



Mechanisms of immune regulation by IVIG

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Purpose of review

In the past few years there have been many advances in our understanding of the mechanisms by which intravenous immune globulin (IVIG) modulates immune function in autoimmune disorders.

Recent findings

Previous investigations have focused on the Fc domain of the IgG molecule, and the role of the FcγRIIB receptor and the sialylated Fc domain that have been shown to mediate the anti-inflammatory effects in certain murine models of autoantibody-mediated diseases. More recent findings have implicated the F(ab')₂ domain in IVIG-induced immune modulation in T-cell-mediated autoimmune disease models in which upregulation of T-regulatory cells and downregulation of the Th17 pathways are important components of this mechanism. The prostaglandin E pathway may be playing a role in the IVIG-induced changes in the T-regulatory pathway.

Summary

Many of the mechanisms proposed for the immune-modulating effects of IVIG demonstrate the complexity of immune effector functions in disease processes. Although controversy exists on the role of the FcγRIIB receptor and the importance of the sialylated Fc domain in human autoimmune disorders, probably no one single mechanism is responsible for the effects of IVIG in autoimmune and inflammatory diseases. The potential role of the prostaglandin E pathway may offer alternative treatments.

Keywords

FcγRIIB receptor, intravenous immune globulin, neonatal Fc receptor, prostaglandin E, sialylation, Th17 cells, T-regulatory cells

INTRODUCTION

In 1981, Imbach *et al.* [1] were treating immune deficiency patients with intravenous immune globulin (IVIG). Several of these patients concomitantly had idiopathic thrombocytopenia purpura (ITP) and after treatment with IVIG, the platelet counts increased dramatically immediately after the IVIG infusion. These observations led to a subsequent study [1] in children with ITP, which demonstrated that the administration of high-dose IVIG led to a dramatic increase in platelet count and often the resolution of the disease process. Subsequently to these observations by Imbach in the early 1980s, there has been an explosion in the use of IVIG in patients with a variety of autoimmune and inflammatory disorders. Today, more than 70% of the IVIG utilized in the United States is for immune modulation in patients with autoimmune and inflammatory disorders. This review will examine the more recent literature on the mechanisms of action of IgG in the modulation of the immune system, and will focus on those mechanisms that affect the Fcγ receptors and T-regulatory (Treg) pathways. A number of mechanisms have been postulated for

the immunomodulatory effects of immunoglobulin. Mechanisms of action of IGIV are as follows:

- (1) blockade of Fc receptors on macrophages of the reticuloendothelial system of liver and spleen,
- (2) restoration of idiotypic-antiidiotypic network,
- (3) suppression or neutralization of cytokines by specific antibodies in the IGIV,
- (4) block binding of adhesion molecules on leukocytes to vascular endothelium,
- (5) inhibit complement uptake on target tissues,
- (6) neutralize microbial toxins,
- (7) block Fas ligand-mediated apoptosis by anti-Fas antibodies in the IGIV,

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Curr Opin Allergy Clin Immunol 2014, 14:509–515

DOI:10.1097/ACI.000000000000116

KEY POINTS

- Although saturation of the FcRn receptor may be an important component of IVIG-induced modulation of antibody-mediated autoimmune disease in experimental models, more studies are needed in human disease.
- Studies in splenectomized mice, with ITP and in patients with immune deficiency and autoimmune disease, have questioned the role of the FcγRIIB receptor and the C-type lectin receptor DC-SIGN in IVIG-induced immune modulation.
- Although the importance of sialylation of the IgG molecule especially of the Fc domain is important in murine models of autoantibody-mediated disease, this mechanism remains controversial in other animal models and in human disease.
- IVIG-induced Treg cells and inhibition of the Th17 pathway appear to be important mechanisms of action of IVIG.
- Several studies have demonstrated the role of the PGE pathway in the immune modulation of IVIG in certain disease models.

- (8) induce apoptosis with anti-Fas antibodies at high concentrations of IGIV,
- (9) neutrophil apoptosis by anti-Siglec-9 antibodies in IGIV,
- (10) saturate the FcRn receptors to enhance the clearance of autoantibodies,
- (11) induction of inhibitory FcγRIIB receptors on effector macrophages,
- (12) neutralization of growth factors for B-cells, for example, B-cell activating factor,
- (13) inhibit T-cell proliferative responses,
- (14) expand and/or activating a population of Treg cells,
- (15) downregulate the Th17 pathway,
- (16) inhibit the differentiation and maturation of dendritic cells.

The reader is referred to other reviews on this topic for a more comprehensive and complete review of the mechanisms of action of immunoglobulin [2,3²²].

THE ROLE OF THE NEONATAL Fc RECEPTOR ON IMMUNE MODULATION

The neonatal Fc receptor (FcRn) is a specialized receptor that binds serum IgG, protects the IgG from degradation inside the lysosomes and returns the IgG intact to the plasma circulation. These specialized receptors account for the long half-life of serum IgG of 21–25 days [4]. In FcRn knockout mice the

half-life of serum IgG is markedly decreased. Yu and Lennon [5] postulated that the administration of IVIG saturates this FcRn receptor found in the endosomes of endothelial cells, resulting in the enhanced catabolism of the autoantibodies in antibody-mediated autoimmune diseases. In mouse models of bullous pemphigoid and arthritis, IVIG treatment resulted in a reduction in pathogenic antibodies to levels beneath the disease-causing threshold, and this effect was attenuated in FcRn-deficient mice [6]. Hansen and Balthasar [7] reported that high-dose IVIG in a rat model of immune thrombocytopenia enhanced the clearance of antiplatelet antibodies by saturation of the FcRn receptor by immunoglobulin, and that this mechanism may account for 50% of the total protective effects of IVIG. These studies were supported by additional observations by Hansen and Balthasar [7] that in an FcRn knockout mouse, IVIG therapy failed to increase the clearance of antiplatelet antibodies. Similarly, using FcRn (–/–) knockout mice Li *et al.* [6] reported that the FcRn receptor saturation by immunoglobulin was critical to protect neonatal mice in a bullous pemphigoid mouse model. However, in these FcRn (–/–) mice models it is difficult to assess the pathogenicity of the autoantibody-inducing disease. In the absence of the FcRn receptor, the clearance of these autoantibodies in these disease models is modified, which affects their pathologic effects. Furthermore, in a different mouse ITP model with absent FcRn, IVIG was still effective in increasing platelet counts [8]. Thus, the role of the FcRn receptor in human autoantibody-mediated diseases modulated by IVIG is unclear (Fig. 1).

Fc RECEPTOR BLOCKADE

Following the administration of 1 to 2 g/kg of IVIG platelet counts rise rapidly in patients with ITP [9]. Fc receptor blockade of the reticuloendothelial system was suggested as the mechanism by which platelet counts rapidly increase after the administration of IVIG [10,11]. Autoantibody-opsonized platelets are destroyed in the spleen and liver by FcγR-mediated phagocytic clearance [8]. Fehr *et al.* [11] showed that the administration of IVIG in patients with ITP prolonged the in-vivo clearance of radiolabeled antibody sensitized red blood cells. Further supporting evidence for Fc receptor blockade on macrophages in the spleen and in other parts of the reticuloendothelial system was reported by Clarkson *et al.* [12] who demonstrated a marked increase in platelet counts in patients with ITP using a monoclonal antibody directed against the FcγRIIIA receptor. Intravenous administration in children with acute ITP of Fcγ fragments prepared

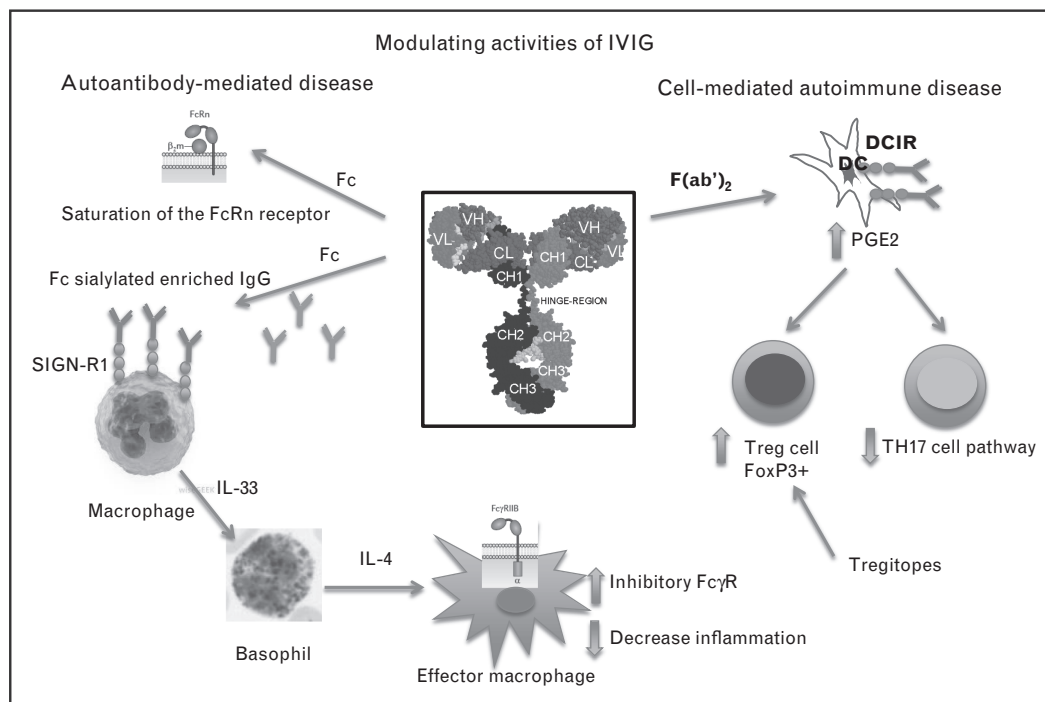


FIGURE 1. Immune modulating activities of IVIG in antibody mediated and cell mediated autoimmune disease.

from IVIG resulted in a rapid increase in platelet counts [13]. The efficacy of using Fc γ fragment therapy in ITP strengthens the hypothesis that Fc γ receptor blockade is the main mechanism of action of IVIG for the immediate rapid increase in platelet counts in ITP. However, this mechanism does not explain the longer-term immune-modulating effects of IVIG therapy in these autoantibody-mediated diseases.

MODULATION OF IMMUNOREGULATORY FUNCTION THROUGH THE Fc RECEPTOR

Although Fc receptor blockade with the administration of IVIG may result in the rapid rise in platelet counts in patients with ITP, studies [10,14] have shown that the levels of antiplatelet antibodies decrease over time. Studies [15,16] addressing these observations suggest that the inhibitory Fc γ RIIB receptors found on a variety of cell types including macrophages, B-cells and a subpopulation of T-cells may be playing a role in the immune modulation of IVIG. This Fc γ RIIB receptor provides an inhibitory signal to cells through a pathway mediated by an immunoregulatory tyrosine-based inhibition motif. In a murine model of immune thrombocytopenia Samuelsson *et al.* [17] reported that the protective effects of IVIG required this inhibitory Fc γ receptor, for example, in which either disruption of Fc γ RIIB receptors in knockout mice or blocking with a monoclonal antibody reversed the therapeutic

effects of IVIG. The protective effects of IVIG were associated with the increased expression of the Fc γ RIIB receptor on splenic macrophages [17]. Subsequently, Kaneko *et al.* [18] showed that the inhibitory properties of IVIG was linked to the sialylation of the glycan component in the CH2 domain of the Fc fragment. Using a K/BxN serum-induced arthritis murine model, Kaneko *et al.* [18] showed that IVIG at 1g/kg inhibited the inflammatory arthritic process. Deglycosylated or neuraminidase-treated IVIGs were unable to inhibit this inflammation. IVIG enriched for the sialylated glycan moiety had comparable inhibitory effects on the inflammatory process at only 1/10th of the dosage used with intact IVIG. This inhibitory activity was dependent on Fc γ RIIB expression on effector macrophages. Anthony *et al.* [19] engineered a recombinant/sialylated human IgG1 Fc protein that had a 35-fold enhanced immune-modulating activity compared with native IVIG. However, antibodies enriched for the sialic acid moiety have reduced binding to the Fc γ Rs [20] that suggested that other receptor(s) are involved in the inhibitory or anti-inflammatory properties of IVIG.

Although in these mouse models of autoantibody mediated disease the role of the sialylated IgG molecule resulting in an increase in the Fc γ RIIB receptor on effector macrophages was important, the intermediary steps leading to changes in this receptor were not clear. Anthony *et al.* [21] performed studies to examine the mechanism by which

the sialylated Fc fragment could mediate its anti-inflammatory activity, and identify the target cell that initiates this anti-inflammatory pathway. They showed that a C-type lectin receptor, for example, specific intercellular adhesion molecule 3-grabbing nonintegrin-related 1 (SIGN-R1) which is expressed primarily on splenic marginal zone macrophages was required for the anti-inflammatory activity of IVIG in concert with its ability to bind to sialylated Fc domains. Furthermore, the 2,6 linkage of the sialylated moiety in the Fc domain was important for the modulating effects of IVIG. Anthony *et al.* [22] demonstrated that the interaction between sialylated IgG Fc and SIGN-R1 leads to the upregulation of the inhibitory FcγRIIB receptor on effector macrophages, and that this effect of IVIG was abrogated in SIGN-R1 knockout mice. Using their K/BxN serum-induced arthritis model in mice, Anthony *et al.* [22] showed that IVIG induced the production of IL-33 from dendritic cells, by binding of the sialylated Fc domain to SIGN-R1, which in turn increased the production of IL-4 from basophils, and upregulated the expression of the FcγRIIB receptor on effector macrophages. It had been demonstrated by others that Th2 derived cytokines, and IL-4 in particular, increase the expression of the FcγRIIB receptor on effector cells.

Does this mechanism of action for IVIG reported by Ravetch and colleagues in several autoantibody-mediated mouse models [18,19,21,22] play a role in humans? In particular is dendritic cell-specific intercellular adhesion molecule-3-grabbing nonintegrin (DC-SIGN), the human orthologue of SIGN-R1 in the mouse, involved in the immune-modulating effects of IVIG in man? Others have questioned whether this lectin receptor has a comparable role for the anti-inflammatory effects of the IgG Fc domain on human macrophages and dendritic cells. SIGN-R1 is mainly expressed on mouse splenic marginal zone macrophages, an important aspect of the model proposed by Ravetch and colleagues. The human spleen differs from that in mice with regard to the presence of marginal zone macrophages. Splenectomized patients with ITP still respond to IVIG therapy. In an ITP mouse model, IVIG still showed efficacy when splenectomized [23,24]. Tjon *et al.* [25^{***}] studied these proposed pathways in patients receiving IVIG treatment for primary immune deficiency disease and autoimmune disease. IVIG therapy increased plasma levels of IL-33, IL-4 and IL-13, but the FcγRIIB receptor was not upregulated on peripheral blood myeloid dendritic cells. There was decreased expression of the activating FcγRIIA receptor and of the IFN-γR2 subunit on myeloid dendritic cells in those patients receiving high-dose IVIG. Using a DC-SIGN

blocking antibody, IVIG still enhanced IL-33 mRNA production by macrophages *in vitro*. These data and other studies [26,27] suggest a DC-SIGN and FcγRIIB receptor independent pathway for the effects of IVIG. In contrast, observations in patients with chronic inflammatory demyelinating polyneuropathy treated with high-dose IVIG demonstrated upregulation of this FcγRIIB receptor on peripheral blood monocytes [28]. Therefore, the pathways by which IVIG modulated immune function may be different in humans compared with mice, a theme that will be expanded upon below in other models on the effects of IVIG-induced immune modulation.

THE SIALYLATION CONTROVERSY

The experimental models of Ravetch and colleagues clearly outline the role of sialylated IgG on the Fc domain in the immunomodulatory properties of IVIG on murine models of antibody-mediated autoimmune disease. IgG is glycosylated in the constant region in the CH2 domain at Asn 297. Glycosylation in the IgG Fc domain modifies antibody effector function by modifying its binding affinity to Fcγ receptors. A fully processed form of the carbohydrate component with a terminal sialic acid moiety is present in only 5% of the total serum IgG. Is this the reason why such large doses of IVIG are required to achieve efficacy in human autoimmune diseases? Several studies have suggested that the Fc sialylated portions of the IgG molecule were not critical for the activity of IVIG. Leontyev *et al.* [23] described a sialylation-independent mechanism for the effects of IVIG in a murine ITP model. Campbell *et al.* [29] explored the effects of high-dose IVIG in two murine models of antibody-mediated inflammation of the joints, models for rheumatoid arthritis: the K/BxN serum transfer murine model used by Ravitch and colleagues, and the collagen antibody-induced arthritis murine model. IVIG was protective in a dose-dependent manner, and the protective effect was linked to the Fc domain of IgG. However, sialylation was not required for efficacy. Also, in contrast to the studies by Anthony *et al.* [22], depleting basophils with a monoclonal antibody did not abrogate the effects of IVIG on its immune-modulating activities. These authors also called into question the role of IL-33 in the immune-modulating process by IVIG. IL-33Rα^{-/-} mice, but not IL-33^{-/-} mice were protected from K/BxN serum transfer-induced arthritis [30]. Bayry *et al.* [26] found that sialylated IgG Fc fragments were not involved in the anti-inflammatory activity of IVIG on human dendritic cells. Furthermore, the variable region domains also have sialic acid rich glycan moieties [31,32] that may be important in engaging C-type

lectin receptors. In several murine and in-vitro human models (see below), the F(ab')₂ fragment of IVIG was involved in the immune modulation of the disease process.

EFFECTS OF IMMUNOGLOBULIN G ON THE T-REGULATORY PATHWAYS

Although many labs have focused on antibody-mediated autoimmune disease, other labs have focused on the effects of IVIG on cell-mediated immune autoimmune disease. One such T-cell-mediated model is experimental autoimmune encephalomyelitis, a murine animal model of multiple sclerosis in which IVIG abrogates the disease progression by expanding CD4+CD25+ forkhead box P3 (FoxP3) Treg cells. Using this animal model, Othy *et al.* [33²²] showed that IVIG inhibits the differentiation of Th17 and Th1 cells, and increases the number of CD4+CD25+ FoxP3+ Treg cells. Even in FcγRIIB^{-/-} mice IVIG decreased the number of Th17 cells, while expanding the number of FoxP3+ Treg cells. Furthermore, this process induced by IVIG was not dependent on the Fc domain as F(ab')₂ fragments led to similar changes in Th17 cells, Treg cells and clinical efficacy in this experimental autoimmune encephalomyelitis model. Desialylated IVIG had the same immune-modulating effects as 'native' IVIG [34]. Kaveri and colleagues [35²³] demonstrated that the mechanism by which IVIG induces Treg cells was by the induction of cyclo-oxygenase dependent prostaglandin E₂ (PGE₂) from human dendritic cells. This process was mediated by F(ab')₂ fragments, but not Fc fragments. In a different in-vitro model, Wiedeman *et al.* [36²⁴] showed that a F(ab')₂ fragment of IVIG inhibited toll-like receptor (TLR)-7 and TLR-9 agonist-induced IFN-α production. This inhibitory activity of IgG was mediated by PGE₂ production by monocytes.

Mazer and colleagues have extensively studied the effects of IVIG therapy in an ovalbumin sensitized mouse model of asthma. IVIG markedly attenuated lung inflammation and decreased bronchial hyperresponsiveness to methacholine [37]. IL-13 and TNF-α levels diminished, Delta-4 (part of the Notch pathway that induces Th1 cells) expression increased whereas Jagged-1 (part of the Notch pathway that induces Th2 cells) expression and GATA-3 mRNA decreased, suggesting that Th2 responses were suppressed. The draining pulmonary lymph nodes of IVIG treated mice showed a significant increase in CD4+CD25+Foxp3+ regulatory cells. IVIG-primed dendritic cells on adoptive transfer to ovalbumin sensitized and challenged mice abrogated airway hyperresponsiveness and induced Treg

cells [38]. In their model system Massoud *et al.* [39²⁵] reported that sialylated IgG bound to a novel C-type lectin receptor, that is the dendritic cell immunoreceptor (DCIR), induced Treg cells and attenuated airway hyperresponsiveness. Interestingly, transfer of IVIG treated myeloid dendritic cell from Fcγ receptor knockout mice still increased Treg cells and abrogated airway hyperresponsiveness. These observations suggest that in this asthma model the effects of IVIG were independent of Fcγ receptors.

The importance of Treg cells in the immune modulation induced by IVIG is also underscored by the studies of de Groot *et al.* [40]. These investigators identified epitopes, that is Tregitopes in both the Fc and F(ab')₂ regions that bind to multiple human leucocyte antigen class II determinants that results in the expansion and activation of FoxP3⁺ Treg cells. Coincubation of these Tregitopes with house dust mite antigen led to expansion of CD4+CD25^{high} Treg cells, and suppressed IL-5 and IFN-γ cytokine secretion, but upregulated IL-10 from peripheral blood mononuclear cells of house dust mites-sensitive individuals. Although not studied directly in their model, antigen-presenting cells or dendritic cells presumably play an important role in this pathway of inducing Treg cells.

In Kawasaki disease and in patients with a vasculitis, clinical improvement with IVIG therapy correlated with increased Treg number and function [41,42]. Tjon *et al.* [43] reported that high-dose, but not low-dose IVIG treatment in patients with immunodeficiency and autoimmune disease enhanced the activation of circulating Treg cells, but the numbers of circulating Treg cells remained unchanged. Thus, depending on the animal model for autoimmune disease and the human autoimmune disorder, IVIG appears to have reciprocal immune-modulating effects by downregulating the Th17 pathway [44] and enhancing or expanding CD4+CD25+ FoxP3 Treg cells.

CONCLUSION

Clearly, IVIG (IgG) has a number of immune-modulating effects (see the above list given in the introduction section). In autoantibody-mediated disease, the Fc domain appears to be the important IgG moiety that leads to immune modulation. The importance of sialylation of the Fc fragment remains controversial, as do the mediators involved, for example, IL-33 and IL4. Differences in animal models, IVIG source, route and timing of the administration of the IVIG, mouse strain and other variables may account for the differences in experimental observations between laboratories. In T-cell-mediated animal models of disease, such as

experimental autoimmune encephalomyelitis, there is strong evidence that there is upregulation of Treg cells and inhibition of the Th17 pathway. These effects may be mediated by the F(ab')₂ portion of the IgG molecule, and not the Fc domain. Furthermore, there is also controversy over the receptor on antigen processing cells, for example, macrophages and dendritic cells that are involved in the immune-modulating process mediated by IVIG. In certain animal models the SIGN-R1 (or in humans DC-SIGN, the orthologue of SIGN-R1 in the mouse) is important, and in other models, for example, murine asthma, a novel C-type lectin receptor (DCIR) appears to be important. These differences undoubtedly relate to the disease model. Two studies have demonstrated the importance of the PGE₂ pathway on IVIG-induced immune modulation mediated by the F(ab')₂ portion of the IgG molecule. These observations may point to the possibility of alternative treatment regimens that employ the selective increase in PGE₂ in certain autoimmune or inflammatory disorders to increase Treg cells and inhibition of the production of certain cytokines. Further clarification will be important in human disease models. These mechanisms are not mutually exclusive, and probably more than one mechanism is playing a role in the efficacy of immunoglobulin therapy in an autoimmune disease process.

Acknowledgements

None.

Conflicts of interest

M. Ballow has received honoraria from CSL Behring, Baxter, Grifols, American College of Allergy, Asthma and Immunology, Kedrion, Up-to-Date, National Institute of Allergy and Infectious Diseases. M. Ballow is currently receiving a grant from CSL Behring, and is on the speaker's bureau for CSL Behring, Baxter and Grifols.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Imbach P, Barandun S, d'Apuzzo V, *et al.* High dose intravenous gammaglobulin for idiopathic thrombocytopenic purpura in childhood. *Lancet* 1981; 1:1228–2132.
2. Ballow M. The IgG molecule as a biological immune response modifier: mechanisms of action of intravenous immune serum globulin in autoimmune and inflammatory disorders. *J Allergy Clin Immunol* 2011; 127:315–323.
3. Schwab I, Nimmerjahn F. Intravenous immunoglobulin therapy: how does IgG modulate the immune system? *Nat Rev Immunol* 2013; 13:176–189.
- Excellent review on the mechanisms of action of IVIG with some interesting insight.
4. Jungmans R, Anderson C. The protective receptor for IgG catabolism is the beta2-microglobulin-containing neonatal intestinal transport receptor. *Proc Natl Acad Sci U S A* 1996; 93:5512–5516.
5. Yu Z, Lennon VA. Mechanism of intravenous immune globulin therapy in antibody-mediated autoimmune diseases. *N Engl J Med* 1999; 340:227–228.
6. Li N, Zhao M, Hilario-Vargas J, *et al.* Complete FcRn dependence for intravenous Ig therapy in autoimmune skin blistering diseases. *J Clin Invest* 2005; 115:3440–3450.
7. Hansen RJ, Balhasar JP. Effects of intravenous immunoglobulin on platelet count and antiplatelet antibody disposition in a rat model of immune thrombocytopenia. *Blood* 2002; 100:2087–2093.
8. Crow AR, Song S, Freedman F, *et al.* IVIg-mediated amelioration of murine ITP via FcR1B is independent of SHIP1, SHP-1, and Btk activity. *Blood* 2003; 102:558–560.
9. Blanchette VS, Luke B, Andrew M, *et al.* A prospective, randomized trial of high-dose intravenous immune globulin G therapy, oral prednisone therapy, and no therapy in childhood acute immune thrombocytopenic purpura. *J Pediatr* 1993; 123:989–995.
10. Bussell J. Modulation of Fc receptor clearance and antiplatelet antibodies as a consequence of intravenous immune globulin infusion in patient with immune thrombocytopenic purpura. *J Allergy Clin Immunol* 1989; 84:566–578.
11. Fehr J, Hofmann V, Kappeler U. Transient reversal of thrombocytopenia in idiopathic thrombocytopenic purpura by high-dose intravenous gammaglobulin. *N Engl J Med* 1982; 306:1254–1258.
12. Clarkson SB, Bussell JB, Kimberly RP, *et al.* Treatment of refractory immune thrombocytopenic purpura with an anti-Fcγ receptor antibody. *N Engl J Med* 1986; 314:1236–1239.
13. Debre M, Bonnet MC, Fridman WH, *et al.* Infusion of Fc gamma fragments for treatment of children with acute immune thrombocytopenic purpura. *Lancet* 1993; 342:945–949.
14. Bussell J, Pahwa S, Porges A. Changes in the vitro antibody synthesis in ITP treated with intravenous gamma globulin are closely linked to long-term outcome. *J Clin Immunol* 1986; 6:50–56.
15. Daron M. Fc receptor biology. *Annu Rev Immunol* 1997; 15:203–234.
16. Kimberly RP, Salmon JE, Edberg JC. Receptors for immunoglobulin G. *Arthritis Rheum* 1995; 38:306–314.
17. Samuelsson A, Towers TL, Ravetch JV. Anti-inflammatory activity of IVIG mediated through the inhibitory Fc receptor. *Science* 2001; 291:484–486.
18. Kaneko Y, Nimmerjahn F, Ravetch JV. Anti-inflammatory activity of immunoglobulin G resulting from Fc sialylation. *Science* 2006; 313:670–673.
19. Anthony RM, Nimmerjahn F, Ashline D, *et al.* Recapitulation of IVIG anti-inflammatory activity with a recombinant IgG Fc. *Science* 2008; 320:373–376.
20. Arnold J, Wormald M, Sim R, *et al.* The impact of glycosylation on the biological function and structure of human immunoglobulins. *Annu Rev Immunol* 2007; 25:21–50.
21. Anthony RM, Wermeling F, Karlsson M, Ravetch J. Identification of a receptor required for the anti-inflammatory activity of IVIG. *Proc Natl Acad Sci U S A* 2008; 105:19571–19578.
22. Anthony RM, Kobayashi T, Wermeling F, Ravetch JV. Intravenous gammaglobulin suppresses inflammation through a novel T(H)2 pathway. *Nature* 2011; 475:110–113.
23. Leontyev D, Katsman Y, Ma XZ, *et al.* Sialylation-independent mechanism involved in the amelioration of murine immune thrombocytopenia using intravenous gammaglobulin. *Transfusion* 2012; 52:1799–1805.
24. Schwab I, Biburger M, Kronke G, *et al.* IVIg-mediated amelioration of ITP in mice is dependent on sialic acid and SIGNR1. *Eur J Immunol* 2012; 42:826–830.
25. Tjon AS, van Gent R, Jaadar H, *et al.* Intravenous Immunoglobulin Treatment in Humans Suppresses Dendritic Cell Function via Stimulation of IL-4 and IL-13 Production. *J Immunol* 2014; 192:5625–5634.
- An important article using human cells in patients treated with high-dose IVIG showing that IVIG modulates the inflammatory responsiveness of myeloid dendritic cell by a DC-SIGN independent process mediated by Th2 cytokines with down-regulation of FcγRIIa and IFN-γR2 receptors but not FcγRIIB.
26. Bayry J, Bansal K, Kazatchkine M, Kaveri S. DC-SIGN and a2,6-sialylated IgG Fc interaction is dispensable for the anti-inflammatory activity of IVIG. *Proc Natl Acad Sci U S A* 2009; 106:E24.
27. Yu X, Vasiljevic S, Mitchell DA, *et al.* Dissecting the molecular mechanism of IVIg therapy: the interaction between serum IgG and DC-SIGN is independent of antibody glycoform or Fc domain. *J Mol Biol* 2013; 425:1253–1258.
28. Tackenberg B, Jelcic I, Baerenwaldt A, *et al.* Impaired inhibitory Fcγgamma receptor IIb expression on B cells in chronic inflammatory demyelinating polyneuropathy. *Proc Natl Acad Sci U S A* 2009; 106:4788–4792.
29. Campbell IK, Miescher S, Branch DR, *et al.* Therapeutic effect of IVIG on inflammatory arthritis in mice is dependent on the Fc portion and independent of sialylation or basophils. *J Immunol* 2014; 192:5031–5038.
30. Martin P, Talabot-Ayer D, Seemayer CA, *et al.* Disease severity in K/BxN serum transfer-induced arthritis is not affected by IL-33 deficiency. *Arthritis Res Ther* 2013; 15:R13.
31. Guhr T, Bloem J, Derksen NI, *et al.* Enrichment of sialylated IgG by lectin fractionation does not enhance the efficacy of immunoglobulin G in a murine model of immune thrombocytopenia. *PLoS One* 2011; 6:e21246.
32. Kasermann F, Boerema DJ, Rueggsegger M, *et al.* Analysis and functional consequences of increased Fab-sialylation of intravenous immunoglobulin (IVIG) after lectin fractionation. *PLoS One* 2012; 7:e37243.

33. Othy S, Hegde P, Topcu S, *et al.* Intravenous gammaglobulin inhibits encephalitogenic potential of pathogenic T cells and interferes with their trafficking to the central nervous system, implicating sphingosine-1 phosphate receptor 1-mammalian target of rapamycin axis. *J Immunol* 2013; 190:4535–4541.

An important article that demonstrates that IVIG inhibits the differentiation of CD4 T-cells into Th17 cells, while inducing the expansion of FoxP3+ Treg cells. The F(ab')₂ fragments were similar to intact IgG in mediating these effects.

34. Othy S, Topcu S, Saha C, *et al.* Sialylation may be dispensable for reciprocal modulation of helper T cells by intravenous immunoglobulin. *Eur J Immunol* 2014; 44:2059–2063.

35. Trinath J, Hegde P, Sharma M, *et al.* Intravenous immunoglobulin expands regulatory T cells via induction of cyclo-oxygenase-2-dependent prostaglandin E2 in human dendritic cells. *Blood* 2013; 122:1419–1427.

A critical article that demonstrates that the IVIG-induced expansion of Treg cells is mediated by the induction of cyclo-oxygenase dependent prostaglandin E2.

36. Wiedeman A, Santer D, Wei Y, *et al.* Contrasting mechanisms of interferon- α inhibition by intravenous immunoglobulin after induction by immune complexes versus toll-like receptor agonists. *Arthritis Rheum* 2013; 65:2713–2723.

In this article the authors report that the inhibitory activity of IVIG on TLR agonist-induced IFN- α requires monocyte production of PGE2.

37. Kaufman GN, Massoud AH, Audusseau S, *et al.* Intravenous immunoglobulin attenuates airway hyperresponsiveness in a murine model of allergic asthma. *Clin Exp Allergy* 2011; 41:718–728.

38. Massoud AH, Guay J, Shalaby KH, *et al.* Intravenous immunoglobulin attenuates airway inflammation through induction of forkhead box protein 3-positive regulatory T cells. *J Allergy Clin Immunol* 2012; 129:1656–1665.e3.

39. Massoud AH, Yona M, Xue D, *et al.* Dendritic cell immunoreceptor: a novel receptor for intravenous immunoglobulin mediates induction of regulatory T cells. *J Allergy Clin Immunol* 2014; 133:853–863.e5.

An important article that demonstrates that a novel C-type lectin receptor for sialic acid enriched IVIG, dendritic cell immunoreceptor, is an important component of IVIG-induced increase in Treg cells and abrogation of the airway hyperresponsiveness in a mouse asthma model.

40. De Groot A, Moise L, McMurry J, *et al.* Activation of natural regulatory T cells by IgG Fc-derived peptide 'Tregitopes'. *Blood* 2008; 112:3303–3311.

41. Olivito B, Taddio A, Simonini G, *et al.* Defective FoxP3 expression in patients with acute Kawasaki disease and restoration by intravenous immunoglobulin therapy. *Clin Exp Rheumatol* 2010; 28:93–97.

42. Tsurikisawa N, Saito H, Oshikata C, *et al.* High dose intravenous immunoglobulin treatment increases regulatory T cells in patients with eosinophilic granulomatosis with polyangitis. *J Rheumatol* 2012; 39:1019–1025.

43. Tjon A, Tha-In T, Metselaar H, *et al.* Patients treated with high-dose intravenous immunoglobulin show selective activation of regulatory T cells. *Clin Exp Immunol* 2013; 173:259–267.

44. Maddur MS, Vani J, Hegde P, *et al.* Inhibition of differentiation, amplification, and function of human TH17 cells by intravenous immunoglobulin. *J Allergy Clin Immunol* 2011; 127:823–830; e1-7.