Clinical applications of immunoglobulin: update

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Human immunoglobulin is the most used blood product in the clinical practice. Immunoglobulin applications have increased quickly since the elucidation of its immunomodulatory and anti-inflammatory properties which turned this blood product into a precious tool in the treatment of numerous diseases that present with humoral immune deficiency or that cause immune system dysfunction. Currently, the approved indications for Ig are: primary immunodeficiencies, secondary immunodeficiencies (multiple myeloma or chronic lymphoid leukemia), Kawasaki syndrome, immune thrombocytopenic purpura, Guillain Barré syndrome, graft-versus-host disease following bone marrow transplantation and repeat infections in HIV children. On the other hand, there are numerous "off-label" indications of immunoglobulin, which represent 20-60% of all clinical applications of this drug. It is important to study all these indications and, above all, the scientific evidence for its use, in order to provide patients with a new therapeutic option without burdening the health system. This review results from a wide selection of papers identified in the Pubmed and Lilacs scientific electronic databases. A group of descriptors were used from human immunoglobulin to the names of each disease that immunoglobulin is clinically applied. Our main objective is to list the numerous indications of immunoglobulin, both authorized and "off-label" and to analyze these indications in the light of the most recent scientific evidence.

Keywords: *Immunoglobulin, intravenous; Plasma; Purpura, thrombocytopenic, idiopathic; Guillain-Barre syndrome; Immune system diseases*

Introduction

In 1990, there was a meeting about the clinical applications of immunoglobulin (Ig) which listed the following indications of this blood product: primary immunodeficiencies, congenital HIV infection with recurrent bacterial infections in children, bone marrow transplantation, chronic lymphoid leukemia, immune thrombocytopenic purpura, Kawasaki disease, chronic inflammatory demyelinating polyneuropathy and Guillain Barré syndrome.[1]

Since then, there has been little change in the main indications of Ig, but there has been a great increase in "off-label" indications. These indications currently represent 20 to 60% of the use of Ig.[2] It is important to point out that Ig can be used as a replacement therapy (Figure 1) or as immunomodulatory and anti-inflammatory agents (Figures 2 & 3).

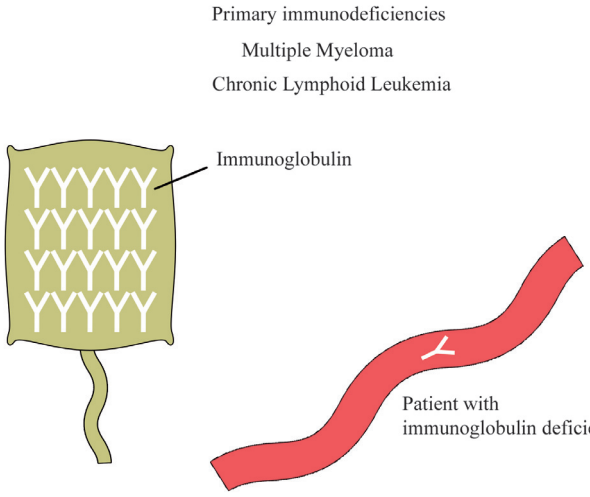

Figure 1 – Immunoglobulin as a replacement therapy for primary immunodeficiencies, multiple myeloma and chronic lymphoid leukemia

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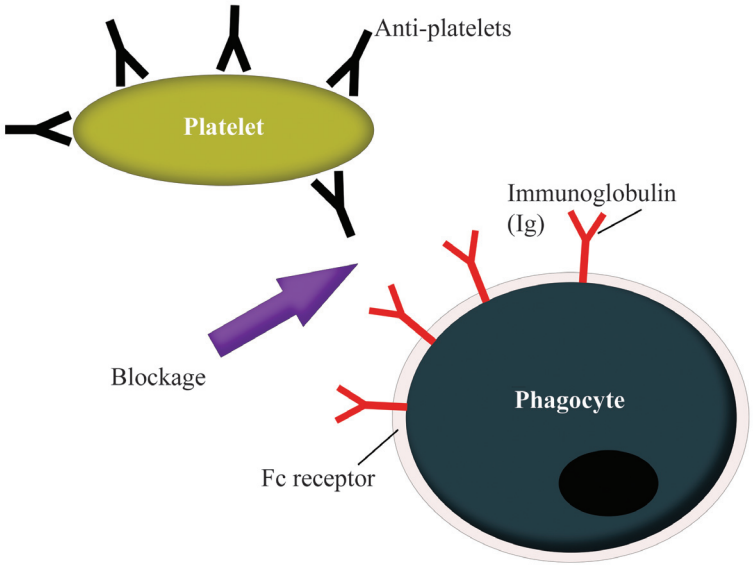

Figure 2 – Fc receptor blockade of phagocytes by Ig in a patient with immune thrombocytopenic purpura (presence of anti-platelet antibodies)

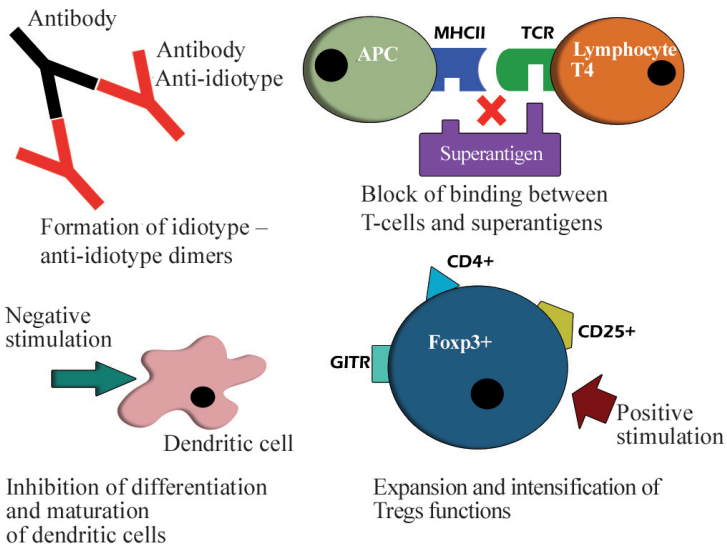

Figure 3 – Anti-inflammatory and immunomodulatory properties of Ig. These Ig properties justify its use in autoimmune diseases

Table 1 - Level of evidence and grades of recommendation

Level of evidence	Source of evidence	Grade of recommendation
Ia	Meta-analysis or randomized clinical trials	A
Ib	At least one randomized clinical trial	A
IIa	At least one study well designed without randomization	B
IIb	At least one study quasi-experimental	B
III	Non-experimental well designed studies, descriptive	C
IV	Expert opinion	C

There are different classifications of indications for Ig in the medical literature. In Brazil, the guidelines of Anvisa (the equivalent of the FDA) written in 2004, classifies indications of Ig in formal, acceptable, experimental and unsubstantiated according to the available scientific evidence.[3]

On the other hand, the British guidelines for Ig, written in 2008, gives explicit indications for Ig with scientific substantiation and discusses other indications that still lack conclusive scientific evidence.[4]

This review will divide the indications of Ig in approved indications ("label") and partially approved indications ("off-label"). It will state the level of evidence that supports each indication and, for this, the classification in Table 1 will be used.

Approved indications for immunoglobulin

Immunodeficiencies

Human immunoglobulin is one of the most important elements used to treat severe antibody deficiencies, which is the commonest type of primary immunodeficiency.

Antibody deficiency syndromes constitute a heterogeneous group of diseases with different etiologies, whose final common consequence is an inability to produce humoral immunity against pathogens. These deficiencies include congenital hypogammaglobulinemia or agammaglobulinemia, severe and combined congenital immunodeficiency and Wiskott Aldrich syndrome. Ig support, in these cases, has improved survival as well as quality of life (Recommendation: Grade B; Evidence: level IIb).

There are primary immunodeficiencies involving low antibody production that are difficult to distinguish clinically. Whenever necessary, especially when there are doubts whether Ig can be used, tests can be applied to demonstrate failure of antibody production with immunization.[4] Ig use in these cases is indicated when antibiotic treatment fails or when bacterial infections are recurrent and severe (Recommendation: Grade C; Evidence: level III).[4]

Besides the use of Ig in primary immunodeficiencies, this blood product is indicated for patients with low levels of IgG after stem cell transplantation (Recommendation: Grade B; Evidence: level IIb) and for patients who lack circulating B cells as a consequence of thymoma (Recommendation: Grade C; Evidence: level III). Patients with multiple myeloma and chronic lymphoid leukemia, when they concomitantly have a low level of immunoglobulins and recurrent bacterial infections, are also candidates for Ig therapy.[5,6]

Kawasaki disease

Kawasaki disease is a systemic vasculitis of unknown cause that occurs mainly during childhood. The major complication of this disease is represented by coronary aneurisms.

There is convincing evidence that Ig use in Kawasaki disease results in lower rates of coronary complications.[7] The use of 2 mg/kg of Ig is recommended with high doses of acetylsalicylic acid as soon as the diagnosis is made (Recommendation: Grade A; Evidence: level Ia). Some patients need an extra dose of Ig when there is no response after the first or when there is relapse of the disease within 48 h after the first infusion.[4]

Immune thrombocytopenic purpura

The first report of the treatment of immune thrombocytopenic purpura (ITP) with Ig was made by Imbach et al. who reported the case of a child whose ITP was quickly reverted after the use of this blood product.[8] Even though the exact mechanism of action of Ig in patients with ITP is not completely understood, it is known that reversion of thrombocytopenia depends on the expression of inhibitory receptors FcR IIB and also on the interaction between Ig and FcR dendritic cells, resulting in macrophagic inhibition.[9]

Studies in children show that Ig has efficacy similar to that presented by corticosteroids, but results in quicker responses.[10,11] As a result, Ig can be used in children with ITP (Recommendation: Grade A; Evidence: level Ib).

In adults, ITP usually has a chronic course, with duration over 6 months. In these cases, the ability of Ig in raising platelet counts is well documented.[12] Ig use in ITP adults can be indicated as first line therapy or as second choice therapy, as long as the treatment is indicated (platelet count below 30,000/mm^3 or bleeding).[13]

Although Ig represents higher costs to the hospital, when compared to corticosteroids, the drawbacks of this blood product are less. On the other hand, its effects are transitory (2-4 weeks). Ig can, as a consequence, be applied in ITP adult patients that require treatment (Recommendation: Grade A; Evidence: level Ia). When quick increases in platelet counts are needed, as for example before surgical procedures, Ig use is especially indicated.[14]

Guillain-Barré syndrome

Guillain-Barré syndrome is an acute immune polyneuropathy, characterized by quick progression and by the presence of limb weakness and areflexia. Sensory disturbances, autonomic dysfunction and respiratory distress may occur during the course of this disease.[15]

Ig was first used to treat this syndrome in 1988. Studies show that Ig and plasma exchange therapy have similar results when applied to treat Guillain-Barré syndrome, but Ig has less side effects.[16,17]

Ig is indicated for the treatment of Guillain-Barré patients with significant impairment; plasma exchange therapy is an alternative treatment. The use of Ig should be started as soon as possible, preferably within the first two weeks of disease (Recommendation: Grade A; Evidence: level Ib).[16] Yet there are not enough studies to conclude whether there is benefit in the administration of Ig in patients with less severe Guillain-Barré syndrome or in the case of patients with the Miller-Fisher variant of the disease.[16] Apparently, there is no additional benefit in administering Ig after the completion of plasmapheresis for patients with indication for treatment.[17] The benefit of Ig in Guillain-Barré syndrome includes pediatric cases.[17]

Prevention of graft-versus-host disease and infections in patients submitted bone marrow transplantation

There is conflicting evidence in the literature that the use of Ig in patients submitted allogeneic bone marrow

Table 2 - "Label" indications of Ig use

Disease	Recommendation of Ig use	Level of evidence	Alternative treatments
Kawasaki disease	Short term	A, Ia	None
Primary immunodeficiency	Long term	B, IIb	None
Immune Thrombocytopenic Purpura - Adults	Short term	A, Ia	Anti-D, corticosteroids, rituximab, splenectomy, immunosuppressive drugs
Immune Thrombocytopenic Purpura - Children	Short term	A, Ib	Anti-D, corticosteroids, rituximab, immunosuppressive agents
Guillain-Barré syndrome	Short term	A, Ia	Plasma exchange therapy
Graft versus host disease after stem cell transplantation	Short term	Ib	Immunosuppressive drugs
Infection after stem cell transplantation	Short term	Ia	Antibiotics, Ganciclovir

transplantation is associated with a lower frequency and severity of cytomegalovirus (CMV) infection and sepsis and a reduction of graft-versus-host disease.[18]

A randomized controlled trial involving 382 patients demonstrated a reduction of CMV infection, infections in general, mortality and interstitial pneumonitis with the administration of Ig up to the ninetieth day after transplantation.[19] Similar results were obtained with a meta-analysis of 12 studies (1282 patients) using Ig as prophylaxis in bone marrow transplantation, which showed a significant reduction in CMV infection, CMV-related pneumonia, pneumonia not related to CMV and total mortality.[20]

However, a meta-analysis by Raanani et al. in 2009 involving 4223 patients, demonstrated no benefit with the administration of Ig in these patients with regard to mortality rate, incidence of infections and incidence of interstitial pneumonitis.[21]

Thus, the role of Ig in preventing infections in bone marrow transplantation is weakened. However, the drug is indicated in patients with low IgG levels after allogeneic bone marrow transplantation (Recommendation: Grade B; Evidence: level IIb).

Children with congenital HIV and severe recurrent infections

The impairment of the immune system of HIV-infected children is more important than in adults with the same disease.

In the era before highly-active antiretroviral treatment (HAART), the use of Ig in children with HIV was associated with lower rates of bacterial infections. The same benefit was not observed in adults with HIV.

The advent of HAART has significantly reduced the morbidity and mortality caused by HIV infection. HAART is associated with partial immune restoration in HIV positive patients. The role of Ig in children with HIV in the era after HAART is controversial. There are no controlled studies documenting the immunomodulatory effect of Ig in patients who are infected with HIV and who concomitantly receive HAART.[22]

Table 2 shows "label" indications of Ig use.

"Off-label" indications for Ig use

Hematology

Low platelet counts in adult patients with HIV

Studies have shown that Ig therapy may be effective in bleeding patients with thrombocytopenia and infection with HIV (Recommendation: Grade A; Evidence: level Ib).[23,24] Moreover, There is evidence that low doses of Ig (0.04 g/kg/week for five weeks) can be used in the treatment of these patients.[24]

Alloimmune thrombocytopenia

Studies show that, during the antenatal period, maternal administration of Ig, alone or in combination with dexamethasone is associated with reduced rates of fetal bleeding and is, therefore, indicated (Recommendation: Grade C; Evidence: level III).[25] The use of Ig in the neonatal period, moreover, is also possible, especially for cases in which compatible platelet transfusions are not available.[3,26,27]

Erythroid aplasia

The use of Ig is indicated in patients with bone marrow analysis compatible with pure red cell aplasia and parvovirus B19 infection confirmed by PCR (polymerase chain reaction) (Recommendation: Grade C; Evidence: level III).[28,29]

Pure red cell aplasia associated with immune deficiency (HIV, hematologic malignancy) or with failure after treatment with steroids also presents a favorable response with the administration of Ig. Fetal hydrops secondary to pure red cell aplasia caused by parvovirus B19 infection also responds to the administration of this medication.[4]

Post-transfusion purpura

Post-transfusion purpura is a rare disorder characterized by severe thrombocytopenia that develops seven to ten days after the transfusion of blood components containing platelets in patients who were previously sensitized via transfusion or pregnancy.[30]

Considering the potential lethality of post-transfusion purpura and its rarity, Ig is indicated for treatment of bleeding associated with this disease, even though evidence in the literature is not abundant (Recommendation: Grade C; Evidence: level III).[30, 31]

Acquired hemophilia

Acquired hemophilia is a rare condition in which there is formation of antibodies against coagulation factors, most often factor VIII. It is a disease with a high incidence of severe bleeding.[32]

Patients with acquired hemophilia and with bleeding associated with the risk of life or limb loss, who have not responded to other treatments (corticosteroids or other immunosuppressive agents), may benefit from the use of Ig (Recommendation: Grade C; Evidence: level III).[4]

Autoimmune hemolytic anemia and Evans syndrome

Autoimmune hemolytic anemia consists in a reduction of erythrocyte survival secondary to the action of autoantibodies. Evans syndrome, in turn, is a disorder that leads to hemolytic anemia and autoimmune thrombocytopenia.

Studies show benefits with the use of Ig in autoimmune hemolytic anemia.[33-35] However, its use is indicated only when the use of corticosteroids fails or there are absolute contraindications to its use and in cases where there is disease relapse after splenectomy (Recommendation: Grade C; Evidence: level III).[36,37]

Series and case reports show the benefit of Ig in Evans syndrome, especially in combination with other immunosuppressive treatments such as corticosteroids and cyclophosphamide (Recommendation: Grade C; Evidence: level III).[38-44]

Hemolytic disease of the fetus and newborn

Two systematic reviews have demonstrated that Ig reduces the need for exchange transfusion in neonates with hemolytic disease of the newborn.[45,46] The drug is indicated in cases of hyperbilirubinemia that progresses despite conventional treatment (Recommendation: Grade C; Evidence: level III).[4]

Acquired von Willebrand Disease

There is some evidence, in the literature, of clinical improvement in patients with acquired von Willebrand disease after Ig use.[47,48] However, there is a lack of prospective randomized studies involving the subject.[4]

Autoimmune neutropenia

The growth-stimulating factor, G-CSF is considered the first-line treatment for autoimmune neutropenia. However, administration of Ig is considered a therapeutic option based on published studies with small numbers of cases.[49]

There are few studies in the literature demonstrating the clinical response to the administration of Ig in patients with autoimmune neutropenia.[50-52] There is, however, no clear evidence that this treatment is superior to the use of corticosteroids or other immunosuppressive agents.[4]

Neurology

Chronic inflammatory demyelinating polyneuropathy

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an acquired disorder secondary to a demyelinating process, leading to sensory loss and dysesthesia as well as muscle weakness.[53]

The three treatments with scientific evidence deriving from randomized controlled trials are: corticosteroids, plasmapheresis and Ig.[53] A metaanalysis of the Cochrane Library demonstrated significant improvement in strength with short term Ig use, while the benefits of this drug's long-term use have been confirmed by recent randomized studies.[53-55] Despite the demonstrated benefits of Ig in CIPD and good tolerability of this drug, corticosteroids and plasmapheresis are also options for treatment, especially in cases unresponsive to Ig.

Thus, the Ig can be used as first choice treatment of CIPD (Recommendation: Grade A; Evidence: level Ib). The choice between Ig and corticosteroids or plasmapheresis should be individualized.[4]

Myasthenia Gravis

Myasthenia gravis is an autoimmune disease caused by autoantibodies against antigens in the neuromuscular postsynaptic membrane. Muscle weakness induced by autoantibodies is the main manifestation of the disease.[16]

Ig may be recommended for patients during myasthenic crises, with this indication supported by the Cochrane systematic review that confirms the benefit of Ig in the treatment of patients with deterioration of the disease. At exacerbation, there is apparently no difference between doses of 1 g/kg or 2 g/kg Ig.[56] There is not, however, scientific evidence to support the use of Ig in chronic myasthenia gravis or evidence to assert its superiority to plasmapheresis in the treatment of exacerbations.[56]

Thus, available evidence indicates that Ig can be used in exacerbations of myasthenia gravis, with good results (Recommendation: Grade B; Evidence: level IIa).[3,56]

Multifocal motor neuropathy

Multifocal motor neuropathy is characterized by progressive weakness, predominantly distal and asymmetric, usually with the presence of multiple partial blocks of motor nerve conduction.

This disease is not responsive to plasmapheresis and may be exacerbated by steroids. Randomized, double-blind, placebo-controlled trials demonstrated improved muscle strength and reduction of disability with the use of Ig.[57,58]

The frequency of maintenance treatment should be guided by the patient's clinical response.[16]

Ig is, therefore, indicated in the treatment of multifocal motor neuropathy (Recommendation: Grade A; Evidence: level Ib).[4]

Paraproteinaemic demyelinating neuropathy

Paraproteins are found in approximately 10% of patients with primary peripheral neuropathies. In about 60% of patients with neuropathies associated with monoclonal gammopathy of undetermined significance, the identified paraprotein belongs to the IgM class. In such cases, the monoclonal immunoglobulin is directed against the myelin-associated glycoprotein, leading to symptoms of neuropathy.[16]

The Cochrane systematic review, involving five major studies, concluded that the use of Ig is safe and effective over the short term in patients with demyelinating neuropathy IgM paraproteinemia.[59] The use of Ig may be considered as a treatment for diagnosed patients and with significant impairment (Recommendation: Grade A; Evidence: level Ib).[60]

Ig may also be used in patients with demyelinating neuropathy associated with IgA or IgG (Recommendation: Grade A; Evidence: level Ib). The Cochrane systematic review showed no differences between Ig alone and Ig with plasmapheresis or corticosteroids in this situation.[55]

Stiff person syndrome

Stiff person syndrome is a neurological disease that leads to stiffness and spasms, and is linked to the presence of anti-GAD65.

There is evidence of benefits in Ig administration when compared with placebo.[61] This benefit is described in terms of reduced rigidity, ability to ambulate, reduced levels of anti-GAD and quality of life.[16] The current indication of Ig is reserved for patients with stiff person syndrome with incomplete response to diazepam and/or baclofen and significant disability (Recommendation: Grade A; Evidence: level Ib).[16]

Eaton-Lambert myasthenic syndrome

Eaton-Lambert myasthenic syndrome is a rare autoimmune disease that leads to muscle weakness and autonomic dysfunction.[62]

A randomized controlled trial and a few smaller studies have shown benefit from the use of Ig in patients with Eaton-Lambert myasthenic syndrome.[63-66] The use of this drug is recommended in cases where the use of cholinesterase inhibitors or 3.4-diaminopyridine failed or proved inappropriate (Recommendation: Grade A; Evidence: level Ib).[4]

Intractable pediatric epilepsy

Intractable pediatric epilepsy is present mainly in Lennox-Gastaut syndrome, West syndrome, early myoclonic encephalopathy and Landau-Kleffner syndrome.[4] A meta-analysis of intractable epilepsy and Ig showed 52% improvement in seizures and 45% improvement in the electroencephalogram.[67] Even so, the indication of Ig in this situation is experimental.[3]

Dermatology

Toxic epidermal necrolysis and Stevens-Johnson syndrome

Toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS) are potentially fatal conditions related to the use of medications. They are related to FAS-mediated apoptosis of epidermal keratinocytes.[68]

Studies show survival rates between 88% and 92% with the use of Ig in severe TEN and SJS cases.[69,70] Ig contains anti-FAS and, experimentally, it is capable of preventing apoptosis when pre-incubated with keratinocytes.[71] Paquet et al. demonstrated that Ig can promote protection of keratinocytes of patients with TEN and, thus, can limit progression of the disease.[72]

Recently, a study of 82 patients demonstrated that the use of Ig associated with corticosteroids results in a better clinical outcome, and lower mortality and hospitalization.[73] However, some other studies showed no benefits from the use of Ig in these syndromes.[74-76]

Thus, Ig can be recommended in the treatment of TEN and SJS, especially when there are contraindications of other treatments or when the clinical situation is severe (Recommendation: Grade B; Evidence: level IIa).[4]

Autoimmune bullous diseases

Autoimmune bullous diseases consist of primary cutaneous manifestations, represented by vesicles and bullae.[77]

Studies show that Ig may be beneficial in the treatment of bullous pemphigoid, pemphigus vulgaris and pemphigus foliaceus.[78-80] Treatment with Ig in these diseases is recommended when there is failure of treatment with corticosteroids or other immunosuppressive agents (example mycophenolate mofetil) (Recommendation: Grade C; Evidence: level III).

Because Ig is considered the adjuvant treatment of autoimmune blistering diseases, it must be administered concomitantly with immunosuppressive treatment which is generally with steroids.[68]

Rheumatology

Dermatomyositis/Polymyositis

Open and controlled studies showed benefits with the use of Ig in severe forms of dermatomyositis.[81-83] This applies to idiopathic, paraneoplastic and juvenile forms of the disease.[68] The current recommendation is that this drug is administered for resistant or aggressive cases. Thus, Ig can be used as second line treatment in the following situations:

when monotherapy treatment with corticosteroids failed to produce clinical improvement after one month, when reducing the steroid dose resulted in relapse of the disease or when side effects limit the use of corticosteroids (Recommendation: Grade B; Evidence: level IIa).[68]

In the case of polymyositis resistant to corticosteroids and other immunosuppressive treatments, the use of Ig has been reported, although only in open studies.[84] In these studies, there was improvement in muscle function and reduction in serum muscle enzymes with the use of Ig.

Thus, dermatomyositis and polymyositis refractory to immunosuppressive and anti-inflammatory treatment are considered acceptable indications for the use of Ig.[3]

Antineutrophil cytoplasmic antibody-positive vasculitis

Studies show that Ig is effective in refractory vasculitis associated with the presence of antineutrophil cytoplasmic antibodies (ANCA) when compared to a placebo.[85,86] The effectiveness was measured by the inflammatory activity.

A prospective study of 22 patients with ANCA-positive vasculitis was recently published. This report presented beneficial effects with the use of Ig (complete remission or partial remission).[87]

Systemic lupus erythematosus

There is little published evidence supporting the use of Ig in systemic lupus erythematosus patients with dysfunctional myocardium, kidneys, nerves or bone marrow.[4] However, most studies with positive results refer to lupus nephropathy.[88-90] Treatment with immunosuppressive agents is still the first choice.[4]

A recent review indicates that the use of high doses of Ig (2 g/kg for five days) is safe and effective in treating patients with systemic lupus erythematosus based on results of case reports and open trials.[91]

Solid organ transplantation

Treatment of acute rejection and antibody-mediated rejection resistant to steroids after solid organ transplantation

Antibody-mediated rejection of solid transplantation leads to the inevitable failure of the graft if not reversed. Positive results come from studies showing benefits with the use of Ig in patients with kidney transplant rejection.[92-95] Apparently, Ig is the most economically viable option to prevent rejection in the context of solid organ transplantation.[4]

Alzheimer's disease

Alzheimer's Disease is the leading cause of dementia and the fourth cause of death among individuals in developed countries. In recent years, researchers have been devoted to assessing the potential immunomodulatory effect of Ig in patients with this disease.

In animals, it has been shown that infusions of Ig decrease amyloid plaques and improve the behavioral activity. An ongoing phase III study of 360 patients may provide valuable information regarding the use of Ig in Alzheimer's disease.[96]

Other "off-label" Ig indications are shown in Table 3.

Table 3 - "Off- label" indications of Ig[4]

Diseases
Pure erythroid aplasia not secondary to parvovirus infection
Acquired Von Willebrand disease
Aplastic anemia
Autoimmune neutropenia
Hemolytic uremic syndrome
Prophylaxis for viral infection after exposition if intramuscular injection is contraindicated or hyperimmune immunoglobulin treatment is not available
Hyperhemolysis after transfusion
Systemic lupus erythematosus with cytopenias
POEMS syndrome
Acute disseminated encephalomyelitis
Acute idiopathic dysautonomia
Bickerstaff encephalitis
Cerebral infarction with antiphospholipid antibodies
Central nervous system vasculitis
Neuromyotonia
Intractable childhood epilepsy
PANDAS (pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection)
Paraneoplastic disorders
Limbic encephalitis not associated with potassium channel antibody
Vasculitic neuropathy
Atopic dermatitis/eczema
Pyoderma gangrenosum
Urticaria
Systemic lupus erythematosus
Other systemic vasculitides
Systemic juvenile idiopathic arthritis
Catastrophic antiphospholipid syndrome

Conclusion

Ig is the blood product with the fastest growing use in the world. The immunomodulatory and anti-inflammatory properties of this drug justify the many indications for its use, with various levels of scientific evidence.

Considering the therapeutic potential of Ig, we can say that there are still many areas in medicine where the drug might be used with possible benefits. However, studies show that there are also many situations where Ig has a small role, or possibly, no therapeutic function. Thus, we need carefully designed clinical studies that accurately establish which situations merit the use of this blood product.

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