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Treatment of Primary Immunodeficiency with Human Gammaglobulin

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Abstract

Primary immunodeficiencies are characterized by recurrent or prolonged infections associated with growth retardation, infections by specific microorganisms or by low virulence germs, inappropriate response to the antibiotics used, a high risk of complications and hospitalization and severe vaccine complications. The evaluation of immunological status is essential for the diagnosis of these diseases.

Immunoglobulin replacement therapy is the best option for most antibody deficiencies and for some diseases that do not belong to this group, like hyper IgM syndrome, immunodeficiency with thymoma and severe combined immunodeficiency. This therapy is a safe procedure that induces dramatic positive changes in the clinical outcome of patients who carry antibody defects.

An early diagnosis of primary immunodeficiencies is essential so that therapeutic measures may be taken quickly, such as the use of immunoglobulin when properly indicated, reducing the risks of death and complications.

Keywords: Immunity; Immunologic deficiency syndromes; Infection; Immunoglobulins; Biological therapy

Introduction

Primary Immunodeficiencies (PID) comprise a genetically heterogeneous group of diseases caused by genetic defects involving one or more sectors of the immunologic response [1]. The relationship between the genetic characteristics and the clinical phenotypes is not linear, but consists of a complex expression of molecular defects caused by endogenous and exogenous factors, possibly justifying the great phenotypic heterogeneity observed [2]. Since the first report of congenital agammaglobulinemia [3], approximately 200 different types of PID have been described, with the identification of more than 120 genes involved, a fact that has rendered the classification of these diseases increasingly complex. Thus, PID is classified according to the immunologic system primarily involved and are divided into 8 groups [4]: 1. Deficiencies predominantly of antibodies; 2. Combined deficiencies (T and B cells); 3. Other well-defined immunodeficiencies; 4. Diseases of immunologic deregulation; 5. Congenital phagocyte defects; 6. Innate immunity defects; 7. Auto-inflammatory diseases; 8. Deficiencies of the complement system.

Except for IgA deficiency, PID is considered to be diseases of low prevalence, affecting approximately 1 individual in 2,000 live borne, especially in populations with a high rate of consanguinity and genetically isolated [5]. Among the different groups, deficiencies predominantly involving antibodies are the most frequent, corresponding to about half the cases of PID [6].

The first step for the diagnosis of PID is recognition. The most typical manifestations of PID are recurrent or prolonged infections associated with weight and height growth retardation, infections caused by specific microorganisms or by germs of low virulence, an inadequate response to habitually used antibiotic therapy, and high risks of complications and hospitalizations [2]. The presence of immunodeficiency in siblings or first degree relatives obligatorily requires clinical and laboratory investigation of the possible presence of PID, even when the patient does not have a history of severe or uncommon infections.

The evaluation of immunologic competence is essential for the diagnostic definition of PID. The recommendation is that laboratory investigation be started with low-cost and easy to perform screening tests based on clinical history and physical examination [2]. The main screening tests for the investigation of PID adopted by the Service of Pediatric Allergy and Immunology of the School of Medicine of Ribeirão Preto-University of São Paulo are listed in table 1.

Treatment

Treatment should be instituted as soon as the diagnosis is confirmed in order to prevent possible complications and to improve quality of life and prognosis. Rigorous measures of environmental and personal hygiene are recommended, as well as education of patients and relatives about the disease, nutritional support; a diet free of raw or poorly cooked foods; frequent nasal washes with physiological saline; draining of secretions by means of respiratory physiotherapy; avoiding vaccines consisting of attenuated agents in some PID, especially severe

1. Complete blood count
2. Determination of serum immunoglobulins (IgG, IgM, IgA and IgE)
3. Cavum and chest X-rays
4. Delayed hypersensitivity skin tests
5. NBT reduction test
6. Total hemolytic complement (CH50)
7. HIV serology

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Table 1: Exams for PID screening.

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Brand	Concentration (%)	Formulation	pH	Sugar	Sodium	IgA (µg/mL)	IgM	Osmolarity (mOsmol/L)
Gamunex®	10	Liquid	4.0-4.5	No	Traces	46	Traces	258
Endobulin®	10	Liquid	4.5-5.1	No	No	≤ 14	Traces	240-300
Kiovig®								
Gammagard®								
Privigen®	10	Liquid	4.6-5.0	No	Traces	≤ 25	Traces	240-440
Gammagard®	-	Lyophilized powder	6.4-7.2	20 mg/mL	8.5 mg/mL	<2.2	Traces	636
Carimune® NF	-	Lyophilized powder	6.4-6.8	1.67 mg sucrose/g protein	< 20 mg/g protein	720	Traces	192 (5%)–1074 (10%)
Octagam®	5	Liquid	5.1-6.0	100 mg/mL maltose	≤30 mMol/L	≤ 200	Traces	310-380
Flebogama®	5	Liquid	5.0-6.0	50 mg/mL sorbitol	< 3.2 mEq/L	≤ 50	Traces	240-350
Carimune®	12	Liquid	5.3	No	< 10 mMol/L	≤ 15	Traces	360
Sandoglobulin®								
Sandoglobulin®								
Sandoglobulin®	-	Lyophilized powder	6.8	Glucose	0.145 mEq/ml (55% solution) 0.28 mEq/ml (10% solution)	<2.2	Traces	636 (5%)-1250 (10%)

Table 2: Characteristics of currently available IGIV products.

cell immunity deficiencies and agammaglobulinemias; infusion of previously irradiated blood derivatives in order to prevent graft-versus-host reactions; aggressive and early treatment of infections with antimicrobial agents based, whenever possible, on previous pathogen isolation by culture of organic fluids and on the antibiogram, and treatment of comorbidities and their complications.

Treatment with human gammaglobulin

Immunoglobulin Replacement Therapy (IGT) is the main therapeutic tool for deficiencies predominantly involving antibodies. However, its use should take into account several aspects related to efficacy and safety [7]. Commercially available preparations mainly contain IgG at sufficient concentrations to protect against sepsis and to reduce recurrent or chronic pulmonary infections, reflecting the immunologic memory of the donors [8].

The characteristics of commercially available preparations are listed in table 2 [9].

Efficacy and safety

IGT has proved to be highly effective by significantly reducing the incidence of acute respiratory infections, especially pneumonias, and reducing the risk for chronic lung disease. In addition, immunoglobulin replacement reduces the frequency of hospitalizations due to infection, with a consequent reduction of mortality and improving quality of life [10].

In a study comparing the efficacy of Intravenous Immunoglobulin (IVIG) and intramuscular immunoglobulin, 23 patients aged 6 to 15 years with agammaglobulinemia or severe hypogammaglobulinemia were treated with IVIG at the dose of 150 to 300 mg/kg every three weeks for a period of at least three years. Compared to the preceding two year period when these patients were treated with intramuscular immunoglobulin and their serum IgG levels remained below 100 mg/dL, there was a significant reduction in the number of infections and in the number of days of hospitalization, as well as an increase in IgG concentrations close to normal levels [11].

A multicenter study compared habitually recommended doses of IVIG (300 mg/kg for adults and 400 mg/kg for children every four weeks) and higher doses (600 mg/kg and 800 mg/kg every four weeks, respectively) in patients with primary hypogammaglobulinemia. There was a significant reduction in the number of infections (3.5×2.5 per patient; (p=0.004) and in their duration (33 days to 21 days [p=0.015]) [12].

The dose and the frequency of application should be tailored to each patient based on his clinical response and on the determination of serum IgG levels, which ideally should be above 500 mg/dL after 4 weeks of infusion. In the presence of acute infections the catabolism of gammaglobulin is usually increased and extra infusions may be necessary. Results from a recent meta-analysis show the importance of a treatment aimed at achieving the desired clinical outcome, as opposed to achieving only a desired plasma IgG level. This study combined results from all available studies evaluating trough immunoglobulin levels and pneumonia incidence in PID patients with hypogammaglobulinaemia who received IVIG. It included results from 17 studies and 676 patients (2127 patient-years of follow-up). These results indicated that the incidence of pneumonia declined by 27% with each 100 mg/dL increment in trough IgG levels. Pneumonia incidence with maintenance trough levels of 500 mg/dL was five times more frequent than with a trough level of 1000 mg/dL (0.113 versus 0.023 cases per patient-year) [13].

Since 1991, Subcutaneous Gammaglobulin (SCIG) started to be used in various countries. SCIG is very practical by facilitating self-application at home without the need for hospitalization and is a safe and effective therapy for the prevention of bacterial infections, also increasing patient satisfaction and quality of life [14-17]. The initial therapeutic scheme of 100 mg/kg every seven days or 200 mg/kg every 14 days permits reaching IgG concentrations similar to those obtained with IVIG. In addition, the IgG values obtained with SCIG are more stable than those obtained with IVIG since the weekly administration of smaller doses prevents maximum and minimum plasma concentrations due to the rapid catabolism of the doses administered [18]. Comparison of serum immunoglobulin levels in patients first treated with IVIG and then with SCIG revealed better immunoglobulin levels during subcutaneous treatment (a mean increase of serum levels from 7.8 to 9.2 g/dL in children and from 8.6 to 8.9 g/dL in adults, p<0.001) [19]. SCIG is as effective as IVIG for the treatment of patients with PID, also having other advantages such as not requiring venous access and the possibility of home treatment [20].

Normally, the side effects of IVIG are infrequent, in most cases being mild and transitory [21]. The most common are fever, nausea, vomiting, and myalgia, especially during or some hours after the first infusions. These reactions are frequently related to the rate of infusion or to the presence of a concomitant infection [22,23]. More serious manifestations such as urticaria, angioedema, bronchospasm and anaphylaxis are rare. These reactions may be the consequence of the presence of IgG aggregates or, more rarely, of anti-IgA antibodies. Other rare manifestations generally associated with high IVIG doses administered for immunomodulating purposes are hematologic (hemolysis with a positive Coombs test); neurologic (aseptic meningitis); vascular (thromboembolism); or renal with transitory increases in serum creatinine levels. Although virus transmission is rare, there are reports of transmission of hepatitis B and C virus [24].

The variables that potentially determine the risks and intensity of the adverse effects associated with IVIG administration include patient age and health conditions, presence of IgA, stabilizing agents and osmolarity of the preparation, and rate of infusion [22].

SCIG replacement treatment has some advantages over IVIG such as a lower frequency of adverse reactions. Thus, this preparation is indicated for patients with a history of severe adverse reactions to the use of IVIG and for patients with difficulties in obtaining venous access. The follow-up of adults and children with PID submitted to replacement with SCIG involved the analysis of 2297 infusions and reported 28 notifications of non-severe systemic adverse reactions (1.2%). The more frequent side effects were local, such as edema, erythema and pain at the site of infusion, which disappeared within 12 to 24 hours, especially during the first weeks of treatment [19]. However, patients who present serious adverse reactions to IVIG should be considered to be at risk also for SCIG. A prospective study evaluated 262 patients with severe combined immunodeficiency. Thirteen patients (4.96%) presented severe adverse reactions during treatment with IVIG. After a period of no IVIG replacement, these 13 patients were submitted to SCIG replacement under in-hospital monitoring. This therapy proved to be a safe option for 11 patients, although serious adverse reactions were observed in two of them [25].

Absolute and relative indications

According to Stiehm et al. [26], the absolute indications for the use of IGT in PID are defects of immunoglobulin production:

- X-linked agammaglobulinemia;
- Common variable immunodeficiency;
- Hyper IgM syndrome;
- NEMO deficiency;
- Severe combined immunodeficiency

However, several conditions represent relative indications for the use of IGT, depending on their severity and number of infections [26,27]:

- Subclass deficiency if associated with specific antibody defect;
- Specific antibody defect with normal immunoglobulin levels;
- IgA deficiency if associated with subclass deficiency or with specific antibody defect;
- Transient hypogammaglobulinemia of infancy;
- Hyper IgE syndrome if associated with specific antibody defect;
- Ataxia-telangiectasia if associated with hypogammaglobulinemia or sp ecific antibody defect;
- Wiskott-Aldrich syndrome;
- WHIM syndrome (warts, hypogammaglobulinemia, infections and myelokathesis);
- DiGeorge syndrome if associated with hypogammaglobulinemia or specific antibody defect;

At this point some considerations are important. Most children with a diagnosis of transient hypogammaglobulinemia do not require IGT. Some patients with IgA deficiency associated with deficiency of IgG subclasses (especially IgG2) or associated with defects in the production of specific antipolysaccharide antibodies with normal immunoglobulin levels can benefit from treatment with gammaglobulin. However caution is needed regarding possible anaphylactic reactions, especially among patients with the presence of circulating anti-IgA antibodies. In these cases, the option should be for IgA-free gammaglobulin preparations or preparations containing very reduced IgA concentrations [27].

Patients with severe combined immunodeficiency, congenital agammaglobulinemia, common variable immunodeficiency and specific deficiency of polysaccharide antibodies, with normal immunoglobulin levels associated with severe asthma frequently show clinical improvement of asthma after IGT. The improvement of clinical parameters observed may have been probably due to the significant reduction of respiratory infections, which play an important role in triggering exacerbation and intensification of the bronchial inflammatory process in these patients [2].

Practical aspects

Before the initiation of IGT, physicians must carry out a detailed clinical evaluation, including laboratory tests, to provide a comprehensive assessment of the patient's health condition7. Such evaluation should include:

- Complete haemoleukogram;
- Serum levels of all immunoglobulins (IgG, IgA, IgM, and IgE);
- Titres of antibodies specific to protein and polysaccharide antigens from vaccines (may not be necessary except in cases of specific antibody deficiencies, since levels <200 mg/dL might give false negative titres);
- Lymphocyte populations in peripheral blood (B, T, and NK lymphocytes);
- Evaluation of the lungs including pulmonary function testing and high-resolution contrasted computed tomography;
- Assessment of hepatic and renal function (total and direct bilirubin, transaminases, gamma glutamyl transferase, lactate dehydrogenase, blood urea nitrogen, and serum creatinine);
- Assessment of blood-acquired diseases such as HIV, hepatitis B, hepatitis C, toxoplasmosis, cytomegalovirus infection, mononucleosis, rubella, Chagas disease, malaria, leishmaniasis, herpes simplex virus infection, or other infectious diseases according to the geographical particularities.

Patients submitted to IGT should be monitored for adverse reactions. According to the Immuno Deficiency Foundation, during the first infusion 30% have side effects that either decrease in severity or do not recur with subsequent treatments, as long as the same product is used [28].

So patients should be submitted to rigorous clinical and laboratory monitoring, as follows [27]:

• Determining vital signs before the beginning of infusion, at each change in rate and 30 minutes after the end of infusion;

• Determining the vital signs immediately if there is a report of any adverse reaction at any time during infusion and 5 minutes after the solution of the problem;

• Performing laboratory tests every 6 months: blood count, erythrocyte sedimentation rate, C-reactive protein and polymerase chain reaction (used to detect sub-clinical infections); measurement of immunoglobulin levels (IgG, IgM and IgA); renal and hepatic function;

In cases of severe reactions, the following measures should be adopted before continuing treatment [14,23,29]:

• Re-evaluating the real need for treatment;

• Determining whether the gammaglobulin brand was changed. If this is the case, the product better tolerated previously should be reinstated;

• Determining the presence of IgA antibodies in gammaglobulin preparation. Although IgE antibodies anti-IgA is the major causes of anaphylactic reactions, the presence of IgG antibodies anti-IgA may also be involved. These patients should be treated with IgA-free preparations;

• Considering pretreatment with antihistamines or corticosteroids before the infusions;

• Replacing IGIV with IGSC using an infusion pump with a number 23 beveled needles or a needle adapted for subcutaneous infusion. This method can also be used when a venous access is inevitable;

• Selecting the patients and evaluating the risks and benefits of the use of IGIV and of alternative treatments. For risk patients such as individuals with renal diseases, dehydration, diabetes mellitus, advanced age, or arterial hypertension, or patients that are being treated with other nephrotoxic medications, the option should be for sucralose-free IGIV preparations infused at a slow rate after appropriate hydration.

Final Considerations

A delayed PID diagnosis is frequently due to the limited knowledge about the existence and clinical heterogeneity of these diseases. This delay extends to treatment, compromising the prognosis and quality of life of the patients. The main therapeutic tool for patients with immunodeficiency predominantly involving antibodies is IGT by the intravenous or subcutaneous route. This treatment has proved to be highly effective in reducing the number and gravity of infections and the number of hospitalizations, in addition to presenting a good safety profile and very low risks for serious adverse reactions.

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