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Abstract

Intravenous immunoglobulin (IVIG) is a pooled preparation of normal immunoglobulin IgG obtained from several thousand healthy donors. It is widely used in the immunotherapy of a large number of autoimmune and inflammatory diseases. The mechanisms of action of IVIG are complex and, as discussed in this review, experimental and clinical data provide an indicator that the therapeutic benefit of IVIG therapy is due to several mutually nonexclusive mechanisms affecting soluble mediators as well as cellular components of the immune system. These mechanisms depend on Fc and/or $F(ab')_2$ fragments. A better understanding of the effector functions of IVIG should help in identification of biomarkers of IVIG response in autoimmune patients.

1. Introduction

The human body contains five classes of immunoglobulins and one class, IgG, represents nearly 80% of the total amount of immunoglobulin. IgG consists of a $F(ab')_2$ fragment that recognizes specific antigens and an Fc fragment that exerts effector functions upon binding to Fcγ receptors (FcγRs). Human immune cells express various receptors for the Fc fragment of IgG that include several activating receptors (e.g. FcγRI, FcγRIIA, FcγRIIC and FcγRIIIA) and an inhibitory receptor (FcγRIIB). The FcγRs in the mouse include FcγRI, FcγRIII and FcγRIV (activating receptors) and FcγRIIB (inhibitory receptor) (1, 2). The activating receptors with the exception of FcγRIIA and FcγRIIC, contain single α-chain that binds to ligands, and dimeric γ-chain that transduces signals and has immunoreceptor tyrosine based activating motifs (ITAMs) in the cytoplasmic domains. FcγRIIA and FcγRIIC have only single α-chain that itself carries ITAM motif in the cytoplasmic domain. In contrast,

inhibitory FcγRIIB possesses immunoreceptor tyrosine based inhibitory motifs (ITIM) in the cytoplasmic domain of a single α-chain (1, 2).

Intravenous immunoglobulin (IVIG) is a pooled preparation of normal human immunoglobulins obtained from the several thousand healthy donors. Besides IgG monomers (>96%), a small percentage of IgG dimers, IgM and IgA can be found in IVIG preparations. IVIG is used as a substitution therapy in primary and secondary immunodeficiencies at low doses (400 mg/kg) and in the immunotherapy of a large number of autoimmune and inflammatory diseases at high doses (1–2 g/kg).

The US Food and Drug Administration (FDA)-approved and the European Medicines Agency (EMA)-approved autoimmune indications for IVIG therapy include immune thrombocytopenic purpura (ITP), Kawasaki disease (KD), chronic inflammatory demyelinating polyneuropathy (CIDP) and multifocal motor neuropathy. Guillain–Barré syndrome (GBS) is approved only by the EMA. However, randomized clinical trials have shown the efficacy of IVIG in other autoimmune and inflammatory diseases such as dermatomyositis, anti-neutrophil cytoplasm antibody-associated systemic vasculitis, autoimmune hemolytic anemia, myasthenia gravis and graft-versus-host disease (3-7). IVIG therapy is generally considered safe although mild adverse reactions might be observed in approximately one in four of the treated patients, mostly due to high levels of IgG reached following therapy (4, 7).

The mechanisms of action of IVIG are complex and a single mechanism might not account for its therapeutic benefit in autoimmune diseases. As discussed in this review, experimental and clinical data provide an indicator that the therapeutic benefit of IVIG therapy is due to several mutually nonexclusive mechanisms affecting soluble mediators as well as cellular

components of the immune system. These mechanisms depend the on Fc and/or the $F(ab')_2$ fragments.

2. The effects of IVIG on soluble mediators

Inhibition of autoantibodies by idiotype networks

One of the earliest identified mechanisms of IVIG was its interaction with idiotypic determinants on pathogenic autoantibodies (and autoantibody-producing B cells). During the early 1980 and 1990s, several reports demonstrated the presence in IVIG **[Au: OK? OK]** of anti-idiotypes against a large number of disease-associated autoantibodies including antibodies to factor VIII, acetylcholine receptor, thyroglobulin, DNA and others (3, 8, 9). In addition, the therapeutic utility of these anti-idiotype antibodies from IVIG was demonstrated in animal models of autoimmune diseases (10).

Modulation of components of the complement

IVIG interacts with complement fragments C3b and C4b that are effectors of the complement cascade; it prevents the formation of C5b–C9 membrane-attack complex and, as a consequence, prevents complement-mediated cell death and tissue damage (11-13) (Fig. 1). Additionally, IVIG neutralizes C3a and C5a anaphylatoxins via a $F(ab')_2$-mediated mechanism (14).

3. The effects of IVIG-Fc fragment at the cell surface

Blockade of activating FcγRs

Initially it was proposed that IVIG blocks activating FcγRs on innate immune cells such as monocytes and macrophages, and reduces the immune complex-mediated activation of these

innate cells. A series of studies demonstrated conclusively that FcγR blockade was integral to the acute increase in platelet numbers seen following IVIG therapy in ITP patients. One of these initial studies employed monoclonal anti-human FcγRIIIA antibody that transiently increased the platelet count in an refractory ITP patient (15). Further, Debré *et al.* demonstrated that infusion of Fcγ fragments in ITP patients increases the platelet count. This study provided additional support for the concept that FcγR blockade is the most important mechanism responsible for the acute increase in platelets in ITP patients following IVIG therapy (16).

Saturation of FcRn

IgG can also bind to an additional receptor FcRn (neonatal Fc receptor). However, unlike other FcγRs, FcRn is not directly implicated in the regulation of activation of immune cells; rather, it acts as a protective receptor by preventing the catabolism of IgG (17). It was shown that saturation of FcRn by IVIG induces accelerated clearance of pathogenic antibodies in murine models of arthritis and autoimmune skin-blistering diseases, and ameliorates arthritis and blistering in these models (18, 19).

These observations were subsequently confirmed in fetal and neonatal ITP models as well (20). However, subsequent studies suggested that FcRn is dispensable for IVIG-mediated improvement of ITP both in wild-type mice (21) and in humanized mice (22), suggesting that FcRn might only have a role in the initial phase of anti-inflammatory mechanisms of IVIG. However, as discussed later, IVIG actively modulates various arms of the immune system to exert beneficial effects. Hence IVIG mechanisms go beyond simple blockade of activating FcγRs and saturation of FcRn.

Upregulating inhibitory FcγRIIB and increasing the threshold of immune-complex-mediated activation of innate cells

Results from Ravetch and colleagues have demonstrated that, in a murine model of ITP, infusion of IVIG or monomeric Fc fragments to wild-type mice or mice with humanized FcγRs inhibit pathogenic autoantibody-triggered consumption of platelets (23). They found that inhibitory FcγRIIB that contains an ITIM motif, was obligatory for this protection. The therapeutic effect of IVIG was abolished in FcγRIIB-deleted mice or if its function was blocked by a monoclonal antibody. Importantly, IVIG-mediated protection was associated with an enhanced expression of FcγRIIB on the surface of splenic macrophages. Subsequent exploration identified colony-stimulating factor-1 (CSF-1)-dependent macrophages as 'sensors' of Fcγ fragments of IVIG that in turn enhance FcγRIIB on CSF-1-independent 'effector' macrophages (24).

IgG molecules are glycosylated at Asn297 in the Fc domain and Ravetch's team reported that the anti-inflammatory action of IVIG is mediated mainly via Fcγ fragments that have terminal α2,6-sialic acid linkages at Asn297 (25). The sialylated fraction accounted for nearly 10% of IgG; recombinant Fc fragments containing terminal α2,6-sialic acid linkages and IVIG with controlled tetra-Fc sialylation could also recapitulate IVIG actions (26, 27).

Mechanistically, sialylated Fc fragments are recognized by SIGN-R1 (specific ICAM-3 grabbing non-integrin-related 1) on marginal-zone macrophages and induce IL-33 in them. This IL-33 acts on basophils to produce IL-4 that enhances FcγRIIB on effector macrophages (28, 29). Accordingly, the anti-inflammatory effects of IVIG were compromised in mice with splenectomy, deficiency of SIGN-R1^{+} cells in the splenic marginal zone, genetic deletion of SIGN-R1, blockade of the domain on SIGN-R1 that recognizes ligands or depletion of

basophils (28, 29). The requirement for terminal sialic acid residues in IVIG-mediated protection was also confirmed by other mouse models of autoimmune diseases (30). Fc variants that mimic structures imparted by sialylation could also mimic the therapeutic effects of Fc-sialylated functions in the K/BxN-induced arthritis model and in experimental autoimmune encephalomyelitis (EAE) (31). Sialylated IVIG was more effective in inhibiting anti-ganglioside antibody-mediated complement deposition *in vitro* (32).

Controversies about the requirement of Fc-sialylation for IVIG-mediated anti-inflammatory effects

It is important to note that aforementioned mechanisms were reported only in murine models and translation of IVIG-sialylation data to humans did not recapitulate those observations. Also, additional reports in animal models questioned the link between Fc-sialylation and anti-inflammatory effects of IVIG (33).

In autoimmune patients, although IL-33 was increased in the blood following IVIG therapy (34, 35), it was not associated with basophil expansion. DC-SIGN [dendritic cell (DC)-specific ICAM-3 grabbing non-integrin] is the human orthologue of SIGN-R1 but IVIG did not induce IL-33 production by DC-SIGN$^+$ innate cells, indicating that non-immune cells such as endothelial cells or epithelial cells contribute to IVIG-induced IL-33 (34). The sialylation levels of therapeutic IVIG did not determine the response to therapy in KD (36) and, in ITP patients, IVIG treatment led to modification in the ratio of activating/inhibitory FcγRs primarily via reducing FcγRIIIA (37). In addition, IVIG could inhibit the activation of DC-SIGN$^+$ human cells, expression of adhesion molecules and chemokine secretion in monocytes, and FcγR-mediated phagocytosis by macrophages independently of IgG-Fc sialylation (38-40). Analysis of splenic macrophages from adult ITP patients did not reveal modulation of

FcγR expression following IVIG therapy (41). Structural and immunological analyses indicated that DC-SIGN-independent cell surface lectin receptors mediate binding of the Fc regions of IVIG (42).

The collagen antibody-induced arthritis, K/BxN serum transfer arthritis, EAE and ITP models in mice in other laboratories failed to prove a role for Fc-sialylation and basophils in the therapeutic effects of IVIG (43-46). It was suggested that the genetic background of mice and dose of IVIG are the important factors that determine the role of FcγRIIB in IVIG-mediated protection (47). Also, anti-inflammatory effects of IVIG via induction of Src homology 2 (SH2)-containing tyrosine phosphatase-1 (SHP-1)-dependent inhibitory ITAM (ITAMi) signaling but independent of ITIM-bearing FcγRIIB have been reported. Binding of IVIG to FcγRIII (either via Fc or natural antibodies that recognize FcγRIII) results in sub-optimal phosphorylation of ITAM in FcγRIII-associated FcRγ chain leading to ITAMi inhibitory signal (48, 49).

In conclusion, all these data indicate that although sialylated Fc has a role in IVIG-mediated anti-inflammatory actions, it does not represent the sole mechanism but rather is one of the several mechanisms of IVIG that act mutually.

4. The effects of IVIG on specific cell types

Effector functions of IVIG on monocytes and macrophages

IVIG inhibits activation of monocytes and macrophages in both mice and humans, and induces anti-inflammatory cytokines like IL-1 receptor antagonist (IL-1RA), TGF-β and IL-10 (50-53) (Fig. 1). These effects are associated with inhibition of NF-κB, ERK1/ERK2 and P38 MAPK pathways (52, 54). However, one of the anti-inflammatory pathways HO-1 (heme

oxygenase 1) is not implicated (53). Gene expression profiles in the monocytes of KD patients, mononuclear cells of patients with chronic heart failure, muscle biopsies of patients with inflammatory myopathies and whole blood of healthy donors indicated suppression by IVIG of a diverse array of activating genes associated with inflammation including chemokines (55-58). Similarly in ITP patients, IVIG abrogated type I IFN response signatures in monocytes (37). Additionally, IVIG contains high affinity natural IgG to various cytokines and these antibodies can exert direct neutralization effect on innate inflammatory cytokines (59).

Regulation of DC functions by IVIG

DCs are professional antigen-presenting cells and key players of autoimmune responses. Exploration of the action of IVIG on DCs revealed that it inhibits differentiation of DCs from human monocytes as well as suppressing DC activation (38, 60) (Fig. 1). IVIG suppressed the expression of maturation markers and the secretion of pro-inflammatory cytokines like IL-12, and inhibited DC-mediated $CD4^+$ T cell proliferation (60-63), CD1-restricted NKT responses and T cell responses (64). The immunosuppressive effects of IVIG on DCs were associated with accumulation of lipid that is known to suppress antigen presentation (65). Although both Fc and $F(ab')_2$ fragments of IVIG are equally effective in inhibiting DC activation, the $F(ab')_2$ fragment-mediated effects on DCs also indicate an Fc-sialylation-independent action of IVIG (38, 60).

The effects of IVIG were not restricted to monocyte-derived DCs. IVIG also diminished the expression of FcγRIIA on circulating myeloid DCs (66) and lessened the production of IFNα by plasmacytoid DCs via two distinct mechanisms: inhibition of immune-complex-mediated IFNα production by blocking FcγRIIA in a sialic acid-independent mechanism; and suppression of TLR-7 or TLR-9-mediated IFNα production via the $F(ab')_2$ fragment (67).

In line with the induction of tolerogenic properties to DCs, upon adoptive transfer, IVIG-treated DCs ameliorated disease in a murine model of ITP (68).

The effect of IVIG on granulocytes

IVIG contains natural anti-Siglec-9 autoantibodies and these antibodies regulate human neutrophil cell death *in vitro* by caspase-dependent and caspase-independent mechanisms (69). We confirmed these studies and also found that IVIG exerts dose-dependent effects on neutrophils (70). In patients with KD, IVIG treatment reduced NO production by neutrophils (71) (Fig. 1).

In vivo results in experimental models shed light on additional roles of IVIG in regulating neutrophil functions. In a sickle-cell disease model, IVIG interfered with the recruitment of neutrophils and their activation by inhibiting adhesion (72). Subsequent study in neutrophil-mediated acute vascular injury model identifies the mechanism by which IVIG inhibits neutrophil recruitment and activation (73). Analogous to FcγRIII-associated ITAMi model detailed earlier (48), this study reports that IVIG interacts and signals through FcγRIII on neutrophils and mediates anti-inflammatory activity by recruiting SHP-1.

The cytotoxic effects of IVIG are not restricted to neutrophils. Eosinophils are also susceptible to IVIG-mediated cytotoxic effects and these effects were mediated via anti-Siglec-8 antibodies present in IVIG (74). The cytotoxic effects of IVIG on granulocytes are greatly enhanced if the cells are primed by cytokines (like IL-5, GM-CSF, IFN-γ or TNF-α) or leptin.

Modulation of NK cells

Women with recurrent spontaneous abortion display a rise in natural killer (NK) cell numbers. The success of IVIG treatment in women with recurrent spontaneous abortion is linked to

significant inhibition of NK cytotoxicity (75) and was confirmed by other groups as well (76) (Fig. 1). In contrast, a significant increase in the activity of NK cells has been observed following IVIG treatment in KD patients (77). Thus, the reported effects of IVIG on NK cells appear to vary, depending on the pathology. Alternatively, these discrepancies might be also attributed to heterogeneity in NK cell subsets. Another report also shows that IVIG promotes apoptosis of DCs via NK cell-mediated antibody-dependent cellular cytotoxicity (78).

Reciprocal regulation of pathogenic and regulatory $CD4^+$ T cells by IVIG

$CD4^+$ T lymphocytes are key effectors of autoimmune responses. $CD4^+$ T lymphocytes are heterogeneous and are divided into various subsets. Th1 and Th17 are the major $CD4^+$ T cell subsets involved in the pathogenesis of autoimmune diseases whereas regulatory $CD4^+$ T cells (T_{reg} cells) are immunosuppressor cells and are key for maintaining immune tolerance. IVIG induces apoptosis of activated effector T lymphocytes via Fas-mediated activation of caspases (79).

Various lines of evidence show that IVIG enhances and restores the functions of T_{reg} cells both in experimental models and in IVIG-treated patients (Fig. 1). IVIG enhances suppressive effects of human T_{reg} cells *in vitro* (80). In EAE and allergic airways disease models, IVIG-mediated protection from the disease was associated with an expansion of T_{reg} cells (81, 82). In an ITP model, IVIG restored splenic T_{reg} populations (83). These results were further consolidated in patients wherein IVIG therapy led to an increase in T_{reg} cells in the peripheral blood (84).

Mechanistically, IVIG-mediated expansion of T_{reg} cells implicates several mechanisms that may work in a mutual manner to exert immune tolerance. These mechanisms include induction of cyclo-oxygenase 2 (COX-2)-dependent production of prostaglandin E_2 (PGE_2) in

human DCs, a mechanisms reliant on DC-SIGN and $F(ab')_2$ fragments of IVIG (35, 85, 86); DC immunoreceptor (DCIR)-dependent induction of murine T_{reg} cells by lung DCs (87); and processing and presentation of T_{reg} epitopes (Tregitopes) in IgG by DCs (88).

In addition to its inhibitory effects on T_h1 cytokines, recent reports demonstrate profound inhibitory effects of IVIG on human T_h17 cell differentiation and amplification both under experimental conditions and in treated autoimmune patients (89-94) (Fig. 1). These effects of IVIG on T_h17 cells are not due to passive neutralization of T_h17 cytokines by IVIG and are mediated by interference with the activation of signal transducer and activator of transcription 3 (STAT3). $F(ab')_2$ fragments of IVIG retain the capacity to regulate T cell subsets (89).

Data from *in vivo* experiments in EAE and experimental autoimmune arthritis demonstrate that IVIG reciprocally regulates encephalopathogenic T_h1 cells, T_h17 cells and T_{reg} cells (45, 95, 96). Either sialylation or FcγRIIB are dispensable for these effects and $F(ab')_2$ fragments of IVIG also preserve the capacity to regulate $CD4^+$ T cell subsets (45, 95). IVIG sequesters T cells in the secondary lymphoid tissues and reduces infiltration of $CD4^+$ T cells into the central nervous system by diminishing the expression of sphingosine-1 phosphate receptor on them (95).

Control of B cell activation and functions

IVIG inhibits the proliferation and antigen-presenting functions of B cells. It also inhibits IL-4 plus CD40-, TLR- and BCR-mediated activation of B cells (97-103) (Fig. 1). IVIG suppresses BCR-mediated B cell activation via down-regulation of tyrosine phosphorylation of Lyn and sustained activation of ERK1/ERK2 (98). These effects of IVIG were dependent on sialylation and its interaction with CD22 (98). B cells are resistant to immunomodulation by 'IVIG-educated' human DCs and this suggests direct modulation of B cells by IVIG (104).

Clinical studies have demonstrated that IVIG therapy in allergic pediatric patients results in reduced IgE levels (105); this was confirmed in *in vitro* studies as well (106). These effects of IVIG were $F(ab')_2$-dependent (106). Another report indicates that although IVIG inhibits B cell proliferation *in vitro*, this was associated with enhancement of the differentiation of plasma cells that may compete with autoantibody-producing plasma cells (107).

IVIG contains neutralizing anti-BAFF (B-cell activating factor) and anti-APRIL (a proliferation-inducing ligand) IgG and hence might affect B cell survival via neutralization of these cytokines (108). In fact, IVIG treatment significantly reduces serum levels of BAFF in CIDP patients (109).

Inhibition of activation of endothelial cells

Endothelial cells contribute to inflammatory responses as in the case of KD by secretion of cytokines and chemokines, and by regulating the rolling and passage of immune cells (110). IVIG inhibits activation of endothelial cells, expression of adhesion molecules and secretion of soluble mediators (111).

5. Conclusions

Although IVIG has been widely used as an immune-modulating agent for more than 30 years, little is known about the factors that predict the success of this therapy. Therefore, exploration of biomarkers that predict responders and non-responders to IVIG therapy remains a major area of research. This highlights the inevitability of exploring the mechanisms of action of IVIG and its translational application in the clinic as a potential biomarker of response to therapy. A number of inflammatory mediators, downstream signaling molecules of

inflammatory cascades and dynamic changes in the frequency and/or activation status of immune cells have shown potential for predicting the response to IVIG therapy (112). A better understanding of the mechanisms of action of IVIG should also reduce empirical use of IVIG and help to determine the appropriate dose, window and duration of IVIG treatment for various autoimmune and inflammatory diseases where this immunotherapy has shown promise (113).

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Abbreviations

APRIL= A proliferation-inducing ligand

BAFF=B-cell activating factor

BCR=B-cell receptor

CIDP=Chronic inflammatory demyelinating polyneuropathy

COX-2=Cyclo-oxygenase-2

DC=Dendritic cell

DCIR=Dendritic cell immunoreceptor

EAE=Experimental autoimmune encephalomyelitis

FcγR=Fcγ receptor

FcRn=Neonatal Fc receptor

GBS =Guillain–Barré syndrome

HO-1=Heme oxygenase-1

IL=Interleukin

IFN=Interferon

ITAM= Immunoreceptor tyrosine based activating motifs

ITIM= Immunoreceptor tyrosine based inhibitory motifs

ITP=Immune thrombocytopenic purpura

IVIG=Intravenous immunoglobulin

KD=Kawasaki disease

NK cell=Natural killer cell

PGE_2=Prostaglandin E_2

SHP-1=Src homology 2 (SH2)-containing tyrosine phosphatase-1

STAT=Signal transducer and activator of transcription

T_h cell=T helper cell

T_{reg} cell=Regulatory T cell

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Figure Legend

Fig. 1. The impact of intravenous immunoglobulin (IVIG) on the innate and the adaptive immune compartments in the context of autoimmune and inflammatory diseases. IVIG inhibits activation and functions of various innate immune cells such as DCs, monocytes, macrophages (MΦ), neutrophils (polymorphonuclear cells; PMN) and NK cells. It neutralizes activated complement components. In addition, IVIG modulates B cell functions and plasma cells (Pl), reciprocally regulates regulatory T_{reg} cells and effector T cells such as T_h1 and T_h17 subsets, and downregulates the production of inflammatory cytokines.