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REVIEW

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Immunomodulation of autoimmune and inflammatory diseases with intravenous immunoglobulin

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Abstract Intravenous immunoglobulin (IVIg) has been used in the treatment of primary and secondary antibody deficiencies for over two decades. Since the early 1980s, the therapeutic efficacy of IVIg has been established in idiopathic thrombocytopenic purpura, Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, myasthenia gravis, dermatomyositis and Kawasaki syndrome, and the prevention of graft versus host disease in recipients of allogeneic bone marrow transplants. Its use has also been reported in a large number of other autoimmune and systemic inflammatory conditions. In this review, we discuss the mechanisms by which IVIg exerts immunomodulatory effects in immune pathologies.

Key words Intravenous immunoglobulin • Autoimmune disorders • Inflammatory diseases • Mechanisms

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Intravenous immunoglobulins

Intravenous immunoglobulin (IVIg) has increasingly been used for the treatment of autoimmune and systemic inflammatory diseases and in supportive therapy of immunodeficient patients [1–3]. The number of diseases in which the effect of IVIg therapy has been demonstrated by large-scale controlled clinical trials remains limited. Available clinical and experimental evidence suggests, however, that a wide spectrum of immune-mediated conditions could benefit from IVIg, including acute and chronic/relapsing diseases, autoimmune diseases mediated by pathogenic autoantibodies or by autoaggressive T cells and inflammatory disorders e.g., an imbalance in cytokine networks [1, 2, 4–8] (Table 1).

IVIg is prepared from pools of plasma of at least 3000–10 000, and sometimes up to 100 000, healthy blood donors. It can thus be assumed that IVIg contains a sampling from the entire array of variable regions of antibodies that would be present in normal serum. Having a large number of donors in the pool adds more individual activities to the IVIg preparation, although it carries the risk of diluting out any useful activity that is rare. Hence, IVIg is comprised of a broad range of immune antibodies directed to pathogens and foreign antigens that are critical for the substitutive treatment of patients with humoral immune deficiencies, as well as of natural antibodies to a number of self-antigens, which are believed to be essential for the immunoregulatory effects of IVIg in immune-mediated disorders.

Table 1 Immune-mediated diseases in which a beneficial effect of IVIg has been reported

Idiopathic thrombocytopenic purpura (ITP)*
Acquired immune thrombocytopenias
Autoimmune neutropenia
Autoimmune haemolytic anaemia
Autoimmune erythroblastopenia
Parvovirus B19-associated red cell aplasia
Anti-factor VIII autoimmune disease
Acquired von Willebrand's disease
Guillain-Barré syndrome*
Chronic inflammatory demyelinating polyneuropathy (CIDP)*
Myasthenia gravis*
Multifocal neuropathy
Polymyositis
Dermatomyositis*
Kawasaki disease*
ANCA-positive systemic vasculitis
Antiphospholipid syndrome
Recurrent spontaneous abortions
Rheumatoid arthritis and Felty's syndrome
JRA
SLE
Thyroid ophthalmopathy
Birdshot retinochoroidopathy*
Graft versus host disease*
Multiple sclerosis
Insulin-dependent diabetes mellitus
Steroid-dependent asthma
Steroid-dependent severe atopic dermatitis
Crohn's disease

*Indicates diseases in which evidence for the effect of IVIg has been obtained in controlled trials

Table 2 Immunoregulatory effects of IVIg

Fc receptor-mediated effects
Blockade of Fc receptors on macrophages and effector cells
Antibody-dependent cellular cytotoxicity
Induction of inhibitory FcγRIIB receptors
Anti-inflammatory effects
Attenuation of complement-mediated damage
Decrease in immune complex-mediated inflammation
Induction of anti-inflammatory cytokines
Inhibition of activation of endothelial cells
Neutralisation of microbial toxins
Reduction in steroid requirements
Effect on B cells and antibodies
Control of emergent bone marrow B-cell repertoires
Negative signalling through Fcγ receptor
Selective down-regulation/up-regulation of antibody production
Neutralisation of circulating autoantibodies by anti-idiotypes
Effect on T cells
Regulation of T helper cell cytokine production
Neutralisation of T-cell superantigens
Cell proliferation/death
Inhibition of lymphocyte proliferation
Regulation of apoptosis
Effect on dendritic cells
Inhibition of differentiation and maturation
Regulation of inflammatory cytokine production
Effect on remyelination

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. Normal human serum contains natural Abs of the IgG, IgM and IgA isotypes. A majority of natural antibodies in the serum of healthy individuals and, as a consequence, in the IVIg pool, are self-reactive (natural autoantibodies, NAbs). As 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 [9, 10]. The half-life of infused IVIg in immunocompetent individuals is three weeks. The preparations contain intact Fc molecules that 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.

The therapeutic efficacy of IVIg has been well established in idiopathic thrombocytopenic purpura, Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, myasthenia gravis, dermatomyositis (DM), Kawasaki syndrome, patients with stiff-person syndrome and reported in a large number of other autoimmune and systemic inflammatory conditions like polymyositis, multifocal motor neuropathy, relapsing-remitting multiple sclerosis, sepsis and other conditions [2, 11].

Mode of action of intravenous immunoglobulin

The mode of action of IVIg is complex, involving modulation of expression and function of Fc receptors, interference with complement activation and the cytokine network, provision of anti-idiotypic antibodies and modulation of T- and B-cell activation, differentiation and effector functions (Table 2) [1, 3, 6, 7, 12–18]. Such a broad range of activities reflects the functions of circulating immunoglobulins in the maintenance of tolerance to self and immune homeostasis in healthy individuals. In this presentation, a brief overview of various mechanisms that may underlie the beneficial effects of IVIg in autoimmune neuromuscular disorders is presented.

Neutralisation of autoantibodies and the regulation of autoreactive repertoires

Interactions between IVIg and variable regions of autoantibodies provide the basis for the ability of IVIg to regulate autoreactive B-cell clones *in vivo*. Several lines of evidence indicate that IVIg recognise idiotypes of disease-associated and of NAbs and antigen receptors on B lymphocytes. We have shown that intact IVIg and $F(ab')_2$ fragments of IVIg neutralise the functional activity of various autoantibodies and/or inhibit the binding of the autoantibodies to their respective autoantigens *in vitro*. Inhibition of autoantibody activity by IVIg has been observed in the case of autoantibodies to factor VIII, thyroglobulin, DNA, intrinsic factor, peripheral nerve, neutrophil cytoplasmic antigens, platelet gpIIb IIIa, acetylcholine receptor, endothelial cells, phospholipids, nephritic factor and retinal autoantigens β [19]. Presence of anti-idiotypes to disease-associated autoantibodies may be relevant in explaining the efficacy of IVIg in myasthenia gravis, Lambert-Eaton myasthenia syndrome and antibody-mediated neuropathies [6].

Induction of anti-inflammatory cytokines

Modulation by IVIg of the production of cytokines and cytokine antagonists is a major mechanism by which immunoglobulin exerts its anti-inflammatory effects *in vivo* [20] in various neuromuscular disorders such as inflammatory myopathies, demyelinating neuropathies, myasthenia gravis etc. [6]. IVIg was shown to selectively trigger the production of interleukin-1 receptor antagonist (IL-1ra), the natural antagonist of interleukin-1 (IL-1), in cultures of purified monocytes, without concomitant effect on the production of the pro-inflammatory cytokines IL-1α, IL-1β, IL-6 and tumour necrosis factor-α (TNFα) [21, 22]. Circulating levels of interleukin-1β decrease after treatment with IVIg in patients with Guillain-Barré syndrome [23]. The anti-inflammatory 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 T helper 1 (Th1) and Th2 cytokine production [24].

Attenuation of complement-mediated damage

The interaction of IVIg with complement prevents the generation of the C5b-9 membrane attack complex and subsequent complement-mediated tissue damage, by scavenging active complement components and diverting complement attack from cellular targets [25, 26]. IVIg binds anaphylatoxins C3a and C5a [27], the activated components C3b and C4b, in a C1q-independent [25] and C1q-dependent [28] fashion, thus preventing the deposition of these fragments on target surfaces of complement activation. This mode of action of IVIg is of relevance in the treatment of patients with severe DM, Guillain-Barré syndrome and myasthenia gravis. Thus the effect of IVIg in DM is associated with decreased plasma levels of C5b-9 and a significant decrease in the amounts of C3b and C5b-9 antigens deposited in endomysial capillaries [29].

Fc-mediated blockade of Fcγ receptors

IVIg is able to transiently block the function of Fcγ receptors on phagocytes by saturating, altering or down-regulating the affinity of the Fc receptors, a process that may render the sensitised phagocytic cells unable to exert their action [30]. Recent studies have further suggested that IVIg could also be effective by up-regulating the expression of FcγRIIB [31–33]. In Guillain-Barré syndrome and chronic inflammatory demyelinating polyneuropathy, a blockade of the Fc receptors on the macrophages could inhibit the macrophage-mediated phagocytosis of antigen-bearing target cells, and might intercept the macrophage-mediated demyelination [30].

Interaction of IVIg with membrane molecules of B and T lymphocytes and antigen-presenting cells

In addition to binding to idiotypes of immunoglobulins, IVIg reacts with a number of membrane molecules of T cells, B cells and monocytes that are relevant for the control of autoreactivity and induction of tolerance to self. Thus, IVIg has been shown to contain antibodies to vari-

able and constant regions of the human T-cell receptor [34], cytokines and cytokine receptors [35–37], CD5 [38], CD4 [39], HLA class I molecules [40], RGD adhesion motif [41], Fas [42–44] and CD40 [45]. We believe that antibodies directed to such functional molecules of lymphocytes are important for the immunomodulatory effects of normal immunoglobulin. IVIg also contains a variable amount of solubilised CD4, CD8, HLA-I and HLA-II molecules that may interfere with antigen recognition by the T cells [10].

Interaction of IVIg with dendritic cells

We have recently examined the effects of IVIg on differentiation, maturation and function of dendritic cells (DC). We have shown that DC are the primary targets for the immunosuppressive effects of IVIg on T-cell activation [37, 46], IVIg inhibits the differentiation and maturation of DC *in vitro*, and abrogates the capacity of mature DC to secrete IL-12 upon activation, while enhancing IL-10 production. IVIg-induced down-regulation of costimulatory molecules associated with modulation of cytokine secretion results in inhibition of auto- and alloreactive T-cell activation and proliferation [37, 46]. Modulation of DC maturation and function by IVIg is of potential relevance to its immunomodulatory effects in controlling specific immune responses in autoimmune diseases, transplantation and other immune-mediated conditions. A recent study by the group of Raju indicates an implication of DC in the beneficial effect of IVIg in DM. Using microarray experiments followed by real-time PCR, they showed, in protected patients, a down-regulation of CCL18, a chemokine secreted by immature DC [47].

Effect on remyelination

Treatment with IVIg suppresses experimental allergic encephalomyelitis and experimental allergic neuritis. It has been proposed that one of the multiple mechanisms by which IVIg improves these experimental models of demyelination may be by exerting a remyelinating effect directly on the myelin sheath [48–51].

Concluding note

Considerable progress has been made in understanding the mechanisms by which IVIg exerts immunomodulatory functions in autoimmune and inflammatory disorders. The mode of action of IVIg is complex, involving modulation of expression and function of Fc receptors, interference with activation of complement and the cytokine network, provision of anti-idiotypic antibodies, regulation of cell growth, and effects on the activation differentiation and effector functions of T and B cells. The therapeutic effects of IVIg most likely reflect the functions of natural antibodies in maintaining immune homeostasis in healthy people. Over the past 20 years, IVIg has become the preferred treatment for Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy and Kawasaki syndrome. The ability of IVIg to interact through V regions with complementary V regions of antibodies and antigen receptors as well as with relevant soluble and surface molecules provides the basis for inducing the selection of immune repertoires. Because IVIg is frequently used to treat autoimmune and inflammatory diseases for which evidence of its efficacy is insufficiently documented, controlled trials, particularly of some neurologic diseases in which IVIg represents a promising but unproved treatment, are imperative.

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