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The role of immunoglobulin therapy in allergic diseases

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Intravenous immunoglobulin (IVIG) has been used for many years to treat patients with primary immunodeficiencies. More recently, IVIG has been shown to have anti-inflammatory activity when used at substantially higher concentrations. A number of studies have examined the efficacy of IVIG in allergic diseases. For patients with severe refractory asthma, sinusitis, atopic dermatitis, and urticaria, IVIG offers an alternative therapy with relatively few side-effects. Although the mechanism by which IVIG may attenuate the allergic response is still undetermined, clinical studies have shown that immunoglobulin therapy can decrease serum IgE levels and increase glucocorticoid binding affinity, while *in vitro* studies have shown that IVIG can decrease T-cell secretion of TH2 cytokines. Further studies are needed to confirm the initial encouraging results seen in allergic patients with severe, resistant disease.

Human immunoglobulin G (IgG) preparations have been used for many years to prevent bacterial and viral infections in patients who cannot produce sufficient amounts of IgG antibody in response to specific challenge. The process by which an IgG concentrate is made from large volumes of human plasma (often derived from greater than 10 000 donors), called cold ethanol fractionation, was developed by E.J. Cohn in the early 1940s. This method primarily isolated IgG, which often aggregated into dimers, causing complement activation *in vivo*. Infusion of this preparation resulted in various serious reactions that precluded intravenous administration. To avoid these complications, IgG replacement therapy was delivered by intramuscular injection, which provided slower absorption into the bloodstream. However, this method of administration was far from

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satisfactory. Injections were painful, the amounts administered were limited, and muscle proteases degraded some of the infused immunoglobulins. Several steps were ultimately added to the fractionation procedure (including extraction at low pH and addition of sugars to decrease aggregation), resulting in a purified product with fewer IgG dimers, and allowing higher doses of immunoglobulin to be safely administered intravenously (IVIG).

It soon became apparent that IVIG had anti-inflammatory and immunomodulatory effects when administered at higher concentrations. It is now known that to exhibit anti-inflammatory potential, IVIG must be given at substantially higher concentrations than used to treat primary antibody deficiencies. For instance, in chronic ITP, the initial effective dose given is 2 gm/kg followed by 1 gm/kg as a monthly maintenance dose after the initial response (1). In Kawasaki disease, where IVIG at high doses has been shown to prevent coronary aneurysms, studies have demonstrated that 100–500 mg/kg of IVIG will have minimal efficacy in preventing coronary aneurysms and that total doses of <1 gm/kg are either ineffective or inferior to the higher doses (2). In light of these findings, most trials of the effectiveness of IVIG in autoimmune and inflammatory diseases have adopted a regimen of 2 gm/kg given in single or multiple doses, generally every 4 weeks. Prospective randomized, controlled trials are lacking in many of these clinical situations, but in diseases such as Kawasaki disease and immune thrombocytopenic purpura (ITP), IVIG has become the standard treatment.

Clinical studies in allergy

Asthma

In the 1950s and 1960s, intramuscular injections of immunoglobulin were frequently used to treat “infectious asthma”. At that time, asthma was subdivided into extrinsic and intrinsic asthma. Intrinsic or infectious asthma was believed to be due to increased numbers of infections despite normal levels of IgG. Thus, patients with intrinsic asthma were thought to have a qualitative defect in their immunity which predisposed them to increased infections. Since immunoglobulin injections were effective in the treatment of immunodeficiency and provided protection against viral infections such as measles and infectious hepatitis, it was believed that immunoglobulin therapy could improve immune function and reduce the incidence of infections in asthmatics.

In 1958, Abernathy et al. (3) published the first double-blind, placebo-controlled study in 22 asthmatic children with normal IgG levels. Half the children received six monthly injections of intramuscular immunoglobulin at the dose recommended for treatment of patients with immunodeficiency, and the other half received saline injections. At the end of the study, there were no significant differences from controls in asthma symptoms, vital capacity, eosinophil counts, or numbers of infections. In fact, both the treatment and placebo groups showed a high rate of improvement. The immunoglobulin group did, however, require substantially fewer days (56 vs 224) of treatment with glucocorticoids. A second double-blind, placebo study by Fontana et al. (4) essentially confirmed these findings.

In 1988, a double-blind, placebo-controlled study was conducted by Smith et al. (5), using low-dose (200 mg/kg) IVIG in 50 children. Patients in the IVIG group required significantly fewer doses of bronchodilators or corticosteroids and had a trend toward less severe asthma symptoms than controls, although this did not reach statistical significance. Other parameters such as pulmonary function were not assessed.

Since the initial use of immunoglobulin for treatment of “infectious asthma”, our understanding of the disease has changed, as has our use of immunoglobulin therapy. With the ability to administer higher doses intravenously as an anti-inflammatory agent, the first studies evaluating the use of high-dose IVIG in asthma emerged.

A number of case reports described dramatic effects of high-dose IVIG when administered to patients with severe asthma. In 1989, Mazer et al. (6) reported the case of a 14-year-old girl with severe asthma who continued to have poor pulmonary function despite treatment with oral steroids. She was treated with high-dose IVIG (2 gm/kg) in seven monthly infusions and was able to decrease her daily steroid use significantly while pulmonary function improved in parallel. A second case study (7) of two teenagers with steroid-resistant asthma was published in 1996. In both patients, maintenance oral steroids were reduced dramatically while pulmonary function increased into the normal range after 2–6 months of high-dose (2 gm/kg) IVIG therapy.

As a follow-up to their earlier report, Mazer & Gelfand (8) published an open-label study in eight children. These children had steroid-dependent asthma (normal pulmonary function maintained only if on oral steroids), but two of the patients had steroid-resistant asthma (poor pulmonary function despite treatment with oral steroids). These patients had been followed as inpatients for a number of

months, and their therapies had been optimized before initiation of IVIG therapy. Each patient received monthly infusions of 2 gm/kg of IVIG for a period of 6 months. All patients had significant decreases in asthma symptom scores. The steroid-dependent patients were weaned to significantly lower daily prednisone doses beginning after 1 month of therapy, while maintaining normal pulmonary function. The two patients with steroid-resistant asthma were able to decrease their steroid dose and normalize their pulmonary function. All patients tolerated the infusions with minimal side-effects. A second open-label study done on similar patients by Landwehr et al. (9) confirmed the steroid-sparing effects found by Mazer & Gelfand.

Jakobsson et al. (10) published an open-label trial in 1994. Nine patients with moderately severe asthma were treated with IVIG for 5 months. This group was compared to a reference group of asthmatics who were not treated. Because of the association with long-lasting severe headaches in these patients, the dose of IVIG that was administered was reduced below 1 gm/kg. At study completion, there was a significant decrease in asthma symptom scores and a significant decline in inhaled steroid dose in the treatment group compared to the reference group. After the infusions were stopped, there was an increase in symptom score and steroid requirements. There was no difference in peak-flow variability or pulmonary function; however, it is unclear whether these patients had normal pulmonary function upon entry into the study.

Niggemann et al. (11) recently published the results of a double-blind, placebo-controlled study comparing high-dose IVIG treatment to serum albumin infusions in 31 asthmatic children and adolescents. These patients also had mild to moderate asthma based on FEV₁ while being maintained on moderate doses of beclomethasone or budesonide (800 µg/day). The groups initially received 1 gm/kg of either IVIG or

albumin for 2 consecutive days (2 gm/kg) and then two more monthly doses of 1 gm/kg. Only mild side-effects were noted with these infusions. In the treatment group, there was a significant decrease in the number of days with upper respiratory infections as well as a trend toward fewer symptoms. There were no significant differences between groups in bronchial reactivity, peak-flow variability, or blood eosinophils. Pulmonary function increased in both the treatment group and the placebo group, so that there was no significant effect of IVIG on pulmonary function. Although not one of the main end points of this study, there was a small decrease in steroid requirement in the treatment group and a slight increase in the control group. This too was not statistically significant.

What are we to conclude from the seemingly different results in these studies? (Table 1). First, it is likely that for effects to be observed in asthma, high doses of IVIG are required, as with other inflammatory diseases. Therefore, it is not surprising that in the studies of Abernathy et al. (3), Fontana et al. (4), and Smith et al. (5), where only low doses of IgG were administered, there were no significant effects on pulmonary function or symptom scores (although even at these doses there was a steroid-sparing effect). Second, unlike Kawasaki disease and ITP, where the effects can be measured soon after the first infusion, there are some parameters such as lung function or steroid reduction which may improve only after 2–4 monthly infusions of high-dose IVIG. This is not entirely surprising since these studies were in chronic asthmatics, and the effects of IVIG in other chronic diseases such as dermatomyositis occurred only after 2–4 months of treatment with 2 gm/kg of IVIG (12). This suggests that short-term studies such as the Niggemann et al. study that was carried out over 2 months would not detect significant improvement in lung function. Most importantly, in both the Jakobsson et al. and

Table 1. IVIG effects in asthma

Study (Ref.)	Type	Duration	Dose	Symptoms	Steroid sparing	PFTs
Abernathy et al. (3)	DBPC	6 months	0.6 cc/kg*	No	Yes	No
Fontana et al. (4)	DBPC	6 months	0.6 cc/kg*	No	?	No
Smith et al. (5)	DBPC	6 months	0.2 gm/kg*	No	Yes	?
Mazer & Gelfand (8)	Open label	6 months	2 gm/kg	Yes	Yes	Yes
Landwehr et al. (9)	Open label	6 months	2 gm/kg	Yes	Yes	Yes
Jakobsson et al. (10)	Open label controlled	5 months	0.8 gm/kg	Yes	Yes	No
Niggemann et al. (11)	DBPC	2 months	1–2 gm/kg	No	No	No

DBPC: Double-blind, placebo-controlled; PFTs: pulmonary function tests.
*Intramuscular dose: approx. 100 mg/kg.

the Niggemann et al. studies, the patients evaluated had milder asthma and were not dependent on oral steroids. These patients contrasted with those in earlier studies where high-dose IVIG seemed to have dramatic effects. Because these were milder asthmatics, it would be difficult to detect changes in lung function or symptom scores. The major effect of any therapy used in combination with inhaled steroids in this group would be on steroid reduction, which was significantly decreased in the Jakobsson et al. study, as it was in the other positive studies. However, the Niggemann et al. study did not use steroid reduction as a primary end point.

The importance of and need for future double-blind, placebo-controlled studies, evaluating high-dose (2 gm/kg) and long-term (at least 4 months) therapy, cannot be overemphasized. These studies should include only patients who are truly steroid-dependent or steroid-resistant in order to determine the steroid-sparing effect of IVIG as well as its effects on pulmonary function. At the present time, when IVIG is both costly and in short supply, it seems appropriate to reserve IVIG treatment for patients who continue to have an oral steroid requirement and/or low pulmonary function while on optimal therapy including high potency inhaled steroids. These patients may benefit from a 3–6-month trial of high-dose IVIG.

Allergic rhinosinusitis

Hamilos & Christensen (13) described the case of a man who had Churg-Strauss vasculitis and a history of chronic allergic rhinosinusitis. This patient was treated with high-dose (2 gm/kg) monthly IVIG for 6 months, resulting in resolution of both lung and nasal symptoms. After cessation of IVIG therapy, nasal symptoms recurred. In the double-blind, placebo-controlled study by Smith et al. noted above, there was a significant decrease in nasal symptom scores in the group that was treated with (low-dose) IVIG compared to the placebo-treated group.

Atopic dermatitis

The first case reports describing the effectiveness of high-dose IVIG in the treatment of atopic dermatitis were observed in those patients undergoing IVIG treatment for Kawasaki disease and ITP who happened to have concurrent severe atopic dermatitis. Kimata (14) reported on the treatment of four infants and toddlers – two of whom were being treated for Kawasaki disease and two for ITP with high-dose (400 mg/kg for 5 days) IVIG. These patients had

atopic dermatitis refractory to treatment with steroid ointments and antihistamines. In these patients, nearly complete resolution of their symptoms occurred after one course of high-dose IVIG therapy. These dramatic improvements were maintained when these children were assessed after 6–12 months.

Gelfand et al. (15) studied three adults with atopic dermatitis which was resistant to topical and oral corticosteroids. These patients received 2 gm/kg of IVIG for 6 months. Average symptom scores in these patients decreased significantly while on IVIG and recurred when IVIG was discontinued. Improvement in overall symptoms occurred by the second or third infusion in these patients.

A recent study published by Wakim et al. (16) examined the effect of high-dose IVIG in an open-label study of children and adults with severe refractory atopic dermatitis. Each patient received high-dose (2 mg/kg) IVIG for seven monthly infusions. Skin scores improved in four patients. The mean prednisone dose among the five patients on oral prednisone decreased from 6.8 to 5.1 mg/day but was not statistically significant. The authors concluded that, unlike the Kimata study, no dramatic improvement in refractory atopic dermatitis was conferred by high-dose IVIG therapy. The discrepancy between these studies is quite striking. Further study of the response of atopic dermatitis to IVIG in younger patients may help clarify these issues.

Chronic urticaria

Chronic urticaria is often termed “idiopathic” since its pathogenesis is usually obscure even after an extensive work-up. It has been postulated that chronic urticaria may in some cases be secondary to an autoimmune disease. In many patients with chronic idiopathic urticaria, one can measure IgG autoantibodies against IgE or against the high-affinity Fc_ϵ receptor (found on mast cells and basophils) (17).

Because IVIG had been found to be effective in a number of autoimmune diseases, including ITP and dermatomyositis, O'Donnell et al. (18) investigated the response of 10 patients with chronic urticaria to treatment with high-dose IVIG. These patients were refractory to treatment with antihistamines, prednisolone, and, in four cases, cyclosporin. They all showed evidence of IgG autoantibodies, as shown by positive autologous intradermal skin tests. Nine showed evidence of anti- Fc_ϵ autoantibodies, and one was thought to have anti-IgE autoantibodies. These patients were treated with high-dose IVIG while they continued on daily antihistamines.

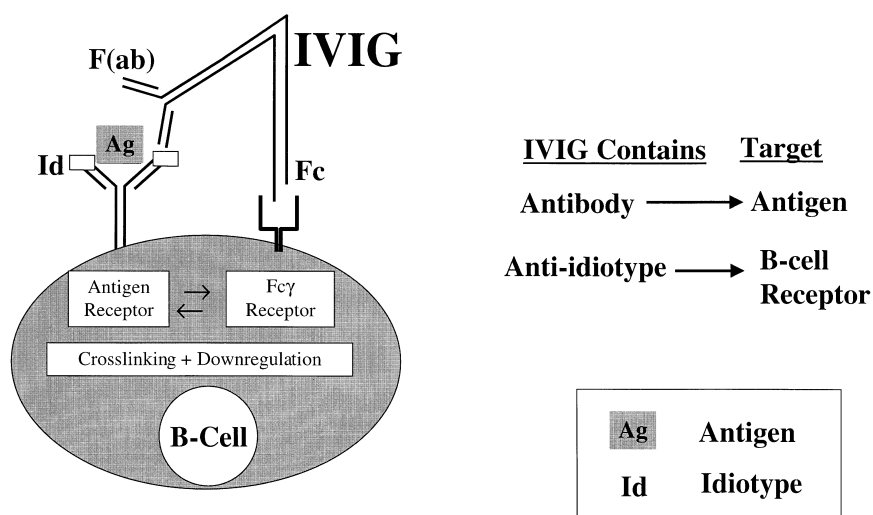


Figure 1. IVIG inhibitory activity on B cells. IVIG contains anti-idiotypic IgG which binds to soluble and membrane-bound antibody. F(ab') portion of idiotypic IgG can therefore bind to immunoglobulin receptor on B cell while Fc portion binds to Fc γ IIB receptor. Alternatively, F(ab') portion of IgG in IVIG can bind to multideterminant antigen which also binds to specific B-cell receptor while Fc portion of IgG binds to Fc γ IIB receptor. When both receptors are co-cross-linked, activating signal from immunoglobulin receptor is attenuated by inhibitory signal from Fc receptor. Thus, the B cell is not activated and undergoes apoptosis.

Eight of the patients had significant responses to IVIG treatment, and five of the patients had complete remission of their symptoms. Two patients demonstrated a striking clinical response, which was sustained for up to 3 years after treatment. Overall, there was a significant improvement in urticaria scores compared to baseline, and in 7/10 patients the autologous intradermal serum tests showed a reduced wheal and flair response. Adverse effects included severe headaches in all patients and low-grade fever and flu-like symptoms in some patients. The authors concluded that IVIG represents an important therapeutic option in patients with chronic urticaria and evidence of anti-Fc ϵ autoantibodies. A double-blind, placebo-controlled study in these patients seems warranted.

Mechanisms of IVIG in allergy

IgG, the main component of IVIG, may affect the immune response in a number of ways. The variable, or F(ab')₂ region of the antibody can bind and neutralize antigen in a specific manner. The Fc region binds to Fc receptors (Fc γ R) on multiple cell types and activates complement, especially when it is aggregated. The Fc portion of the IgG also allows different IgG antibodies to act nonspecifically and bind immune cells through the Fc γ receptor.

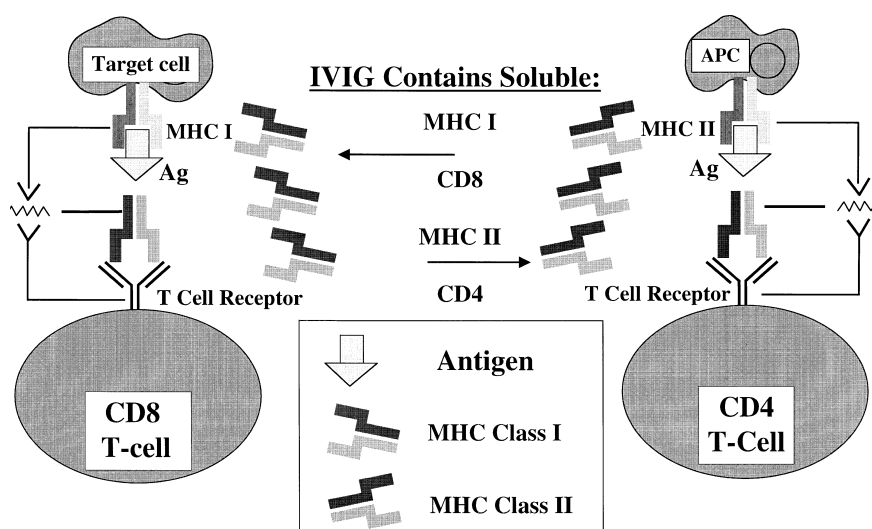
How may IVIG affect allergic responses and why are such high doses apparently needed? It is interesting to note that in many clinical studies the administration of IVIG is associated with a decrease in circulating levels of IgE antibody (8, 10, 14, 15). Although IVIG does not contain specific IgG which could bind to and neutralize allergen (19), it does contain antibodies which bind to other antibodies

(anti-idiotypes). The amount of these anti-idiotypic antibodies increases when high doses of IVIG are administered (20). Therefore, administration of high-dose IVIG may provide circulating antibodies which bind to IgE and remove them from the circulation.

A recent study by Sigman et al. (21) has shown that incubation of tonsillar B cells with high doses of IVIG blocks IgE production. Although this is unproven, IVIG may terminate IgE production by binding to the Fc receptor on B cells (Fc γ IIB). This Fc γ receptor can attenuate signaling when it is cross-linked to another receptor. For example, if the Fc γ IIB receptor is cross-linked to the antigen receptor on mouse B cells, signaling through the antigen receptor is attenuated and the cell is not fully activated (22). Thus, anti-idiotypic IgG found in IVIG could inhibit B-cell activation by binding to the Fc receptor through its Fc portion while cross-linking the antigen receptor through its F(ab') portion (Fig. 1). Because these Fc receptors found on B cells have a low binding affinity, they can bind only to immune complexes or high concentrations of IgG.

As we now know, allergic diseases such as asthma and atopic dermatitis are not solely IgE-mediated. Indeed, it now seems that the major component which drives these diseases is the production of TH2 cytokines. In asthma, T-cell production of IL-4 not only stimulates IgE production by B cells but also induces IL-5 production and the migration into the airway of eosinophils – the major effector cell in asthma. In atopic dermatitis, in addition to the markedly elevated levels of serum IgE, there is a marked increase in IL-4 production and a reduction in interferon-gamma production (23). A number of *in vitro* studies have demonstrated that IVIG reduces cytokine production, including IL-4, in T cells. Studies by Amran et al. (24) and Modiano et al. (25)

Figure 2. IVIG inhibitory activity on T cells. IVIG contains soluble CD4, CD8, MHC I, and MHC II. Soluble CD4 binds to MHC II on antigen-presenting cell (APC). Soluble MHC II binds to CD4 receptor on T-helper cell; thus, APC/T-helper cell interaction is blocked. Soluble MHC I binds to CD8 receptor on T-cytolytic cell while soluble CD8 binds to MHC I on target cell, thus blocking T-cytolytic cell/target cell interaction.



demonstrated that IVIG blocks post-transcriptional activation of cytokine production, decreasing amounts of IL-2 and IL-4 released by T cells. It is unclear, however, how IVIG interacts with T cells since they do not express Fc receptors. One explanation may be associated with the findings (26) of low amounts of soluble MHC I and II and CD4 and CD8 in IVIG. These cell-surface molecules could interfere with antigen presentation by blocking MHCI/II interactions with CD8/CD4 *in vivo* and possibly block mitogen interaction with the T-cell receptor *in vitro* (Fig. 2). Because the concentrations of these molecules are low in IVIG preparations, these effects may not be seen unless high doses of IVIG are given.

A number of studies have investigated the steroid-sparing effect of IVIG in asthma. How could IVIG affect steroid insensitivity in asthmatics? A recent study by Spahn et al. (27) demonstrated that treatment with IVIG resulted in a significant reduction in oral glucocorticoid use, number of glucocorticoid bursts, and hospitalizations after 6 months of therapy in severe, steroid-dependent asthmatics. In studying the mechanisms of this decrease, Spahn et al. demonstrated that IVIG, at pharmacologic doses (1–10 mg/ml), acted synergistically with dexamethasone in suppressing PHA-induced proliferation in peripheral blood mononuclear cells (PBMC). Because a defect in steroid binding to its receptor has been found to be associated with steroid-insensitive asthmatics, it was significant that in this study these patients demonstrated significantly improved glucocorticoid receptor binding affinity after 6 months of IVIG therapy. Although not yet defined, the mechanism whereby IVIG increases glucocorticoid receptor binding may occur indirectly, since IVIG decreases production of the two cytokines

known to alter glucocorticoid receptor binding – IL-2 and IL-4 (28).

Conclusion

High-dose IVIG has been shown to exhibit anti-inflammatory and immunomodulatory properties in a number of acute and chronic diseases. Besides its ability to bind to and facilitate clearing of extracellular pathogenic antigens, IVIG has been shown to decrease cell activation and cytokine secretion *in vitro*. In asthma and allergy, IVIG may decrease IgE synthesis and TH₂ cytokine secretion through one or both of these mechanisms. Additionally, IVIG may potentiate the effect of steroids by increasing steroid binding affinity to the glucocorticoid receptor. Unfortunately, since we have limited knowledge of the pathogenesis of many inflammatory diseases, including the allergic diseases, it is difficult to say which mechanism predominates.

In allergic diseases, a number of clinical studies have shown that IVIG may be beneficial to patients who do not respond to conventional therapies. In atopic dermatitis, chronic rhinosinusitis, and chronic idiopathic urticaria, IVIG may decrease symptoms, sometimes dramatically. In patients with severe, steroid-dependent asthma, high-dose IVIG therapy has been shown to increase pulmonary function and decrease the amount of oral steroid required to control this disease. In each of these diseases, placebo-controlled studies in these severely refractory patients are necessary to confirm the initial encouraging results.

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