Clin. exp. Immunol. (1991) **86,** 192-198

REVIEW

Intravenous immunoglobulins (IVIg) in the treatment of autoimmune diseases

S.-V. KAVERI, G. DIETRICH, V. HUREZ & M. D. KAZATCHKINE
INSERM U28 and Unité d'Immunopathologie, Hôpital Broussais, Paris, France

(Accepted for publication 22 July 1991)

SUMMARY

Intravenous immunoglobulin (IVIg) therapy is increasingly used in autoimmune diseases. Although its efficacy has only been established in a few specific antibody-mediated autoimmune conditions, accumulating evidence on the regulatory role of circulating immunoglobulins in the selection of peripheral B cell repertoires makes it an attractive potential therapeutic option to clinical immunologists. This overview briefly discusses the current use of IVIg in human autoimmune diseases with a particular emphasis on the possible mechanisms by which IVIg could suppress pathological autoimmune responses.

Keywords intravenous immunoglobulins (IVIg) autoimmunity idiotypic regulation

INTRODUCTION

The concept of immunoregulation of autoimmune responses with IVIg has been gaining increasing interest in the last 10 years since the first report of their use in idiopathic thrombocytopenic purpura (Imbach *et al.*, 1981). The beneficial effect of IVIg in certain autoimmune diseases has opened up novel approaches for the treatment of autoimmune disorders and for understanding the basic mechanisms regulating the expression of the physiological and pathological autoimmune repertoires.

INTRAVENOUS IMMUNOGLOBULINS

IVIg are therapeutic preparations of normal polyspecific IgG obtained from plasma pools of over 20000 healthy blood donors. Currently used preparations are made of intact IgG with a distribution of subclasses corresponding to that of normal serum and a half-life of 3 weeks *in vivo* for Igb1, Igb2 and Igb4, and somewhat less for Igb3. Most of the preparations contain only traces of IgA, IgM and of Fc-dependent IgG aggregates (Table 1). IVIg contain up to 30% of $F(ab')_2$-$F(ab')_2$ dimers as assessed by size-exclusion chromatography and electronmicroscopy. The dimers are the consequence of V-region complementarity between immunoglobulins in the pool (Roux & Tankersley, 1990). Owing to the large number of donors, IVIg represent a wide spectrum of the expressed normal human IgG repertoire, including antibodies to external antigens, autoreactive antibodies and anti-antibodies.

Correspondence: Professor Michel D. Kazatchkine, Unité d'Immunopathologie, Hôpital Broussais, 96 Rue Didot, 75674 Paris, Cedex 14, France.

THE USE OF IVIg IN THE TREATMENT OF AUTOIMMUNE DISEASES

The clinical use of IVIg in autoimmune disorders has been summarized in several reviews (Gordon, 1987; Eibl & Wedgwood, 1989; Berkman, Lee & Gale, 1990; Schwartz, 1990) and volumes (Morell & Nydegger, 1986; Bona & Kohler, 1989; Imbach, 1991). Infusion of IVIg has resulted in clinical improvement and/or a decrease in autoantibody titre (Fig. 1) in the autoimmune diseases listed in Table 2. In this list, 'autoimmune diseases' is used in a broad sense including diseases associated with pathogenic autoantibodies, diseases which are most probably T cell mediated and diseases for which the evidence for a pathogenic autoimmune process is only indirect. The beneficial effect of IVIg has been established by controlled trials against placebo or against conventional treatment in a few of these diseases including childhood acute idiopathic thrombocytope-

Table 1. Characteristics of commonly used IVIg preparations

IVIg	Fragments (%)	Aggregates (%)	IgA (μg/ml)	Monocyte FcR-binding efficiency (graded 1-7)
Sandoglobulin®	< 10	1·0	610	2
Gammagard®	0	0·4	2	1
Gammimmune®	5-8	3·6	170	5
Gammimmune N®	1	0·5	74	NT
Endobulin®	24	0	< 50	4

NT, not tested.

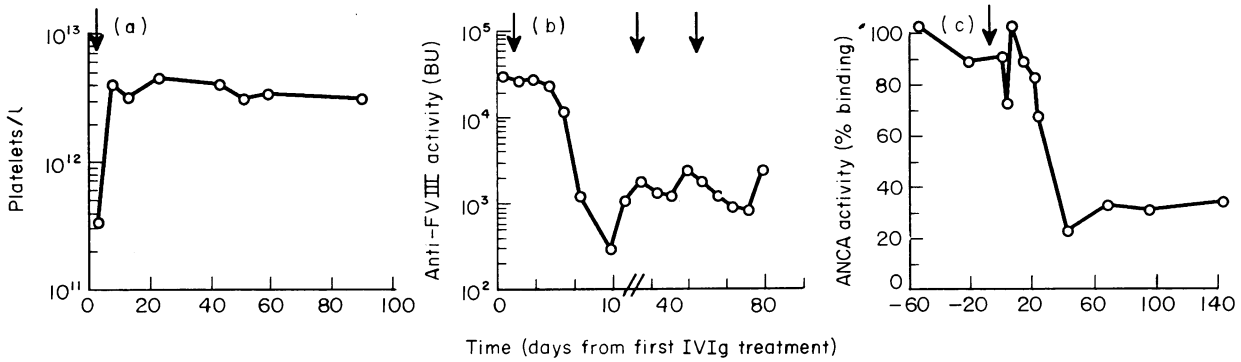

Fig. 1. Treatment with IVIg of patients with autoimmune diseases. (a) Kinetics of increase in platelet number in a patient with ITP (adapted from Imbach *et al.*, 1981). (b) Kinetics of decrease in anti-factor VIII antibody titre in a patient with anti-factor VIII autoimmune disease (adapted from Sultan *et al.*, 1984) (BU, Bethesda units). (c) Kinetics of decrease in ANCA activity in a patient with systemic vasculitis (adapted from Lockwood, 1991). Arrows depict infusions of IVIg (0·4 g/kg per day for five consecutive days).

Table 2. Reported beneficial effect of IVIg in human autoimmune diseases*

Idiopathic thrombocytopenic purpura (Imbach *et al.*, 1981, 1985; Bussel *et al.*, 1983; Newland *et al.*, 1983)
Autoimmune haemolytic anaemias (Bussel, Cunningham-Rundles & Abraham, 1987)
Autoimmune neutropenia (Hilgartner & Bussel, 1987)
Autoimmune erythroblastopenia (McGuire *et al.*, 1987)
Myasthenia gravis (Arsura, 1989)
Guillain–Barré syndrome (Lundkvist *et al.*, 1989)
Chronic inflammatory demyelinating polyneuropathy (Lundkvist *et al.*, 1989)
Multiple sclerosis
Monoclonal gammopathies with anti-mag activity (Cook *et al.*, 1990)
Adrenoleucodystrophy
Grave's disease
Systemic lupus erythematosus (Jordan, 1989; Akashi *et al.*, 1990; Maier *et al.*, 1990)
Anti-cardiolipin antibodies and recurrent abortions (Carreras *et al.*, 1988)
Refractory polymyositis (Cherin *et al.*, 1991)
Juvenile rheumatoid arthritis (Groothoff & Van Leeuwen, 1988)
Rheumatoid arthritis (Mitropoulou, Becker & Helmke, 1987)
Felty's syndrome (Breeveld, Brand & Aken, 1985)
Ulcerative colitis
Crohn's disease (Knoflach, Muller & Eibl, 1990)
Certain glomerulonephritides
ANCA positive systemic vasculitis (Jayne *et al.*, 1991)
Kawasaki's disease (Newburger *et al.*, 1986; Newburger *et al.*, 1991)
Anti-factor VIII autoimmune disease (Sultan *et al.*, 1991)
Birdshot retinopathy (Le Hoang, Jobin & Kazatchkine, 1991)

*Autoimmune diseases in which a clinical improvement and/or decrease in autoantibody titre has been established or suggested. The upper part of the table lists peripheral autoimmune cytopenias.

nic purpura (ITP) (Imbach *et al.*, 1985), chronic inflammatory demyelinating polyneuropathy (CIDP) (Van Doorn *et al.*, 1990) and Kawasaki's disease (Newburger *et al.*, 1991). In most diseases, however, the evidence for the beneficial effect of IVIg comes from open trials or anecdotal reports. There are major difficulties at the present time in conceiving adequate protocols for controlled trials of IVIg in autoimmune diseases since information is still missing on the amount of IVIg that should be given, the frequency of administration, and the mechanisms of action of IVIg. These parameters may differ between diseases and, possibly, between patients within a given pathological entity.

Since the first reports of the use of IVIg in patients with ITP, IVIg are usually given at a daily dosage of 0·4 g/kg body weight for 5 days; IVIg are often administered every 4 weeks in patients requiring repeated infusions. In acute ITP and autoimmune neutropenia, the increment in the target cell counts occurs within hours after infusion and is most often only transient, lasting for a few days. In diseases other than peripheral cytopenias, the effect of IVIg may be either short-term and requiring repeated treatment, e.g. in CIDP, or long-lasting (e.g. in anti-factor VIII autoimmune disease) indicating that the treatment has resulted in down regulation of autoantibody synthesis. Reviews or selected reports of the use of IVIg in diseases are listed in Table 2. The present review focuses on the mechanisms by which IVIg may exert an immunomodulatory action in autoimmune diseases.

V-REGION-DEPENDENT MODULATION OF THE EXPRESSION OF THE AUTOIMMUNE REPERTOIRE BY IVIg

Several mutually non-exclusive mechanisms of action of IVIg in autoimmune diseases have been proposed. These include the reversible blockade of Fc receptors on cells of the reticulo-endothelial system by Fc fragments of injected immunoglobulins; Fc-dependent feedback inhibition of autoantibody synthesis by B cells and modulation of suppressor or helper T cell functions; interference of IVIg with complement-mediated damage; modulation by IVIg of cytokine secretion; V-region-dependent modulation by IVIg of the expression of the autoimmune repertoire. We have concentrated on the latter hypothesis which is in agreement with the observed heterogeneity of clinical responses to IVIg treatment and corroborates the experimental evidence indicating a role for circulating immunoglobulins in the selection of the expressed repertoire.

The presence in IVIg of anti-idiotypic antibodies directed against pathological autoantibodies was first suggested during the investigation of two patients with autoantibodies to Factor

Table 3. Affinity chromatography of IgG or $F(ab')_2$ autoantibodies on Sepharose-bound $F(ab')_2$ fragments of IVIg

Patients' autoantibody	Specific autoantibody activity	
	Loaded specific	Acid-eluted specific
Anti-F VIII $F(ab')_2$	0·80 BU/mg†	38·09 BU/mg
Anti-thyroglobulin $F(ab')_2$	1·26 AU/mg‡	18·20 AU/mg
Anti-DNA IgG	0·31 AU/mg	10·80 AU/mg
Anti-intrinsic factor IgG	3·26 AU/mg	4·32 AU/mg
ANCA IgG	1·12 AU/μg	3·40 AU/μg
Anti-retinal S antigen $F(ab')_2$	1·08 AU/mg	6·17 AU/mg

*IgG or $F(ab')_2$ fragments containing autoantibody activity were chromatographed on Sepharose-bound $F(ab')_2$ fragments from IVIg. The columns were washed until no protein was found in the effluent and then eluted at pH 2·8. Autoantibody activity was measured in the loaded material and in the acid-eluted fractions.

†Bethesda units.

‡Autoantibody activity was expressed as the optical density obtained in the ELISA at a given input of autoantibody in each assay. This concentration was in the linear portion of the ELISA curves. Arbitrary units were calculated relative to the OD obtained in the corresponding assay with a fixed input of a standard IgG.

VIII (Sultan *et al.*, 1984). The direct interaction between infused IVIg and circulating autoantibodies was demonstrated by the dose-dependent neutralization of autoantibody activity *in vitro* upon incubation of $F(ab')_2$ fragments of patients' IgG with $F(ab')_2$ fragments of IVIg. In further studies, the ability of IVIg to interact with the combining site of autoantibodies was also observed with anti-thyroglobulin autoantibodies from patients with Hashimoto's thyroiditis, anti-neuroblastoma antibodies from patients with Guillain–Barré syndrome and CIDP, anti-neutrophil cytoplasm antibodies (ANCA) autoantibodies from patients with Wegener's granulomatosis, anti-intrinsic factor autoantibodies from patients with megaloblastic anaemia, anti-gp IIb IIIa autoantibodies from patients with idiopathic thrombocytopenic purpura, anti-DNA autoantibodies from patients with SLE, cytotoxic antibodies from patients with autoimmune erythroblastopenia and anti-retinal antigen autoantibodies from patients with Birdshot retinopathy (McGuire *et al.*, 1987; Rossi, Sultan & Kazatchkine, 1988; Rossi & Kazatchkine, 1989; Berchtold *et al.*, 1989; Van Doorn *et al.*, 1990; Rossi *et al.*, 1991). In almost all instances, inhibition of autoantibody activity by IVIg was dose-dependent with a bell-shaped pattern of inhibition curves and a maximum inhibition occurring at a specific molar ratio between patients' IgG and IVIg.

Three additional lines of evidence demonstrate that IVIg contain anti-idiotypes against autoantibodies. First, IVIg coupled to an immuno-affinity matrix specifically retain autoantibodies. Thus, acid eluates from affinity chromatography of autoantibodies on Sepharose-bound $F(ab')_2$ fragments of IVIg contain 1·3–50-fold higher autoantibody activity than unchromatographed material (Table 3). These experiments indicate that IVIg contain antibodies that bind with high affinity to antigenic determinants located within, near or outside the paratope in variable regions of autoantibodies. Second, IVIg do not contain detectable antibodies against the most commonly expressed allotypes in the $F(ab')_2$ region of human IgG (Rossi *et al.*, 1988). Third, IVIg recognize idiotypes defined by heterologous anti-idiotypic antibodies on autoantibodies. Thus, IVIg has been shown to compete with monoclonal or polyclonal anti-idiotypic reagents for binding to anti-FVIII (Dietrich *et al.*, 1990) and to anti-thyroglobulin (Dietrich & Kazatchkine, 1990) autoantibodies. The target idiotypes on autoantibodies are either binding-site related (β and γ type) or located outside the antibody combining site (α type). In the case of anti-thyroglobulin autoantibodies, IVIg recognize an immunodominant, cross-reactive alpha idiotype that is specifically expressed by antibodies from patients with Hashimoto's disease and not by natural anti-thyroglobulin autoantibodies from healthy individuals. The expression of this disease-associated idiotype correlates with the recognition of restricted epitopic determinants on human thyroglobulin (Dietrich *et al.*, 1991a). Cross-reactive idiotypes are frequently observed on human autoantibodies (Matsuyama, Fukumuri & Tanaka, 1983; De La Fuente & Hoyer, 1984; Delves & Roitt, 1984; Isenberg *et al.*, 1984; Fong *et al.*, 1986; Dang *et al.*, 1988; Lefvert, 1988; Ruiz-Arguelles, 1988). Since these idiotypes are phenotypic markers of rearranged V region genes, their occurrence indicates that they originate from a potential repertoire shared by a large number of non-related individuals. The idiotypes would not be expressed in healthy individuals due to specific idiotypic regulation. Thus, the finding in IVIg of anti-idiotypes against disease-specific cross-reactive idiotypes of autoantibodies may be indicative of the presence in normal human IgG of anti-idiotypes that control expression of the autoimmune repertoire.

Several factors account for the presence in IVIg of anti-idiotypic activity against disease-associated autoantibodies. One of the factors may be the presence among the individuals contributing to the IVIg pool of 'privileged' donors with respect to anti-idiotype content of serum IgG: such privileged donors could be individuals who have recovered from autoimmune diseases through autologous idiotypic suppression or aged individuals over 50 years whose serum IgG exhibits an increased frequency of anti-idiotypes against autoantibodies (Sultan, Rossi & Kazatchkine, 1987; Dietrich, Kaveri & Kazatchkine, 1991b). Another major factor is the synergistic effect that is obtained by the complementation of individual antibody sources in the pool. We have recently found that mixing purified IgG from as few as two or three donors may be sufficient for the acquisition by the mixture of an anti-idiotypic activity that is not detected in individually tested IgG. Roux & Tankersley (1990) have clearly demonstrated that the proportion of dimers in IVIg increases with the number of donors contributing to the pool. The dimers form as a consequence of V-region-dependent interactions between IgG molecules in the pool. Thus, anti-idiotypic activity of IVIg would depend on the number of donors and on the occurrence of relevant idiotypes in the donor population. This would imply that IVIg contain high amounts of anti-idiotypes directed against cross-reactive idiotypes.

The subtle limits that exist between pathological autoimmunity and physiological autoreactivity are still not clearly understood (Huetz *et al.*, 1988a). In the last few years, evidence has accumulated demonstrating the physiological presence of autoreactive antibodies in the serum of healthy individuals (Avrameas, 1991). Natural autoreactive antibodies are of IgM, IgG and IgA isotypes; the autoantibodies are directed against evolutionarily conserved molecules (e.g. cytoskeletal proteins

and nuclear antigens), against antigens which may become targets of antibodies in autoimmune diseases (e.g. thyroglobulin, neutrophil cytoplasmic antigens, intrinsic factor) and often display polyreactivity. From experiments in mice, it has been postulated that recognition of self represents the physiological basis of the autonomous internal activity of the immune system (Varela & Coutinho, 1991). Naturally activated, autoreactive B cells are highly connected within a network of V-region-dependent interactions, providing a basis for the control of the expression of the autoimmune repertoire under physiological conditions and for the prevention of the emergence of pathological recognition of self. Pathological autoantibodies may arise as a result of an abnormal expansion of germline-encoded natural autoreactive clones (Sanz & Capra, 1988) or of somatically mutated, possibly autoantigen-driven, autoreactive clones (Davidson *et al.*, 1987). In either case, the emergence of pathological autoimmunity could be the consequence of a primary or secondary defect in the network regulatory mechanisms which control the expression of the autoimmune repertoire in healthy individuals.

In addition to their ability to interact with pathological autoantibodies, IVIg recognize idiotypic determinants on natural, IgM and IgG autoantibodies from healthy individuals. The ability of IVIg to interact idiotypically with natural autoantibodies is not correlated with the polyreactivity of the autoreactive antibodies (Rossi *et al.*, 1990). Idiotypic interactions also connect a subset of normal serum IgG as indicated by the presence in IVIg of natural IgG autoantibodies and complementary IgG molecules (Rossi, Dietrich & Kazatchkine, 1989). By reacting with natural, autoreactive IgM and IgG antibodies, IVIg may alter the available immune repertoire.

T lymphocytes are involved in the regulation of the expression of the autoreactive B cell repertoire. Activation of some autoreactive B cell clones in mice has been shown to require the help of naturally activated T cells (Huetz *et al.*, 1988b). A number of experimental and human autoimmune diseases are probably caused by the activation of autoreactive and autoaggressive T cell clones. Studies on the suppression or prevention of autoimmune disease (e.g. experimental allergic encephalomyelitis (EAE)) after vaccination with T lymphocytes suggest a regulatory role on the expression of autoreactivity for an idiotypic T cell network integrated within complex physiological, regulatory interactions that occur among lymphocytes and between lymphocytes and antibodies (T–T and T–B network) (Kumar *et al.*, 1989; Varela & Coutinho, 1991).

Idiotypic suppression can be achieved in adults by treatment of newborn mice with a natural syngeneic connected anti-idiotypic MoAb (Sundblad *et al.*, 1989). Infusion of non-autoimmune mice with pooled normal murine IgG induces a selective stimulation of peripheral autoreactive B cells and $CD4^+$ T lymphocytes (Sundblad *et al.*, 1991), and alters the V_H gene usage of autoantibodies (Freitas *et al.*, 1991). These observations provide direct evidence for the ability of natural IgG to modulate the expressed autoimmune repertoire.

Changes in the dynamic behaviour of disease-associated and of natural autoantibodies upon infusion of IVIg provide further evidence for the interference of IVIg with the regulatory function of the immune network *in vivo* (Varela *et al.*, 1991). Autoantibody activity fluctuates in serum with a well defined periodicity in healthy individuals. The dynamics of spontaneous fluctuations appear to be clearly different between healthy individuals and patients with autoimmune diseases. As shown in Fig. 2, infusion of IVIg in patients with Birdshot retinopathy, a human disease resembling an experimental model of autoimmune uveitis (EAU), alters the dynamics of expression of disease-related autoantibodies (i.e. antibodies to retinal antigens) and also the dynamics of natural autoantibodies of irrelevant specificities (anti-thyroglobulin autoantibodies). These data indicate that infusion of IVIg modifies the endogenous regulation of the expressed repertoire in treated patients. In this context, IVIg therapy could be envisaged as a substitutive therapy providing an autoimmune patient with normal regulatory elements of the functional immune network (Dietrich *et al.*, 1991b).

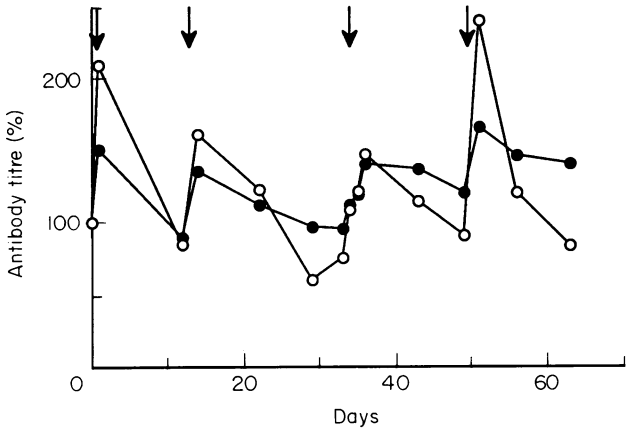

Fig. 2. Time course of the relative variations of anti-retinal S antigen activity (○) and anti-thyroglobulin autoantibody activity (●) in serum during the treatment with IVIg of a patient with Birdshot retinopathy. Antibody titres are expressed as per cent of the pretreatment titre. Arrows denote infusions of 0·4 g/kg body weight of IVIg for 4 days.

Fc-DEPENDENT MECHANISMS OF ACTION OF IVIg

The V-region-dependent immunoregulatory effects of IVIg discussed above are probably best achieved with intact IgG since the modulatory effects of anti-idiotypic antibodies on B and T cell functions *in vitro* often require binding of the antibody to the target cell via both the antibody combining site and the Fc portion (Uher & Dickler, 1986) and since idiotypic suppression in animals requires intact IgG.

Several mechanisms of action of IVIg exclusively implying the role of the Fc portion of infused IgG have also been postulated (Table 4). Fc receptor blockade by the Fc portion of infused IgG appears to be an important mechanism for the short-term rapid elevation of the platelet counts in patients with ITP treated with IVIg and is probably critical for the beneficial effect of IVIg in peripheral autoimmune cytopenias in general. The clearance of autologous erythrocytes coated with anti-Rhesus D antibodies was found to be decreased for about 4 weeks following treatment with IVIg (Fehr, Hofmann & Kappeler, 1982). Platelet survival is prolonged in patients with ITP treated with IVIg. *In vitro* studies have shown that peripheral blood monocytes from IVIg-treated patients with ITP exhibited a decreased ability to form rosettes with IgG-coated erythrocytes (Kimberly *et al.*, 1984). Furthermore, *in vivo*

Table 4. Possible Fc-dependent mechanisms by which IVIg may exert immunoregulatory functions

Reversible blockade of FcγR on phagocytic cells
Non-specific induction of suppressor cell function
Inhibition of antibody synthesis by B cells
Modulation of the synthesis and release of interleukins and of inflammatory mediators
Idiotypic regulation of B and T cell functions
Inhibition of the binding of complement components to targets of complement activation
Alteration of the structure and solubility of immune complexes

blockade of FcR on macrophages following treatment of Rh-D$^+$ ITP patients with anti-D antibodies (Salama, Muller-Eckhart & Kiefel, 1983) or treatment with a MoAb directed against FcγRIII (Clarkson *et al.*, 1986), mimicked the effect of IVIg, by inhibiting the accelerated splenic clearance of antibody-coated platelets.

It is conceivable that the binding of IVIg to FcR on monocytes and lymphocytes would modulate the synthesis and/or the release of proinflammatory and immunoregulatory cytokines. However, evidence for such an effect of IVIg *in vitro* and *in vivo* is still weak. IVIg were suggested to exert anti-pyretic activity in *in vivo* experiments in rabbits (Iwata *et al.*, 1987) and this could be related to the observed inhibition by IVIg of TNF-α and IL-1 production by LPS-stimulated peritoneal exudate cells *in vitro* (Shimozato *et al.*, 1991). The beneficial effect of IVIg that has been reported in patients with asthma (Smith *et al.*, 1988; Mazer, Giclas & Gelfand, 1989) could be due to down regulation of the release of mediators involved in immediate hypersensitivity reactions and late phase allergic responses.

Independently of their ability to bind to FcR, Fc fragments of IVIg may interfere with pathogenic processes by altering the physico-chemical properties of immune complexes and by interacting with complement components in the fluid-phase and/or on the target surface of complement activation. Recent studies have shown a dramatic effect of IVIg in improving the survival of guinea pigs injected with lethal doses of anti-Forssman antibodies (Basta, Kirshborn & Frank, 1989). The protective effect of IVIg was dependent on the uptake of nascent C3b and C4b by infused IVIg, thus diverting complement deposition and attack from target cell membranes.

Intravenous immunoglobulins are the definitive substitutive treatment for primary and secondary humoral immune deficiencies. Their efficacy has been proven, observed in uncontrolled studies or only suggested in isolated reports in a large number of autoimmune diseases. Some of the evidence summarized in this review suggests to us that treatment with IVIg may be viewed as an active immunotherapy aimed at stimulating regulatory mechanisms which control the expression of the autoimmune repertoire. A number of additional or alternative mechanisms of action of IVIg may be effective. The investigation of the effect and mechanisms of action of IVIg in autoimmune diseases in the coming years will provide non-immunosuppressive approaches to treatment and a better understanding of the molecular and cellular events leading to the shift from physiological autoreactivity to pathological autoimmunity.

ACKNOWLEDGMENTS

This work was supported by Institut National de la Santé et de la Recherche Médicale (INSERM), France, and the Central Laboratory of the Swiss Red Cross, Bern, Switzerland. The authors wish to thank A. Brand, A. Coutinho, D. Jobin, C. M. Lockwood, I. Lundkvist, U. Nydegger, F. Rossi and F. Varela for helpful suggestions and collaboration in this work.

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