

IVIG: A Brief Introduction

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Intravenous immune globulin (IVIG) is used to treat a wide variety of clinical conditions resulting from dysregulation of the immune system. IVIG contains the pooled polyclonal IgG fraction from the sera of several thousand individuals¹⁻³ IVIG is FDA approved for a limited list of indications, including idiopathic (immune) thrombocytopenic purpura (ITP), Kawasaki's vasculitis, and primary immunodeficiencies.^{1,2,4} In addition, as shown in table 1, IVIG has numerous off-label uses.^{4,5} The cost of IVIG therapy depends on the dosage and duration of treatment. The standard dose of IVIG in cases of primary immunodeficiency ranges from 0.2 to 0.8 gm/kg, given every four weeks.⁴ A higher dose of IVIG, usually 1 to 2 gm/kg given over the course of one to five days, is administered when treating ITP or other autoimmune related conditions.^{1,4,5} The cost of treatment is not insignificant; for an adult with ITP, a four-dose course of IVIG may cost as much as \$25,000; for conditions that require more chronic treatment, the total cost may be even greater.⁶

Most adverse reactions to IVIG are clinically minor and occur in approximately 10% of recipients.⁵ These include headache, fever, chills, myalgia, or chest discomfort.^{3,5} More serious reactions are rare and include renal tubule necrosis, associated with high sucrose IVIG preparations, and thromboembolic events, especially in patients with increased serum viscosity or with a history of stroke or coronary artery disease.^{3,5} In addition to IgG immunoglobulins, IVIG preparations include a small amount of IgA, which may result in severe anaphylactic reactions in patients with selective IgA deficiency.⁵

The mechanism by which IVIG achieves its therapeutic effect is not entirely clear. The antibodies of healthy people include a small population of autoantibodies whose Fab portions bind to self-antigens, as well as antibodies produced in response to exogenous antigens.² Naturally occurring low-titer autoantibodies are classified as idiotype and anti-idiotypic antibodies. The Fab portion of idiotype autoantibodies are directed to such human proteins as CD4, Fas receptors, and cytokines.^{2,5} Anti-idiotypic antibodies are directed against the unique antigen binding site (Fab) of idiotype autoantibodies. Furthermore, anti-anti-idiotypic antibodies are produced whose Fab region is specific to the Fab antibodies of the anti-idiotypic antibodies.⁷ These antibodies form a complex network postulated to contribute to the regulation of physiologic feedback cycles.^{5,7} Dysregulation of this system is believed to be an important contributor to the pathogenesis of autoimmune diseases.⁷

In the treatment of ITP, it is widely accepted that the Fc immunoglobulin region, rather than the Fab region, is responsible for the therapeutic effect of IVIG. In this model, the Fc regions in IVIG provide a competitive blockade of Fc receptors, inhibiting Fc mediated

phagocytosis of autoantibody-opsonized platelets in the spleen and liver.^{1,5} Evidence for this is provided by experiments that show decreased efficacy of IVIG treatment in ITP in mouse models that lack specific Fcγ-receptors.^{1,3} Fc receptors are also expressed in high levels on vascular endothelial cells and serve a protective function by sequestering IgG antibodies in endocytic vesicles before returning them intact to the circulation.^{3,5} The IgG immunoglobulin in IVIG is believed to saturate these protective niches, resulting in destruction of pathologic as well as non-pathologic IgG.^{2,3,5}

Additional proposed therapeutic mechanisms of IVIG include suppression of antibody production, cellular immunosuppression, and release of anti-inflammatory cytokines.^{1,2,4,5} For a more complete discussion, one can refer to any of the excellent reviews referenced below.^{1-3,5}

Understanding of the precise mechanisms responsible for IVIG therapeutic efficacy is still evolving. Most likely, mutually non-exclusive mechanisms exist by which IVIG modulates the recipient's immune response. Knowledge of the current state of IVIG research and appropriate therapeutic use will enhance patient care and optimize management of hospital resources.

References:

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Table 1. Indications for IVIG Therapy (adapted from Leong et al. 2008)

FDA Labeled Indications <ul style="list-style-type: none">• Primary immunodeficiency• Idiopathic thrombocytopenic purpura (ITP)• Kawasaki disease• Chronic lymphocytic leukemia• Pediatric HIV (to decrease bacterial infections)
Off-label Uses of IVIG <ul style="list-style-type: none">• Accepted use:<ul style="list-style-type: none">○ Chronic inflammatory demyelinating polyneuropathy○ Churg-Strauss syndrome○ Epidermolysis bullosa acqvista○ Graves ophthalmology○ Guillain-Barré syndrome○ Pemphigus○ Posttransfusion purpura○ Toxic necrotizing fascitis due to group A streptococcal bacteria• May be beneficial:<ul style="list-style-type: none">○ Autoimmune hemolytic anemia○ Dermatomyositis, polymyositis○ Lambert-Eaton myasthenic syndrome○ Multifocal motor neuropathy○ Multiple myeloma○ Multiple sclerosis○ Myasthenia gravis○ Renal transplant, prevention and treatment of humoral rejection• Not recommended:<ul style="list-style-type: none">○ Acquired hemophilia○ Acute viral myocarditis○ Diabetes mellitus○ Epilepsy○ Pure red cell aplasia○ Stevens-Johnson syndrome