

The Use of Intravenous Immunoglobulins (IVIG) in Immunological Mediated Diseases and Possible Mechanisms of Actions

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Abstract Intravenous immunoglobulin (IVIG) is a product prepared from fractionation of pools of thousands of plasma donations collected at blood transfusion services. IVIG has been used in the treatment of neurological disorders, primary and secondary immunodeficiency, skin disorders, autoimmune disorders, immunologic abortion, and as anti-cancer and anti-inflammatory therapy. In this paper we listed a number of diseases for which the use of IVIG has been successful and the most mentioned mechanisms of actions of this immunotherapy. IVIG has different modes of actions involving interference with activation of complement components and the cytokine network; effects on regulatory T cells (Tregs) subset; expression of Fc receptors; modulation of idiotype network; and activation, proliferation and effector functions of B and T lymphocytes and of antigen-presenting cells such as dendritic cells and macrophages. We concluded that IVIG has proven to be efficacious in the treatment of immunodeficiency, autoimmunity, infections and inflammatory disorders over the last three decades. To date IVIG has been used to treat more than 80 diseases. Although some of the mechanisms of actions of IVIG are obscure in nature, the fact that many patients improved with it when all other options of treatment were exhausted, make the use of IVIG an important alternative. On the other hand, treatment with IVIG is expensive. We are hopeful that in near future new horizons will be open for the acquisition and use of a cheaper IVIG to treat weak immune system or as immunosuppressive drug in the treatment of autoimmune and inflammatory disorders.

Keywords: intravenous immunoglobulins (IVIG), immunological diseases, immunotherapy, autoimmunity, immunodeficiency

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1. Introduction

IVIG is a product prepared from fractionation of pools of thousands of plasma donations collected in blood transfusion services [1-4]. Along with purified IgG, other proteins are present in the IVIG in small amounts, for example: traces of IgM and IgA [5], immunomodulating peptides, and various cytokines [6]. IVIG demand worldwide is coupled with shortages and concerns about potentially infected blood from which it may be prepared [7]. This has obligated National Health Authorities to produce guidelines for the better use of IVIG, for example England and Wales regulations [8] and the Canadian guidelines [9]. In this paper we listed a number of diseases for which the use of IVIG has been successful and the most mentioned mechanisms of actions of this immunotherapy.

2. Use of IVIG in Immunological-Mediated Diseases

As shown in Table 1, IVIG has been used in the treatment of neurological disorders, primary and secondary immunodeficiency, skin disorders, autoimmune disorders, immunologic abortion, and as anti-cancer and anti-inflammatory therapy.

The worldwide consumption of IVIG in 1980 was 300 kg per year and it increased to 100 tonnes per year in 2010 [24]. The mechanisms of action of IVIG reflect the importance of natural antibodies in the maintenance of immune homeostasis [25]. Side effects from IVIG are mild and transient and mostly rare. Adverse effects can be minimized by administration of slow infusion rate of 0.4 g/Kg body weight IVIG for 5 consecutive days, and given in monthly cycles. The high price is the only downside of IVIG treatment [27]. The risk of transmission of microorganisms appears only theoretical [31].

IVIG was not recommended for 8 conditions including amyotrophic lateral sclerosis, autism, adrenoleukodystrophy, critical illness polyneuropathy, intractable childhood epilepsy, inclusion body myositis, paraproteinemic neuropathy (IgM variant), and POEMS syndrome (this name is an acronym deriving from some of the main features of this

syndrome: Polyneuropathy, Organomegaly, Endocrinopathy or Edema, M-protein and Skin abnormalities). Dissemination and development of evidence-based clinical practice guidelines may facilitate appropriate IVIG use [9]. The immunomodulatory mechanisms of

action of IVIG are not well-understood and unclear because of the diversity and often contradictory Fc, F(ab')(2), and non-IgG-related mechanisms. Results obtained in various *in vitro* and *in vivo* experimental models have been contradictory [3].

Table 1. Use of IVIG in a number of immunological mediated-diseases

Diseases	References
Immune thrombocytopenic purpura (ITP)	8, 10, 11,2, 3, 16, 22-24, 28
Guillain-Barré syndrome	8, 10, 16, 25, 28, 32, 54
Chronic inflammatory demyelinating polyneuropathy	8-10,16, 28, 32
Systemic lupus erythematosus (SLE)	8, 10, 25, 29
Idiopathic inflammatory myopathies	8
ANCA-associated vasculitides	8
Multiple motor neuropathy	10, 9
Multiple sclerosis	10, 9
Myasthenia gravis	10, 9, 16, 25, 28, 32
Kawasaki disease	10, 16, 25, 28, 32, 38
Autoimmune uveitis	10
Dermatomyositis	10, 9, 13-15, 16, 28, 32
Systemic sclerosis	10
Sjögren syndrome	10
Antiphospholipid antibody syndrome	10
Still's disease	10
Acute disseminated encephalomyelitis	9
Diabetic neuropathy	9
Lambert-Eaton myasthenic syndrome	9
Opsoclonus-mycoclonus	9
Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections	9
Polymyositis	9, 13-15
Rasmussen's encephalitis	9
Stiff person syndrome	9
Primary immunodeficiency disorder	11, 21, 22, 25, 26, 30, 37, 54
Secondary immunodeficiency disorder	11, 2, 25, 26, 30, 37, 54
Chronic lymphocytic leukemia	11, 2
Bone marrow transplantation	11, 28, 32
Treatment-induced neutropenia and thrombocytopenia	11
AIDS	11
Autoimmune thyroiditis	12
Inclusion-body myositis	13-15
Graft versus host disease	16, 28
Recurrent pregnancy loss	17, 19, 20
Cancer	17, 18
Severe infections	21, 25, 52, 53
Toxic epidermal necrolysis	33-35
Stevens-Johnson syndrome	33-35
Multiple sclerosis	36
Neonatal hemochromatosis	55

3. Mechanisms of Actions of IVIG

The gamma globulin therapy began in 1930 when, in Finland, Cohn, Bruton and Imbach carried out the treatment of pneumococcal pneumonia in patients with equine serum. This improved notably the survival rate of this type of pneumonia. Originally IVIG was used to treat immunodeficiencies. Later, the IVIG use was extended for the treatment of autoimmune disorders and inflammatory diseases [27]. IVIG has been used successfully to treat SLE patients with a broad spectrum of clinical manifestations, such as pancytopenia, refractory thrombocytopenia,

secondary antiphospholipid syndrome, central nervous system (CNS) involvement and lupus nephritis [29]. The different mechanisms of actions of IVIG are listed in Table 2.

IVIG has different modes of action that involve interference with activation of complement components and the cytokine network; effects on Tregs, expression of Fc receptors, modulation of idiotype network, among others mechanisms as shown in Table 2. The IVIG therapeutic effects most likely reflect the functions of natural antibodies, which play an important role in the maintenance of the immune homeostasis in healthy individuals.

Table 2. Mechanisms of actions of IVIG in immunological mediated disorders

Mechanisms of action of IVIG	References
Effects of IVIG on activated B lymphocytes	3, 49
Possible involvement of autoantibodies of IgG isotype (auto-IgG) in the immunomodulatory effects of IVIG	3, 12
Inhibition by F(ab)2 from IVIG of the binding of F(ab)2 autoantibodies to their autoantigens	39
Anti-idiotypic specificities that may not necessarily be detectable in plasma from single healthy individuals	39, 41, 16
Retention of autoantibodies on affinity columns of Sepharose-bound F(ab')2 fragments of IVIG	40
Recognition of the same idiotypic determinants on autoantibodies by heterologous anti-idiotypic antibodies and by IVIG	40
Interaction with V regions of autoantibodies and with surface molecules of lymphocytes in vitro	12, 41-43
Infusion of IVIG results in suppression of specific auto-IgG clones in vivo	41, 42, 44, 45, 50
IVIG reacts with framework and constant regions of the beta chain of the alpha beta T cell receptor	42, 45
Interaction of the IgG Fc fragment with Fc receptors on leucocytes and endothelial cells	4, 43, 7, 47
Interaction of infused IgG with complement proteins	4, 43-46, 7, 16, 17, 47, 21, 49
Monocyte and lymphocyte modulation of synthesis and release of cytokines and cytokine antagonists	4, 43, 45, 22, 49, 26
Modulation of cell proliferation and apoptosis	43, 7
Remyelination	43, 7
Neutralizes pathogenic autoantibodies	44-46, 7, 17, 22, 27
Interferes with antigen presentation	44, 49
Functional blockade of Fc receptors on splenic macrophages	45, 16, 17, 21, 26
Interaction with surface molecules of T cells, such as the alpha beta TCR, CD5, CD4, non-polymorphic determinants of MHC class I molecules and adhesion molecules of T and B cells	45, 7, 46, 16
Selection of immune repertoires	7
Neutralisation of bacterial toxins and superantigens	46, 21
Effects on the Fas apoptotic pathway via agonistic and antagonistic anti-Fas autoantibodies	16
Hindrance of natural killer cell activity	17, 49, 27
Inhibition of matrix metalloproteinase-9	17
Suppression of NFkB activation and Ikb degradation	17
G1 cell cycle arrest	17, 47, 48
Prevention of tumor growth	17, 27
It might increase the survival rate of the embryo in the uterus	19, 20, 27
IVIg protects keratinocytes from pathogenic autoantibodies by preventing the autoantibody-induced of apoptosis and oncosis	33
Enhances the expansion of Tregs, which induce of suppressive functions	51, 36-38

The use of IVIG as a therapeutic option in arthritis is significant. In the United States of America the prevalence of this disorder is quite high and varies according to ethnicity. Helmick and colleagues reported in 2008 that 21% of USA adults (46.4 million persons) were found to have self-reported doctor diagnosed arthritis. They estimated that rheumatoid arthritis affects 1.3 million adults, juvenile arthritis affects 294,000 children, spondyloarthropathy affect from 0.6 million to 2.4 million adults, systemic lupus erythematosus affects from 161,000 to 322,000 adults, systemic sclerosis affects 49,000 adults, and primary Sjögren's syndrome affects from 0.4 million to 3.1 million adults [56]. All of these conditions may benefit from the use of IVIG, in addition to many other autoimmune disorders, immunodeficiency and inflammatory disorders. The IVIG worldwide shortage is an issue of concern in specialized areas of medicine that has to be overcome in the near future.

4. Conclusions

We concluded that IVIG has proven to be efficacious in the treatment of immunodeficiency, autoimmunity, infections and inflammatory disorders. To date more than 80 diseases have benefited from the use of IVIG. Its modes of action must be clarified for a wider and better use in immunological mediated diseases.

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