Therapeutic indications and adverse reactions to intravenous gammaglobulin

Indicações terapêuticas e reações adversas da gamaglobulina intravenosa

Núria Matamoros Florí[1]

ABSTRACT

The first therapeutic indication, and still currently the most applied of gamma globulin, is the one which uses its substitutive capacity in patients with antibodies deficiencies. Its immunomodulatory effectiveness with pro and anti-inflammatory activity holds a second place in their indications, in autoimmune and inflammatory illnesses. The first gamma globulin to be used in patients with agammaglobulinemia in the 50's, were of intramuscular administration, with significant limitations on the volume and the infusion's amount, as well as being painful . For over 20 years intravenous immunoglobulin (IVIG) has been widely used in human pathology. The first proteolytic enzyme-treated intravenous immunoglobulins allowed large doses infusions, thereby getting higher levels of IgC circulating in plasma, a subclass profile similar to the normal population, as well as a much higher average life expectancy. The pharmaceutical industry efforts brought about new more purified and viral safer immunoglobulins. The Cohn and cold ethanol methods were quickly supplemented with ulterior procedures that strengthened the viral safety of these products. The application of molecular techniques to the screening study of plasma donors, as well as incorporating new viral inactivation procedures during its manufacture, have made of IVIG a safe product whose consumption has exponentially increased in recent years. IVIG's high cost, the hypothetical plasma supply problems and risks associated to its administration made essential the writing of usage protocols for official agencies, which, besides, hospitals also adopted.

Key-words: Immunoglobulins. Biological Therapy. Immune Function.

Introduction

The IVIG restoration therapy in primary immunodeficiencies (PID) achieves replacing the lack of antibodies in these patients, preventing the occurrence of infections and long-term complications, especially digestive and lung related. Most IVIG have its origin in plasma fractionation derived by Cohn-ethanol's method or some of its modifications. These first products presented with aggregated of IgG and anti-complementary activity, which could cause anaphylactic reactions. Current IVIG have been suitably modified

1. Servei d'Inmunología. Hospital Universitari Son Espases. Spain.

Dra. Núria Matamoros
Cap de Servei d'Immunologia
Hospital Universitari Son Espases
Ctra. de Valldemossa, 79
07010 Palma de Mallorca
0034-871205120

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to solve these problems. Viral inactivation processes have been supplemented with adding new treatments such as using solvent-detergent, nanofiltration or pasteurization. From 1982 the WHO has been recommending a 90% monomeric IgC constitution for IVIG as well as for them to present less than 5% aggregated IgG. IgG must maintain its bacterial toxins and viruses neutralization capabilities, as well as its opsonizing ability mediated by phagocytes. Despite IgG's wealth in different IVIG presentations being close to 98% small quantities of IgA can be found, as well as some coagulation's cascade proteins. Since discovering in the early 80's the immunomodulatory properties of IVIG, its application in autoimmune and inflammatory diseases has greatly increased.

Indications for IVIG therapy

IVIG is currently used in hospitals as a replacement therapy in primary and secondary immunodeficiencies, as well as an immunomodulatory therapy and / or anti-inflammatory in different pathologies. Currently there are seven indications for an IVIG treatment (replacement and immunomodulatory) approved by the European Medicines Agency (EMEA) (1, 2). However, its actual field of application is much broader. In a daily practice is used on more than 50 diseases not recognized by the EMEA, in which the scientific evidence of its benefits is highly variable (3, 4, 5, 6, 7, 8, 9, 10). All of the above, the product's high price, its production limitation and the risks arising from its use, have made increasingly necessary drafting indication strict hospital protocols.

Proposed Protocol of IVIG Indications and prescription at the University Hospital Son Espases (HUSE)

For the development of this therapeutic guide a complete review on the use of IVIG published in recent years was conducted. Moreover it was contrasted with the indications commonly used in our hospital. Following the last protocol's pattern performed at Son Dureta Hospital on the issue (December, 2000), indications were divided into 1) approved indications: the one numerically most important, the ones with an oldest establishment, recommended and accepted by international therapeutic guidelines; 2) other approved indications, with a current rating making them elective treatments and, finally; 3) technically unapproved indications but supported by controlled clinical trials which, theoretically, would require following the compassionate use procedure. All entries accepted at the Hospital follow the EMEA recommendations and those not recognized as off-label, require the compassionate use application. In addition, the Pharmacy and Therapeutics Hospital Committee must establish the conditions of use for which the drug can be applied on patients in which the medication's advantages and benefits can be significantly clinically objectified and with a valued cost. In cases in which the clinical trials results provide enough evidence, it may be possible to consider the applications, which allows a rational drugs use, on those patients who really have shown a significant or probable clinical benefit.

Requirements for compassionate use of IVIG

There are not considered clinical conditions for IVIG use in the data sheet that require performing a compassionate use application. At the Hospital an application form for compassionate use of drugs can be found. These forms provide the request to be justified and for the necessary information to be furnished, literature (evidence on the efficacy and safety), conditions of use and other relevant data for the compassionate use indication to be made with clinical accuracy.

Situations that require the evaluation committee's authorization

An AD Hoc Evaluation Committee consisting on specialist Pharmacy Services and Hospital Immunology Department experts will intervene in all cases in which the benefit of treatment with IVIG is unlikely (even being its indication approved by the EMEA) but there may be some special medical condition that advises its use. The assessment ought to be made on a case by case basis. The specialist requiring the suitability of the treatment will also participate in the evaluation; the Evaluation Committee may summon an expert from another specialty as a consultant if it sees fit.

Application for an IVIG use authorization to the Evaluation Committee will also be mandatory in pathologies not included in this document or in those

where the potential benefit of an IGIV treatment is not adequately supported by any of the three criteria mentioned above. These special situations may include conditions, such as prevention of recurrent genital herpes or prevention of recurrent pulmonary infection in patients with hypogammaglobulinemia and impaired secondary antibody response to immunosuppressive therapy in COPD.

Being IVIG a derived product from human plasma it can, for various reasons, present with shortages or scarcity; the Evaluation Committee may prioritize indications in these situations. This Protocol shall be updated at least every two years, including the amendments which have arisen from new indications as well as removing those that have proven unsuccessful. In all cases the practice of Evidence and Ethics Based Medicine and must always take into account the patient's clinical benefit.

Approved indications at Hospital Universitari Son Espases

Immunology

- **Primary immunodeficiencies**
  - Predominantly antibody deficiencies. Severe Combined immunodeficiencies
  - Well defined syndromes with immunodeficiency and others immunodeficiencies
- **Secondary immunodeficiencies**
  - Antibody deficiencies secondary to LLC. Antibody deficiency secondary to Mieloma
  - Secondary antibody deficiency to anti-CD20 monoclonal antibody treatment
- **Hematology**

  Idiopathic thrombocytopenic purpura.
- **Neurology**
  - Guillain–Barre syndrome. Multifocal motor neuropathy. Chronic inflammatory demyelinating neuropathy. Other immunomediated demyelinating neropathy (CIDP-like)
  - Myastenia gravis. Lambert –Eaton Syndrome. Multiple sclerosis. Stiff-person disease
- **Autoimmunity**
  - Peripheral or CNS affectation in autoimmune diseases. Dermatomyositis. ANCA positive systemic vasculitis. Severe infections in out –break autoimmune disease
- **Pediatrics**
  - Kawasaki disease. Neonatal sepsis

Immunoglobulins for subcutaneous use

For several years there has now been another type of presentation for human gamma globulin with a via-subcutaneous use (IGSUBCU) (11,12).

This alternative therapy has been put into practice as a replacement therapy in patients with primary and secondary antibody immunodeficiencies; little by little the number of patients receiving it has expanded. Continuing learning on the infusion's mechanics is taught at our Day Care Hospital. Teaching is performed by specialized personnel and every 6 months the patient must come to the hospital to receive an infusion so to ensure a successful procedure. Treatment is usually performed at home, which prevents the patient's displacement to the hospital. It is particularly suitable for children and adults with a less than 50-60 kilos weight. The infusion is carried out by special pumps through special tracts, usually injecting the abdomen, the thighs, the hips or the arm; more than one infusion point may be used simultaneously. Treatment should be done on a weekly basis. Experience has shown that through these subcutaneous gamma globulins the replacement effect is generally successful and IgG pre-infusion levels are achieved and sometimes even higher ones than those obtained with the same dose of IVIG provided every 21-28 days. To the Hospital it represents a lower use of the Day Care Hospital's resources. There are, as well as with the intravenous one, different concentrations of subcutaneous gammaglobulin. In the Spanish market 20% concentration type can be found. They are usually very well tolerated by patients; however they sometimes present with after infusion discrete local reactions.

Secondary adverse reactions to IVIG administration

IVIG infusion is not without side effects. The most common adverse reactions are closely related to the infusion's rate. Most of these reactions are mild and reversible and occur in about 15-20% of all infu-

sions. They can't be foreseen, but they usually appear at the end of the infusion when speed at its highest; they can also reveal themselves over 24 hours following the infusion. Special care must be taken when these reactions take place, during the first infusion in newly diagnosed patients or those chronically infected or acute infected at the time of infusion. The most effective measure to take at the onset of these reactions is to slow down or stopping the infusion whether symptoms do not disappear. If patients were to repeat these reactions on subsequent infusions, the speed ought to be lowered to the maximum tolerated by the patient; it can sometimes be premedicated with nonsteroidal anti-inflammatory drugs or antihistamines. The most common reactions reported in literature are: fever, chills, flushing, tachycardia, palpitations and chest pain. To a lesser extent but also often they may present with high anxiety, nausea, abdominal pain, dyspnea, arthralgia / myalgia. Exceptionally hypotension and shock occur. The etiology of these reactions has been linked to the formation of antigen-antibody complexes, immunoglobulin recognizing the antigens present on the infectious agent may be another possible mechanism of complement activation or the presence of vasoactive amines contaminants in the product. Infrequent reactions and having a higher severity are: aseptic meningitis, neutropenia, urticaria and maculopapular rash, leukocytoclastic vasculitis, thromboembolic events, which can manifest as deep as in thrombosis vein or myocardial infarction reach and very rarely with renal failure. Occasionally these reactions are related to characteristics of the product, but especially with infusion of high doses of IVIG (13,14).

Our experience at the University Hospital Son Espases between 1982-2012 showed that from a total of 30,600 infusions about 20-30% are to provoke frequent mild reactions and less than 1% rare or severe reactions.

Conclusions

IVIG is an product with few side effects and an excellent safety standards. In the last years a rapid expansion in the use of IVIG for an important number of conditions was appeared The major impact of IVIG treatment applied to neurology, haematology, immunology, rheumatology and dermatology. Many of the side effects related to IVIG treatment were mild and with a easy control in a day care hospital. The limitations for IVIG treatments are the cost, it is necessary to maintain a good hospital organization for its administration. The future availability of IVIG product has been a concern, especially for primary immunodeficiency patients since at this moment there are not alternative therapies for these patients.

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RESUMO

A primeira indicação terapêutica e, ainda hoje, a mais utilizada da gamaglobulina humana é aquela que usa a sua capacidade de substituição em pacientes com deficiências de anticorpos. Sua capacidade imunomoduladora, com atividades pro e anti-inflamatória, ocupam segundo lugar dentro de suas indicações, em doenças autoimunes e inflamatórias. As primeiras gamaglobulinas que foram utilizadas nos anos 50 em pacientes com agamaglobulinemia, tinham aplicação intramuscular, com limitações significativas relativas à dor, ao volume e a quantidade de infusão. Durante os últimos 20 anos, as imunoglobulinas intravenosas (IVIG) têm sido amplamente utilizadas em patologias humanas diversas. As primeiras IVIG tratadas por enzimas proteolíticas permitiram a infusão de grandes quantidades, obtendo assim níveis mais elevados de IgG sérica circulante, com um perfil de subclasses semelhante ao da população normal e uma vida média muito superior. O esforço da indústria farmacêutica fez com que aparecessem novas imunoglobulinas mais purificadas e com maior segurança contra infecções virais. Os métodos de Cohn e *cold etanol* foram rapidamente complementados com outros procedimentos que reforçavam a segurança antiviral desses produtos. A aplicação de técnicas moleculares para o estudo de rastreio do plasma dos doadores, bem como a incorporação de novos processos de inativação viral durante seu processo de fabricação, faz das IVIG um produto seguro cujo consumo tem aumentado exponencialmente nos últimos anos. O alto custo das IVIG, os hipotéticos problemas de desabastecimento de plasma e os riscos associados à sua administração tornaram essencial a redação de protocolos de uso para as agências oficiais que os hospitais também adotaram.

Palavras-chave: Imunoglobulinas. Terapia Biológica. Função Imunológica.

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