IVIG THERAPY

Intravenous immunoglobulins in Autoimmune Disease

Immunoglobulins are proteins manufactured in the body that the immune system uses to produce antibodies and various factors. These factors, which are called cytokines, are used to communicate with immune system cells and modify the immune reaction. The term immunoglobulin and antibody are sometimes used interchangeably.

Immunoglobulin Subtypes

There are 4 immunoglobulin subtypes, immunoglobulin M (IgM), immunoglobulin A (IgA), immunoglobulin G (IgG or gamma globulin) and immunoglobulin E (IgE). IgG are the basic component used in the manufacture of long-acting antibodies.

Immune Globulin

Immune globulin products derived from human plasma were first used in 1952 to treat patients with conditions of immune deficiency and chronic lymphocytic leukemia. These first immune globulin transfusions were administered intramuscularly.

In the early 1980s intravenous preparations of immune globulin (IVIG) were first used to treat patients with idiopathic thrombocytopenic purpura, an autoimmune condition causing platelet deficiencies. Today, IVIG is used in many different autoimmune disorders, and most IVIG is produced from pooled human plasma derived from multiple blood donors. IVIG typically contains more than 95 percent unmodified IgG with intact immune signaling functions along with trace amounts of IgA and IgM, cytokines, soluble complement, and HLA molecules.

Intravenous Immunoglobulins (IVIG)

IVIG is an immunomodulator in that it balances the immune system, strengthening immune systems that are too weak and reducing activity in overactive immune systems. IVIG also contains anti-idiotypes that neutralize various autoantibodies. The activities or benefits of IVIG therapy include: modulation of the immune chemical known as complement; suppression of autoantibody production; saturation or blocking of signaling Fc receptors on macrophage cells and B lymphocytes; and suppression of inflammatory chemicals, such as the cytokines, chemokines, and metalloproteinases.

Blocking the Fc signal receptors is one of the primary benefits of IVIG therapy because it interrupts the normal immune process that results in tissue cell destruction in autoimmune disorders. Autoantibodies and toxins are also thought to be neutralized by IVIG. Immune complexes composed of antigens and antibodies are also reduced. In patients with immune deficiency syndromes, IVIG boosts immune function and provides resistance to infection. In patients with autoimmune disorders, IVIG binds to Fc receptors on cells within the reticuloendothelial system modulating their immune effects.
IVIG is approved by the FDA for treating: primary immunodeficiency; autoimmune thrombocytopenia; the vascular disorder Kawasaki disease; hematopoietic stem cell or bone marrow transplantation in patients older than 20 years; chronic B-cell lymphocytic leukemia, prevention of graft vs host disease in transplant patients, and pediatric HIV-1 infection.

**Off Label Uses**

IVIG is also used off-label in the treatment of aplastic anemia, red blood cell aplasia, autoimmune hemolytic anemia, hemolytic disease of the newborn, patients with acquired clotting factor inhibitors, acquired von Willebrand disease, immune-mediated neutropenia (deficiency of polysegmented white blood cells), pemphigoid disorders, refractoriness to platelet transfusions, blood transfusion reactions or consequences, Graves' ophthalmopathy, pretibial myxedema, multiple sclerosis, CIDP, and various systemic autoimmune rheumatological conditions including rheumatoid arthritis, dermatomyositis and systemic lupus erythematosus (SLE), and in patients at risk for infectious diseases become of compromised immune systems such as patients with burns, trauma, low birth weight or HIV infection. IVIG has the potential to benefit any severe autoimmune disease.

**Side Effects**

IVIG therapy can cause a number of potential adverse effects and its cost is often prohibitive. The annual cost of IVIG therapy is often more than $50,000, and in many disorders, there have been no controlled studies to determine efficacy of this treatment. Adverse effects are reported to occur in about 15 percent of patients receiving IVIG. These effects include: fevers, flushing, chest pain, muscle aches, headaches, and shortness of breath. These effects are related to the activation of the complement cascade, which is a normal immune mechanism involved in healing.

The aggregation of immunoglobulin in IVIG triggers this response. Redness, pain, phlebitis, and eczema may also occur at the infusion site. Because some IVIG preparations contain sucrose, the potential for sucrose uptake by renal tubules resulting in renal failure is another potential adverse effect. Worldwide, 114 conditions of acute renal failure resulting in 17 deaths have been reported in patients using IVIG therapy. Preparations using the highest concentrations of sucrose have the highest association with renal failure. Renal failure is most likely to occur in older patients and in patients with impaired renal function.

**Need for Future Studies**

Randomized clinical trials are needed to determine the efficacy of IVIG therapy when used off-label. Trials are especially needed in conditions such as CIDP, in which high doses of IVIG are used. In studies of children using IVIG, immediate adverse reactions are seen in up to 10 percent of patients, and delayed reactions, including fatal reactions,
are seen in up to 41 percent of children. As with any therapy, the potential benefits must be weighted against potential adverse effects.