

Globulin, Immune

Brand Name: Gamimune N, Gammagard S/D, Gammar-P I.V., Ivegam EN, Polygam S/D, Venoglobulin-S, Carimune, Gamunex, Panglobulin

Drug Description

Immune globulin intravenous (IGIV) preparations consist of concentrated immunoglobulins, principally IgG, with a subclass distribution that largely reflects that of IgG in normal human serum. Pooled serum is collected from large numbers of donors, ranging from 1000 to more than 50,000, depending on the manufacturer. All U.S. IGIV manufacturers use Cohn-Oncley ethanol fractionation (fraction II) as an initial step in the preparation of immunoglobulin. Subsequent steps differ among preparations and include ion exchange chromatography, ultrafiltration, enzymatic digestion, manipulation of the pH and salt concentration, and organic solvent-detergent partitioning. These procedures remove contaminants, minimize the concentration of IgG aggregates, and deactivate viral contaminants, such as hepatitis B and C viruses and HIV. Donor serum samples are screened for antibodies to HIV, HCV, and hepatitis B surface antigen and for elevated levels of alanine aminotransferase. [1]

HIV/AIDS-Related Uses

Children and young adults with symptomatic HIV infections who are immunosuppressed in association with AIDS or other clinical manifestations of HIV infection are at increased risk of serious complications from infection.[2] IGIV was approved by the FDA on December 27, 1993 for use in HIV-infected children to reduce the risk of serious bacterial infections. However, there is no evidence to suggest that IGIV confers incremental benefit to antiretroviral therapy and prophylactic antibiotics administered according to current standards of practice. In children with advanced HIV disease who are receiving zidovudine, IGIV decreases the risk of serious bacterial infections. However, this benefit is apparent only in children who are not receiving sulfamethoxazole-trimethoprim as prophylaxis and for children with a CD4 count of greater than 200 to 400 mm³. [3]

Non-HIV/AIDS-Related Uses

IGIV provides passive immunity in susceptible individuals exposed to certain infectious disease when there is no vaccine available for active immunization against the disease, when the susceptible individual is allergic to a vaccine component, or when there is insufficient time for active immunization to stimulate antibody production.[4] IGIV can replace or boost immunoglobulin G (IgG) in individuals with antibody-deficiency syndromes resulting from defective antibody synthesis, such as congenital agammaglobulinemia, hypogammaglobulinemia, common variable immunodeficiency, X-linked immunodeficiency with hyperimmunoglobulin M, severe combined immunodeficiency, and Wiskott-Aldrich syndrome. IGIV is indicated for the treatment of idiopathic thrombocytopenic purpura when a rapid rise in the platelet count is required, such as prior to surgery, to control excessive bleeding, or to defer or avoid splenectomy.[5]

In conjunction with aspirin, IGIV is used in the treatment of Kawasaki's disease. Use of this combination within the first 10 days of illness significantly reduces the prevalence of coronary artery abnormalities associated with this condition, and IGIV has been shown to decrease the prevalence of giant coronary artery aneurysms associated with the highest morbidity and mortality rates in Kawasaki's disease.[6]

IGIV is used as a treatment adjunct for the prevention of recurrent bacterial infections in patients with hypogammaglobulinemia associated with B cell chronic lymphocytic leukemia. IGIV is also used to prevent the risk of acute graft-versus-host disease, associated interstitial pneumonia, and infections (e.g., cytomegalovirus infection, varicella-zoster infection, recurrent bacterial infection) after bone marrow transplantation in patients 20 years of age or older.[7]

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Pharmacology

IGIV is used to provide passive immunity by increasing an individual's antibody titer and antigen-antibody reaction potential. The IgG antibodies present in IGIV help to prevent or modify certain infectious diseases in susceptible individuals. The mechanisms by which IGIV exerts a therapeutic effect in many disease states are unknown, but various immunomodulatory actions operate alone or in combination.[8] [9]

The mechanism by which IGIV increases platelet counts in the treatment of idiopathic thrombocytopenic purpura has not been fully elucidated. It has been suggested that IGIV may saturate Fc receptors on cells of the reticuloendothelial system, resulting in a decrease in Fc-mediated phagocytosis of antibody-coated cells. This Fc receptor blockade on macrophages may occur in bone marrow, spleen, and other parts of the reticuloendothelial system and may occur through competition for Fc receptors by increased serum concentrations of IgG or by circulating immune complexes. Altered Fc-receptor affinity for IgG or suppression of antiplatelet antibody production may also be involved.[10]

The more long-term effects of IGIV can be attributed to the immunomodulatory effects of IGIV on T cells and macrophages, particularly on cytokine synthesis, and B cell immune function and its regulatory action on the membrane-damaging components of the complement system. In contrast, the effects of IGIV on Kawasaki disease and perhaps other diseases may be caused by the presence of specific antibodies in the IGIV that are capable of neutralizing bacterial or even viral toxins that can affect the host's immune and inflammatory systems. It is likely that no single mechanism accounts for all of the immune modulating effects of IGIV in inflammatory and autoimmune processes.[11]

Following intravenous (IV) administration of IGIV, IgG appears in serum immediately; serum concentrations of IgG attained with IGIV appear to be directly related to the dose. IGIV reportedly has a half-life of about 21 to 29 days following IV

administration; however, interindividual variation in the half-life has been reported, especially in patients with immunodeficiencies.[12] After an intravenous infusion of IGIV 2 g/kg of body weight, the patient's serum IgG level increases fivefold and then declines by 50% in 72 hours before returning to pretreatment level in 21 to 28 days. The marked initial decrease reflects extravascular redistribution. The IgG in the infusion easily enters the cerebrospinal fluid (CSF). During the first 48 hours of the infusion, when the serum IgG level is high, the concentration of IgG in the CSF increases as much as twofold, but returns to normal within a week.[13]

Immune globulin is in FDA Pregnancy Category C. Adequate and well-controlled studies have not been done in pregnant women. It is not known whether immune globulin can cause fetal harm or affect reproduction capacity.[14] [15] IGIV should be given to a pregnant woman only if clearly needed. Intact immune globulin crosses the placenta from maternal circulation increasingly after 30 weeks gestation. In cases of maternal idiopathic thrombocytopenia purpura in which IGIV was administered to the mother prior to delivery, the platelet response and clinical effect were similar in the mother and neonate.[16] [17] It is not known if IGIV is distributed into breast milk; however, problems in humans have not been documented.[18]

During their circulating life span, IgG antibodies repeatedly exit and enter the vascular compartment. Most antibodies never encounter their specific target antigen and are eventually removed from the circulation and degraded at an unknown site. The rate of IGIV degradation is determined by the Fc region and by the IGIV concentration; degradation is accelerated in hypergammaglobulinemia and reduced in hypogammaglobulinemia. The half-life of most IGIV preparations is 18 to 32 days, similar to that of native IgG. The half-life of IGIV in neonates is similar to that in adults. There is, however, considerable individual variability, which reflects several factors, including the immunoglobulin level before infusion, the peak immunoglobulin level after infusion, the presence

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Pharmacology (cont.)

of infection or burns, the reliability in determined immunoglobulin levels, and other factors.[19]

Adverse Events/Toxicity

IGIV is a pooled plasma product, collected from a large number of donors. Although potential blood donors are screened for antibodies to hepatitis B and C viruses and HIV, the risks of viral transmission cannot be ruled out.[20]

The reported incidence of adverse effects associated with the administration of IGIV ranges from 1% to 15%, but usually is less than 5%. Most of these reactions are mild and self-limited. Severe reactions occur very infrequently and usually do not contraindicate further IGIV therapy.[21] Most adverse reactions to IGIV appear to be related to the rate of administration rather than the dose, and may be relieved by decreasing the rate of administration or by temporarily stopping the infusion.[22]

Adverse effects seen with immune globulin use include dyspnea; tachycardia; burning sensation in the head; cyanosis; faintness or lightheadedness; fatigue; wheezing; arthralgia; backache or pain; headache; malaise; myalgia; nausea or vomiting; chest or hip pain; leg cramps; redness, rash, or pain at the injection site; and urticaria.[23]

Drug and Food Interactions

Antibodies contained in immune globulin may interfere with the immune response to certain live virus vaccines (e.g., measles virus vaccine live, mumps virus vaccine live, rubella virus vaccine live) and these vaccines should not be administered simultaneously with or for specified intervals before or after administration of IGIV. Administration of vaccines containing measles virus vaccine live should be deferred for at least 8 months following administration of IGIV for replacement therapy of immunodeficiencies; for at least 8 to 10 months following administration of IGIV for the treatment of idiopathic

thrombocytopenic purpura; and for at least 11 months following administration of IGIV for Kawasaki's syndrome. Although specific information regarding the effect of immune globulin preparations on the immune response to mumps virus vaccine and rubella virus vaccine live are not available, there is potential for interference since immune globulin preparations contain antibodies to these viruses.[24]

In contrast to live virus vaccines, administration of IGIV preparations has not been demonstrated to cause significant inhibition of the immune responses to inactivated vaccines and toxoids.[25]

Contraindications

IGIV products carry the following black box warning: IGIV products have been reported to be associated with renal dysfunction, acute renal failure, osmotic nephrosis, and death. Patients predisposed to acute renal failure include patients with any degree of pre-existing renal insufficiency, diabetes mellitus, age greater than 65, volume depletion, sepsis, paraproteinemia, or patients receiving known nephrotoxic drugs. Especially in such patients, IGIV products should be administered at the minimum concentration available and the minimum rate of infusion practicable. While these reports of renal dysfunction and acute renal failure have been associated with the use of many of the licensed IGIV products, those containing sucrose as a stabilizer accounted for a disproportionate share of the total number.[26] [27]

IGIV is contraindicated in individuals who have had anaphylactic or severe systemic reaction to immune globulin or any ingredients in the formulations (e.g., thimerosal, maltose). Epinephrine should be available for immediate treatment of an anaphylactic reaction if it occurs. Most IGIV preparations are contraindicated in individuals with selective IgA deficiencies, since these individuals may have serum antibodies to IgA or may develop antibodies following administration of immune globulin intramuscular (IGIM) or IGIV and anaphylaxis could result following

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Contraindications (cont.)

administration. IGIV occasionally causes a precipitous fall in blood pressure and the clinical manifestations of anaphylaxis; these appear to be related to the rate of administration of the drug and therefore the recommended rate of infusion should not be exceeded. Patients with agammaglobulinemia or extreme hypogammaglobulinemia who have not previously received IGIV or who have received this drug within the preceding 8 weeks are at particular risk of developing these reactions.[28]

IGIV should be administered with extreme caution in patients with a history of cardiovascular disease and/or thrombotic episodes. Patients with thrombotic risk factors, including advanced age, hypertension, cerebrovascular disease, coronary artery disease, diabetes mellitus, high serum levels of monoclonal protein, a history of prolonged immobilization (e.g., bed-bound), and/or a history of thrombotic episodes should be carefully evaluated before IGIV administration and such patients should only receive infusion solutions of IGIV with a protein concentrations of 5% or less. Gamimune N 5% and 10% have a pH of 4 to 4.5 and consideration should be given to the effect of the additional acid load if the drug is used in patients with limited or compromised acid-base compensatory mechanisms.[29]

Clinical Trials

For information on clinical trials that involve Globulin, Immune, visit the ClinicalTrials.gov web site at <http://www.clinicaltrials.gov>. In the Search box, enter: Globulin, Immune AND HIV Infections.

Dosing Information

Mode of Delivery: Intravenous.[30]

Dosage Form: By protein mass in powder form: 1, 2.5, 3, 5, 6, 10, and 12 g of protein.[31]

By mass per volume in solution form: 50 mg per

ml, 100 mg per ml.[32]

Other Names

IGIV[33]

Immune Globulin Intravenous (Human)[34]

IVIG[35]

Further Reading

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Manufacturer Information

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Manufacturer Information (cont.)

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Gammar-P I.V.
Aventis Behring
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Venoglobulin-S
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Gamunex
Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175
(800) 288-8371

Panglobulin
American Red Cross
National Headquarters Biomedical Services
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For More Information

Contact your doctor or an AIDSinfo Health Information Specialist:

- Via Phone: 1-800-448-0440 Monday - Friday, 12:00 p.m. (Noon) - 5:00 p.m. ET
- Via Live Help: http://aidsinfo.nih.gov/live_help Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

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