

Clinical Application and Functional Mechanisms of Intravenous Immunoglobulin: an Overview

Kaveh Tari¹, Ali Jalili², Ali Akbar Pourfathollah³, Amir Atashi^{1*}
Saeid Abroun¹, Masoud Soleimani¹

1. Department of Hematology, Faculty of Medical Sciences, Tarbiat Modares University, Tehran, Iran.

2. Department of Immunology and Hematology, Faculty of Medicine, Kurdistan University of Medical Sciences, Kurdistan, Sanandaj, Iran.

3. Department of Immunology, Faculty of Medical Sciences, Tarbiat Modares University, Tehran, Iran.

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Previous, Intravenous Immunoglobulin (IVIG) has been used for treatment of patients with immunodeficiency. However, recent studies have shown that IVIG is a suitable approach for treatment of inflammatory and autoimmune diseases. Although the exact mechanism of IVIG action is not well known, but recent findings have demonstrated the IVIG effects on expression and function of FC receptors of immunoglobulins, modulation of complement activation and cytokines. In addition, IVIG regulates the cell proliferation, and it can affect T, B and dendritic cells differentiation. Correspondingly, its side effects are classified into three categories, including immediate side effects (which can occur during infusion, including anaphylaxis reactions, facial flushing, and dyspnea), delay effects (which occurs in a few hours or a few days after the injection as side effects on the skin, lung, kidney, aseptic meningitis, arthritis, cerebral symptoms, leukopenia, and hemolysis) and late side effects (such as transmission of infectious agents). In this review, we are summarizing recent applications, mechanism and side effects of IVIG.

Keywords: Intravenous immunoglobulin, replacement therapy, immune modulation, side effects

Immunoglobulin products were produced of human's plasma since 1952, and they were used for the treatment of immune deficiency. Intravenous immunoglobulin (IVIG) products are sterile, purified from human's plasma accumulation and typically contain more than 95% immunoglobulin G (IgG). However, there are minor amounts of immunoglobulin A (IgA) or immunoglobulin M (IgM) (1). Relatively, IVIG contain large amounts

of different types of antibodies against foreign antigens as well as natural antibodies (natural antibody). A natural antibody recognizes many self-antigens, which is believed to be related to their immunomodulatory effects. IVIG has several functions that include modulation of the complement system, inhibition of idiopathic antibodies, typically saturate Fc receptors on macrophages, and inhibits multiple inflammatory

* Correspondence: Department of Hematology, Faculty of Medical Sciences, Tarbiat Modarres University, Tehran, Iran.
E-mail: Atashia@modares.ac.ir

mediators such as cytokine, chemokine and metalloproteinase proteins. IVIG also contains cytokines and antibodies with unclear clinical features (perhaps neutralizing) against macrophage-granulocyte colony stimulating factor, Inter-IFN and IL-6 (2, 3).

IVIG is used to treat various diseases, including autoimmune, infectious, and idiopathic diseases (unknown cause). Also, IVIG is prescribed for treatment of graft-versus-host disease (GVHD) and idiopathic thrombocytopenia purpura (ITP), Kawasaki and Guillain Barre Syndrome and polymyositis/ dermatomyositis. Beneficial effects of intramuscular immunoglobulin as preventive therapy in patients with immune deficiency syndrome has also been proven (1).

Natural antibodies

Natural antibodies that are mainly produced by B1 cells are part of the serum antibodies. It is estimated that approximately 5-15% approximately 5-15% of spleen B cells produce antibodies naturally (4, 5).

The main function of this antibodies is regulating immune homeostasis as their main role is to prevent the proliferation and the proliferation of self-reactive B cells (auto reactive) (4).

In addition, these antibodies bind to microbial epitopes that are similar to self-epitopes, thereby hindering the development of autoimmune diseases. Many natural antibodies against molecules involved somehow in immune system regulation are known. For example, natural antibodies against Ig, T cells receptor, CD5, CD4, CD95, FCR, MHC, cytokines and their receptors have been identified (6-9).

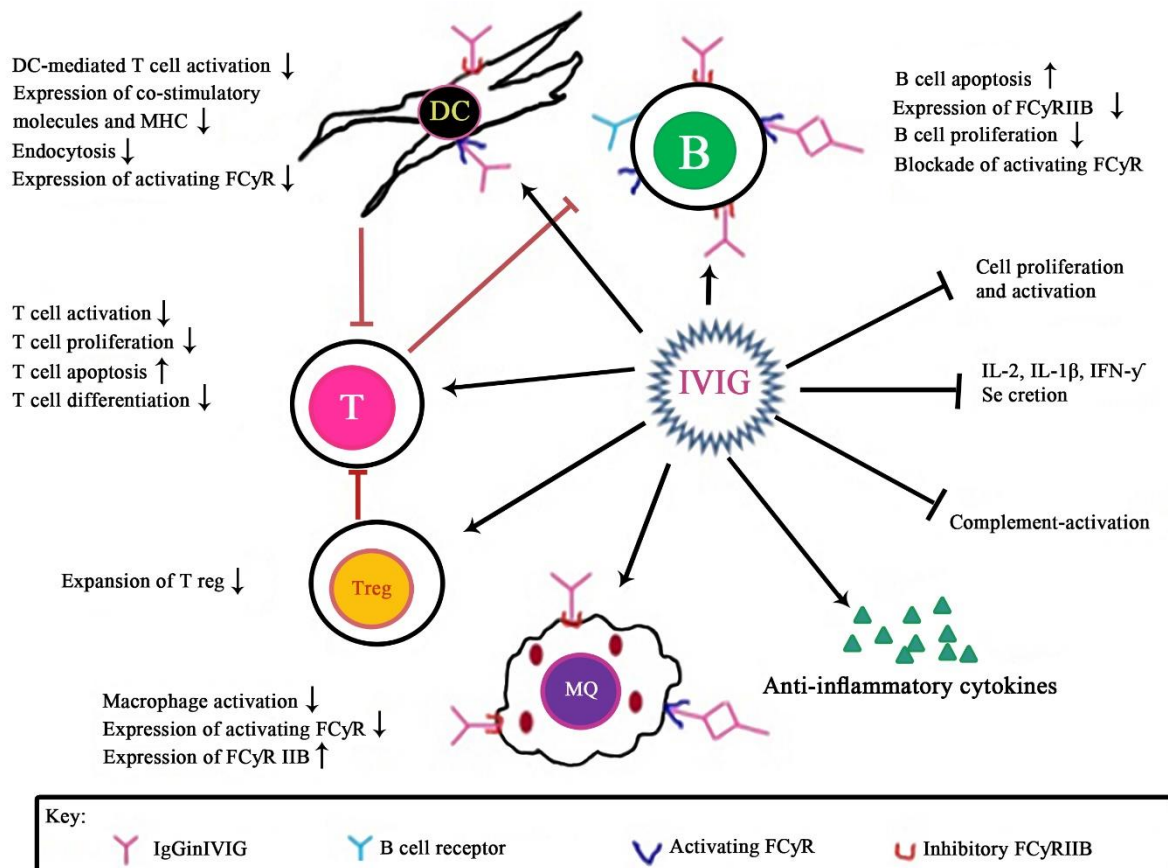


Figure 1. IVIG effects on immune cells, IVIG affects directly and indirectly the immune system, immune cells and cytokines. On one hand IVIG reduces cytokine production, inhibits the complement system, immune cells growth and the differentiation and maturation of T cells and DCs. On the other hand IVIG increases the inhibitory receptors FCyRIIB, increases Treg cells, macrophages and B cells and suppresses the binding of antibodies to FCyRs the surface of these cells.

Functional mechanisms of IVIG

The mechanisms of action of IVIG are very complex, as shown in (Figure 1). The functions of IVIG include modulating the expression and function of FC receptors, affecting the complement system and cytokine network activity, modulating maturation, differentiation and function of dendritic, T and B cells. Some of these IVIG functions are briefly described below.

Effect on antibodies FC receptor

IgG has a Fab portion that is responsible of identifying the antigenic index and a sector that contributes the binding of IgG to the receptor of FC IgG () on the surface of phagocytic cells, particularly macrophages. So far, four FC γ Rs types, FC γ RI, FC γ RII, FC γ RIII and FC γ RIV are known. Among them, FC γ RI, FC γ RII A, FC γ RIII and FC γ RIV act as activating receptor while FC γ RIIB acts as inhibiting receptor (10).

The immune response modulating activity of IVIG is related to the interaction between IVIG and FC γ Rs of target cells. For example, in ITP disease, the binding of FC portion of IgG molecules to macrophages of reticuloendothelial system, leads to the removal of the platelets. During IVIG treatment, many antibodies present in IVIG, bind to the FC γ Rs of macrophages and inhibit the binding of anti-platelet antibodies. In addition, by saturating the FC γ Rs of macrophages, IVIG may increase the expression of FC γ R IIB on macrophages (11).

IVIG effects on dendritic cells

Dendritic cells (DCs) have a crucial role in stimulating T cells. An important part of the immune suppressing effects (immunosuppression) of IVIG is related to the inhibitory effect of the antibody on T cells. IVIG inhibits T cell differentiation, decreases IL-12 production, and increases IL-10 production. It also reduces the expression of co-stimulatory

molecules and finally, reduces the production of cytokines by DCs (12, 13).

For example, in patients with systemic lupus erythematosus (SLE), usage of high-dose IVIG can prevent DCs differentiation and decreased expression of CD80, MHC II and CD86 on the cell, while active DCs are reduced. However, low dose IVIG is mainly used for increasing DCs activity during the treatment of immune deficiency disorders. For instance , DCs differentiation in patients with common variable immune deficiency (CVID) is impaired, but when IVIG is given to patients, the molecules associated with DCs activity such as CD86, CD40, CD86 and MHCII are increased in many subjects (14, 15).

IVIG effects on the complement system

The IVIG inhibits the formation of the membrane attack complex (MAC). It also can bind to the C3b and C4b to prevent the molecules' meeting on the membrane of target cells (16).

Cytokine production modulation and performance

One of the main actions of IVIG in the treatment of neuromuscular disorders, such as myasthenia gravis and inflammatory myopathies, is modulating cytokine production. Also, IVIG causes IL-1 receptor antagonist (IL-1ra) production increase by monocytes. IVIG also reduces the amount of serum IL-1b in patients with Guillain-Barre syndrome (17).

Laboratory criteria for the use of intravenous immunoglobulin

There are several experimental criteria that predispose patients receiving IVIG. The most important criteria include specific hypogammaglobulinemia (IgG levels less than 200 mg/ dl or total immunoglobulin less than 400 mg/ dl), the absence or low levels of antibodies, the lack of response or

Table 1. Cases IVIG use as replacement therapy

Bruton's agammaglobulinemia	Chronic lymphocytic leukemia
Common variable immunodeficiency	Multiple myeloma
Hyper-IgM syndromes	HIV infection
Severe combined immunodeficiency	

poor response to tetanus and pneumococcal vaccines and lack of antibody response to infection before injecting these products. Also, there are several laboratory tests to be performed, among which the evaluation of liver function, the performance of the kidney, complete blood count (CBC) to investigate cell differentiation , hepatitis screening to assess the risk of disease transmission by IVIG and assessment for detection of immunoglobulin IgA deficiency are the most Important ones (3).

IVIG applications

IVIG was primarily used for the treatment of immune deficiency, but it is also used for many autoimmune and inflammatory diseases treatment now. IVIG is used in two different doses. The low-dose is known as replacement therapy and following the injection of 500 mg/ Kg of patient body weight, serum IgG level increases to 12-14 mg/ml (18). –In high-dose therapy, also called immune modulator, the amount of serum IgG reaches 25-35 mg/ml upon the injection of 2 g/ Kg of body weight of IVIG into the patient (19).

The applications of any of the above IVIG treatment methods are briefly described below.

Replacement therapy

In this method, IVIG is used to treat patients with immunodeficiency. It has been shown that IVIG infusion to patients with primary defects of the immune system helps to protect them against respiratory infections. It appears that a serum IgG level above 500 mg/ dl is sufficient to prevent respiratory infections. Furthermore, the injection of

300-500 mg/ Kg of patient weight in a month is essential to achieve this serum level of IgG (20, 21).

In many secondary immune deficiencies that are mainly due to the lack of antibodies, IVIG is used as replacement therapy. For B cell cancers such as chronic lymphocytic leukemia (CLL) and multiple myeloma, it is noted that prophylactic treatment with IVIG reduces the incidence of infectious diseases in those patients. Also, IVIG replacement therapy in children with HIV infection reduces mortality and it can improve the quality of life. Recent studies suggest that IVIG infusion in patients who received bone marrow transplantation leads to a reduction of infections, septicemia, acute GVHD and need to platelets (22-24).

(Table 1) summarizes the diseases in which IVIG is routinely given as replacement therapy.

Immune modulation therapy

High-dose IVIG is used for the treatment of autoimmune and inflammatory diseases which are summarized in (Table 2).

Blood diseases

The first report of treatment of patients with ITP by IVIG, was introduced in 1981 by Imbach et al. Results of this research indicate that administration of IVIG resulted in rapid improvement in children with ITP (25).

Phagocytic cells such as monocytes and macrophages that have a large number of receptors for FC γ R have been seen in the spleen. These cells can attach to opsonized platelets and destroy them. Although platelets are destroyed in most organs, but

Table 2. Cases of IVIG treatment as immune modulator

Hematological diseases	Neuroimmunological diseases	Rheumatic diseases	Transplantation	Others
Acquired von Willebrand's disease	Guillain–Barre' syndrome	Kawasaki disease	Graft versus host disease (GVHD)	Toxic epidermal necrolysis
Antifactor VIII autoimmune disease	Chronic inflammatory demyelinating	ANCA-positive systemic vasculitis	Antibody-mediated rejection (AMR) of the graft	Autoimmune skin blistering diseases
Parvovirus B19-associated red cell aplasia	polyneuropathy	Systemic lupus erythematosus (SLE)		Streptococcal toxic shock syndrome
Autoimmune hemolytic anemia	Multifocal motor neuropathy	Felty's syndrome		Sepsis syndrome
Autoimmune neutropenia	Multiple sclerosis	Rheumatoid arthritis and		
Idiopathic thrombocytopenic purpura (ITP)	Myasthenia Gravis	Recurrent spontaneous abortions		
Acquired immune thrombocytopenia		Antiphospholipid syndrome Dermatomyositis		

splenectomy in ITP is a successful treatment in most cases. In 1982, Fehr and his colleagues showed that in cases of ITP without splenectomy, injected IVIG can decrease the clearance of red blood cells sensitized with antibodies labeled with radioactive materials inside the body (26).

Possible mechanisms of action of IVIG include: 1- the presence of small amounts of Ig dimers and multimers in the IVIG products which however are important and are able to bind to FcRs and therefore inhibit platelets clearance. 2- IgG molecules present in IVIG might bind either to host antigens and form immune complexes and/ or to, FcRs competing with platelets sensitized with monoclonal antibodies, resulting in a longer lifetime of platelets (27).

Rheumatic diseases

Several clinical and laboratory findings have shown that IVIG is a reliable treatment for many rheumatic diseases. For example, administration of IVIG in early Kawasaki disease is beneficial. It also significantly improves muscle strength and neuromuscular symptoms in patients with dermatomyositis and polymyositis (28).

Considerably, it has been shown that IVIG is a successful treatment for patients with vasculitis with Anti-neutrophil antibody (anti neutrophil cytoplasmic antibody-positive systemic vasculitis) who do not respond to conventional therapy. Despite the promising findings, the therapeutic effect of IVIG in many other rheumatic diseases such as SLE and Sjogren's syndrome is not fully proven yet (29)

Although some studies have shown the efficacy of IVIG in treatment and recovery of the symptoms of symptoms of SLE and Sjögren's syndrome (30, 31).

Mortality associated with coronary heart disease in many autoimmune diseases such as rheumatoid arthritis and lupus is higher than in the normal population. In these patients, administration of IVIG helps to prevent atherosclerosis progression. It has been shown that IVIG prevents the formation of foam cells in vessels as well as neutralizing antibodies against oxidized LDL (anti-ox LDL) (32).

Graft

Recent studies have shown that high-dose IVIG for people who have received allogeneic bone marrow transplantation can reduce the disease severity as well as GVHD, and prevents them from getting infections (33).

The new findings suggest that IVIG can increase the lifetime of renal and heart transplantation in patients who previously have been sensitized to HLA antigens and present anti-HLA antibodies in their sera. So, administration of IVIG is effective in reducing the severity of antibody-mediated transplant rejection (34).

Studies in animal models showed that administration of IVIG resulted in greater survival of xenograft transplantation (pigs to monkeys) (35).

Side effects

Side effects of IVIG are classified into three categories, including immediate side effects (which can occur during infusion, including anaphylaxis reactions, facial flushing, and dyspnea), delay effects (occur in a few hours to few days after the injection in the skin, lung, kidney, aseptic meningitis, arthritis, cerebral symptoms, leukopenia, and hemolysis) and late side effects (such as transmission of infectious agents) (36).

The most common side effects that have been

observed immediately following injection, include headache, flushing, chills, wheezing, tachycardia, lower back pain, nausea, and hypotension. If hypotension occurs during injection, the injection should be discontinued or continued slowly (37). If symptoms are anticipated, the intravenous hydrocortisone and antihistamines may be given to the patient. Side effects of IVIG infusions in a classification based on the severity of mild and severe complications can be divided into two categories. The most severe side effects and disorders include headache, nausea, vomiting, restlessness, muscle aches, low-grade fever, anxiety, abdominal cramps, rash, and leukopenia in different regions of the body and severe complications include acute renal failure, stroke, thrombosis deep venous, pulmonary embolism, anaphylaxis and aseptic meningitis (38).

Complications occurring in IVIG infusions are varied and in numerous reports, the incidence has been reported between 1-81%. While others reported an incidence of 30-40% (39). Complications depend on infusion rate, age, injection conditions, dose, concentration of IgA, and concentration of stabilizing agent (40).

In some cases, such as acute renal failure and renal disease, risk factors such as older age (more than 65 years), diabetes mellitus, hypertension and increased blood viscosity, have a crucial role in complication occurrence (41).

In addition, IVIG can trigger reactions in patients with IgA deficiency. This disease occurs in a one patient out of 500 to 1000. Acute inflammatory response to IVIG infusions occur soon. Anaphylaxis associated with susceptibility to IgA in patients with IgA deficiency can be prevented by using immunoglobulin without IgA. Non-infectious meningitis is a rare but well known complication of IVIG treatment. This complication

may be associated with fever, stiff neck, headache, dizziness, nausea, and vomiting (42).

IVIG therapy can also cause hyperproteinemia, increased serum viscosity and decreased false blood sodium, after its injection. Berard and colleagues, according to a survey conducted on four patients have demonstrated that IVIG infusion can cause hemolytic anemia (43).

It has been observed in During Guillain-Barre syndrome treatment, acute encephalopathy caused by IVIG has been observed (44). In addition, high-dose IVIG can expedite acute myocardial infarction (45).

Conclusions

IVIG is one of the drugs that can modify the immune system and is used to treat diseases such as blood disorders and rheumatic diseases. Such mechanisms can be used to modulate the immune system and reduces cytokines production. However, this drug has remarkable side effects among which, anaphylactic shock, aseptic meningitis and brain disorders are the most important ones.

Conflict of interests

The authors declared no conflict of interests.

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