

Evaluation of the Immunoglobulin Use in Inflammatory Systemic and Immuno-Mediated Illnesses in a Tertiary Hospital

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Abstract: The object of this study is to assess the IvIg (intravenous immunoglobulin) use in inflammatory systemic and immune-mediated illnesses, in patients older than 18 years in a tertiary hospital. The assessment also intends to ensure if the clinical indications matched with the evidence-based clinical guidelines recommendations of use. Analytical, observational, transversal and retrospective study carried out during 2012. Patients with inflammatory systemic and immuno-mediated illnesses, older than 18 years old, were included. The data collected were: age, sex, number of administrations, dosage, frequency, commercial brand and the indication for what the IvIg treatment has been prescribed. As a reference guide the British Health Department Clinical Guidelines for Immunoglobulin Use (2nd edition, 2008, and 2nd edition update 2011) and its Spanish adaption were used. The IvIg treatment was justified by a grade of recommendation A, B or C in 41% of the indications. Thus in 59% (grey indications or unclear diagnosis) the IvIg use would be questionable because of its weak evidence. It was found one indication for what the prescription of IvIg was clearly not recommended. The inflammatory systemic and immune-mediated diseases include many pathologies for what the IvIg use has not been properly studied. There is a need of consensus guidelines for IvIg use to guide doctors and pharmacists in their clinical practice. Moreover, it is important to prioritize which indications and circumstances are of first importance to have their supply guaranteed.

Key words: Intravenous immunoglobulin, immune-mediated diseases, clinical guidelines, systemic and inflammatory diseases.

Abbreviations

IvIg	intravenous immunoglobulin
ITP	immune thrombocytopenic purpura

1. Introduction

IvIg (intravenous immunoglobulin) is a blood-derivative product that is widely used as the treatment of choice for patients with antibody deficiencies. The replacement therapy for humoral immunodeficiency, consisting of a 3-4 weekly, 200-400 mg IvIg/kg body weight doses, has been for years almost the solely clinical indication for the IvIg preparations. Nevertheless, IvIg is becoming more and more frequent associated to complex immuno-mediated diseases. Since the initial use of IvIg

for ITP (immune thrombocytopenic purpura) in children [1], IvIg preparations are used as an immunomodulatory agent in an increasing number of immune and inflammatory disorders, following higher dose schedules 2 g IvIg/kg body weight. While in the antibody deficiencies ground there is room for a limited number of diseases, in the second main clinical use there could be a wide range of diseases whose physiopathology in many cases is not fully understood [2-7].

Among this second main clinical use, many inflammatory systemic and immune-mediated illnesses could potentially benefit from the IvIg treatment. It has become an appealing therapeutic option for clinicians when previous first-line treatments have failed as IvIg is a product with an excellent safety profile, without the side effects of steroids or other immunosuppressive agents. This fact might explain the striking fact that,

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according to the British Third National Immunoglobulin Database Report (2012), only 14% of prescribing in neurology was for life-threatening symptoms, suggesting that up to 86% of prescribing could have been considered for alternative treatments [6-10].

Nevertheless, IvIg prescription it is not always based on high quality evidence, due either to the scarce studies supporting its use and to the low prevalence of some inflammatory systemic and immune-mediated illnesses. Besides, there is a mistaken perception of its harmlessness, so either the benefit-risk or the benefit-cost is not always taken into account. Despite being a secure product, some patients can experience side effects, which are normally dose-related. They can be from mild (flu-like symptoms, muscle ache or headache) to more serious or life-threatening (anaphylaxis, aseptic meningitis or thrombosis, par example). As any blood product, not only are the careful donor selection and the purification and sterility of the pooled plasma formed of an extremely importance, but also having the IvIg supply guaranteed is a highly-critical issue. In order to avoid shortages, the best prevention is a rational use as the number of donators can't be easily increased [2-7, 11].

All things considered, there is an urgent need for consensus among the clinicians in order to prioritize the indications whose treatment with IvIg is of maximum priority as the source of supply is limited and the economic impact on the health system budget is notorious. Some excellent guidelines have already been done, for example the British Health Department Clinical Guidelines for Immunoglobulin Use [2, 3] (2nd edition, 2008, and 2nd edition update 2011) and the Criteria for the Clinical Use of Intravenous Immunoglobulin in Australia (2nd edition 2012) [7], but a lot more work is to be done by health professionals, including clinical pharmacists.

Finally, besides prioritizing indications, it is also of public concern to know how IvIg is currently used in the daily practice. Thus, the main purpose of the study

is to describe the indications for what IvIg treatment was prescribed in patients with inflammatory systemic and immuno-mediated illnesses, older than 18 years. The indications belonging to the neurology field, which are often controversial, were studied apart due to their complexity. The assessment also intends to ensure if the clinical indications matched with the evidence-based clinical guidelines recommendations of use.

2. Methods

Analytical, observational, transversal and retrospective study carried out during 2012 in a tertiary hospital of 600 beds. The study was favorably evaluated by the Institution's Ethics Committee. All patients older than 18 years old with inflammatory systemic and immune-mediated illnesses, who had at least received one IvIg administration according to the Pharmacy Service records, were initially selected. Immunodeficiencies and neurological indications (such as Guillain-Barré syndrome, multifocal motor neuropathy, myasthenia gravis or chronic inflammatory demyelinating polyradiculoneuropathy) were excluded in order to focus on inflammatory systemic diseases.

Clinical records were consulted and the data collected were as follows: demographic data (age, sex and weight), the clinical indication for what the IvIg treatment has been prescribed, medical specialty prescribing the IvIg treatment, if it consisted of an outpatient or hospitalized patient, total number of administrations, length of treatment, dosage, frequency and commercial brand used.

In order to evaluate the suitability of the indication, the British Health Department Clinical Guidelines for Immunoglobulin Use [2, 3] (2nd edition, 2008, and 2nd edition update 2011) and its Spanish adaption [4] were used as the reference guide. According to these guidelines, indications were standardized so it could be possible to compare them with the indications classified in the guidelines (Table 1).

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Table 1 Classification of clinical indications for IvIg according to the Clinical Guidelines for Immunoglobulin Use.

The classification consisted of:	
	Short treatment
If the indication is recommended or not for:	Long treatment
	Depending on the patient's circumstances
Depending on the grade of strength of recommendation or evidence:	A-C
	I-III
Depending on the treatment's priority:	Red: maximum priority, severe illness without therapeutic alternative
	Blue: although there is evidence of its efficacy, there are other therapeutic alternatives.
	Grey: because of the low incidence of these pathologies, there are few studies to assess the efficacy of the treatment.
	Black: its use is not recommended.

Data from all clinical records selected were processed and a data file was created to properly manage all information collected. A suitable descriptive statistics—mainly frequency tables was performed in order to accurately show the outcomes.

3. Results

298 patients were evaluated in order to be included in the study as they had received IvIg treatment according to the Pharmacy Service records. 100 patients were included in the study as they had an inflammatory systemic disease and the IvIg administration was confirmed. The reasons for excluding the rest of the patients were: no evidence of the IvIg administration (25), neurological indications (70) or immunodeficiencies (103).

The mean age was 54.6 (19-87) years old, and 57 (57%) were women. 31 (31%) patients received the IvIg administration during hospitalization, but the majority were outpatients (69%).

Among the top-ranking diagnoses, the administration related to kidney, liver or lung transplantation was found in first place (32%). In second and third place were inflammatory myopathies

(13%) and dermatomyositis (11%). 9% of patients had a diagnosis of systemic lupus erythematosus, and 5% suffered from scleroderma.

It is to highlight that among these most frequent indications it is found a black indication, rheumatoid arthritis (4%). Two indications belonged to the hematology field, immune thrombocytopenic purpura (4%) and autoimmune hemolytic anemia (3%). Also three patients (3%) had a diagnosis of autoimmune membranous glomerulonephritis. These nine indications represented the reason for administering the IvIg in 84 patients (84%) (Table 2).

The 16 patients left suffered from 16 different minority pathologies. Some interesting minority indications were *Parvovirus B19* infection, Susac's syndrome, systemic vasculitis, acquired haemophilia, Von Willebrand syndrome and eosinophilic fasciitis, among others.

When the quality of the evidence and the grade of strength of recommendation of the indications for what the IvIg treatment was prescribed in the 100 patients were analyzed, we found that in a 41% the strength of recommendation was A/B/C (Ia-III), which can be considered reliable enough. It is to highlight the great percentage of grey indications (42%), which means weak evidence, for what more trials are required in order to show significant effectiveness. In four patients (4%) the IvIg wasn't recommended as they had rheumatoid arthritis, which is a black indication (Table 3).

Table 2 Classification of the most frequent clinical indications among the inflammatory systemic and immune-mediated diseases.

Pathology	Percentage (%)
Related to liver, lung or kidney transplantation	32
Inflammatory myopathies	13
Dermatomyositis	11
Systemic lupus erythematosus	9
Scleroderma	5
Rheumatoid arthritis	4
ITP (immune thrombocytopenic purpura)	4
Autoimmune hemolytic anemia	3
Autoimmune membranous glomerulonephritis	3
Total	84

Table 3 IvIg indications grouped by strength of evidence or recommendation.

Strength of evidence or recommendation	Percentage (% , over the 100 patients)	
A + B + C (Ia-III)	41%	
Grey	42%	IvIg use that should be reviewed: 59%
Black	4%	
Others (unclear diagnosis, etc.)	13%	

4. Discussion

Historically, the first therapeutic use of the IvIg treatment was as replacement therapy in immunodeficiencies. Later, the first non-replacement therapy indication was ITP [1], and from this moment, many immuno-mediated inflammatory disorders have benefited from the IvIg treatment.

A trend to increase the IvIg prescription has been observed in the last decades as it is regarded as a secure product that can turn out to be an interesting therapeutic alternative for the treatment of many immunological disorders. Nevertheless, there are some inconvenience that should prevent health professionals from its indiscriminate use: its high cost, the possibility of the appearance of side effects, the lack of studies supporting its use in some of the low-prevalent pathologies and the limited supply as in any other blood product.

The main limitation of the study would be the study design as it consists of a single-center and retrospective study. Being a single-center represents a bias as other hospitals may have other ways of processing the IvIg management and some different patient's profile. Moreover, being a retrospective study conditions the data collection, as well as the difficulty to evaluate the scientific evidence due to the lack of studies for some of the indications conditions the results.

5. Conclusion

After matching the indications with the reference clinical guidelines [2-4], it has been observed that the most part of the prescriptions were not evidence-based (grey and black indications plus others with unclear

diagnosis: 59%). For these doubtful indications the benefit-risk should be taken into account by an expert committee before its prescription depending on each patient's circumstances.

All in all, it can be concluded that in the field of the inflammatory systemic and immune-mediated diseases there is a lot of room for research. More clinical trials are needed to cast light on the still weak evidence-based indications. It is also important to highlight the necessity of consensus guidelines for IvIg use to guide doctors and pharmacists in their clinical practice and to prioritize which indications and circumstances are of first importance to have their supply guaranteed.

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