Intravenous immunoglobulin

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Intravenous immune globulin (IVIG) is a blood product administered intravenously. It contains the pooled IgG immunoglobulins (antibodies) extracted from the plasma of over one thousand blood donors. IVIG's effects last between 2 weeks and 3 months. It is mainly used as treatment in three major categories:

- Immune deficiencies - Immune deficiencies such as X-linked agammaglobulinemia, hypogammaglobulinemia (primary immune deficiencies), and acquired compromised immunity conditions ([secondary immune deficiencies), featuring low antibody levels.
- Inflammatory and autoimmune diseases.
- Acute infections.

Contents

Mechanism of action

IVIG is given as a plasma protein replacement therapy (IgG) for immune deficient patients who have decreased or abolished antibody production capabilities. In these immune deficient patients, IVIG is administered to maintain adequate antibodies levels to prevent infections and confers a passive immunity. Treatment is given every 3–4 weeks. In the case of patients with autoimmune disease, IVIG is administered at a high dose (generally 1-2 grams IVIG per kg body weight) to attempt to decrease the severity of the autoimmune disease.

The precise mechanism by which IVIG suppresses harmful inflammation has not been definitively established but is believed to involve the inhibitory Fc receptor.[1][2] The actual primary target(s) of IVIG in autoimmune disease are still unclear, however. IVIG may work via a multi-step model where the injected IVIG first forms a type of immune complex in the patient. [3] Once these immune complexes are formed, they interact with activating Fc receptors on dendritic cells[4] which then mediate anti-inflammatory effects helping to reduce the severity of the autoimmune disease or inflammatory state.

Additionally, the donor antibody may bind directly with the abnormal host antibody, stimulating its removal. Alternatively, the massive quantity of antibody may stimulate the host's complement system, leading to enhanced removal of all antibodies, including the harmful ones. IVIG also blocks the antibody receptors on immune cells (macrophages), leading to decreased damage by these cells, or regulation of macrophage phagocytosis.

IVIG may also regulate the immune response by reacting with a number of membrane receptors on T cells, B cells, and monocytes that are pertinent to autoreactivity and induction of tolerance to self.[5]

A recent report stated that IVIG application to activated T cells leads to their decreased ability to engage microglia. As a result of IVIG treatment of T cells, the findings showed reduced levels of tumor necrosis factor-alpha and interleukin-10 in T cell-microglia co-culture. The results add to the understanding of how IVIG may affect inflammation of the central nervous system in autoimmune inflammatory diseases. [6]

IVIG is useful in some acute infection cases such as in Kawasaki's Disease and pediatric HIV infection.

IVIG notes

- IVIG is an infusion of IgG antibodies only. Therefore, peripheral tissues that are defended mainly by IgA antibodies, such as the eyes, lungs, gut and urinary tract are not fully protected by the IVIG treatment.
- XLA patients are immune to the most virulent adverse effect, anaphylactic shock, as they do not have the antibodies to react against the treatment. Anaphylactic shock has a higher chance to occur in IgA deficient patients which do have other antibody types.
- In case of recurring side effects, it is recommended to slow the pace of the IVIG administration and to reduce the dosage. It is also advisable to change IVIG brand, as some people react against to a specific brand.
- If the patient is diabetic, he should take into consideration the medium in which the antibodies are solubilized in the IVIG treatment, as some brand solubilize antibodies with high concentrated sugars (such as sucrose and maltose).
- U.S. Food and Drug Administration (FDA) guidelines for IVIG state the product should be:
  - Prepared out of at least 1,000 different human donors.
  - All four IgG subgroups (1-4) should be present.
  - The IgG should maintain biological activity and lifetime of at least 21 days.
  - Does not contain samples which are HIV, hepatitis B, hepatitis C positive.
  - Screened and treated in a manner that destroys viruses.
- IVIG is also considered a modulator of the immune system and was shown to be beneficial in treating numerous autoimmune diseases such as relapsing and remitting multiple sclerosis (MS), myasthenia gravis, pemphigus, polymyositis (PM), dermatomyositis (DM), Wegener's granulomatosis (WG), Churg-Strauss syndrome, chronic inflammatory demyelinating polyneuropathy (CIDP) and more.
- IVIG can be given to pregnant women.
- IVIG is also used as a treatment for unexplained recurring miscarriages. The effectiveness of the therapy is controversial.
- IVIG cost is climbing and well over $50/g. ($10,000 for a 220lbs person at 2g/kg)

Uses of IVIG

Dosage of IVIG is dependent on indication.

For primary immune dysfunction 100 to 400 mg/kg of body weight every 3 to 4 weeks is implemented.

For neurological and autoimmune diseases 2 grams per kilogram of body weight is implemented for

three to six months over a five day course once a month. Then maintenance therapy of 100 to 400 mg/kg of body weight every 3 to 4 weeks follows.

FDA-approved indications

- Allogeneic bone marrow transplant
- Chronic lymphocytic leukemia
- Idiopathic thrombocytopenic purpura
- Pediatric HIV
- Primary immunodeficiencies
- Kawasaki disease
- Chronic inflammatory demyelinating polyneuropathy (CIDP)
- Kidney transplant with a high antibody recipient or with an ABO incompatible donor

In 2004 the FDA approved the Cedars-Sinai IVIG Protocol which has been 90-95% successful in removing antibodies from the blood of kidney transplant recipients so that they can accept a living donor kidney from any healthy donor no matter blood type (ABO incompatible) or tissue match.

In Phase III testing in the US (as of December 2008)

- Alzheimer's Disease

Off-label uses

- Chronic fatigue syndrome
- Clostridium difficile colitis
- Dermatomyositis and polymyositis
- Graves' ophthalmopathy
- Guillain-Barré syndrome
- Muscular Dystrophy
- Inclusion body myositis
- Lambert-Eaton syndrome
- Lupus erythematosus
- Multifocal motor neuropathy
- Multiple sclerosis
- Myasthenia gravis
- Neonatal alloimmune thrombocytopenia
- Parvovirus B19
- Pemphigus
- Post-transfusion purpura
- Renal transplant rejection
- Spontaneous Abortion/Miscarriage
- Stiff person syndrome
- Opsoclonus Myoclonus
- Severe sepsis and septic shock in critically ill adults[7]
- Toxic epidermal necrolysis
- In chronic lymphocytic leukemia and multiple myeloma, as well as various rare deficiencies of immunoglobulin synthesis (e.g. X-linked agammaglobulinemia, hypogammaglobulinemia), IVIG is administered to maintain adequate immunoglobulin levels to prevent infections.

Complications and side effects

Although routine use of IVIG is common practice, sometimes for long term treatments, and is considered safe, complications of IVIG therapy are known and include:

anaphylactic shock, especially in IgA deficient patients, who by definition can still produce IgG antibodies. IgA deficient patients are more likely to produce IgG against the IVIG administration than normal patients.

- headache
- dermatitis - usually peeling of the skin of the palms and soles
- infection (such as HIV or viral hepatitis) by contaminated blood product; there is also an as yet unknown risk of contracting variant CJD (vCJD).
- pulmonary edema from fluid overload, due to the high colloid oncotic pressure of IVIG
- allergic/anaphylactic reactions
- damage such as hepatitis caused directly by antibodies contained in the pooled IVIG
- acute renal failure
- venous thrombosis
- aseptic meningitis

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