were identified retrospectively using the hospital computer system. Their charts were subsequently reviewed. We collected data pertaining to patients' demographics, indication of IVIG, dose regimen and physician specialty. Indications were categorized into 4 different categories: US Food and Drug Administration (FDA)-labeled; off-label recommended as first line; off-label recommended as alternative; and not recommended.

Results: A total of 305 patients were identified. Intravenous immunoglobulin was given to 109 (35.7%) patients for FDA-labeled indications, 29 (9.5%) patients for off-label recommended as first line indications, 97 (31.8%) for off-label recommended as alternative indications, and 70 (23%) for not recommended indications. The amount of IVIG consumed during the study period was 43.65 Kgs with an estimated cost of $1.75 million, 24.4% of which was considered inappropriate use. Hematologists and neurologists were the most frequent prescribers.

Conclusions: A significant amount of IVIG was prescribed for inappropriate indications. This had a large financial burden on an already strained hospital budget.

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From the Departments of Pediatircs (Alangari), and Pharmacy (Albarraq), College of Medicine, and the Department of Clinical Pharmacology (Abutaleb, Aldhowailie), College of Pharmacy, King Saud University, Riyadh, Kingdom of Saudi Arabia.

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Address correspondence and reprint request to: Dr. Abdullah A. Alangari, Department of Pediatrics, College of Medicine, King Saud University, PO Box 2925, Riyadh 11461, Kingdom of Saudi Arabia. Tel. +966 (1) 4670807. Fax. +966 (1) 4679463. E-mail: alangari100@hotmail.com

Intravenous immunoglobulin (IVIG) is a plasma product prepared from the serum of thousands of donors.[1] It is primarily composed of IgG. Intravenous immunoglobulin is mainly used as a replacement therapy in patients with primary or secondary immunodeficiency or as an immunomodulatory therapy in many other conditions. Since its introduction in 1980, the use of IVIG has grown steadily to the point in which it has over taken albumin (human) in commercial importance among fractionated plasma products.[2] This has been attributed to the expanding list of clinical conditions for which it may help.[3] However,

there are only a limited number of approved indications by well-recognized licensing agencies. For example, the FDA has only 6 approved indications. Nevertheless, in the USA or Canada, more than half of the IVIG dispensed to inpatients or outpatients is given for off-label indications.[3-6] Most of these indications were, however, based on scientific evidence. Intravenous immunoglobulin is also an expensive medication. The estimated cost per gram ranges from $40-$80. In one major hospital in the USA, the annual acquisition cost of infused IVIG was estimated to be $4 million, making it the most expensive blood product dispensed in that institution.[7] We sought to evaluate the utilization of IVIG in King Khalid University Hospital, a tertiary care teaching hospital in Riyadh, Saudi Arabia. The hospital has 850 inpatient beds and is part of the College of Medicine, King Saud University, Riyadh, Saudi Arabia.

Methods. This is a retrospective chart review study. The medical records of all patients who received IVIG in the period from January 2003 to December 2005 were identified using the hospital computer system. A total of 305 patients were identified. For 284 patients, charts were available for review and for the rest (21 patients) information was taken from the electronic data, which were less accurate. Patients' demographics, indication of IVIG, dose regimen, and the physician specialties were recorded. Similar to the University Health System Consortium classification,[5] we categorized our identified indications into 4 different categories: a) FDA-labeled, b) off-label recommended as fist line, c) off-label recommended as alternative, and d) not-recommended. Indications in category C were further subdivided based on whether the IVIG was given as a first line or second line treatment. US Food and Drug Administration-labeled indications include: 1) Primary immunodeficiency, 2) Secondary immunodeficiency due to chronic lymphocytic leukemia (CLL), 3) Pediatric human immunodeficiency virus (HIV) infection, 4) Prevention of graft versus host disease (GVHD) and infection in adult bone marrow transplantation (BMT), 5) Immune thrombocytopenic purpura, and 6) Kawasaki syndrome. Our decisions of categorizing other indications into B, C, or D categories were mainly based on the recent review of evidence of the use of IVIG in human disease by the primary immunodeficiency committee of the American Academy of Allergy, Asthma, and Immunology[8] and other recent literature reviews of IVIG clinical uses.[1,7,9] If there is a strong evidence to justify the use of IVIG for a particular condition as a first line therapy or there is no alternative to IVIG, the condition will be considered for category B. If evidence suggests that IVIG is very effective or partially effective in the treatment of a particular condition but not sufficient to justify its use as a first line or in case this was a controversial issue it was considered for category C. Other conditions where there is no evidence to support IVIG use in their management were considered for Category D. Appropriate use of IVIG was defined as indications in categories A, B, or C if used as a second line. Inappropriate use was defined as indications in category C if used as a first line, or category D. This work was conducted in compliance with the requirements of the Ethical Committee at the College of Medicine and King Khalid University Hospital. The authors have no conflict of interest with the company producing the IVIG.

Results. A total of 305 patients received IVIG in our institution during a-3-year period. Among the patients, there were 164 (53.8%) males and 141 (46.2%) females. There were 170 (55.7%) child, 63 of whom were infants; and 135 (44.3%) adults. The distribution of indications within each category and the number of patients received IVIG for each indication is shown in **Table 1.** The category A included 5 conditions, as there is no BMT service in our hospital. In category B, toxic epidermal necrolysis was included since there is no alternative to IVIG in the treatment of this condition. The evidence that supports IVIG as an alternative in the management of conditions in category C varied in strength from one condition to the other. Category D included many conditions. Some of them are listed. Those included in "others" represent 21 different conditions for most only one patient received IVIG per condition. None of these conditions have any evidence to justify their use. The brand of IVIG used in our hospital during the study period was Octagam® (Octapharma, Switzerland). The average cost per gram was $40.5, which is relatively low. There are more patients who received IVIG for labeled indications (category A) than any other category. Most IVIG was dispensed for appropriate indications (**Table 2**). However, approximately one third of patients received IVIG for inappropriate indications. This corresponded to about one quarter of the amount of IVIG dispensed, the cost of which is nearly half a million US dollars. Among various subspecialties, hematologists prescribed IVIG the most (31%) followed by neurologists (19.6%), neonatologists (10.8%), rheumatologists (7.2%), immunologists (4.6%), and nephrologists (3.3%). When major specialties were considered, internal medicine and pediatrics had most of the share (47% and 46%).

Discussion. Intravenous immunoglobulin is an essential blood product that is used in the treatment of an increasing number of conditions.[1,10,11] Thus, there is an increasing demand on this product every year. In many institutions or countries, policies have been

Table 1 - Distribution of patients who received intravenous immunoglobulin (IVIG) during the study period based on indication in categories A and B, and categories C and D. Category C patients were subdivided based on whether they received IVIG as first line or second line.

Categories	No. (%)	
Category A		
1. Primary immunodeficiency	18 (5.9)	
2. Secondary immunodeficiency due to chronic lymphocytic leukemia	9 (3.0)	
3. Pediatric human immunodeficiency virus	1 (0.3)	
4. Idiopathic thrombocytopenic purpura	60 (19.7)	
5. Kawasaki disease	21 (6.9)	
Total	**109 (35.7)**	
Category B		
1. Guillian-Barre syndrome	26 (8.5)	
2. Chronic inflammatory demyelinating polyneuropathy	2 (0.7)	
3. Toxic epidermal necrolysis	1 (0.3)	
Total	**29 (9.5)**	
Category C	Fist line	Second line
1. Dermatomyositis/polymyositis	4 (1.4)	2 (0.6)
2. Myasthenia gravis	1 (0.3)	6 (2)
3. Intractable childhood epilepsy	0 (0)	6 (2)
4. Autoimmune hemolytic anemia	2 (0.7)	3 (1)
5. Pure red cell aplasia	0 (0)	2 (0.7)
6. Post-transfusion purpura	0 (0)	1 (0.3)
7. Neonatal alloimmune thrombocytopenia	0 (0)	1 (0.3)
8. Post-renal transplant rejection	0 (0)	1 (0.3)
9. Acute demyelinating encephalomyelitis	2 (0.7)	2 (0.7)
10. Pemphgus vulgaris	2 (0.7)	3 (0.3)
11. Systemic lupus erythematosus	0 (0)	26 (8.5)
12. Neonatal alloimmune hemolysis	14 (4.6)	10 (3.3)
13. Preterm neonatal sepsis	1 (0.3)	6 (2)
14. Hemophagocytic lymphohistiocytosis	0 (0)	2 (0.7)
Total	**26 (8.5)**	**71 (23.3)**
Category D		
1. Acute lymphoblastic leukemia	3 (1)	
2. Acute myelogenous leukemia	1 (0.3)	
3. Rapidly progressive glomerulonephritis	8 (2.6)	
4. Recurrent spontaneous abortions	11 (3.6)	
5. Sepsis (in term neonates and older)	9 (3)	
6. Viral myocarditis	2 (0.7)	
7. Prophylaxis for preterm sepsis	2 (0.7)	
8. Heparin induced thrombocytopenia	2 (0.7)	
9. Pulmonary lymphangectasia	1 (0.3)	
10. Opsoclonus-myoclonus syndrome	1 (0.3)	
11. IgA nephropathy	1 (0.3)	
12. Cutaneous granulomatous vasculitis	1 (0.3)	
13. Aplastic anemia	2 (0.7)	
14. Neuroblastoma	1 (0.3)	
15. Lymphoma	3 (1)	
16. Thrombotic thrombocytopenic purpura	1 (0.3)	
17. Others	21(6.9)	
Total	**70 (23.0)**	

developed to monitor and control the dispensing process of IVIG.[7,11] At our institution IVIG was dispensed mostly based on physician's prescription. There is a little role for the pharmacy or any other service in controlling its use. This, at least partly, explains why there were many conditions for which IVIG was prescribed unnecessarily. In comparison with other reports in the literature, the number of conditions for which IVIG was inappropriately used at our institution is unacceptably high. This was clearly reflected on the high cost of the IVIG given for those indications. In a report by the University HealthSystem Consortium that included 251 patients who received IVIG in 1996, only 14% of IVIG was used for non-recommended reasons.[5] This represented a clear improvement compared to a multi-center report in 1994 by a different group in the US.[12] In a study by Hanna et al,[13] that looked at IVIG use in 10 institutions in Canada from 1997-

Table 2 - Amount of IVIG given for indications of each category with the cost and number of patients during the 3 years study period.

Categories	Quantity in Kgs (%)	Cost in US dollars	Number of patients (%)
A	18.00 (41.4)	729,000	109 (35.7)
B	4.50 (10.31)	182,250	29 (9.5)
C (as 2nd line)	10.50 (24.5)	425,250	71 (23.3)
Total appropriate use	33.00 (75.6)	1,336,500	209 (69.0)
C (as 1st line)	3.25 (7.45)	131,625	26 (8.5)
D	7.40 (16.95)	299,700	70 (23.0)
Total inappropriate use	10.65 (24.4)	431,325	96 (31.0)
Total	43.65 (100)	1,746,000	305 (100)

1999, 53% of adults and 38% of children received IVIG for off-label indications. However, 89% of the dispensed IVIG was considered appropriately used. In a different Canadian study by Pendergrast et al[14] on IVIG prescribing patterns in the period from 1995-2000 in 4 Toronto teaching hospitals, over 80% of the 429 patients in the study were determined to have received IVIG for appropriate reasons. A report from Spain by Badia et al,[11] that looked at IVIG use from 2000-2004 and included 273 patients found that 86% of IVIG courses were for labeled indications, which were similar to FDA-labeled indications with the addition of Guillian Barre syndrome. Moreover, 96% of IVIG courses were considered appropriate. Finally, in a report from New Zealand by Lee et al[10] that examined IVIG clinical usage in 4 different centers in Auckland in 1996, 116/131 (88.5%) of patients were given IVIG for appropriate indications. In terms of the prescription of IVIG by specialty, our results were mostly consistent with that of the literature. In the multi-center study from Toronto, Canada[14] hematology and neurology patients constituted half the patients for which IVIG was prescribed with equal share for each group. In 2 other Canadian multi-center studies hematologists and neurologists were the 2 most prevalent prescribers of IVIG as well.[13,15] One of the main reasons many of the above mentioned reports demonstrate that most of their IVIG was dispensed for appropriate reasons is the existence of a strict approval system for IVIG prescriptions for off-label indications or at least those that are not supported by sound scientific evidence. In the report from Massachusetts General Hospital they relayed their finding that the majority of IVIG use matches guidelines to the institution of a prerelease review process. Every order by a clinician needs to be reviewed by a physician from the blood transfusion service and approved before release.[7] In the report from the Spanish institution, upon receiving a prescription, the pharmacist assesses the indication and categorizes it. When IVIG request is for an indication without scientific evidence supporting its use, the pharmacist contacted the prescribing physician to obtain the documentation required to request authorization from the health authorities for compassionate use.[11] In fact, at another institution in Riyadh, Saudi Arabia there was a clear improvement in labeled to unlabeled uses ratio and correct dosing for various indications after the adoption of an IVIG indication form which physicians must fill when prescribing IVIG and obtain approval from the clinical research committee for any unlabeled indication.[16] Physicians education by distributing guidelines of appropriate IVIG use and getting feedback was also found to significantly reduce inappropriate use.[15] On the other hand, the rapid expansion of IVIG use for some conditions based on weak scientific evidence during the late 1990's when there was a severe shortage of IVIG supply has made some authors believed that it would seem unlikely that stricter enforcement of transfusion guidelines, at least within the academic hospital environment, would have a large effect on IVIG use. Instead, they suggested that efforts may be more successfully directed towards improving the quality of evidence upon which the transfusion guidelines are based.[14] We think that both strategies are needed for optimal IVIG utilization. Our study is one of a few to touch on this important subject in this part of the

world. It included a reasonably good number of patients who received IVIG for a wide variety of indications in a tertiary academic center. However, it is limited by its retrospective nature. Occasionally, during chart review process some information may have been missing or not very accurately recorded. Therefore the amount of data that was collected from those patients' charts was limited. We also did not perform year-by-year analysis to see if there is any change of IVIG use over the study period.

In conclusion, we have shown that there is a relatively high amount of IVIG dispensed at our institution for inappropriate indications. This has a great cost burden on the hospital and may reflect similar attitude in many other institutions in the area. Implementing an approval form and obtaining expert permission to use IVIG for off-label indications especially when the scientific evidence is limited or not conclusive may improve this behavior.

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