



INTRAVENOUS IMMUNOGLOBULIN THERAPY IN MEDICAL PRAXIS

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ABSTRACT

Intravenous immunoglobulin (IVIG) is a blood product prepared from the serum of a thousand or more blood donors. The IVIG that is available contains complete immunoglobulin G (IgG) molecules which has intact Fc-dependent effector functions. The IgG subclasses match those in normal human serum. It is the main treatment for patients with antibody deficiencies. High dose IVIG (hdIVIG), is used as an immunomodulatory agent in an increasing number of immune and inflammatory disorders. The clinical specialities using the largest amounts of IVIG are neurology, haematology, immunology, nephrology, rheumatology and dermatology. In this paper, we review recent developments in the understanding of mechanisms of action of IVIG and the major clinical areas of use.

Keywords: immunology, intravenous immunoglobulin

INTRODUCTION

Immunoglobulin (IVIG) are products obtained from human serum and were first used in 1952 to treat immune deficiency. They contain the pooled immunoglobulin G (IgG) immunoglobulins from the serum of between 1000 and 15 000 blood donors. IVIGs are sterile, purified IgG products manufactured and typically contain more than 95% unmodified IgG, which has intact Fc-dependent effector functions and only trace amounts of immunoglobulin A (IgA) or immunoglobulin M (IgM). (1) The IVIG that is available contains complete IgG molecules. The IgG subclasses match those in normal human serum. Most preparations contain trace amounts of IgA, which can sensitize IgA-deficient persons during treatment. Immune globulin also contains trace amounts of cytokines, soluble CD4, CD8, and HLA molecules. The large number of donors in the pool increases the number of individual antibody activities in the preparation. [1] In healthy persons they last approximately 22 days; however, in persons with certain illnesses, they can last as few as 6 days.

IVIG therapy should be monitored, and obtaining a history and performing a physical examination, with an emphasis on obtaining information regarding hepatic or kidney disease or a history of reactions to blood products or transfusion reactions.

For the patients with antibody deficiency IVIG is used at a 'replacement dose' of 200–400 mg/kg body weight, given 3-weekly. In contrast, 'high dose' IVIG (hdIVIG), given at 2 g/kg/month, is used as an immunomodulatory agent

in an increasing number of immune and inflammatory disorders

They are administered as slow intravenous infusion. There are separate preparations of immunoglobulin for subcutaneous application which are given as a replacement therapy in children and young adults. Both mode of application provide good infections prevention

Mechanisms of action of IVIG

As a replacement therapy IVIG is used to replace missing immunoglobulin in serum of the patients with immunodeficiency. The entire array of variable regions of antibodies in normal serum is contained in IVIG. The large number of donors in the pool increases the number of individual antibody activities in the preparation. [2] However there are significant variations from batch to batch in the concentration of particular antibodies. [1]

As an immunomodulatory therapy IVIG is used for: modulation of complement activation, suppression of idiotypic antibodies, saturation of Fc receptors on macrophages, and suppression of various inflammatory mediators, including cytokines, chemokines, and metalloproteinases. [3]

Uses of intravenous immunoglobulin

The US Food and Drug Administration has approved the use of IVIG for the following conditions: 1) treatment of primary immunodeficiencies; 2) prevention of bacterial infection in patients with hypogammaglobulinemia due to B cell chronic lymphocytic leukemia; 3) prevention of coronary artery aneurysms in Kawasaki disease; 4) prevention of infections and graft versus host disease after bone marrow transplantation; 5) reduction of serious bacterial infection in HIV-infected children; and 6) increasing platelet count in idiopathic thrombocytopenic purpura to prevent bleeding. Not all currently available products are approved for each of these indications and physicians should review specific product information. [4]

IVIG in primary and secondary antibody deficiencies

IVIG are used to reduce severity and frequency of infections in patients with primary and secondary immunodeficiencies where there is impairment of quality or quantity patients immunoglobulins and they are used as replacement therapy. Patients with low levels of immunoglobulins depend on IVIG for their survival. [5]

IVIG are used in antibody deficiencies in primary

immunodeficiencies, X-linked agammaglobulinemia, [5, 6, 7] Common variable immunodeficiency (CVID), HyperIgM syndrome [5]. IgG subclasses deficiencies where total level of immunoglobulins could be normal. [8] Severe combined immunodeficiency (SCID). Transient hypogammaglobulinemia of infancy and small children under the age of two with recurrent infections. [9]

IVIG are indicated in secondary hypogammaglobulinemias due to protein losing enteropathy in gastrointestinal disorders and cardiopathies in children if antibody deficiency is significant and followed by recurrent infections. [10] Some medications as corticosteroids, cytostatics, anticonvulsives may cause hypogammaglobulinemia. [11] In those cases first step is to stop particular medication. IVIG are part of the standard therapy in pediatric HIV patients

IVIG in prophylaxis and therapy of sepsis and severe infections

Maternal transfer of IgG to the fetus occurs after 32 weeks of gestation and there has been much interest in the role of IVIG as prophylaxis against infection in preterm babies. Although early studies suggested some benefit, a Cochrane meta-analysis of 19 studies [12] including approximately 5000 preterm babies has shown that IVIG makes a marginal reduction to the frequency of sepsis but importantly does not reduce associated morbidity or overall mortality. The meta-analysis concluded that there is no justification for further randomized trials of IVIG in preterm or low birth weight infants. Equally, the role of IVIG as adjunctive therapy for suspected or proven neonatal sepsis is not supported by a recent Cochrane meta-analysis [13] which showed that the reduction of mortality with IVIG was only of marginal significance. Another Cochrane meta-analysis in effects of IVIG in sepsis and septic shock in adults and neonates shows reduction of mortality in adults, but not in neonates [14] If IVIG preparations that are used for sepsis and septic shock in adult and neonates are enriched with immunoglobulin, which improves their opsonic activity, it is shown that there is reduction of mortality by 30 % [15] IVIG is not standard therapy for sepsis in children and adults and further investigations in their role and potential benefits are required.

Autoimmune diseases and IVIG

IVIG are used in treatment of idiopathic thrombocytopenic purpura where improves number of thrombocytes acting like immunomodulatory agents. [16] Some reports that are not evidence based show positive effects of IVIG in immune hemolytic anemia. [17] In systemic lupus they show positive effects on nephritis, myocarditis, polyradiculopathy and bone marrow suppression but potential for thromboembolic complication and acute renal failure demands extreme precaution. [18] There are several reports that show potential benefits in systemic sclerosis [19] and Still's

disease [20], but lack of evidence for their efficiency make their use limited.

In patients with asthma who are on high doses of corticosteroid for symptoms control different studies have shown different results [21] and routine use of IVIG is not recommended. Patients with immunodeficiency who have asthma-like symptoms have benefits from IVIG administration.

Neurological diseases

IVIG have shown positive effects in treatment of inflammatory demyelinating diseases of the central and peripheral nervous system especially on Guillain-Barre Syndrome and they are used as first line drugs with fewer side effects than corticosteroids and plasmapheresis. [22, 23] In myasthenia gravis they can be used when other therapeutic options has failed. [24] IVIG can be potential second line drug of choice in relapsing remittent form of multiple sclerosis. [25] It is used but without sufficient evidence in intractable epilepsy of childhood. [26]

Transplantation of hematopoietic stem cells and solid organs

IVIG can be used in selected patients with hematologic malignancies in the first 100 days after stem cell transplantations, [27] IVIG and can be effective in solid organ transplantations during rejection of the transplant or in high HLA sensitized persons [28]

Dermatological diseases and Kawasaki syndrome

Given as immunomodulatory agents in first ten days after onset of fever in Kawasaki syndrome IVIG prevents the development of coronary aneurism. [29] In Steven-Johnson syndrome and toxic epidermal necrolysis they are given in immunomodulatory doses regarding high mortality. [30] In dermatology IVIG are used in bullous dermatosis when other therapeutically options failed [31] Studies of IVIG therapy in autistic spectrum didn't show positive effects. [32]

CONCLUSION

There is rapid expansion in clinical uses of intravenous immunoglobulins. IVIG are safe preparations which enable medical professionals to avoid negative effects of corticosteroids and other immunosuppressive drugs during treatment of patients. Our understanding of mechanisms of action of IVIG in various diseases is growing, but there are many more things yet to be learned. IVIG are used predominantly in neurology, haematology, immunology, rheumatology and dermatology.

Their use in many diseases is not always evidence based, but it is clear that it is important that controlled trials should be performed in large number of rare diseases and conditions to document their clinical efficiency.

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Please cite this article as: Kareva L. Intravenous immunoglobulin therapy in medical praxis. *J of IMAB*. 2016 Oct-Dec;22(4):1403-1406. DOI: <https://doi.org/10.5272/jimab.2016224.1403>

Received: 13/10/2016; Published online: 21/12/2016



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