

EDITORIAL

Is Steroid-Dependent Asthma a Disease Treatable with Intravenous Immunoglobulin?

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The prevalence of asthma has increased substantially in the last 2 decades from 4.8% among 6–11 year olds in 1971–1974 in the U.S. to over 7% over the past few years (1, 2). Recognition that asthma is a chronic inflammatory disease of the airways has only occurred in the past decade. Recent elucidation of the pathogenesis of asthma and a better understanding of the immune and inflammatory events in the lungs have shaped our therapeutic approach in the treatment of asthma (1, 2). Inhaled corticosteroids have become the cornerstone of current anti-inflammatory therapies in asthma. Indeed, corticosteroids are well suited as an anti-inflammatory agent in asthma because of their many known effects on a broad range of proinflammatory and immune-modulating cytokines (3). Nevertheless, a small group of individuals with asthma require high doses of inhaled steroids or even oral steroids in order to control their asthma. These high doses of steroids lead to systemic effects on the hypothalamic–pituitary–adrenal axis as well as other end organs and tissues to produce a number of undesirable side effects, particularly in children (4). Alternative anti-inflammatory agents, including methotrexate, gold salts, and cyclosporine, have been tried in steroid-dependent asthma with mixed results (5). Another treatment modality first suggested by Mazer and Gelfand as a steroid-sparing agent is intravenous immunoglobulin (IVIG) (6).

The initial observations of Imbach in 1981 that IVIG produced a marked increase in platelet counts in children with immune thrombocytopenia marked the beginning of a virtual explosion of the use of IVIG in a variety of autoimmune and inflammatory diseases. Over the past decade our knowledge has increased substantially on the mechanisms of action by which IVIG modulates the inflammatory process (7). Kawasaki syndrome has been the prototype inflammatory disease that responds well to high-dose IVIG. Although complex, it is believed that one of the major mechanisms of action of IVIG in this disease is its modulation of cytokine production. Others have shown that IVIG

in vitro can decrease cytokine synthesis, resulting in diminished B-cell immunoglobulin production and altered T-cell function (7). These effects may be mediated by the immune-modulating activity of the Fc portion of IVIG on the Fc γ receptors on immune and inflammatory cells.

Several studies have suggested that the immunomodulating effects of IVIG are mediated by the binding of IVIG to the Fc γ receptors on B-cells (8–11). The mechanism for Fc receptor-mediated suppression of B-cell function by IVIG has recently been elucidated. While immune complexes can be potent activators of phagocytic cells through the Fc γ RIII receptor, immune complexes can be negative regulators of B-cells as a consequence of coligation of the B-cell antigen receptor (BCR) and the Fc γ RIIB receptor (12). The mechanism for this “negative signaling” in B-cells is thought to occur by the immunoreceptor tyrosine-based inhibition motif (ITIM), which is known to be associated with the intracytoplasmic domain of the Fc γ RIIB receptor. Coligation of the BCR and Fc γ RIIB could be induced by the binding of IVIG through the Fc moiety of the IgG to the Fc γ RIIB receptor and the anti-idiotypic antibody specificity of the IgG molecule to the BCR. This FcR “off signal” mediated through the Fc γ RIIB receptor can even accelerate early entry of B-cells into apoptosis (13). IVIG could thus provide an off signal to the B-cell to inhibit B-cell proliferation and immunoglobulin production. Recent studies by Sigman *et al.* (14) showed that IVIG *in vitro* inhibits IgE production by B-cells paralleling the clinical observation in asthmatic patients treated with IVIG in which the serum IgE levels markedly decreases (6). In fact, this ITIM-bearing negative receptor pathway is also present in mast cells (15). Thus, IVIG could modulate mast cell cytokine production and other inflammatory mediators to potentially be of benefit in patients with chronic severe asthma.

In 1991 Mazer and Gelfand (6) published an open-label study of IVIG in 8 children ages 6 to 17 with

severe steroid-dependent asthma to reduce their oral steroid requirements. Six monthly infusions of 2 g/kg of IVIG were administered. The average alternate-day oral steroid dose decreased from 32.5 mg during the 2-month run-in period to 11.5 mg at the end of 6 months of IVIG treatment; reductions in steroid use were seen in all 8 patients. Similarly, prior to IVIG therapy patients required a monthly average of 158 mg of oral corticosteroids for asthma exacerbation, which decreased with IVIG treatment to 49.2 mg/month. Improvements in peak expiratory flow rates and in symptom-score rating were also observed. Immunologically, serum IgE levels decreased from 324 IU prior to therapy to 133 IU after 6 months on IVIG. Immediate hypersensitivity skin testing to allergens decreased by 100-fold. This provocative report was followed by other anecdotal experiences suggesting that IVIG had a steroid-sparing effect in severe steroid-dependent asthma (16–19). These studies suggested the need for a larger placebo-controlled trial of IVIG in glucocorticoid-dependent asthma. In 1997 at the American Academy of Allergy, Asthma and Immunology meetings in San Francisco, two abstracts (20, 21) of placebo-controlled trials of IVIG in severe oral steroid-dependent asthma were presented, one of which is published in this issue of *Clinical Immunology* as part of a full-length article (22). In the Boston study (21), IVIG was given as a loading dose of 2 g/kg followed by 400 mg/kg every 3 weeks for a total of 9 months. IVIG treatment appeared to be significantly effective only in a subgroup of asthmatic patients on higher doses of oral steroids. In the study by Kishiyama *et al.* (22) no significant difference was found between the placebo group and the two IVIG treatment groups, e.g., 1 and 2 g/kg. However, the study did not reach statistical power estimates of 63 evaluable patients (21 patients in each group) because the study was terminated for severe adverse reactions, including 3 patients with aseptic meningitis syndrome. The incidence of adverse reactions was extraordinarily high compared to other studies using high-dose IVIG in patients with autoimmune disease and may be related to the particular preparation of IVIG used in this study (Venoglobulin-I, Alpha Therapeutics Corp., Los Angeles, CA). Two other factors may have compromised this study to lead to negative results. The base-line or run-in period was only 2 months, perhaps too short to optimize the reduction of oral steroid dependency prior to randomization into the three treatment groups. Furthermore, the patient population was principally adults with a mean age of 40, much higher than that of the study by Mazer and Gelfand and others (6) in which the study was composed of children and adolescents. The age group, children vs adults, may be an important factor in the response of the asthmatic inflammatory process to treatment with IVIG.

Much has happened in the treatment of patients with severe asthma since the report by Mazer and Gelfand in 1991. Potent inhaled steroids and leukotriene modifiers are available to help the clinician reduce the oral steroid requirements of severe asthmatics. This may make it very difficult to achieve an additional therapeutic "measure" with IVIG as a further oral steroid sparing modality. A larger placebo-controlled trial is needed to determine the efficacy of IVIG therapy in oral steroid-dependent asthmatics. Further studies need to consider the patient population, study design, including the run-in period and IVIG dosages, and, especially important, cost effectiveness and other outcomes measures. We are currently experiencing a shortage of IVIG product in the United States. The off-label use of IVIG for patients with asthma has to be scrutinized very carefully. Physicians need to consider that all other treatment options and management approaches have been pursued and optimized for the patient with severe asthma.

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LETTER TO THE EDITOR

To The Editor:

The editorial by Ballow (1) on the report by Kishiyama *et al.* (2) about the use of intravenous immunoglobulin (IVIG) in asthma in the May 1999 issue of *Clinical Immunology* misses the mark. The editorial finds no merit in this study, which did not demonstrate any benefit of IVIG in severe steroid-dependent asthma in 40 patients (6 to 66 years of age) in a randomized, double-blinded and placebo-controlled study design. The tone of the editorial implies that open-label and anecdotal studies demonstrating a beneficial effect of IVIG in steroid-resistant asthma (3–7) are likely true, and the Kishiyama paper failed to refute them because of an older subject group, shorter baseline IVIG run-in period, and early closure of the study because of side effects.

While it is possible to speculate that IVIG may be more effective in different study populations, in different study designs, or with different preparations, we do not believe that it is responsible to promote such hypotheses in the absence of carefully controlled trials. We believe that open-label studies and anecdotal case reports share a major flaw because they are not suitably controlled; moreover, they have a very limited value in medicine, in that they serve as pilot studies, not as efficacy studies. As the Kishiyama article clearly demonstrates, without a true placebo control, it is easy to demonstrate an apparent efficacy in using IVIG to treat steroid-resistant asthma.

The article by Niggeman *et al.* (7), which was quoted by Ballow as an anecdotal study supporting the use of IVIG as a steroid-sparing treatment in severe asthma, was actually a double-blinded and placebo-controlled study which did *not* show any benefit for bronchial hyperactivity but a benefit only with regard to the duration of upper respiratory infections. The Salmun *et al.* study quoted by Ballow, which was double-blinded and placebo-controlled, showed only a modest steroid-sparing effect (16.4 to 3 mg/day) in 9 of 38 subjects, but objective and subjective assessments of asthma severity were unchanged (8). Although the editorial states that the Kishiyama study was “compromised” compared to results of uncontrolled trials, we believe that it is a valuable study which strongly suggests that IVIG is equivalent to placebo in its ability to reduce daily

doses of oral corticosteroids. Over the 7-month treatment period, the mean dose of daily prednisone-equivalent requirement fell by approximately 35% (6 mg) in each of the three study groups (2 g IVIG/kg vs. 1 g IVIG/kg vs. 2 g iv albumin/kg; $P = 0.97$). The mean percentage of predicted FEV1 fell in all three groups during the study period, but there were no significant differences between the study arms ($P = 0.83$). There was also no significant difference in the percentages of subjects requiring hospitalization and emergency room visits or missing days of work/school among the three treatment groups. Because of unacceptable side effects, the study had to be terminated somewhat short of its targeted enrollment, which would have permitted statistical power confirmation of its findings.

We do agree with Ballow that with the recent availability of newer asthma treatments, it will be difficult to prove the role of IVIG (if any) in the treatment of steroid-dependent asthma. The current shortage of IVIG brought about in large part by the unproven use of IVIG in many diseases only exacerbates the problem of attempting to perform additional double-blind and placebo-controlled studies in steroid-dependent asthma. Pending this study, physicians who treat steroid-dependent asthma with IVIG need to be mindful of the infrequent but serious side effects of IVIG administration, such as the recently reported cases of renal failure (9), and to carefully explain these risks to their patients.

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