Intravenous Immunoglobulin: Mechanism of Action in Autoimmune and Inflammatory Conditions

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Abbreviations

IVIG Intravenous Immunoglobulin

KD Kawasaki Disease

ITP Immune thrombocytopenic purpura

GBS Guillain–Barré syndrome GBS,

CIDP Chronic inflammatory demyelinating polyneuropathy

SLE Systemic lupus erythematosus

CIA Collagen Induced Arthritis

IL Interleukin

PBMC Peripheral blood mononuclear cells

DC Dendritic cells

pDC Plasmacytoid dendritic cells

EAE Experimental Autoimmune Encephalitis

MISC Multisystemic Inflammatory Syndrome in Children

NET Neutrophil extracellular traps

Key words: Intravenous immunoglobulin, inflammation, autoimmunity, innate immunity, adaptive immunity, Regulatory T cells, IVIG

Clinical Commentary: *JACI in practice*

Abstract: IVIG is the mainstay of therapy for humoral immune deficiencies and numerous inflammatory disorders. Although the use of IVIG may be supplanted by several targeted therapies to cytokines, the ability of polyclonal IgG to not only act as an effector molecule but as a regulatory molecule is a clear example of the polyfunctionality of IVIG. This article will address the mechanism of action of IVIG in a number of important conditions that are otherwise resistant to treatment. In this commentary we will highlight mechanistic studies that shed light on the action of IVIG. This will be approached by identifying effects that are both common and disease specific, targeting actions that have been demonstrated on cells and processes that represent both innate and adaptive immune responses.

Introduction

IgG plays multiple roles in the immune system. Best known as an effector molecule in host defense, infusions of polyclonal IgG have been employed as the mainstay of treatment for patients with immunodeficiency diseases affecting the humoral immune system. Preparations of human IgG are available for intravenous (IVIG) or subcutaneous SCIG) administration, which has allowed individuals with both primary and secondary immune defects to achieve much improved outcomes.[1] In addition, IVIG has been employed as a regulator of a large number of autoimmune and inflammatory conditions since the 1980's[2]. IVIG contains a broad spectrum of antibodies, as it is fractionated from plasma pools that include several thousand donors or more[3]. IVIG has been consistently and successfully used for numerous conditions, including Immune thrombocytopenic purpura (ITP), Kawasaki Disease (KD), Guillain–Barré syndrome, chronic inflammatory demyelinating polyneuropathy (CIDP), systemic lupus erythematosus, dermatomyositis, and other autoimmune and neurologic disorders[4]. Indeed, the number of conditions for which IVIG is used "off label" outnumbers those that have regulatory approval[5,6]. However, pressures on the plasma fractionation system leading to shortages of raw materials for IVIG, particularly during the recent pandemic period, demand that practitioners carefully scrutinize their use and employ caution both in prescribing, and in over-rationing this essential therapy, to the detriment of patients with primary antibody immune deficiency[7]. More thorough mechanistic understanding of the role of IVIG as an immune regulator can provide better rationale and determine the optimal use for this increasingly scarce resource.

IVIG has been used in two distinct dose regimes: low-dose (400-800 mg/kg) replacement therapy in primary immunodeficient patients and high-dose (1-2 g/kg) in autoimmune and inflammatory diseases.[1] As IVIG contains antibodies to diverse pathogens, the main goal of low-dose replacement therapy is to prevent recurrent infections in primary immunodeficient patients or in patients with recurrent infections with secondary immunoglobulin deficiencies. Several lines of evidence also suggest that low-dose IVIG

therapy can exert positive effects on the cellular immune compartment, depending on underlying immunodeficiency[8-12]. In contrast, most autoimmune conditions require high dose therapy. As will be discussed below, this is likely due to the need for specialized antibody contents that represent a small percentage of polled IVIG, such as anti-idiotype antibodies, fractions that have specific glycosylation, and other components[2].

Autoimmune and inflammatory diseases are characterized by perturbed immune tolerance and aberrant activation of immune and nonimmune cells, inflammation, and tissue damage. Despite the significant number of novel, biological therapies that target cytokines and small-molecule inhibitors aimed at signaling pathways, IVIG continues to have an important therapeutic niche in these diseases. The rationale behind the extensive use of IVIG is due to a combination of relatively low therapeutic toxicity[13,14] with a very broad spectrum of immunoregulatory actions.

IgG molecules are complex glycoproteins, structured to both interact with target antigens via their variable regions, and with cells that express Fc receptors via their constant regions (Figure 1). These are complemented by multiple glycosylation sites which increase the mobility of the molecule and mediate interaction between IgG and lectin receptors on cells in the immune system. As demonstrated in Figure 1, IVIG has been implicated in multiple critical immune processes that can mitigate inflammatory responses in autoimmune diseases. These actions encompass both the innate and adaptive immune systems. In this commentary we will address several of the key mechanisms of action which can provide direction for the continued use of IVIG and assist in potentially developing therapeutic substitutes for this critical therapy.

IVIG modulates structural cells

Structural cells like epithelial cells, fibroblasts and endothelial cells express a wide range of immune genes and respond to the inflammatory stimuli. Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and SJS/TEN overlap syndrome are rare severe skin reactions, in most cases triggered by medications, with high morbidity and mortality of up to 40% for TEN. IVIG is one of several therapies, utilized after corticosteroids, which have been shown to improve outcomes, reduce hospital stays and decrease time for the skin to heal.[15,16] The therapeutic benefits of IVIG in TEN is suggested to be due to inhibition of Fas-mediated keratinocyte death[17,18]. A different mechanism is seen in experimental models of bullous pemphigoid, an autoimmune blistering disease, for which IVIG suppressed inflammatory cytokines like IL-6 from keratinocytes[19]. In pathologies associated with fibrosis such as systemic lupus erythematosus and Sjögren's syndrome, IVIG therapy may reverse fibroblast proliferation[20], and also inhibited early fibrogenic changes in experimental models of Systemic Sclerosis[21].

Endothelial cells function as a barrier between the bloodstream and tissue. They actively contribute to inflammatory processes by secretion of cytokines and chemokines, and by regulating the adhesion and mobility of various immune cells. By activating mitochondrial apoptotic signalling pathways, IVIG induced apoptosis of TNF-α-stimulated umbilical vein endothelial cells [22]. IVIG inhibited TNF-α-induced activation of NF-κB [23] and as a consequence inhibited inflammatory cytokine-mediated proliferation of endothelial cells, and expression of adhesion molecules, inflammatory cytokines and chemokines[24-26]. Similarly, in a murine model of stroke, IVIG suppressed ischemia-induced enhancement of markers of endothelial cell adhesion and lymphocyte infiltration[27].

IVIG can inhibit inflammatory processes of endothelial cells via specific antibodies in its repertoire that interact with target molecules. Specifically, anti-IL-1α IgG antibodies in IVIG have been shown to inhibit IL-1α-mediated activation of endothelium and consequently, reduce neutrophil adhesion[28]. In a murine

model of antiphospholipid antibody syndrome, IVIG inhibited antiphospholipid antibodies-induced endothelial cell activation and thrombosis *in vivo*[29]**.** IVIG also increased HLA-DR expression in endothelial cells, decreased IL-6 and promoted endothelial cell amplification of Treg cells, all of which may assist in maintenance of allograft tolerance [30]**.** Thus, by targeting endothelial cells, IVIG not only reduces endothelial cell function but also mitigates the influx of immune cells to sites of inflammation.

Innate immunity and IVIG

The innate immune compartment, including soluble factors such as complement molecules and innate immune cells, plays a key role in the initiation and propagation of pathogenic immune responses through the secretion of inflammatory mediators like cytokines and chemokines, recruiting effector cells, mediating T cell differentiation and programming, and by causing tissue damage. Innate immune cells include antigen presenting cells such as dendritic cells (DC), monocyte/macrophages; NK cells, and granulocytes like neutrophils, eosinophils, and basophils. IVIG actively regulates several key components of the innate immune system.

IVIG and complement pathways

The complement pathway is composed of a complex network of proteins that interact with each other in a sequential manner to produce a variety of biological responses. Well known for its crucial role in host defense against infections, the complement pathway also contributes to a range of diseases. IVIG contains antibodies that exert complement scavenging effects[27,31-33]. By interacting with C3b complement components and preventing the binding of activated C3 to C5 convertase, IVIG inhibited the deposition of C5b-C9 membrane attack complexes on endomysial capillaries, restoring the capillary network and reducing microvasculopathy, a characteristic feature of dermatomyositis[31]. Another report showed that IVIG diminished complement amplification in dermatomyositis patients by reducing the

154 concentration of C3 convertase precursors in blood [32]. In both dermatomyositis and KD patients, IVIG
155 therapy suppressed expression of multiple genes for complement products and their receptors [34,35].
156
157 In a murine model of stroke, IVIG protected against experimental stroke by scavenging C3b and
158 preventing complement-mediated neuronal cell death[27]. IVIG also neutralized anaphylatoxins C3a and
159 C5a, and suppressed their effector functions both in vitro and in vivo animal models [33]. Thus, IVIG exerts
160 diverse actions on the complement system to attenuate inflammation.
161
162 ***Monocytes/Macrophages and Dendritic cells:***
163 IVIG inhibited activation of monocytes and macrophages both in mice and humans, and induced anti-
164 inflammatory cytokines like IL-1 receptor antagonist (IL-1RA), TGF-β and IL-10[36-41]. IVIG induced
165 Fas-mediated apoptosis of innate cells and neutralized various innate inflammatory cytokines by virtue
166 of high-affinity anti-cytokine IgG antibodies[42]. IVIG also promoted an expansion of monocytic myeloid-
167 derived suppressor cells[43]. Interestingly, induction of IL-10 by IVIG in TLR-4 activated monocytes is
168 dependent on FcγRI (CD64) and FcγRIIb (CD32B), and is impaired in high affinity genetic FCGRIIA
169 risk variants (H131R polymorphism, rs1801274)[38].
170
171 The effect of IVIG therapy on monocytes may be a biomarker in KD. Single cell RNA sequencing-based
172 profiling of PBMCs from acute KD patients revealed that monocytes are the major source of
173 inflammatory mediators in these patients[35]. IVIG therapy reduced $CD14^+$ monocytes/macrophages and
174 $CD16^+$ positive inflammatory monocytes in circulation [35,44-46], as well as expression of calgranulin genes
175 [35,47] and high affinity FcγRI receptors[45]. Microarray data confirmed that IVIG therapy downregulated
176 *MAPK14, TLR5 and MYD88*, the signaling and adapter proteins involved in TLR and IL-1 receptor
177 signaling[48] which affects multiple signal transduction pathways[38,49,50]. In line with these observations,
178 analyses of M1(inflammatory macrophages which cause tissue damage) and M2 (regulatory

179 macrophages which induce tissue repair) macrophages in KD patients revealed that during acute phases
180 of the disease, transcripts of both M1 and M2 markers were increased, then declined following IVIG
181 therapy[51]. IVIG mediated epigenetic regulation of target genes in macrophages via hypermethylation of
182 CpG sites at its promoter region[51].
183
184 DC are the major professional antigen presenting cells which direct both immune tolerance and primary
185 and memory T-cell responses. IVIG suppressed expression of DC co-stimulatory molecules CD40, CD80
186 and CD86, and HLA-DR in vitro [52], leading to a tolerogenic DC phenotype. Adoptive transfer of IVIG-
187 treated $CD11c^+$ DC led to amelioration of ITP in mouse[53]. IVIG therapy in CIDP patients reduced levels
188 of inflammatory $CD16^+$ myeloid DC[54], and reduced inflammatory cytokines like IL-12 and TNF[52,55],
189 while enhancing IL-10[52]. IL-10 was also induced by IVIG in two myeloid DC subsets in KD patients in
190 the subacute phase of recovery[56]**.** IVIG suppressed IFNα production in pDC via two mechanisms: in SLE
191 patients, IVIG inhibited FcγRIIa and IFNα production induced by SLE immune complexes; additionally
192 IVIG contained $F(ab')_2$ residues which induced PGE_2 in monocytes, leading to suppression of TLR-7 or
193 TLR-9 agonist-induced IFNα production[57].
194
195 Initial reports on successful clinical use of Fc fragments of IVIG for the treatment of ITP suggested that
196 IVIG blocked Fcγ receptors and hence prevented immune complex-mediated activation of innate
197 immune cells[58]. Subsequent studies, particularly in experimental animal models, reported that terminal
198 α2,6-sialic acid-linked residues on the Fc portion of IgG may mediate some of these immunoregulatory
199 functions of IVIG (Figure 1), suggesting possible enrichment of IgG preparations for sialic acid
200 containing fractions, and thus more targeted usage. However, the importance of the α2,6-sialic acid
201 linked residues appears to be disease and possibly model specific. Murine studies suggest that the α2,6-
202 sialic acid portion of IVIG enhances the inhibitory FcγRIIb in effector splenic macrophages [59-62]. α2,6-
203 sialic acid linkages may induce IL-33 in marginal-zone macrophages via SIGN-R1 signaling (or in

204 humans, DC-SIGN) or CD23[59,63,64]. IL-33 activates basophils via the ST2 receptor to induce IL-4 [63,64]
205 which in turn enhances FcγRIIb expression on effector splenic macrophages. Several animal models such
206 as K/BxN-induced arthritis, experimental autoimmune encephalomyelitis (EAE), ITP and experimental
207 allergic bronchopulmonary aspergillosis (ABPA) have validated the requirement of sialylated Fc region
208 or sialylated IgG in imparting protective effects [61,63-69]. In allergic airways disease, a second sialic acid
209 receptor, DCIR, was shown to mediate the effects of sialylated IgG in abrogating airway inflammation[70].
210 In contrast, models of autoimmune diseases such as K/BxN serum transfer arthritis, collagen-induced
211 arthritis (CIA), ITP and EAE reported that neither sialylation of Fc fragments nor FcγRIIb are mandatory
212 for the anti-inflammatory effects of IVIG [71-74]
213
214 In human studies have also not been as conclusive. Flow cytometry and cellular surface plasmon
215 resonance imaging did not find evidence to support CD23 or DC-SIGN as receptors for human IgG
216 irrespective of glycosylation properties on $F(ab')_2$ or Fc[75]. Both FcγRIIb or Fc-sialylation were
217 dispensable for IVIG to inhibit IgG-mediated phagocytosis by human macrophages [76]. Although IL-33
218 was induced by IVIG in autoimmune patients, it was not produced by DC-SIGN$^+$ innate cells [77]. IL-33
219 did not induce activation of human basophils nor production of IL-4[78], suggesting that the action of IVIG
220 modulating human basophils would be via different mechanisms. Sialic acid moieties on IgG were also
221 not required for activation of the Wnt/β-catenin pathway, autophagy and immune complex-mediated
222 induction of type I IFN by human pDC[57,79,80]. DC-SIGN on human monocyte-derived DC played a key
223 role in inducing COX-2-mediated PGE_2 production and regulatory T cell (Treg) expansion[81]. But unlike
224 mice, interaction with DC-SIGN was mediated by $F(ab')_2$ fragments rather than Fc, suggesting that either
225 sialic acid molecules on Fab or anti-DC-SIGN IgG antibodies could mediate these effects. More work is
226 needed to define the role of sialylated Fc fragments in mediating immunoregulatory functions of IVIG.
227
228 ***Granulocytes:***

Neutrophils: Neutrophils have a role in inflammatory diseases such as KD through recruiting other innate immune cells to the site of inflammation, secreting inflammatory mediators and causing tissue damage. IVIG therapy exerted cytotoxic effects on neutrophils in KD patients[82,83] possibly through anti-Fas and anti-Siglec9 IgG via caspase-dependent and caspase-independent pathways, respectively[84]. IVIG also reduced neutrophil nitric oxide in KD patients[85]. In multisystem inflammatory syndrome in children (MIS-C)[86], IVIG targeted IL-1β$^+$ neutrophils via PI3K- and NADPH oxidase-dependent cytotoxicity, and suppressed their activation[82]. IVIG inhibited neutrophil extracellular trap (NET) formation in anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis *in vivo*[87]. This may be due to IVIG inducing lactoferrin in neutrophils that negatively regulates NET formation[87,88].

The immunoregulatory role of IVIG on neutrophils goes beyond cytotoxicity. In a mouse model of sickle cell disease, IVIG interfered with recruitment of neutrophils in inflamed venules by increasing rolling velocity of granulocytes and reducing adhesion to venules[89]. Using a neutrophil-mediated acute vascular injury model the effect of IVIG on neutrophil adhesion and activation was dependent on FcγRIII via recruitment of SHP-1[90].

Basophils: IVIG induces the activation marker CD69 as well as IL-4 and other cytokines in IL-3-primed human basophils via $F(ab')_2$- and Syk-dependent mechanisms by interacting with surface-bound IgE[78]. Induction of CD69 was also observed in IVIG-treated myopathy patients[78]. IL-4 produced by basophils might dampen inflammation by enhancing FcγRIIb and antagonizing Th1 and Th17.

Eosinophils: IVIG induces ROS-dependent cytotoxic effects on eosinophils in the presence of inflammatory cytokines both by caspase-dependent and caspase-independent pathways, via anti-Siglec-8 IgG[91]. IVIG therapy in Churg-Strauss syndrome patients decreased CD69$^+$ activated eosinophils[92]

253 suggesting functional anti-Siglec-8 IgG-mediated cytolysis. Similarly, in moderate to severe childhood
254 atopic dermatitis patients, IVIG therapy caused a decline in peripheral blood eosinophil counts[93].
255
256 Other positive effects of IVIG on eosinophils have also been observed. Eosinophil levels are frequently
257 significantly higher in KD patients compared to control subjects[94]. In work by Kuo et al, IVIG therapy
258 induced IL-5 and elevated eosinophil counts, which were positively correlated with successful IVIG
259 therapy[95]. Mechanistically, increased IL-5 (or other eosinophil chemotactic factors) without increased
260 eosinophil activation factors was correlated with post-IVIG therapy eosinophilia[96] and mitigated Th1
261 inflammation. Th2 cytokines following IVIG therapy were proposed to also help decrease coronary
262 artery lesions.
263
264 ***Natural Killer cells****:*
265 Classically known for their ability to kill malignant and virus-infected cells by cytotoxic effects, Natural
266 Killer (NK) cell activation also leads to secretion of pro-inflammatory cytokines. IVIG inhibits direct
267 cytotoxicity and ADCC function of human NK cells in vitro[97] associated with apoptotic cell death in
268 $CD56^{dim}$ NK cells[98]. Reduced NK cell function following IVIG therapy was reported in ITP[99],
269 CIDP[100,101], and KD, all associated with reduced cytotoxic $CD56^{dim}$ NK cell subsets, while preserving or
270 increasing regulatory $CD56^{bright}$ NK cells[101,102].
271
272 Some women with multiple high-risk pregnancies have elevated preconception peripheral NK cells; trials
273 of IVIG therapy significantly improved the delivery birthweight of babies born to women with high risk
274 of low birthweight infants[103]**.** A murine model of recurrent pregnancy loss was associated with increased
275 $CD44^{bright}$ NK cells; IVIG reduced spontaneous abortion rates while suppressing increases in the
276 $CD44^{bright}$ NK cell subset[104]. Women with recurrent spontaneous abortion similarly display increased NK
277 cells but exhibit reduced NK cell cytotoxicity; IVIG therapy significantly increased the live birth rate[105-

[108], as well as increasing expression of inhibitory receptors and decreased activating receptors of NK cells[105]**.** Further detailed investigation on the regulation of NK cells by IVIG is needed.

Adaptive Immunity: Human studies

Treg/Th17 axis: $CD4^+$ T cells are heterogenous and various subsets have been identified. Tregs are necessary for the control of inflammation, while, aside from controlling infection, Th1, Th2 and Th17 cells can promote tissue damage, and are associated with autoimmunity[109,110]. Early studies indicated that IVIG therapy balances Th1 and Th2 cells[111]. Experimental studies have further reported that IVIG suppressed the differentiation, expansion and function of human Th17 cells in an $F(ab')_2$-dependent manner by inhibiting STAT-3 phosphorylation[112]. KD has been a paradigm for understanding the role of IVIG in the Treg/Th17 axis. While Th17 cells, as well as cytokines IL-17, IL-22, and IL-23, can be elevated in acute KD, these cytokines were downregulated up to eight weeks following IVIG therapy[113]. Analyses of mRNA in a group of KD subjects revealed that there were no significant changes in the frequency of Th17 cells before and after IVIG therapy; however, Treg-related IL-10 and FoxP3 levels increased 3 days after IVIG, and plasma IL-17 levels significantly decreased after 3 weeks[114]. Single-cell RNA sequencing has also demonstrated increased *FOXP3* mRNA levels after IVIG treatment[35]. Franco et al.[115] found that two weeks after IVIG therapy, KD patients without coronary artery lesions presented an expansion of a Treg population that produced IL-10 and low amounts of IL-4 but no TGF-β. In contrast, patients with arterial inflammation did not exhibit this profile, reinforcing the idea that Tregs are key for controlling the vascular inflammation and may be associated with KD resolution[115]. Additionally, two myeloid DC subsets ($CD14^+$ cDC2 and ILT-4^+ $CD4^+$ tmDC) from KD patients internalized IgG in vitro through FcγR, secreted IL-10 and expanded Fc-specific Tregs[56].

The effects of IVIG on Treg are not restricted to KD. Women with recurrent pregnancy loss (RPL), ITP patients successfully treated with IVIG, or ex vivo IVIG-treated healthy donor T cells, showed increased Tregs as well as enhanced in vitro Treg activation and increased suppressive function[35,116-118]. In GBS patients, IVIG reciprocally regulated Th1/Th17 and Tregs[119] suggesting that Treg frequency represents a potential immunological biomarker to predict clinical response to IVIG therapy[120]. Similarly, patients with CIDP and dermatomyositis showed increased frequency of Tregs following IVIG[102]. In vitro stimulation with IVIG of PBMC from GBS patients resulted in increased in vitro secretion of IL-10 and TGF-β1[121] and expansion of Tregs[121]. Reduced frequency of circulating Tregs in myasthenia gravis was corrected by IVIG and induced expansion of circulating $CD4^+CD25^+FoxP3^+$ and $CD4^+CD25^+FoxP3^+$ CTLA-4^+ T cells.

B cells and humoral antibody responses:

Potential mechanisms through which IVIG regulates the humoral immune system include the (i) neutralization of pathogenetic autoantibodies via anti-idiotype antibodies[122], (ii) acceleration of the catabolism of pathogenic autoantibodies by saturation of FcRn[123], (iii) interaction with inhibitory Fc receptors, (iv) the reset of immunoglobulin repertoires[124], and (v) inhibition of activation and proliferation of B-cells by recruiting phosphatases[125,126].

IVIG suppressed B-cell activation and proliferation through agonistic binding to inhibitory receptors such as CD22 and FcγRIIb, while antagonizing signaling through BCR or TLRs[126], although this is not a consistent finding in human B-cells[105]. Compared to healthy controls, patients with CIDP display reduced expression of FcγRIIb on the surface of naïve and memory B-cells; this can be rescued following treatment with IVIG, resulting in upregulation of FcγRIIb on both B-cell subsets[124]. Treatment of GBS

with IVIG promoted rapid expansion of plasmablasts one week after onset of treatment[124]. In addition, IVIG may reduce B-cell survival by neutralization of BAFF, as demonstrated in CIDP patients[127,128].

Adaptive Immunity: Murine studies

Using a collagen induced arthritis (CIA) model, it was demonstrated that IVIG affected T-cell and germinal center responses[129], and that IVIG-mediated attenuation of CIA was IL-10 dependent and associated with increased frequencies of Tregs and decreased Th17 in the spleen, coupled with a decrease in splenic germinal center B- and T-follicular helper (Tfh) cells. Further, IVIG attenuates murine allergic airways disease (AAD) by inducing highly suppressive antigen specific Tregs[130-132] This entails modification of DC and is driven at least in part by Fc-sialic acid residues[70,130,133]. IgG-derived Tregitopes (T-regulatory epitopes), which can be produced synthetically[134], can reproduce the effects of IVIG in allergic airways disease[135]. IVIG had a positive effect on proliferation of natural Tregs[136] and reciprocally regulated pathogenic Th1/Th17 in experimental models of autoimmune diseases like EAE by regulating T-cell trafficking[73]; this effect was independent of IgG sialylation[74]. Other mechanisms including modulation of prostaglandin E2 have been reported by which IVIG induces and /or expands Tregs[70,81,134].

Anti-idiotype antibodies are naturally occurring antibodies against various molecules including normal cytokines, receptors and pathogenic autoantibodies; anti-idiotype antibodies in IVIG may help in regulating inflammatory responses. From as early as 1984, with the discovery of anti-idiotypic antibodies in IVIG against idiotypes of anti-VIII autoantibodies, multiple candidate anti-idiotypic antibodies have surfaced as highly relevant molecules[52,122,137-139]. For example, anti-anti-citrullinated-protein antibodies fractionated from commercial IgG (ACPA-sIVIG) was as effective as high-dose IVIG at Treg induction, reduced anti-collagen and anti-ACPA antibody responses, increased anti-inflammatory cytokine (IL-10 and TGF-β), and decreased pro-inflammatory cytokine (TNFα and IL1β) production in the CIA model [140]. Similarly, another study showed that anti-anti- β_2GPI specific fraction of IVIG, was highly effective

at preventing fetal loss and repairing fecundity in mice with experimental antiphospholipid syndrome (APS)[141]. These studies provide insight into the need to understand potential bioactive fractions within normal human immune globulin that can mitigate disease.

Conclusion

There has been extensive mechanistic study in animal models of disease and observation in IVIG-treated individuals. In this clinical commentary, we addressed pertinent studies that provide clues to biomarkers that track the effects of IVIG in autoimmune and inflammatory conditions. IVIG therapy can be best utilized if there will be clearer guidance for ancillary measures of immunological effectiveness to complement clinical observations. To summarize over 30 years of use of this therapy in a brief commentary does not do justice to the extensive amount of work that has been performed. However, the take home message is that there has been significant animal and human study of IVIG mechanistic biomarkers that we can use for clinical application. For example, measuring monocyte subsets or NK cells, as has been demonstrated in KD, in arthritis models and in high-risk pregnancies, may give practitioners more information regarding the likelihood of treatment success. Moreover, the accumulated evidence on induction of Tregs by IVIG suggests that there is a role for monitoring Treg in patients for whom there are questions on the effectiveness of IVIG therapies; this could be a target for validation in larger cohorts. Considering IVIG as a scare resource argues for development of distinct guidelines not simply for disease indications, but for baseline evaluation and follow-up of individuals who have IVIG therapy initiated for autoimmune and inflammatory diseases. This will not only provide a method of monitoring success or failure of therapy but will allow for accrual of evidence that can advance the care of those who are treated with human immunoglobulin.

Further mechanistic study will also improve the chances of understanding various fractions of IVIG that have specific bioactivity. The study of sialic acid linkages may address a need for a fraction of IgG that

376 can target specific conditions, but it also has increased the sophistication of preparation of other antibody
377 therapies, which require proper glycosylation to have maximum effect. Other modalities such as
378 Tregitopes or anti-idiotype antibodies such as targeted anti-endothelial antibodies, as examples, can
379 reduce reliance on the plasma supply. Until such time as a true substitute is found through clinical trials,
380 IVIG will continue to be a mainstay of therapy for multiple autoimmune conditions.
381

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383

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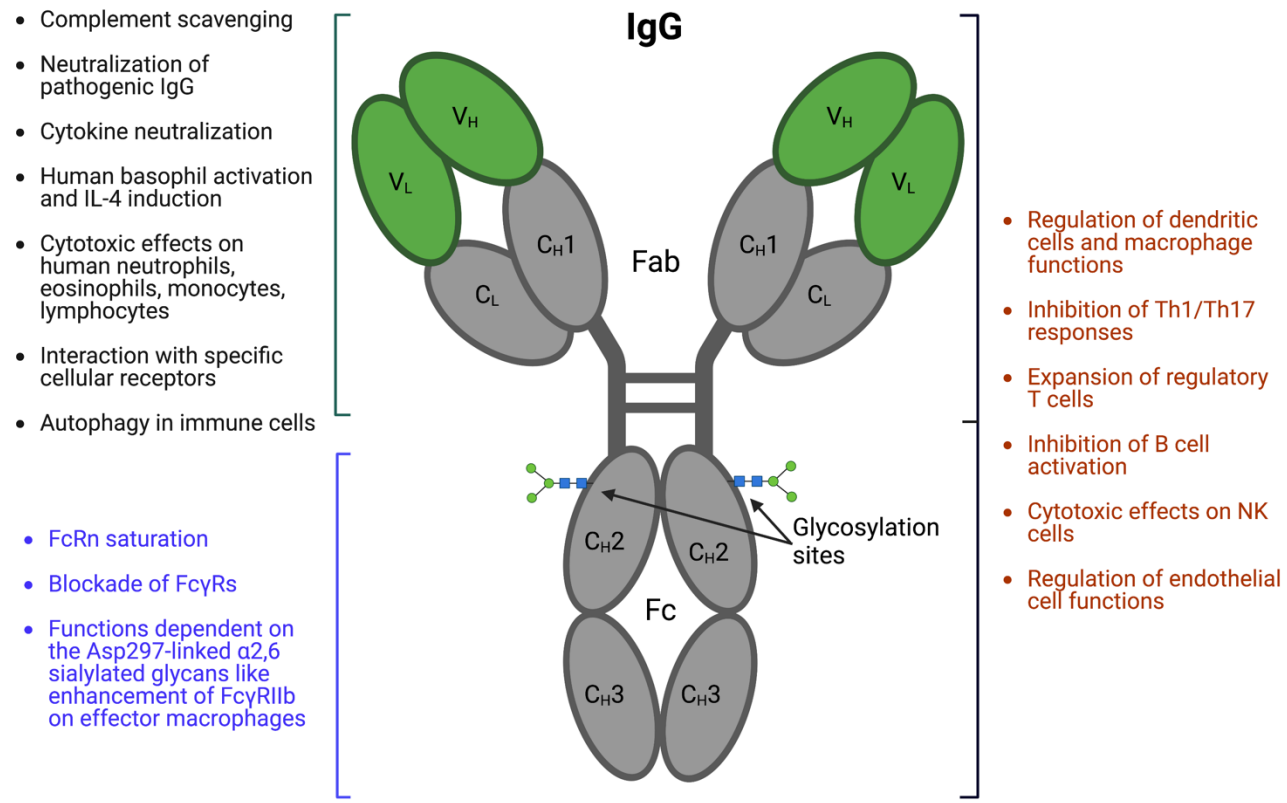
Figure Legend:

Figure 1: **The current knowledge on the implication of either F(ab')$_2$, Fc or both in the mechanisms of action of IVIG.** IgG contain Fab and Fc regions. Several mechanisms of IVIG are mediated by F(ab')$_2$ fragments. Some of the Fc-mediated functions also implicit the involvement of α2,6-sialic acid linkages at Asn297. However, mechanisms of IVIG for dendritic cells, various T cell subsets and B lymphocytes are dependent on both F(ab')$_2$ and Fc fragments. V_H, heavy chain variable domain; V_L, light chain variable domain; C_H, heavy chain constant domain; C_L, light chain constant domain. Figure created in BioRender.com.


IgG
Fab
Fc
V_H
V_L
C_H1
C_L
C_H2
C_H3
Glycosylation sites
Complement scavenging
Neutralization of pathogenic IgG
Cytokine neutralization
Human basophil activation and IL-4 induction
Cytotoxic effects on human neutrophils, eosinophils, monocytes, lymphocytes
Interaction with specific cellular receptors
Autophagy in immune cells
FcRn saturation
Blockade of FcγRs
Functions dependent on the Asp297-linked α2,6 sialylated glycans like enhancement of FcγRIIb on effector macrophages
Regulation of dendritic cells and macrophage functions
Inhibition of Th1/Th17 responses
Expansion of regulatory T cells
Inhibition of B cell activation
Cytotoxic effects on NK cells
Regulation of endothelial cell functions

832 **Table 1**: **Landmark studies on the mechanisms of action of IVIG**
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Innate Immune Compartment	**References**
Blockade of Fcγ receptors	Debré et al. 1993[58]
Induction of apoptosis of immune cells by Fas apoptosis pathway	Prasad et al. 1998[142]
Induction of anti-inflammatory IL-1 receptor antagonist (IL-1RA) in monocytes	Ruiz de Souza et al. 1995[36]
Suppression of an array of immune activation genes in monocytes of Kawasaki disease	Abe et al. 2005[47]
Regulation of dendritic cell functions	Bayry et al. 2003[52,55] Siragam et al. 2006[53] Wiedeman et al. 2013[57]
Inhibition of NK cytotoxicity	Ruiz et al. 1996[108]
Cytotoxic effects on neutrophils by anti-Siglec-9 autoantibodies	von Gunten et al. 2006[84]
Inhibition of neutrophil extracellular trap (NET)	Uozumi et al. 2020 [87]
Cytotoxic effects on eosinophils by anti-Siglec-8 autoantibodies	von Gunten et al. 2007[91]
IL-3-dependent induction of human basophil activation and IL-4 secretion via anti-IgE IgG	Galeotti et al. 2019 [78]
Fc-Sialylation-dependent anti-inflammatory mechanisms in Mice	Kaneko et al. 2006 [61] Anthony et al. 2011 [63] Fiebiger et al. 2015[64]
Identification of receptors for sialylated Fc fragments of IgG	Anthony et al. 2008[143] Séïté et al. 2010[126] Massoud et al 2014 [70] Fiebiger et al. 2015[64]
Induction of inhibitory ITAM signaling through FcγRIII	Aloulou et al. 2012[144]
Induction of autophagy in innate immune cells	Das et al. 2020[87]
Epigenetic regulation of macrophages	Guo et al. 2020[51]

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Innate Immune Compartment	**References**
Regulation of Th1/Th2 balance	Graphou et al 2003**[111]**
Inhibition of Th17 differentiation, expansion and function	Maddur et al. 2011**[112]**
Enhancement of regulatory T cells	Kessel et al. 2007 **[118]** Ephrem et al. 2008 **[136]**
Reciprocal regulation of Th17/Treg cells	Othy et al. 2013 **[73]** Lee et al 2014 **[129]** Guo et al. 2015[114]

Identification of mechanisms of Treg expansion in human and mouse	De Groot et al. 2008 [134] Trinath et al. 2013 [81] Massoud et al 2014 [70] Fiebiger et al. 2015 [64]
Suppression of IL-4- and CD40-induced B-lymphocyte activation	Zhuang et al. 2002 [125]
Inhibition of TLR9 signaling by recruiting phosphatases	Séïté et al. 2011[126]

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Soluble/Humoral Factors	**References**
Neutralization of pathogenic autoantibodies by anti-idiotype antibodies	Sultan et al. 1984 [122]
Neutralization of various cytokines by virtue of high-affinity anti-cytokine IgG antibodies	Svenson et al. 1993 [42]
Complement scavenging effects	Basta and Dalakas. 1994 [31] Basta et al. 2003 [33]

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Structural Cells	
Modulation of endothelial functions	Xu et al. 1998 [25]
Inhibition of toxic epidermal necrolysis by blockade of Fas-mediated keratinocyte death	Viard et al. 1998[18]
Saturation of FcRn	Akilesh et al. 2004 [123]
Modulation of immunoregulatory or structural muscle genes in the patients with inflammatory myopathies	Raju and Dalakas 2005 [34]

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