Journal of Clinical Immunology, Vol. 27, No. 3, May 2007 (© 2007)
DOI: 10.1007/s10875-007-9088-9

Intravenous Immunoglobulin: An Update on the Clinical Use and Mechanisms of Action

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Received February 20, 2007; accepted February 21, 2007
Published online: 11 March 2007

Initially used as a replacement therapy for immunodeficiency diseases, intravenous immunoglobulin (IVIg) is now widely used for a number of autoimmune and inflammatory diseases. Considerable progress has been made in understanding the mechanisms by which IVIg exerts immunomodulatory effects in autoimmune and inflammatory disorders. The mechanisms of action of IVIg are complex, involving modulation of expression and function of Fc receptors, interference with activation of complement and the cytokine network and of idiotype network, regulation of cell growth, and effects on the activation, differentiation, and effector functions of dendritic cells, and T and B cells.

KEY WORDS: Intravenous immunoglobulins; autoimmunity; inflammation; immune-modulation .

INTRODUCTION

Intravenous immunoglobulin (IVIg) is a therapeutic preparation of normal human polyclonal IgG obtained from plasma pooled from a large number of healthy blood donors. Initially introduced as a replacement therapy for patients with primary and secondary immune deficiencies, IVIg is now widely used for the treatment of a number of autoimmune and systemic inflammatory diseases (1–3). The available clinical and experimental evidence suggests that besides these, many other immune-mediated conditions could benefit from IVIg. These include acute and chronic relapsing diseases, autoimmune disorders mediated by pathogenic autoantibodies or autoaggressive T cells, and inflammatory disorders with an imbalance in cytokine networks.

IVIg is prepared from pooled plasma obtained from thousands of healthy blood donors. The large donor pool ensures the diversity of immunoglobulin repertoire that far exceeds that of an individual. Thus, IVIg contains a sampling from the entire array of variable regions of antibodies, expected to be present in normal serum. Hence, IVIg is comprised of a broad range of immune antibodies directed against pathogens and foreign antigens. Their presence is critical for the substitutive treatment of patients with humoral immune deficiencies. Presence of natural antibodies (NAbs) to a number of self-antigens is believed to be essential for the immunoregulatory effects of IVIg in immune-mediated disorders.

NATURAL ANTIBODIES (NAbs)

Natural antibodies (NAbs) constitute a large fraction of serum immunoglobulin (Ig). The autoreactive antibody secreting B lymphocytes (B1 B cells) found in healthy individuals produce NAbs (4). It has been estimated that 5–15% of splenic B-cells activated *in vivo*, can secrete NAbs (5) and up to 20% circulating human B cells are autoreactive (6).

Several functions have been proposed for NAbs under physiological conditions. NAbs function primarily to control autoreactivity and maintain immune homeostasis in healthy individuals. They have an important role in

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the selection of autoreactive B cells and prevention of uncontrolled expansion of specific autoreactive clones. NAbs, through V region-dependent complementary interactions, control the autoreactivity in serum under physiological conditions (5). In addition, they may prevent the occurrence of pathological autoimmunity by binding to microbial epitopes similar or identical to self-antigens. The immunomodulatory effect of systemic administration of intravenous immunoglobulin (IVIg) in inflammatory disorders provides evidence that normal circulating immunoglobulin has antiinflammatory properties. As IVIg is a therapeutic preparation of pooled normal polyspecific human IgG, it contains a wide spectrum of NAbs expressed in normal human serum.

A number of NAbs against soluble and membrane-associated self-molecules, involved in immune regulation, have been characterized in IVIg. These include autoantibodies to idiotypes of immunoglobulins and B-cell antigen receptors (7, 8) to $\alpha\beta$ T-cell receptor (9), CD5 (10), CD4 (11), cytokines and cytokine receptors (12, 13), nonpolymorphic determinants of MHC class I molecules (14), Fcγ receptors, the Fas molecule (CD95) (15, 16), and the Arg-Gly-Asp (RGD) motif of integrins (17). NAbs and their target molecules are directly relevant to the immunomodulatory effects of IVIg. The ability of IVIg to interact with idiotypes of autoantibodies accounts for its ability to neutralize circulating autoantibodies in certain autoantibody-mediated autoimmune diseases. A therapeutic role for antagonistic anti-Fas antibodies present in IVIg has been suggested in toxic epidermal necrolysis (TEN) (Lyell syndrome) (16).

CLINICAL USES OF IVIg

Initially used as a replacement therapy for immunodeficiency diseases, IVIg is now widely used for a number of autoimmune and inflammatory diseases. IVIg is used in two distinct dosing schedules, (i) low dose or "replacement" therapy and, (ii) high dose or "immunomodulatory/antiinflammatory therapy" (Table I).

Table I. Clinical Uses of IVIg

A. Replacement (low dose) therapy
I. Primary immunodeficiency diseases
II. Secondary immunodeficiency
B-cell malignancies (CLL, MM)
HIV infection
B. Immunomodulator (high dose) therapy
I. Hematological diseases
Idiopathic thrombocytopenic purpura (ITP)[a]
Acquired immune thrombocytopenias
Autoimmune neutropenia
Autoimmune hemolytic anemia
Parvovirus B19-associated red cell aplasia
Antifactor VIII autoimmune disease
Acquired von Willebrand's disease
II. Neuroimmunological diseases
Guillain–Barré syndrome (GBS)[a]
Chronic inflamatory demyelinating polyneuropathy (CIDP)[a]
Multifocal motor neuropathy (MMN)[a]
Multiple sclerosis
Myasthenia Gravis[a]
Lambert–Eaton syndrome
Stiff person syndrome
III. Rheumatic diseases
Kawasaki disease[a]
ANCA-positive systemic vasculitis
Polymyositis
Dermatomyositis[a]
Antiphospholipid syndrome
Recurrent spontaneous abortions
Rheumatoid arthritis and Felty's syndrome
Systemic lupus erythematosus (SLE)
Juvenile idiopathic arthritis (JIA)
IV. Dermatological diseases
Toxic epidermal necrolysis (TEN)
Autoimmune skin blistering diseases (BP, PF, PV)[a]
Streptococcal toxic shock syndrome
Steroid-dependent severe atopic dermatitis
V. Other conditions
Graft versus host disease[a]
Antibody-mediated rejection (AMR) of the graft
Sepsis syndrome

[a]Indicates diseases in which evidence for the effect of IVIg has been obtained in controlled trials.

Replacement Therapy

Primary Immunodeficiencies. IVIg is used to prevent infections in patients with primary immunodeficiency diseases (18–20). Following the introduction of IVIg therapy, the incidence of pulmonary infections has reduced significantly. Trough serum levels of IgG above 500 mg/dL appear to be adequate for preventing pulmonary infections and its complications (21). To achieve this level, a 300–500 mg/kg body weight of IVIg every 3–4 weeks is recommended (22, 23).

Secondary Immunodeficiencies. Secondary immunodeficiency in B-cell malignancies (CLL, Multiple myeloma), results in severe and recurrent bacterial infections due to reduced antibody synthesis (24). Prophylactic IVIg therapy has reduced the incidence of infectious complications in these patients (25, 26).

IVIg replacement therapy in pediatric HIV infection has resulted in reduced incidence of bacterial infections, decreased morbidity, and improved quality of life (27). Following bone marrow transplantation, IVIg therapy is reported to reduce the incidence of infections, septicemia, platelet transfusion requirement, and acute GVHD (28). However, with the availability of newer antimicrobials (gancyclovir, fluoroquinolones, antifungal agents) and the risk of veno-occlusive disease associated with IVIg use, it is not routinely recommended for infection prophylaxis

(29). It may be reserved for hypogammaglobulinemic patients (IgG < 4g/L) after bone marrow transplantation (30).

Immunomodulator/Immunoregulatory Therapy

High-dose IVIg is used to treat many autoimmune and inflammatory disorders.

Hematological Disorders. ITP was the first autoimmune disease successfully treated with IVIg (31–33). IVIg improves the platelet count in both childhood and adult ITP (34, 35). The ITP patients having anti-Gp Ib/IX antibody in their serum may be less responsive to IVIg (36). It is also helpful in Parvovirus-19-related pure red cell aplasia (PRCA) (37), autoimmune neutropenia (AIN) (38), and autoimmune hemolytic anemia (AIHA) (39). Antifactor VIII autoimmune disease and acquired von Willbrand's Disease also respond to IVIg therapy (40).

Neuroimmunological Disorders. IVIg is as effective as plasma exchange in the treatment of acute paralytic Guillain–Barre syndrome (GBS) (41). It is the treatment of choice in multifocal motor neuropathy with conduction blocks (MMN). Treatment with steroids has little effect and may even worsen the disease. IVIg improves muscle strength and neurological disability scores and may reverse conduction blocks in this disease (42, 43). In Chronic Inflammatory Demyelinating Polyneuropathy (CIDP), IVIg is increasingly supplanting traditional steroid therapy. Evidence from randomized controlled trials (44, 45) indicates that IVIg is as effective as steroids and plasma exchange, at least in the short term.

The efficacy of IVIg is similar to plasma exchange for myasthenic crisis (46). It produces short-term improvement in muscle strength in Lambert–Eaton Syndrome (47) and significantly reduces muscle stiffness in stiff person syndrome (48).

The beneficial effects of IVIg in reducing the frequency of relapses, improving neurological status and disability in relapsing remitting multiple sclerosis (MS) is similar to that achieved with beta-interferon and glatiramer acetate (49). It also reduces the pregnancy and postpartum-related relapses (50). In contrast, IVIg is of no demonstrable benefit in secondary progressive MS (51).

Rheumatic Diseases. Clinical and experimental evidence suggest that IVIg may be a viable therapy for several rheumatic diseases (52, 53). IVIg given in the first 10 days of acute illness is effective in Kawasaki disease (54). In dermatomyositis, it significantly improves the muscle strength and neuromuscular symptom scores of patients (55). In polymyositis, up to 70% improvement in muscle strength has been reported (3). The benefit of high-dose IVIg therapy in inclusion body myositis was found to be modest and transient (56, 57).

IVIg is shown to be a useful adjunctive therapy in antineutrophil cytoplasmic antibody (ANCA)-positive systemic vasculitis (AASV), refractory to standard immunosuppressive therapy (58–60). Its use as the single drug in AASV without vital organ involvement also produced encouraging results (61). However, the use of IVIg in mixed cryoglobulinaemic vasculitis is fraught with danger. There is a risk of acute renal failure caused by the deposition of immune complexes formed by exogenous IgG and the intrinsic IgM rheumatoid factor component of mixed cryoglobulins (62).

Despite encouraging reports, the clinical value of IVIg is not well established in systemic lupus erythematosus (SLE) (53, 63). IVIg is used either in nonresponsive severe cases, or as a steroid-sparing agent. However, the efficacy of IVIg therapy in maintaining remission in patients with lupus nephritis has been demonstrated (64). Patients with other rheumatic diseases, such as JIA, Sjogren's syndrome, antiphospholipid syndrome, and fibrosis-associated disorders have been reported to benefit from IVIg (3, 54, 65–68).

Several autoimmune rheumatic conditions, including rheumatoid arthritis, systemic lupus erythematosus, and antiphospholipid syndrome, are characterized by enhanced atherosclerosis and consequently higher cardiovascular morbidity and mortality rates. IVIg has been shown to reduce the process of atherosclerosis likely via inhibitory effects on foam-cell formation and neutralizing the pathogenic anti-oxLDL antibodies (69, 70).

Immunological Diseases of the Skin. Uncontrolled studies have shown a reduction in blistering and mortality with IVIg therapy in Steven Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) (71, 72). Autoimmune blistering disorders [Pemphigus vulgaris (PV), Pemphigus foliaceus (PF), Bullous pemphigoid (BP)] were shown to improve with high-dose IVIg therapy (73, 74). In a mouse model of PV, IVIg as a whole and its $F(ab')_2$ portion inhibited the binding of antidesmoglein-3 antibody to recombinant desmoglein-3 in a dose-dependent manner. IVIg prevented acanthylosis and IgG deposition in the intercellular spaces (75). Other skin conditions where IVIg is reported to be useful are, atopic dermatitis (76), chronic immune urticaria (77), scleromyxoedema (78), pyoderma gangrenosum (79), erythema multiforme, and psoriasis (80).

Transplantation

Graft versus Host Disease (GVHD). Several large controlled studies showed that intravenous immunoglobulin not only prevented infections but also reduced the

incidence and severity of GVHD in patients older than 20 years undergoing allogenic, unrelated-donor, bone marrow transplantation, especially those not receiving T-cell depleted marrow (81, 82). In this high-risk group, increasing the dose of IVIg to 500 mg/kg appeared to be associated with a lower incidence of acute GVHD (82). However, IVIg has not been shown to reduce GVHD in HLA identical sibling donor transplantation (29, 81). In one study, use of higher doses of IVIg was found to be associated with severe (grade 3) veno-occlusive disease (29). Besides, long-term administration of IVIg beyond 3 months has been found to delay the recovery of humoral immunity (83).

Antibody-Mediated Transplant Rejection (AMR). IVIg therapy given to highly sensitized patients leads to reduction in allo-sensitization, reduced ischemic-perfusion injuries, fewer acute rejection episodes, and better long-term results for cardiac and renal allograft recipients (84–86). In pig-to-baboon xenotransplants, IVIg treatment significantly prolonged the survival of graft through inhibition of complement-mediated endothelial cell injury (87). IVIg has the ability to inhibit antibody-mediated injury to vasculature through inhibition of antibody production and inhibition of complement-mediated lysis of target cells (88). A recent multicenter, double-blinded, placebo-controlled trial concluded that IVIg is superior to placebo in reducing anti-HLA antibody levels and improving successful transplantation rates in highly sensitized patients with end-stage renal disease (ESRD) (89).

Miscellaneous. IVIg therapy is reported to be useful in patients with streptococcal toxic shock syndrome (STSS) (90). IVIg contains superantigen neutralizing antibodies and plasma from patients with STSS after IVIg administration completely blocks the streptococcal toxin-induced cytokine production (91). In transgenic model of STSS, IVIg neutralized superantigens and reduced systemic inflammatory response (92).

The efficacy of IVIg as adjunct therapy in sepsis has long been debated. Clinical trials have yielded contradictory results. IVIg administration is reported to be a significant predictor for survival in Pediatric intensive care units (93).

IVIg is useful in HIV-associated PRCA, immune thrombocytopenia, and GBS (37). It has also been found to temporarily control HIV replication in AIDS patients (94).

COMPOSITION OF INTRAVENOUS IMMUNOGLOBULIN

All available preparations of IVIg consist of intact IgG molecules with a distribution of IgG subclasses corresponding to that of normal human serum. IVIg, like normal human serum, is rich in self-reactive natural antibodies of the IgG, IgM, and IgA isotype. Since there is a high content of NAbs in IVIg, a significant fraction of IVIg consists of antibodies capable of interacting with variable regions (idiotypes) of other antibody molecules present in the preparation to form variable region-dependent (idiotypically complementary) dimers. The content in such dimers in the IVIg pool increases with the number of donors contributing to the pool. The formation of idiotype-idiotype dimers may account for some of the clinical effects of IVIg. IVIg has also been shown to contain trace amounts of soluble CD4, CD8, and HLA molecules and of certain cytokines such as TGF-β (95, 96). The preparations contain intact Fc molecules which allow IVIg to interact with and signal through Fc receptors on Fcγ receptor-expressing cells, including phagocytes and B cells, and with a number of Fc-binding plasma proteins, e.g., components of the complement system.

IVIg DOSAGE

Intravenous immunoglobulin (IVIg) is widely used as supportive therapy for many immunodeficiency disorders and as treatment of different autoimmune disorders in two distinct dose regimens (1, 3). The plasma IgG level reached in immunodeficient patients, immediately following infusion of IVIg as a "replacement" dose (300–500 mg/kg), is 12–14 mg/mL. It is higher (25–35 mg/mL) when administered as a "therapeutic" immunomodulator (2 g/kg) dose in autoimmune and inflammatory disorders (97).

The immunomodulatory therapeutic dose of IVIg may be infused as five daily doses of 400 mg/kg each. However, some studies found a superior effect of IVIg when given as a single full dose rather than divided doses (1, 3, 73). For the maintenance of therapeutic response, repeated infusions of IVIg, usually 2 g/kg at 4–6-week intervals, are needed. More studies are required to confirm the optimum dose and appropriate time period for IVIg treatment for induction and maintenance of immune response in these diseases. The half-life of infused IVIg in immunocompetent individuals is 3 weeks.

SAFETY OF IVIg

IVIg therapy is relatively safe. Adverse reactions to IVIg occur in 5–10% of patients (1, 3). Common and mild side effects include headache, nausea, chills, myalgia, low-grade fever, urticaria, arthralgia, and increased blood pressure following IVIg infusion in patients at high

risk of hypertension. These symptoms can be relieved either by reducing the infusion rate or temporarily stopping the infusion. Mild reactions to IVIg are more frequent, occur within the first 30 min of infusion, and may be relieved by reducing the rate or temporarily stopping the infusion. Acute meningeal inflammation with aseptic cerebrospinal fluid pleiocytosis may occur within 48–72 h after administration of IVIg. The symptoms resolve spontaneously and may be prevented by antiinflammatory agents (98). It is possible that *in vivo* activation of TNFα-primed neutrophils, by atypical antineutrophil cytoplasmic antibodies (ANCA) present in IVIg may contribute to the side effects of IVIg therapy (99). Rare but serious side effects including anaphylactic reactions occur in patients with IgA deficiency which is associated with the development of anti-IgA antibodies that react with IgA in the IVIg preparation. This can be prevented by using IgA-depleted IVIg (1). Flares of disease or appearance of immune-mediated diseases such as SLE, vasculitis, and uveitis are other potential serious complications (53, 63). Elderly patients, patients with diabetes or preexisiting impairment in renal function are at risk of acute renal failure, which is usually limited to a transient increase in creatinine levels within 2–5 days after infusion of IVIg (100). Renal failure is related to tubular damage induced by sucrose used as a stabilizer in some IVIg preparations. A close follow-up of renal function is recommended in patients at risk. IVIg has rarely been associated with arterial or venous thrombosis, pulmonary embolism, myocardial infarction, stroke, or retinal artery or vein occlusion. These thromboembolic events occur in patients at high risk of thrombosis due to IVIg-associated increase in plasma viscocity or anticardiolipin antibodies (101). There is no report of transmission of HIV by IVIg, although several outbreaks of hepatitis C associated with its administration were reported in the mid-'90s (102). The risk of viral transmission has been eliminated to a large extent by rigorous donor selection and introduction of new manufacturing processes. Despite increased public concern about emerging and re-emerging infectious diseases and a debate on the risk of blood-borne transmission of variant Creutzfeldt–Jakob disease, IVIg has an excellent safety record through the last decade (103).

MODE OF ACTION OF IVIg

The mode of action of IVIg is complex. It is found to exert its effect through modulation of expression and function of Fc receptors, interference with complement activation and the cytokine network, provision of antiidiotypic antibodies, modulation of dendritic cell, T and B cell activation, differentiation, and their effector functions (1, 3, 18, 104) (Fig. 1). Thus, IVIg has multiple modes of action, thought to act synergistically. Such a broad range of activity reflects the importance of circulating immunoglobulins in the maintenance of tolerance to self and immune homeostasis in healthy individuals. A brief overview of mechanisms that may underlie the benefits of IVIg in autoimmune and inflammatory diseases is presented as follows.

Fc-Mediated Effects of IVIg

IgG consists of Fab regions that recognize antigenic targets and provide diversity to antibodies, and Fc region that allows antibody to interact with Fc gamma receptors (FcγR) on phagocytes. Currently, four classes of FcγR are identified: FcγRI, FcγRII, FcγRIII, and FcγRIV (105). Of these, FcγRI, FcγRIIA, FcγRIIIA, and FcγRIV are "activating receptors" while FcγRIIB is an "inhibitory receptor." Activating FcγRs for IgG are primary mediators of proinflammatory activity in autoimmune diseases (106). Mice rendered genetically deficient in activating FcγRs are protected from pathogenic antibodies (105). Interaction between the Fc portion of IVIg and FcγR on target cells, governs some of the antiinflammatory mechanisms of IVIg. These activities were first applied for the treatment of ITP characterized by platelet clearance mediated by pathogenic antiplatelet antibodies. This platelet clearance is probably mediated by interactions between autoantibodies and FcγR expressed on monocytes or macrophages in the reticuloendothelial system (RES). The competitive blockade of these FcγRs by IVIg has long been considered to be the primary mechanism whereby IVIg may render the sensitized cells of RES unable to exert their function of phagocytosis or antibody-dependent cellular cytotoxicity (ADCC), leading to an increase of platelet count in patients with ITP. Infusion of purified Fc fragments of IVIg ameliorates acute immune thrombocytopenic purpura (ITP) in children and in murine models, as with IVIg (107).

Mice deficient in neonatal Fc Receptor (FcRn) are protected from pathogenic IgG autoantobodies. The long serum half life of autoantibodies results from their interaction with FcRn present on endothelial cells. Normal FcRn binds to the internalized IgG inside lysosomes and prevents its intracellular degradation. Thus, the FcRn saturation by IVIg would result in the accelerated clearance of IgG and therefore reduce the level of pathogenic autoantibodies (108, 109).

In addition to FcγR saturation, IVIg might also modulate the expression of these receptors. In animal model of ITP, the protective effect of IVIg or IVIg Fc is associated

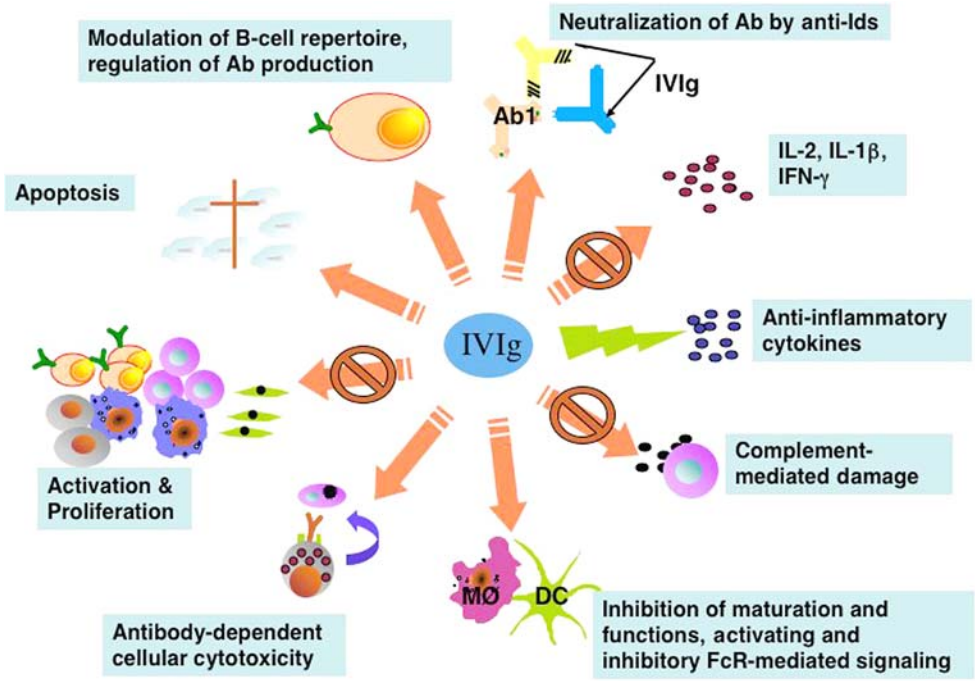

Fig. 1. Schematic representation of proposed mechanisms of action of IVIg in autoimmune and inflammatory diseases. The mechanisms underlying beneficial effects of IVIg in autoimmune and inflammatory diseases involve its direct interaction with various cellular and soluble components of the immune system and modulation of the functions of the immune system. IVIg is found to exert its effect through modulation of expression and function of Fc receptors, interference with complement activation and the cytokine network, provision of antiidiotypic antibodies, modulation of dendritic cell, T and B cell activation, differentiation, and their effector functions.

with upregulation of the inhibitory receptor FcγRIIB on splenic macrophages and is abrogated in mice lacking FCGRIIB gene (110). A recent study of a murine model of nephrotoxic nephritis has suggested that IVIg could be effective by both upregulating the expression of inhibitory FcγRIIB and downregulating the activating FcγRIV (111).

The mechanism of IVIg protection appears to be independent of both the antibody specificity and the site of macrophage activation and is likely to represent a general mechanism for IVIg protection in antibody-triggered autoimmune diseases. However, in some models, FcγRIIB-dependent effects of IVIg are dependent of the presence of a particular population of macrophages, the "regulatory" (CSF-1 dependent) macrophages (112).

Recently, a role for both activating and inhibitory FcγR in the control of ITP has been reported (113). It has been shown that the transfer of IVIg-primed CD11c$^+$ dendritic cells drives the amelioration of ITP through the engagement of activating FcγR expressed on dendritic cells by IVIg as a first event (113), suggesting that ITAM-bearing receptors are also involved in the inhibition of immune responses.

Furthermore, Park Min *et al*. (114) have described the role of small immune complexes and FcγRIII in negative regulation of IFN-γ mediated inflammation which contributes to therapeutic efficacy of IVIg, independent of FcγRIIB expression. Thus, its FcγRIIB and FcγRIII-dependent actions may be complementary.

Recently, Kaneko *et al*., have reported that antiinflammatory activity of IVIg results from Fc sialylation (115). Recombinant sialylated Fc fragments of IgG could, therefore, be an attractive therapeutic alternative that could help to overcome the shortage of IVIg for several autoimmune or inflammatory pathologies. Moreover, this study suggests that like monoclonal antibodies (MAbs), the pattern of N-glycosylation of the Fc of polyclonal immunoglobulins could be engineered in order to optimize IVIg efficacy (116).

The Immunoregulatory Role of Antiidiotypic Antibodies Present in IVIg

Interactions between IVIg and idiotypic determinants of autoantibodies provide the basis for the ability of IVIg to regulate autoreactive B cell clones *in vivo*. Several lines

of evidence indicate that antibodies in IVIg recognize idiotypes of disease-associated and natural autoantibodies, and antigen receptors on B lymphocytes. Intact IVIg and $F(ab')_2$ fragments of IVIg neutralize the activity of various autoantibodies and/or inhibit the binding of autoantibodies to their respective autoantigens *in vitro*. Inhibition of autoantibody activity by IVIg is observed in the case of autoantibodies to factor VIII, thyroglobulin, DNA, intrinsic factor, peripheral nerve, neutrophil cytoplasmic antigens, platelet gpIIb/IIIa, the acetylcholine receptor, endothelial cells, phospholipids, nephritic factor, and retinal autoantigen-β (117). Reduction in the autoantibody titer *in vivo*, is observed in several conditions following IVIg therapy (118, 119). Presence of antiidiotypes to disease-associated autoantibodies may explain the efficacy of IVIg in myasthenia gravis, Lambert–Eaton syndrome, and antibody-mediated neuropathies (120, 121). However, Fab-mediated effects are unlikely to be solely responsible for the effect of IVIg.

Attenuation of Complement-Mediated Damage

The interaction of IVIg with complement prevents the generation of C5b-9 membrane attack complex and subsequent complement-mediated tissue damage, by scavenging active complement components and diverting complement attack from cellular targets (122). IVIg binds the activated components C3b and C4b in a C1q-independent (123) and C1q-dependent (124) fashion, thus preventing the deposition of these fragments on target surfaces of complement activation. This action of IVIg is relevant in the treatment of patients with severe dermatomyositis, Guillain–Barré syndrome, and myasthenia gravis. Recently, a $F(ab')_2$-mediated neutralization of C3a and C5a anaphylotoxins has been proposed as an effector function of IVIg (125).

Modulation of the Production of Cytokines

Modulation of the production of cytokines and cytokine antagonists by IVIg is a major mechanism by which immunoglobulin exerts its antiinflammatory effects *in vivo* (126) in neuromuscular disorders like inflammatory myopathies, demyelinating neuropathies, and myasthenia gravis (120, 127). IVIg was shown to selectively trigger the production of interleukin-1 receptor antagonist (IL-1ra), the natural antagonist of IL-1, in cultures of purified monocytes, without concomitant effect on the production of the proinflammatory cytokines IL-1α, IL-1β, IL-6, and TNF-α (128, 129). Circulating levels of interleukin-1β in patients with the Guillain–Barré syndrome decrease after treatment with IVIg (130). The antiinflammatory effects of IVIg relating to modulation of cytokine production are not restricted to monocytic cytokines, but are also largely dependent on the ability of IVIg to modulate Th1 and Th2 cytokine production (131).

Interaction of IVIg with Membrane Molecules of Antigen Presenting Cells, B and T Lymphocytes

Besides binding to idiotypes of immunoglobulins, IVIg reacts with a number of membrane molecules of T cells, B cells, and monocytes, which are relevant to the control of autoreactivity and induction of tolerance to self. Thus, IVIg is shown to contain antibodies to variable and constant regions of the human T-cell receptor (9), cytokines and cytokine receptors (12, 13), CD5 (10), CD4 (11), HLA class I molecules (14), RGD adhesion motif (17), the chemokine receptor CCR5 (132), CD40 (133), and Fas (16). Antibodies directed to such functional molecules of lymphocytes may be important to the immunomodulatory effect of normal immunoglobulins. IVIg inhibits toxic epidermal necrolysis (TEN) (Lyell's syndrome) by blocking the interaction of Fas with its natural ligand, Fas ligand (Fas L) (16). While Fas receptors are normally expressed in keratinocytes, high levels of soluble Fas ligand were observed in the sera of patients with TEN. The observed beneficial effect of IVIg in TEN is believed to be due to the presence of naturally occurring antibodies against Fas in IVIg that block Fas–Fas L interaction (16).

Interaction of IVIg with Dendritic Cells

Because of their capacity to stimulate naive T cells, dendritic cells (DC) have a central role in the initiation of primary immune responses and are considered promising targets for immunotherapy (134). Dendritic cells (DC) are the primary mediators for the immunosuppressive effect of IVIg on T-cell activation (97, 135). IVIg inhibits the differentiation and maturation of DC *in vitro*, abrogates the capacity of mature DC to secrete IL-12 upon activation, while enhancing IL-10 production. IVIg-induced downregulation of costimulatory molecules, associated with modulation of cytokine secretion results in inhibition of auto- and alloreactive T-cell activation and proliferation (135). At "therapeutic" high dose, IVIg interferes with the differentiation of DC in SLE patients, along with an inhibition of the expression of HLA and CD80/CD86 molecules. IVIg-treated immature DC also display reduced ability to ingest nucleosomes (97). Given the critical role of HLA molecules and costimulatory signals delivered by CD80 and CD86 for optimal antigen presentation and T-cell activation, the inhibition of expression of these molecules by IVIg offers a plausible explanation for the efficacy of IVIg in SLE and other immunoinflammatory conditions.

Contrary to its inhibitory effect on DC with "therapeutic" high dose, IVIg exerts an agonistic effect on the differentiation of DC with "replacement" low dose. DC from patients with common variable immunodeficiency (CVID) show defective differentiation (136). In the presence of IVIg, the DC from CVID patients show upregulation of CD1a (marker of differentiated DC) and costimulatory molecules CD80, CD86, and CD40 (molecules critical in DC–T-cell cross-talk) as compared to DC in the presence of autologous plasma alone. Partial restoration of DC phenotypes in primary immunodeficiency patients, points toward the role of IVIg in maintaining immune homeostasis, through its interaction with the cellular compartment (137, 138). Thus, IVIg replacement therapy is much more than a mere transfer of antibodies in immunodeficient patients.

Effect on Remyelination

In addition to the immunomodulating effects, immunoglobulins seem to have a remyelinating potential. In Theiler's virus-induced murine encephalomyelitis (TMEV), an animal model of MS, myelin protein antibodies, hyperimmune serum, as well as pooled immunoglobulins from donor mice promote and improve remyelination (139, 140). Similar results have been observed in experimental autoimmune neuritis (EAN), the animal model of GBS (141). Little is known about the exact mechanism behind this phenomenon. It is possible that immunoglobulins may, through improved opsonization of myelin and axons, lead to a limited secondary cellular infiltration and thus to protection from further injury. Removal of myelin-associated inhibitors that are known to be present in central nervous system (CNS) and peripheral nervous system (PNS) lesions may, in addition, play a role in this process. Immunoglobulins lead to increased uptake of myelin debris by macrophages *in vitro* (142). The phagocytosis of myelin debris by macrophages in demyelinating diseases may lead to removal of inhibitory factors. It may also lead to production of growth factors by macrophages, such as platelet-derived growth factor, ciliary neurotrophic factor, or insulin growth factor (143). Further studies are necessary to investigate the effects of immunoglobulins on macrophages and the role of this cell in remyelination.

CONCLUSION

Considerable progress has been made in understanding the mechanisms by which IVIg exerts immunomodulatory effects in autoimmune and inflammatory disorders. Its mechanism of action is complex, involving modulation of expression and function of Fc receptors, interference with activation of complement and the cytokine network, provision of antiidiotypic antibodies, regulation of cell growth, and effects on the activation, differentiation, and effector functions of DC, T and B cells. The therapeutic effects of IVIg in all likelihood reflect the functions of natural antibodies in maintaining immune homeostasis in healthy people.

Over the past two decades, IVIg has become the preferred treatment for Guillain–Barré syndrome, chronic inflammatory demyelinating polyneuropathy, and Kawasaki disease. The ability of IVIg to interact through complementary V regions of antibodies, antigen receptors, and relevant soluble and surface molecules, provides the basis for re-emergence of normal immune repertoire in treated patients.

ACKNOWLEDGMENTS

This work was supported by grants from Institut National de la Santé et de la Recherche Médicale INSERM-Indian Council of Medical Research (ICMR) collaborative project and Centre National de la Recherche Scientifique (CNRS), France; Laboratoire Français du Fractionnement et des Biotechnologies, Les Ulis, France; CSL Behring AG, Switzerland; Octapharma, Austria; and Talecris, USA. While we do not intend to undermine the value of uncited studies, we regret that due to space limitations, we could not cite all relevant published work.

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