

Mechanisms of action of intravenous immune serum globulin in autoimmune and inflammatory diseases

Mark Ballow, MD *Buffalo, N.Y.*

Intravenous immune serum globulin (IVIG) is primarily used as replacement therapy in patients with hypogammaglobulinemia. It has been over 15 years since IVIG was first shown to be effective in the treatment of patients with autoimmune thrombocytopenic purpura. Over the past decade, IVIG has been used in the treatment of a number of autoimmune and systemic inflammatory disorders. Although the use of IVIG in many of these immune-mediated disorders was purely speculative initially, we now have a much better understanding of the mechanisms by which IVIG exerts its effects in these autoimmune diseases. IVIG exhibits a number of immune modulatory activities that are mediated by the Fc portion of IgG through the Fc γ receptor on a variety of cell types. Although the major component in IVIG is IgG, other minor components such as solubilized lymphocyte surface membrane determinants and specific antibodies to lymphocyte surface molecules may have important immunoregulatory effects on T- and B-cell immune responses. This review discusses the proposed mechanisms of action of IVIG in autoimmune and inflammatory disorders. (*J Allergy Clin Immunol* 1997;100:151-7.)

Key words: Intravenous immune serum globulin (IVIG), γ -globulin, immune therapy, autoimmune disease, immune modulation, cytokines, complement, Fc receptors

The objective of this review is to present the mechanisms by which intravenous immune serum globulin (IVIG) may modulate autoimmune and various inflammatory disease processes. To achieve this objective I will discuss several autoimmune disorders in human beings, and in some cases animal models of disease, which exhibit various immune pathogenic processes, and develop the mechanisms by which IVIG may be acting in modulating these diseases.

Fc RECEPTOR BLOCKADE AND MODULATION

In 1981 Imbach et al.¹ made a serendipitous observation that the infusion of IVIG in children with immune thrombocytopenia (ITP) produces a marked improvement in platelet counts. ITP was the first autoimmune

Abbreviations used

ANCAs:	Anti-neutrophil cytoplasmic antibodies
EAE:	Experimental allergic encephalomyelitis
IL-1ra:	IL-1 receptor antagonist
ITP:	Immune thrombocytopenic purpura
IVIG:	Intravenous immune serum globulin
KS:	Kawasaki syndrome
TNF:	Tumor necrosis factor

disorder in which IVIG was used as an effective treatment modality. The mechanism by which IVIG increases the platelet count is thought to occur by blockade of the Fc receptors on phagocytic cells, which prevents the removal of sensitized platelets by the reticuloendothelial system in the liver and spleen. This leads to prolonged survival of autoantibody-coated platelets^{2,3} and explains the very rapid changes in platelet counts that occur with the administration of IVIG.⁴ In a recent study by Debré et al.,⁵ 11 of 12 children with acute ITP treated intravenously with purified Fc γ fragments prepared from Cohn fraction II γ -globulin showed an increase in platelet counts. These studies with Fc γ fragments provide direct support for the hypothesis that Fc γ receptor blockade by IVIG is responsible for the improvement of the platelet counts in ITP. In addition, these investigators showed a rise in serum-soluble Fc γ RIII (CD16) concentrations, which correlated with the rise in the platelet count. No sFc γ RIII was detected in the Fc γ fragment preparation, which suggested that the source of these sFc γ RIII receptors was the phagocytic cells of the reticuloendothelial system. An additional mechanism postulated by these investigators was that these soluble Fc γ receptors could act as competitors with the cell membrane Fc γ receptors of the reticuloendothelial system and prevent the clearance of circulating IgG-sensitized platelets.

IVIG is mostly monomeric IgG (>95%) with small amounts of dimeric and aggregated IgG. However, after infusion, some of the monomeric IgG becomes dimeric or complexed to circulating antigens found in the patient. IgG monomers predominantly bind to Fc γ RI found mainly on monocytes; whereas Fc γ RII and Fc γ RIII on monocytes, neutrophils, and other cells interact with polymeric IgG or immune complexes. Fc γ R expression and receptor-mediated phagocytosis are decreased in peripheral blood monocytes treated with

From the Division of Allergy, Immunology and Pediatric Rheumatology, Children's Hospital of Buffalo, State University of New York at Buffalo, School of Medicine and Biomedical Sciences.

Received for publication Dec. 18, 1996; revised Apr. 8, 1997; accepted for publication Apr. 9, 1997.

Reprint requests: Mark Ballow, MD, Division of Allergy, Immunology and Pediatric Rheumatology, Department of Pediatrics, Children's Hospital, 219 Bryant St., Buffalo, NY 14222.

Copyright © 1997 by Mosby-Year Book, Inc.

0091-6749/97 \$5.00 + 0 1/1/82529

polymeric IgG.^{6,7} Kimberly et al.⁸ used peripheral blood mononuclear cells to demonstrate that IVIG decreased Fc γ -receptor affinity. In addition to Fc receptor blockade, Fc γ -receptor downregulation or changes in receptor affinity are other mechanisms by which IVIG may be operating in ITP and other autoimmune cytopenias. Other monocyte Fc receptor-mediated functions are also diminished by IVIG. For example, monocyte-dependent antigen-induced T-cell proliferative responses are decreased.⁶ Changes in accessory cell function mediated by modulation of the Fc γ -receptor family may be important in affecting both T- and B-cell immune responses.

INHIBITION OF B-CELL FUNCTION MEDIATED THROUGH THE Fc γ RIIB RECEPTOR

Fc receptor blockade does not explain the long-term changes produced by IVIG in patients with ITP. Several studies have reported a decrease in the levels of antiplatelet antibody in patients with ITP treated with IVIG.^{2,3} Consequently, it has been proposed that IVIG-induced immunoregulatory effects on the function of T and B cells results in a decrease in antiplatelet antibodies after IVIG therapy. The addition of IVIG *in vitro* suppresses lymphocyte proliferative responses to a variety of T-cell mitogens.^{9,10} This suppressive activity is dependent on the Fc portion of IVIG in that F(ab')₂ fragments of IgG have no effect. Other studies suggest that the target cell for inhibition is the B lymphocyte rather than the T cell.^{11,12} A number of studies have demonstrated that the inhibitory effect is mediated by the binding of IVIG to the Fc γ receptors on B cells.^{7,9,13,14}

The mechanism for Fc receptor-mediated suppression of B-cell function by IVIG has recently been elucidated. Although immune complexes can be potent activators of phagocytic cells through the Fc γ RIIB, immune complexes can be negative regulators of B cells as a consequence of coligation of the B-cell antigen receptor and the receptor Fc γ RIIB.¹⁵ This FcR "off signal" can be circumvented by IL-4 or blocking the Fc γ RII¹⁶ receptor with specific antibodies to this receptor. The mechanism for this "negative signaling" in B cells is thought to be mediated by tyrosine phosphorylation of a novel inositol polyphosphate 5-phosphatase (SHIP)¹⁷ and inhibition of Ca⁺⁺ influx.¹⁸ Coligation of the B-cell antigen receptor and Fc γ RIIB could be induced by the binding of IVIG through the Fc moiety of the IgG to the Fc γ RIIB receptor and the anti-idiotypic antibody specificity of the IgG molecule to the B-cell antigen receptor. This FcR off signal mediated through the Fc γ RIIB receptor can even accelerate early entry of B cells into apoptosis.¹⁹ IVIG could thus provide an off signal to the B cell to inhibit B-cell proliferation and immunoglobulin production.

INDUCTION OF T-CELL SUPPRESSOR ACTIVITY

Our laboratory showed that IVIG could induce changes in T-cell suppressor activity in patients with

common variable immunodeficiency who were receiving IVIG as replacement therapy.²⁰ Further experiments demonstrated that the increased suppressor activity resided in the CD8 T-cell population. Leung et al.²¹ made similar observations in patients with Kawasaki syndrome (KS). Before therapy, patients with KS had increased numbers of circulating activated CD4+ T cells but a deficiency of CD8+ suppressor/cytotoxic T cells. There was also an increased number of circulating spontaneous IgG- and IgM-producing peripheral blood mononuclear cells. By day 4, the patients treated with a combination of aspirin and IVIG had a significant decrease in the activated CD4+ T-helper cells, an increase in CD8+ suppressor cells, and interestingly, a decrease in spontaneous IgG and IgM production. These results suggest that the combination of IVIG and aspirin has profound effects on the immunoregulatory abnormalities of patients with acute KS. KS is a complex immune inflammatory disease in which a number of immune mechanisms may contribute to the disease process.^{21,22} IVIG may modify a number of immune pathways in KS as discussed below.

RESTORATION OF THE IDIOTYPE NETWORK

The pathophysiology of several autoimmune diseases may be related to perturbations in the idiotypic network.²³ A number of groups have postulated that IVIG contains anti-idiotypic antibodies that downregulate the immune response.^{24,25} Using commercial sources of IVIG, Kazatchkine et al.²⁵ prepared F(ab')₂ fragments that could neutralize or bind to known autoantibodies, such as anti-factor VIII, anti-thyroglobulin, anti-DNA, anti-intrinsic factor, and anti-neutrophil cytoplasmic antibodies (ANCA). A number of diseases may serve as models for this mechanism of action for IVIG including conditions in which patients have circulating autoantibody inhibitors to factor VIII activity, systemic lupus erythematosus, and ANCA-associated vasculitides. The presence of anti-idiotypic antibodies in IVIG was first suggested by the response to IVIG therapy of patients with autoimmunity to factor VIII.^{26,27} The treatment of two patients who had high titer autoantibodies to factor VIII activity with high-dose IVIG resulted in a rapid and prolonged suppression of this autoantibody.²⁶ Further investigations by Sultan et al.²⁷ showed that IVIG could also inhibit the activity of factor VIII autoantibody *in vitro* and that the inhibitory effect resided with the F(ab')₂ fragment, thus indicating that IVIG contained an anti-idiotypic antibody, which could bind to and interrupt the function of this pathogenic autoantibody.

ANCA-associated vasculitis may be an example of the possible therapeutic effects of anti-idiotypic antibodies found in IVIG. The systemic vasculitides are a group of disorders in which an inflammatory process involves the blood vessels.²⁸ ANCA occur in patients with several forms of systemic necrotizing vasculitis. Among patients with ANCA-associated vasculitis, the most universal pathologic lesion is a necrotizing vasculitis that affects arteries, arterioles, capillaries, or venules. ANCA acti-

vate neutrophils and thereby produce endothelial damage.²⁸ Recently, several reports have shown that IVIG may be beneficial in the treatment of patients with ANCA-positive vasculitis that is refractory to conventional therapy.^{29, 30} Rossi et al.²⁴ have demonstrated that anti-idiotypic antibodies against a specific ANCA activity exist in normal pooled γ -globulin and have suggested that IVIG could prevent the biologic consequences of ANCAs by binding to these autoantibodies and neutralizing their inflammatory activities. Although IVIG contains anti-idiotypic antibodies to a variety of human autoantibodies that could potentially have immune-modulating effects in certain human autoimmune diseases, the amounts of these anti-idiotypes in IVIG remain small. However, perhaps these anti-idiotypic antibodies act in concert with their effects on the Fc γ RIIb receptor to amplify a negative off signal to the B cells synthesizing these autoimmune antibodies.

MODULATION OF CYTOKINE PRODUCTION

Several studies have shown that IVIG can modulate cytokine production. IVIG produces a dose-dependent decrease in IL-6 production, but not tumor necrosis factor-(TNF) α in lipopolysaccharide-stimulated peripheral blood mononuclear cells.³¹ Shimozato et al.³² demonstrated that both intact IVIG and Fc fragments suppress TNF- α and IL-1 synthesis by lipopolysaccharide-stimulated rabbit peritoneal macrophages. IVIG inhibits mitogen- and antigen-stimulated T-cell proliferation, an effect mediated by the regulation of IL-2 and IL-4 production.³³ Andersson et al.³⁴ studied the effects of IVIG on in vitro induced cytokine production at the single-cell level. Anti-CD3-stimulated T cells produced significantly less IL-2, IL-10, interferon- γ and TNF- β in the presence of IVIG. IVIG added to cultures of human peripheral blood monocytes produces a selective release of IL-1 receptor antagonist (IL-1ra).³⁵ In patients receiving IVIG, plasma concentrations of IL-1ra are increased, resulting in 1000-fold molar excess of IL-1ra to IL-1 β .³⁶ These studies suggest that IVIG can have an important modulating effect on the proinflammatory cytokines. In the acute phase of KS there are elevated serum levels of TNF- α and IL-6, and peripheral blood mononuclear cells produce high levels of IL-1 β and TNF- α . Leung et al.^{37, 38} showed that IVIG with aspirin reduced elevated cytokine levels in patients with KS. From these observations, Leung²² postulated that IVIG regulated cytokine production or activity and that the reduction in coronary artery aneurysms in KS is mediated by IVIG-induced modulation of cytokine production.

Asthma is a disease in which a number of proinflammatory and immune-modulating cytokines are important.³⁹ Results of preliminary studies of IVIG therapy in asthma suggest that IVIG can modify the inflammatory responses and reduce immediate skin test reactivity.⁴⁰ However, direct evidence of both the efficacy of IVIG in asthma (by placebo-controlled, double-blind studies) and the mechanisms by which IVIG exerts its antiinflam-

matory effects in asthma is not available and requires further study. Thus the effects of IVIG on cytokine production may be one important mechanism in regulating immune and inflammatory responses.

MODULATION OF COMPLEMENT UPTAKE ON TARGET CELLS

Studies in both human beings and animals show that IVIG can inhibit complement uptake on target cells. In a guinea pig model of Forssman shock, Frank et al.⁴¹ demonstrated that high-dose IVIG prevented death through inhibition of complement uptake and activation on endothelial cells, thereby preventing tissue damage. These investigators postulated that very high levels of serum IgG from IVIG therapy prevented active C3 and C4 fragments from binding to target cells, which results in the modulation of acute complement-dependent tissue injury. Basta et al.⁴² showed that IVIG also inhibited the uptake of C4 fragments onto antibody-sensitized cells.

Dermatomyositis is an inflammatory myopathy characterized by complement-mediated endomysial vasculitis.⁴³ Activation of complement components C5b to C9, which generate the membrane attack complex (MAC) on skeletal muscle capillaries, leads to destruction of endothelial cells, microinfarcts within the muscle fascicles, muscle ischemia, inflammation, and ultimately muscle atrophy. Patients with dermatomyositis unresponsive to conventional therapies show improvement with high-dose IVIG.⁴⁴ The mechanism by which IVIG is thought to act in dermatomyositis is through the prevention of complement-mediated immune damage of the vessels in the musculature. Muscle biopsy specimens obtained from patients with dermatomyositis treated with IVIG show disappearance of C3b and membrane attack complex deposits on endomysial capillaries with restoration of the capillary network.⁴⁴ It is likely that IVIG inhibits or interferes with the uptake of C4b and C3b fragments by forming complexes between these complement fragments and a specific acceptor site within the immunoglobulin molecule.⁴⁵ This process results in the unavailability of C3b and C4b activation fragments for incorporation into C5 convertase, which is necessary for triggering membrane attack complex assembly.

Another possible mechanism by which IVIG might modify complement uptake on vascular endothelium is through the presence of solubilized complement receptors in IVIG. Although soluble complement receptors have not been sought in IVIG preparations, there is evidence that IVIG does contain other solubilized cell membrane components.⁴⁶⁻⁴⁸ Several observations both in vitro and in animal models suggest that soluble complement receptor 1 can bind fluid-phase C3b to reduce the inflammatory potential of this complement activation product.^{49, 50}

MODULATION OF T-CELL FUNCTION

IVIG contains a number of factors other than IgG including trace amounts of other immunoglobulin iso-

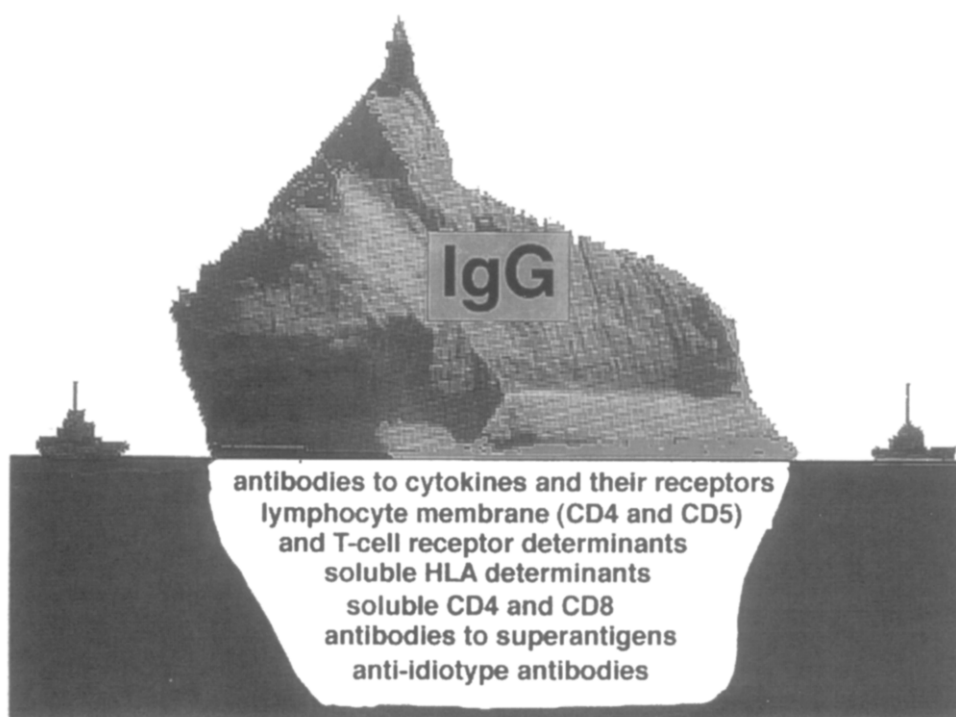


FIG. 1. The major component of IVIG is IgG. This IgG may be just the "tip of the iceberg" in our appreciation of the biologic effects of the "minor" components in IVIG. These other factors, specific antibodies to idiotypes, and lymphocyte surface molecules in IVIG may have important antiinflammatory and immune-modulating effects in autoimmune diseases. Modified from Ballow M. Clinical implications of the mechanisms of action of intravenous immunoglobulin in autoimmune and inflammatory diseases. In: Morell M, Kazatchkine MD, editors. *Intravenous immunoglobulin: research and therapy*. Interlaken: Parthenon Publishing Group; 1997.⁷⁰

types (e.g., IgA), solubilized membrane products, and even HLA determinants, which can interfere with the communication between T cells and accessory or antigen-presenting cells. Lam et al.⁴⁸ and Blasczyk et al.⁴⁶ found that commercial IVIG preparations contain solubilized CD4, solubilized CD8, HLA class I determinants, and HLA class II determinants. These cell surface molecules could interfere with antigen presentation by blocking the interaction between HLA class II and membrane-bound CD4 on T cells or between HLA class I and CD8 in T-cell-mediated cytotoxicity. Additionally, IVIG contains antibodies against lymphocyte surface determinants involved in immunoregulation including CD5,⁵¹ CD4,⁵² and HLA determinants.⁴⁷

Kaveri et al.⁴⁷ demonstrated that IVIG contains antibodies that recognize a highly conserved peptide sequence of the $\alpha 1$ helix of the HLA class I molecule. These anti-peptide antibodies isolated by affinity chromatography from IVIG bind to soluble and membrane-associated HLA class I antigens and inhibit CD8-mediated cytotoxicity of an influenza virus-specific human T-cell line. In addition, these investigators showed that IVIG contains antibodies to CD4 that can bind to CD4+ T cells, suppress mixed lymphocyte proliferative responses, and inhibit infection of CD4+ human T cells with human immunodeficiency virus.⁵² These antibodies in IVIG, which interact with cell surface molecules,

could have important immunoregulatory effects on immune responses in graft-versus-host disease^{53, 54} and a variety of T-cell-mediated autoimmune diseases.

The epidemiology of KS and its clinical presentation suggest that the immune stimulation in acute disease may be triggered by bacterial toxins that have superantigen properties (e.g., staphylococcal enterotoxins and streptococcal pyrogenic exotoxins acting as superantigens).⁵⁵ These bacteria-derived enterotoxin and exotoxin superantigens selectively stimulate T cells expressing certain specific T-cell-receptor- β chain-variable region gene segments and HLA-DR determinants on monocytes and macrophages.⁵⁵ Supporting this hypothesis is the finding of increased circulating levels of V β 2⁺ and V β 8⁺ T cells during the acute phase of KS, which return to normal during the convalescent phase of the disease.^{56, 57} Takei et al.⁵⁸ reported that IVIG contains antibodies to staphylococcal superantigens, which can block the T-cell stimulatory activities of these T-cell superantigens. These data suggest that the beneficial effects of IVIG in KS, and perhaps in toxic shock syndrome, can be due to the presence of specific antibodies in IVIG that neutralize these bacterial superantigen enterotoxins, in addition to the effects of IVIG on inflammatory cytokines.

Experimental uveitis is an animal model of human autoimmune uveitis in which immunization with retinal

TABLE I. Possible mechanism(s) of IVIG action in human disease

Disease	Mechanism(s) of IVIG effects	References
ITP	Fc receptor blockade	4,5
	Changes in Fc γ receptor affinity	8
	Suppression of B-cell function mediated through Fc γ RIIb receptor	15-19
Autoimmune hemophilia	Anti-idiotypic antibodies in IVIG to disease-associated autoantibodies	24-27
	Modulation of B-cell function via Fc γ RII b receptor	15-19
ANCA-associated vasculitis	Anti-idiotypic antibodies in IVIG	24-27
	Modulation of B-cell function via Fc γ RIIb receptor	15-19
Dermatomyositis	Inhibition of complement uptake on endomysial capillaries	44,45
KS	Augmentation of T-cell suppressor activity	20,21
	Modulation of cytokine production	22
	Neutralization of bacterial superantigens	58
Graft-versus-host disease	Solubilized HLA class I and II determinants	46,48
	Antibodies to membrane CD4 and HLA determinants	47,52
	Cytokine inhibition	33,34,53
Multiple sclerosis	Modulation of Fc γ receptor on microglia	6,7
	Inhibition of cytokine production	33,34,66
	Modulation of T-cell function	64,66
Autoimmune uveitis	Modulation of T-cell function	59
Virus-induced autoimmune myocarditis	Modulation of T-cell function	61

S antigen produces a diffuse choroidal infiltrate of T cells. A recent preliminary study suggests that IVIG may be useful in the treatment of autoimmune uveitis.⁵⁹ Another disease entity that may respond to IVIG is virus-induced autoimmune myocarditis. In mice, enterovirus infection can cause an autoimmune carditis that is mediated by CD8+ T cells. Myocardial injury is thought to be caused by virus-specific, class I major histocompatibility complex-restricted cytolytic T cells.⁶⁰ Recently, Drucker et al.⁶¹ reported that high-dose IVIG in the treatment of acute myocarditis was associated with improved recovery of left ventricular function and better survival in the first year after presentation.

Experimental allergic encephalomyelitis (EAE) is a neurologic disease that can be induced in animals by immunization with myelin basic protein and adjuvant.^{62, 63} Autoimmune T-cell responses against myelin in nerves lead to abnormalities of nerve conduction and clinical neurologic deficits. EAE can be transferred to other animals by myelin antigen-specific CD4+ T cells. The treatment of myelin-immunized rats with IVIG prevents the development of EAE.⁶⁴ These investigators found that IVIG treatment also downregulated TNF- α production by autoreactive T cells. In a preliminary study in human beings, IVIG reduced the number of acute relapses in patients with multiple sclerosis, the human counterpart of the EAE animal model.^{65, 66} The effects of IVIG in these T-cell-mediated autoimmune disorders are probably mediated by several mechanisms, including inhibition of cytokine production and the regulation of other T-cell functions by soluble lymphocyte membrane receptors or antibodies to cell membrane determinants on T cells.

SUMMARY

Over 90% of IVIG is monomeric IgG with small amounts of the other immunoglobulins such as IgA and IgM and possibly even IgE. We now know that the IgG in IVIG is just the tip of the iceberg (Fig. 1). IVIG contains "contaminating factors," such as solubilized membrane components, and possibly other important solubilized receptors, as well as specific antibodies to HLA determinants and lymphocyte surface molecules. The studies reviewed in this article suggest that it may be these contaminating molecules that are important in regulating or modifying the immune inflammatory response in autoimmune disease. This may explain why large amounts of IVIG (i.e., 1 to 2 gm/kg) are required for the immune-modulating or antiinflammatory effects of IVIG. Table I contains a partial list of the possible mechanisms by which IVIG may exert its effects in certain human diseases.* Because the pathogenesis of many autoimmune diseases in human beings is most probably multifactorial and not entirely known, delineation of the possible mechanisms of action of IVIG in such diseases is complex. We are just now gaining knowledge about the pathophysiology and the immune pathways responsible for tissue damage in autoimmune disease. A better understanding of the antiinflammatory and immune-modulating effects of IVIG could lead to a better definition of the immunobiology of these complex diseases and could result in a better and more specific form of immunotherapy.

*Although the efficacy of IVIG in various autoimmune disorders is of interest to readers, this discussion is beyond the scope of this review. The reader is referred elsewhere for this information.⁶⁷⁻⁶⁹

I thank Drs. Kathleen O'Neil and Tom Fleisher for reviewing this manuscript and for their very helpful suggestions.

REFERENCES

- Imbach P, d'Apuzzo V, Baumgartner C. High dose intravenous gammaglobulin for idiopathic thrombocytopenic purpura in childhood. *Lancet* 1981;1:1228-30.
- Bussel J, Pahwa S, Porges A. Changes in the *in vitro* antibody synthesis in ITP treated with intravenous gamma globulin are closely linked to long-term outcome. *J Clin Immunol* 1986;6:50-6.
- Bussel JB. Modulation of Fc receptor clearance and antiplatelet antibodies as a consequence of intravenous immune globulin infusion in patients with immune thrombocytopenic purpura. *J Allergy Clin Immunol* 1989;84:566-78.
- Fehr J, Hofmann V, Kappeler U. Transient reversal of thrombocytopenia in idiopathic thrombocytopenic purpura by high-dose intravenous gammaglobulin. *N Engl J Med* 1982;306:1254-8.
- Debré M, Bonnet M-C, Fridman W-H, Carosella E, Phillippe N, Reinert P, Vilmer E, et al. Infusion of Fcγ fragments for treatment of children with acute immune thrombocytopenic purpura. *Lancet* 1993;342:945-9.
- Mannhalter JW, Eibl MM. Down regulation of Fc receptors by IVIgG. *Int Rev Immunol* 1989;5:173-9.
- Mannhalter J, Ahmad R, Wolf HM, Eibl MM. Effect of polymeric IgG on human monocyte functions. *Int Arch Allergy Appl Immunol* 1987;82:159-64.
- Kimberly RP, Salmon JE, Bussel JB, Crow MK, Hilgartner MW. Modulation of mononuclear phagocyte functions by intravenous gamma globulin. *J Immunol* 1984;132:745-50.
- Hashimoto F, Sakiyama Y, Matsumoto S. The suppressive effect of gamma globulin preparations on *in vitro* pokeweed mitogen-induced immunoglobulin production. *Clin Exp Immunol* 1986;65:409-15.
- Antel J, Medof M, Oger J, Kuo H, Arnason B. Generation of suppressor cells by aggregated human globulin. *Clin Exp Immunol* 1981;43:351-6.
- Kondo N, Ozawa T, Mushiaki K, Motoyoshi F, Kameyama T, Kasahara K, et al. Suppression of immunoglobulin production of lymphocytes by intravenous immunoglobulin. *J Clin Immunol* 1991;11:152-8.
- Stohl W. Cellular mechanisms in the *in vitro* inhibition of pokeweed mitogen induced B cell differentiation by immunoglobulin for intravenous use. *J Immunol* 1986;136:4407-13.
- Heyman B. Fc-dependent IgG-mediated suppression of the antibody response: Fact or artefact? *Scand J Immunol* 1990;31:601-7.
- Fridman WH. Regulation of B-cell activation and antigen presentation by Fc receptors [review]. *Curr Opin Immunol* 1993;5:355-60.
- Phillips N, Parker D. Cross-linking of B lymphocyte Fcγ receptors and membrane immunoglobulin inhibits anti-immunoglobulin-induced blastogenesis. *J Immunol* 1984;132:627-32.
- Phillips N, Gravel K, Tumas K, Parker D. IL-4 overcomes Fcγ receptor-mediated inhibition of mouse B lymphocyte proliferation without affecting inhibition of *c-myc* mRNA expression. *J Immunol* 1988;141:4243-9.
- Chacko G, Tridandapani S, Damen J, Liu L, Krystal G, Coggeshall K. Negative signaling in B-lymphocytes induces tyrosine phosphorylation of the 145-kDa inositol polyphosphate 5-phosphatase, SHIP. *J Immunol* 1996;157:2234-8.
- Diegel M, Rankin B, Bolen J, Dubois P, Kiener P. Cross-linking of Fcγ receptor to surface immunoglobulin on B-cells provides an inhibitory signal that closes the plasma membrane calcium channel. *J Biol Chem* 1994;269:11409-16.
- Ashman R, Peckham D, Stunz L. Fc receptor off-signal in the B-cell involves apoptosis. *J Immunol* 1996;157:5-11.
- White WB, Desbonnet CR, Ballow M. Immunoregulatory effects of intravenous immune serum globulin therapy in common variable hypogammaglobulinemia. *Am J Med* 1987;83:431-6.
- Leung DY, Burns JC, Newburger JW, Geha RS. Reversal of lymphocyte activation *in vitro* in the Kawasaki syndrome by intravenous gammaglobulin. *J Clin Invest* 1987;79:468-72.
- Leung DYM, Kurt-Jones E, Newburger JW. Endothelial cell activation and high interleukin-1 secretion in the pathogenesis of acute Kawasaki disease. *Lancet* 1989;2:1298-302.
- Shoenfeld Y. Idiotypic induction of autoimmunity: a new aspect of the idiotypic network. *FASEB J* 1994;8:1296-301.
- Rossi F, Kazatchkine MD. Anti-idiotypes against autoantibodies in pooled normal human polyspecific IgG. *J Immunol* 1989;143:4104-9.
- Dietrich G, Kazatchkine MD. Normal immunoglobulin G (IgG) for therapeutic use (intravenous Ig) contains anti-idiotypic specificities against an immunodominant, disease-associated, cross-reactive idio-type of human anti-thyroglobulin autoantibodies. *J Clin Invest* 1990;85:620-5.
- Sultan Y, Kazatchkine MD, Maisonneuve P. Anti-idiotypic suppression to autoantibodies to factor VIII by high-dose intravenous immunoglobulin. *Lancet* 1984;2:765-8.
- Sultan Y, Rossi F, Kazatchkine MD. Recovery from anti-VIIIc (anti-hemophilic factor) autoimmune disease is dependent on generation of anti-idiotypes against anti-VIIIc autoantibodies. *Proc Nat Acad Sci USA* 1987;84:828-31.
- Jennette JC. Pathogenic potential of anti-neutrophil cytoplasmic autoantibodies. In: Gross WL, editor. ANCA-associated vasculitides: immunological and clinical aspects. New York: Plenum Press; 1993. p. 7-14.
- Jayne DRW, Lockwood CM. Pooled intravenous immunoglobulin in the management of systemic vasculitis. *Adv Exp Med Biol* 1993;336:469-72.
- Lockwood CM. New treatment strategies for systemic vasculitis: the role of intravenous immune globulin therapy. *Clin Exp Immunol* 1996;104(suppl 1):577-82.
- Andersson JP, Andersson UG. Human intravenous immunoglobulin modulates monokine production *in vitro*. *Immunology* 1990;71:372-6.
- Shimozato T, Iwata M, Kawada H, Tamura N. Human immunoglobulin preparation for intravenous use induces elevation of cellular cyclic adenosine 3':5'-monophosphate levels, resulting in suppression of tumour necrosis factor alpha and interleukin-1 production. *Immunology* 1991;72:497-501.
- Amran D, Renz H, Lack G, Bradley K, Gelfand EW. Suppression of cytokine-dependent human T-cell proliferation by intravenous immunoglobulin. *Clin Immunol Immunopathol* 1994;73:180-6.
- Andersson J, Skansen-Saphir U, Sparrelid E, Andersson U. Intravenous immune globulin affects cytokine production in T lymphocytes and monocytes/macrophages. *Clin Exp Immunol* 1996;104(suppl 1):S10-S20.
- Ruiz-de-Souza V, Carreno M, Kaveri S, Kazatchkine M. Selective induction of IL-1ra and IL-8 in human monocytes by normal polyspecific immunoglobulin G for therapeutic use. *Eur J Immunol* 1995;25:1267-73.
- Aukrust P, Froland SS, Liabakk N-B, Muller F, Nordoy I, Haug C, et al. Release of cytokines, soluble cytokine receptors, and interleukin-1 receptor antagonist after intravenous immunoglobulin administration *in vivo*. *Blood* 1994;84:2136-43.
- Leung DYM. Kawasaki syndrome: immunomodulatory benefit and potential toxin neutralization by intravenous immune globulin. *Clin Exp Immunol* 1996;104:49-54.
- Leung DY. The immunoregulatory effects of IVIG in Kawasaki disease and other autoimmune diseases. In: Ballow M, editor. IVIG therapy today. Totowa (NJ): Humana Press; 1992. p. 93-103.
- Barnes P. Cytokines as mediators of chronic asthma. *Am J Respir Crit Care Med* 1994;150:S42-S49.
- Mazer B, Gelfand E. An open-label study of high-dose intravenous immunoglobulin in severe childhood asthma. *J Allergy Clin Immunol* 1991;87:976-83.
- Basta M, Kirshborn P, Frank MM, Fries LF. Mechanism of therapeutic effects of high-dose intravenous immunoglobulin. Attenuation of acute, complement-dependent immune damage in a guinea pig model. *J Clin Invest* 1989;84:1974-81.
- Basta M, Fries LF, Frank MM. High doses of intravenous Ig inhibit *in vitro* uptake of C4 fragments onto sensitized erythrocytes. *Blood* 1991;77:376-80.
- Dalakas MC. Polymyositis, dermatomyositis, and inclusion-body myositis. *N Engl J Med* 1991;325:1487-98.
- Dalakas MC, Illa I, D'Ambrosia JM, Soneidan SA, Stein DP, Otero

- C, et al. A controlled trial of high-dose immune globulin infusions as treatment for dermatomyositis. *N Engl J Med* 1993;329:1993-2000.
45. Basta M, Dalakas MC. High-dose intravenous immunoglobulin exerts its beneficial effect in patients with dermatomyositis by blocking endomysial deposition of activated complement fragments. *J Clin Invest* 1994;94:1729-35.
46. Blasczyk R, Westhoff U, Grosse-Wilde H. Soluble CD4, CD8, and HLA molecules in commercial immunoglobulin preparations. *Lancet* 1993;341:789-90.
47. Kaveri S, Vassilev T, Hurez V, Lengagne R, Lefranc C, Cot S, et al. Antibodies to a conserved region of HLA class I molecules, capable of modulating CD8 T cell-mediated function, are present in pooled normal immunoglobulin for therapeutic use. *J Clin Invest* 1996;97:865-9.
48. Lam L, Whitsett C, McNicholl J, Hodge T, Hooper J. Immunologically active proteins in intravenous immunoglobulin [letter]. *Lancet* 1993;342:678.
49. Swift AJ, Collins TS, Bugelski P, Winkelstein JA. Soluble human complement receptor type 1 inhibits complement-mediated host defense. *Clin Diag Lab Immunol* 1994;1:585-9.
50. Couser WG, Johnson RJ, Young BA, Yeh CG, Toth CA, Rudolph AR. The effects of soluble recombinant complement receptor 1 on complement-mediated experimental glomerulonephritis. *J Am Soc Nephrol* 1995;5:1888-94.
51. Vassilev T, Gelin C, Kaveri S, Zilber MT, Boumsell L, Kazatchkine MD. Antibodies to the CD5 molecule in normal human immunoglobulins for therapeutic use (intravenous immunoglobulins, IVIg). *Clin Exp Immunol* 1993;92:369-72.
52. Hurez V, Kaveri SV, Mouhoub A, Dietrich G, Mani JC, Klatzmann D, et al. Anti-CD4 activity of normal human immunoglobulin G for therapeutic use (intravenous immunoglobulin, IVIg). *Ther Immunol* 1994;1:269-77.
53. Sullivan K. Immunomodulation in allogeneic marrow transplantation: use of intravenous immune globulin to suppress acute graft-versus-host disease. *Clin Exp Immunol* 1996;104(suppl 1):S43-S48.
54. Sullivan K, Kopecky K, Jocom J. Immunomodulatory and antimicrobial efficacy of intravenous immunoglobulin in bone marrow transplantation. *N Engl J Med* 1990;323:705-9.
55. Kotzin BL, Leung DY, Kappler J. Superantigens and human disease. *Adv Immunol* 1993;54:99-146.
56. Abe J, Kotzin BL, Jujo K. Selective expansion of T cells expressing T cell receptor variable regions VB2 and VB8 in Kawasaki disease. *Proc Natl Acad Sci USA* 1992;89:4066-70.
57. Abe J, Kotzin BL, Meissner C. Characterization of T cell repertoire changes in acute Kawasaki disease. *J Exp Med* 1993;177:791-6.
58. Takei S, Arora YK, Walker SM. Intravenous immunoglobulin contains specific antibodies inhibitory to activation of T cells by staphylococcal toxin superantigens. *J Clin Invest* 1993;91:602-7.
59. Saoudi A, Hurez V, De Kozak Y, Kuhn J, Kaveri SV, Kazatchkine MD, et al. Prevention of experimental autoimmune uveoretinitis by infusions of human therapeutic intravenous immunoglobulins in rats. *Transplant Proc* 1993;25:2838-9.
60. Rose N, Hill S. The pathogenesis of postinfectious myocarditis. *Clin Immunol Immunopathol* 1996;80:S92-S99.
61. Drucker NA, Colan SD, Lewis AB, Beiser AS, Wessel DL, Takahashi M, et al. γ -Globulin treatment of acute myocarditis in the pediatric population. *Circulation* 1993;89:252-7.
62. Acha-Orbea H, Mitchell DJ, Timmermann L, Wraith DC, Tausch GS, Waldor MK, et al. Limited heterogeneity of T cell receptors from T lymphocytes mediating autoimmune encephalomyelitis allows specific immune intervention. *Cell* 1988;54:263-73.
63. Ben-Nun A, Wekerle H, Cohen IR. The rapid isolation of clonable antigen-specific T lymphocytes capable of mediating experimental autoimmune encephalomyelitis. *Eur J Immunol* 1981;11:195-9.
64. Achiron A, Margalit R, HersHKovits R, Markovits D, Reshef T, Melamed E, et al. Intravenous immunoglobulin treatment of experimental T-cell mediated autoimmune disease. *J Clin Invest* 1994;93:600-4.
65. Achiron A, Pras E, Gilad R, Ziv J, Mandel M, Gordon CR, et al. Open controlled therapeutic trial of intravenous immune globulin in relapsing-remitting multiple sclerosis. *Arch Neurol* 1992;49:1233-6.
66. Achiron A, Barak Y, Goren M, Gabbay U, Miron S, Rotstein Z, et al. Intravenous immune globulin in multiple sclerosis: clinical and neuroradiological results and implications for possible mechanisms of action. *Clin Exp Immunol* 1996;104(suppl 1):S67-S70.
67. Buckley R, Schiff R. The use of intravenous immune globulin in immunodeficiency diseases. *N Engl J Med* 1991;325:110-7.
68. NIH Consensus Conference. Intravenous immunoglobulin: prevention and treatment of disease. *JAMA* 1990;264:3189-93.
69. Ratko T, Burnett D, Foulke G, Matuszewski K, Sacher R, the University Hospital Consortium Expert Panel for Off-label Use. Recommendations for off-label use of intravenously administered immunoglobulin preparations. *JAMA* 1995;273:1865-70.
70. Ballow M. Clinical implications of the mechanisms of action of intravenous immunoglobulin in autoimmune and inflammatory diseases. In: Morell A, Kazatchkine MD, editors. *Intravenous immunoglobulin: research and therapy*. Interlaken, Switzerland: Parthenon Publishing Group; 1997. p.123-7.

Bound volumes available to subscribers

Bound volumes of *The Journal of Allergy and Clinical Immunology* are available to subscribers (only) for the 1997 issues from the Publisher, at a cost of \$88.50 for domestic, \$116.10 for Canadian, and \$108.50 for international subscribers for Vol. 99 (January-June) and Vol. 100 (July-December). Shipping charges are included. Each bound volume contains a subject and author index, and all advertising is removed. Copies are shipped within 30 days after publication of the last issue in the volume. The binding is durable buckram with the journal name, volume number, and year stamped in gold on the spine. *Payment must accompany all orders.* Contact Mosby-Year Book, Inc., Subscription Services, 11830 Westline Industrial Dr., St. Louis, MO 63146-3318; phone 1 (800) 453-4351 or (314) 453-4351.

Subscriptions must be in force to qualify. Bound volumes are not available in place of a regular journal subscription.