Gammaglobulin for primary immunodeficiency: when should it be used?

Gamaglobulina para imunodeficiência primária: quando usar?

Pérsio Roxo-Junior[1]

ABSTRACT

Antibodies are an essential component of the adaptative immune response and hold long-term memory of the immunological experiences throughout life. Antibody defects represent approximately half of the well-known primary immunodeficiencies requiring gammaglobulin replacement therapy.
On the other hand this therapy can be used 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 and induces dramatic improvement in the clinical outcome of patients, reducing the risks of death and complications.

Key-words: Immunity. Immunologic Deficiency Syndromes. Infection. Immunoglobulins. Biological Therapy.

Primary immunodeficiencies (PID) are a heterogeneous group of diseases caused by genetic defects involving one or more sectors of the immunologic response.[1,2] Since the first report of congenital agammaglobulinemia[3] in 1952, approximately 180 different types of PID have been described.

PID are classified and divided into 8 groups according to the immunologic system primarily involved (Table 1).[4]

PID are considered to be diseases of low prevalence, affecting approximately 1 individual in 2,000 liveborns, especially in populations with a high rate of consanguinity.[5] Deficiencies predominantly involving antibodies are the most frequent, corresponding to about half the cases.[6]

Table 1: Classification of PID.

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

Adapted from Chapel, 2012[4].

1. Assistant Professor, Department of Pediatrics. Responsible for the Service of Pediatric Allergy and Immunology. Ribeirão Preto Medical School, University of São Paulo, Ribeirão Preto, São Paulo, Brazil.

Corresponding:
Department of Pediatrics. Ribeirão Preto Medical School,
University of São Paulo
Avenida Bandeirantes, 3900,
code 14049-900, Ribeirão Preto, São Paulo State, Brazil.
persiorj@fmrp.usp.br

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The most typical manifestations of PID are recurrent or prolonged infections caused by specific microorganisms or by germs of low virulence, weight and height growth retardation, an inadequate response to habitually used antibiotic therapy, high risks of complications and hospitalizations and severe reactions to attenuated vaccines.[2]

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. 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[2] are listed in Table 2.

Table 2: Exams for PID screening.

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

Adapted from Roxo-Jr, 2009[2].

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 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.

Gammaglobulin Replacement Therapy

Standard human gammaglobulins were first developed in the 1950s, while the introduction of intravenous (IVIG) and subcutaneous (SCIG) preparations in the 1980s.

The first immunological description of PID was made by Ogden Bruton in 1952 in a patient who presented with recurrent infections and several episodes of sepsis. The disease was termed agammaglobulinaemia, as it was identified by the absence of the gamma fraction after immunoelectrophoresis of serum from the patient. Eventually, he was treated with human gammaglobulin and this intervention led to a decrease in the frequency of infections.[3]

Gammaglobulins are now employed to treat a wide range of other conditions that are associated with hypogammaglobulinaemia, including graft versus host disease, multiple myeloma, and chronic lymphoid leukaemia, as well as diseases in which their ''immunomodulatory'' properties have a major impact such as idiopathic thrombocytopenia purpura, Kawasaki disease, Guillain-Barré syndrome, and polymyositis/dermatomyositis.[7]

Gammaglobulin replacement therapy (GRT) is the main therapeutic tool for deficiencies pedominantly involving antibodies. However, its use should take into account several aspects related to efficacy and safety.[8] 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.[9]

GRT 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, this procedure reduces the frequency of hospitalizations due to infection, with a consequent reduction of mortality and improving quality of life.[8]

The decision to offer GRT should be based on: the patient's diagnosis; proper assessment of serum immunoglobulin levels; other immunological parameters[10]; and on secondary causes of hypogammaglobulinaemia.

The absolute indications for the use of GRT in PID are defects of immunoglobulin production[10] and are represented in Table 3.

Several conditions represent relative indications for the use of GRT, depending on their severity and number of infections[10,11] and are represented in Table 4.

Table 3: Absolute indications for GRT in PID.

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

Adapted from Stiehm et al, 2010[10].

Table 4: Relative indications for GRT in PID.

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 specific antibody defect
Wiskott-Aldrich syndrome
WHIM syndrome (warts, hypogammaglobulinemia, infections and myelokathesis)
DiGeorge syndrome if associated with hypogammaglobulinemia or specific antibody defect

Adapted from Stiehm et al, 2010[10] and from Condino-Neto et al, 2013[11].

Some considerations are relevant. Children with a diagnosis of transient hypogammaglobulinemia just require GRT when they present severe respiratory infections. Patients with IgA deficiency just benefit from treatment with gammaglobulin if associated with deficiency of IgG subclasses or associated with defects in the production of antipolysaccharide antibodies with normal immunoglobulin levels. 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 low IgA concentrations.[11]

Patients with hypogammaglobulinemia or with specific deficiency of polysaccharide antibodies with normal immunoglobulin levels associated with severe asthma frequently show significant clinical improvement of asthma after GRT. This improvement 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]

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.

In general the recommended dose of IVIG for patients with PID is 400 to 600 mg/kg, but it may vary depending on the severity of the infections and hypogammaglobulinaemia. The infusions shoud be every three to four weeks to maintain IgG levels adequate to prevent severe infections.[11]

The initial therapeutic scheme of SCIG is 100 mg/kg every seven days or 200 mg/kg every 14 days. This procedure permits reaching IgG concentrations similar to those obtained with IVIG. Thus SCIG is as effective as IVIG for patients with PID, also having other advantages such as not requiring venous access and the possibility of home treatment.[12]

The most common side effects of IVIG 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.[13] Some reactions like urticaria, angioedema, bronchospasm and anaphylaxis may occur due to the presence of IgG aggregates or anti-IgA antibodies, however fortunately they are uncommon. On the other hand, high IVIG doses administered for immunomodulating purposes can cause some rare manifestations like hemolysis with a positive Coombs test; aseptic meningitis; thromboembolism; or increases in serum creatinine levels. Moreover there are rare reports of transmission of hepatitis B and C virus.[14]

SCIG has a lower frequency of adverse reactions than IVIG. Thus SCIG is indicated for patients with severe adverse reactions to IVIG and for patients with difficult venous access. The more frequent side effects of SCIG are local like edema, erythema and pain at the site of infusion, especially during the first weeks of treatment.[15]

Monitoring of patients

Some laboratory tests are recommended before the initiation of GRT to provide a comprehensive assessment of the patient's health condition[8]. 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.

With aim of verify the occurrence of adverse reactions, patients should be submitted to rigorous clinical and laboratory monitoring, as follows[11]:

- 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.

Final considerations

The main therapeutic tool for patients with hypogammaglobulinemia is GRT by the intravenous or subcutaneous route. The benefits of this treatment are well established. Patients present reduction of number of infections as well as the severity and number of hospitalizations. The primary consequence is a better prognosis and lower mortality.

RESUMO

Anticorpos são componentes essenciais da resposta imunológica adaptativa e apresentam memória imunológica em longo prazo. Defeitos de anticorpos representam aproximadamente metade das imunodeficiências primárias conhecidas e requerem terapia de reposição de gamaglobulina.
Por outro lado, esta modalidade terapêutica pode ser usada para algumas outras doenças que não pertencem a este grupo, como síndrome de hiper IgM, imunodeficiência com timoma e imunodeficiência combinada grave. Este tratamento é um procedimento seguro e acarreta em significativa melhora clínica dos paceintes, reduzindo os riscos de morte e complicações.

Palavras-chave: Imunidade. Síndromes de Deficiência Imunológica. Infecção. Imunoglobulinas. Terapia Biológica.

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