

Effect of intravenous immunoglobulin on steroid consumption in patients with severe asthma: A double-blind, placebo-controlled, randomized trial

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Background: There is a significant group of patients with severe asthma who require chronic use of systemic steroids for control of their disease. These patients are at risk for severe side effects from oral steroids. Intravenous immunoglobulin (IVIG) has immunomodulatory properties, and a few open-label trials have suggested its possible benefit in individuals with severe asthma.

Objective: This study was designed to assess the potential benefit of IVIG as a steroid-sparing agent in patients with severe asthma.

Methods: Thirty-eight immunocompetent steroid-requiring patients with severe asthma were randomly enrolled in a double-blind, placebo-controlled trial of IVIG.

Results: Of the 38 patients enrolled, 28 patients completed the study. A significant reduction in oral steroid requirement was observed in both the IVIG-treated ($n = 16$) and the placebo-treated ($n = 12$) patients. Further exploration of the results showed that IVIG, but not placebo, had a significant steroid-sparing effect in patients requiring high doses of oral steroids (ie, >2000 mg in the year before the study). Within this subgroup, IVIG treatment ($n = 9$) resulted in a significant decrease in oral steroid requirement, with a median of 16.4 mg/day during the pretreatment period to 3 mg/day during the treatment phase ($P = .0078$). No significant decrease in oral steroid requirement was observed in placebo-treated patients ($n = 8$) within this subgroup. Objective and subjective parameters of the patients' asthma were unchanged in spite of the steroid tapering achieved in the group treated with IVIG.

Conclusion: IVIG may be a useful steroid-sparing agent in patients with severe asthma requiring high doses of oral steroids. (*J Allergy Clin Immunol* 1999;103:810-5.)

Key words: Asthma, intravenous immunoglobulin, steroids

Abbreviations used

IVIG: Intravenous immunoglobulin

PEFR: Peak expiratory flow rate

The prevalence of asthma is 4% to 5% in the United States,¹ and the number of individuals with asthma has increased by 60% in the past decade.² Asthma is the most common pediatric chronic lung disorder in the United States and is responsible for significant school absenteeism, morbidity, and mortality.³ Despite the fact that several new drugs and delivery systems have been introduced in the past 20 years for the treatment of asthma, a decrease in the number of hospital admissions for asthma has not occurred.³ Treatment of asthma includes topical anti-inflammatory therapy and bronchodilators. Nonetheless, a subpopulation of asthmatic subjects have extremely severe respiratory symptoms and require frequent hospitalizations and/or systemic steroids for control of their illnesses. These patients are at high risk for severe side effects because of the chronic or frequent use of systemic steroids. These include growth retardation, cataracts, hypertension, diabetes, suppression of the pituitary-adrenal axis, and osteoporosis complicated by recurrent bone fractures. Intravenous immunoglobulin (IVIG) has been shown to possess immunomodulatory properties,⁴⁻⁷ and 2 recent open-label trials suggested a benefit of using this agent in subjects with severe asthma.^{8,9}

The objective of this study was to assess the efficacy of IVIG as a steroid-sparing agent in patients with severe steroid-dependent asthma. We now report the first double-blind, placebo-controlled, randomized trial of IVIG in patients with severe steroid-dependent asthma.

METHODS

Study design

The study was a double-blind, placebo-controlled, randomized trial of patients with steroid-dependent asthma. A computer-generated randomization scheme was prepared, allowing for randomization in blocks. Patients who met the eligibility criteria were assigned a study number in strict sequential order.

The trial spanned 4 phases, each 3 months long. Phase I consisted of a 3-month observation period in which each patient continued to receive his or her standard medications. Initially, both steroids and other asthma medications (β -agonists, theophylline prepara-

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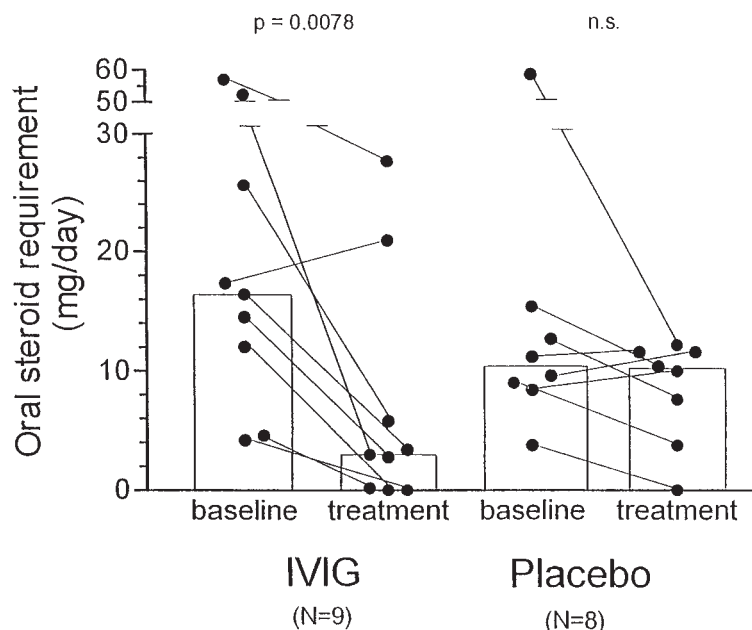


FIG 1. Oral steroid requirements (mg/day) in all patients who completed the study. Filled circles indicate average values in each patient during phases I (baseline) and IV (treatment). Median values for each group are indicated by open bars.

tions, and cromolyn sodium) were, to the extent possible, held at stable dosages. At week 6, if the patient was clinically stable and the peak expiratory flow rate (PEFR) was more than 60%, an attempt was made to decrease the steroid dose by approximately 2.5 to 5.0 mg every 10 days. If a patient was successfully weaned off steroids during phase I, he or she was withdrawn from the study. The patient entered phase II when his or her asthma symptoms worsened significantly on the basis of his or her diary symptom scores or when his or her PEFR dropped below 60% of predicted value. Patients who were not receiving oral steroids at entry, but who required at least 30 days of oral steroids per year despite chronic use of inhaled steroids, were observed for 12 weeks to document their requirement for intermittent oral steroids to control their asthma. If no oral steroids were required during this 12-week period, the patients were withdrawn from the study.

At completion of phase I, all patients were assigned to one of two groups, with one group receiving IVIG and the other receiving placebo by intravenous infusion, all in a blinded manner. During phase II, steroids and other asthma medications were monitored and, to the extent possible, maintained at stable dosages. All enrolled patients were evaluated at 3-week intervals, with an emphasis on steroid requirements, days of wheezing, other pertinent symptoms, and pulmonary function.

After completion of phase II, patients continued to receive 400 mg/kg IVIG or placebo every 3 weeks for the next 6 months (phases III and IV). In these phases the patients were eligible to have their doses of both oral and inhaled steroids reduced at each visit, as long as their symptoms remained above baseline. The clinical assessments were similar to phase II. The level of comedication was, to the extent possible, kept at stable dosages and monitored. The decision of whether to increase or decrease steroid medication in the forthcoming 3 weeks, and if so, by how much, was made by the physician, depending on the patient's clinical status and PEFR values.

Subjects

Thirty-eight immunocompetent patients, aged 5 to 35 years with a clinical diagnosis of severe steroid-dependent asthma, were

enrolled in this study. All patients met the diagnostic criteria for asthma as defined by the American Thoracic Society.¹⁰ For the purpose of this study, immunocompetency was defined as lack of a significant history of recurrent infections and normal immunologic laboratory evaluation, including normal serum IgG, IgA, IgM, and IgG subclasses and specific antibody titers. Steroid-dependent patients were defined as patients who required oral steroids on a daily or alternate day basis for at least 6 months before study entry or patients who required at least 30 days of oral steroids per year despite chronic use of inhaled steroids. In addition, at least one unsuccessful attempt had to be made to lower the patient's steroid dosage during the 6 months before enrollment.

Patients who tolerated an oral theophylline preparation had levels maintained between 10 to 20 μ g/mL. If either inhaled cromolyn or ipratropium was used, the patient continued to take these agents at the same dose throughout the study. Cigarette smokers were not eligible. With the exception of allergic disorders, the patients were otherwise in good health. The study protocol was approved by the Committee on Clinical Investigation at Children's Hospital, Boston. A written informed consent was obtained from all patients and/or their parents at study entry.

Eight patients did not enter phase II of the trial, either because of voluntary withdrawal ($n = 7$) or because of successful discontinuation of their steroids during this phase ($n = 1$). In addition, 2 other patients were discontinued during phase II. One was discontinued because of relocation and the other because of the diagnosis of ciliary dyskinesia, which excluded him from the study. Therefore analysis was done on the 28 remaining patients.

Study drug

Iveegam Immune Globulin Intravenous (Human) 5% was the study medication, and 5% albumin served as the placebo. Both drugs were supplied by Immuno Clinical Research Corporation. The two drugs were supplied, packaged, and labeled in an identical manner. Tinted bottles and infusion sets were used to guarantee that the solution was not identified.

Patients received a loading dose of 2 g/kg body weight initially

TABLE I. Baseline demographics

	IVIG	Placebo	All patients
Sex			
M	6	4	10
F	10	8	18
Race			
White	11	11	22
Hispanic	2	2	4
African American	1	0	1
Asian	1	0	1
Age (y)			
Mean	15.5	19.7	17.3
SD	6.6	9.7	8.2
Range	5-27	5-35	5-35
Oral steroid dose (mg/day)			
Mean	15.1 ± 17.0	13.7 ± 14.8	14.5 ± 15.8
Median	10.1	9.3	9.3
Range	1.4-57.2	3.8-58.9	1.4-58.9
Pulmonary function tests (mean ± SD)			
FVC (L)	2.9 ± 0.7	3.4 ± 1.1	3.1 ± 0.9
FEV ₁ (L)	2.2 ± 0.4	2.3 ± 0.5	2.2 ± 0.5
FEF ₂₅₋₇₅ (L/sec)	2.0 ± 0.7	1.8 ± 0.7	1.9 ± 0.7
Positive skin test responses	9/14*	9/12	18/26

FVC, Forced vital capacity.

*In 2 patients skin test responses were not interpretable, one because of dermatographism and one because of a negative histamine control.

(of either IVIG or albumin) and 400 mg/kg body weight every 3 weeks thereafter for a total of 9 months. The infusion rate was 2 mL/min. Patients with a body weight of more than 50 kg received the loading dose on 2 consecutive days.

Patient evaluation

Assessment of disease activity. A symptom score card that rated coughing, shortness of breath at rest, wheezing, exercise tolerance, chest pain or tightness, and sleep disturbance caused by asthma was completed daily by the patients. A record was also kept of medications used, school days lost, days in hospital, allergic symptoms including rhinitis, and allergic conjunctivitis. An Assess Home Peak Flow Meter¹¹ was provided to each patient for twice daily PEF monitoring at home. Clinical assessment by a physician and spirometry were performed at entry and every 3 weeks throughout the study.

Immunology and allergy evaluation. At entry, serum IgG, IgA, IgM, and IgG subclasses were measured by radial immunodiffusion. *Hemophilus influenza* type b antibody level and tetanus toxoid antibody level were done by ELISA. RAST testing to mites, ragweed, and grasses, as well as serum IgE by ELISA, was performed at baseline and repeated at week 24 and at study completion.

Skin prick testing with the Multi-Test Device (Lincoln Diagnostics, Decatur, Ill) to a panel of 30 inhalant allergens (Hollister Stier) was performed at entry, at week 24, and again at completion of the study in all patients.

Laboratory studies

To evaluate possible adverse effects of the study drug, complete blood count with differential, chemistry profile, and hepatitis B surface antibody were performed at entry and every 3 months through-

out the study. In addition, alanine-aminotransferase was performed every 3 weeks during phases 2, 3, and 4.

Statistical analysis

Because of the uneven distribution of the doses of oral steroids, median values were used for each group. For statistical analysis of the primary endpoint "dosage of oral steroids consumed," other medication use, parameters of clinical symptomatology, and pulmonary function tests, the comparison between the average of the 3 baseline months (phase I) and the average of months 6 to 9 of treatment (phase IV), as recorded daily in the patients' diaries, was evaluated in a paired design by using the Wilcoxon signed-rank test. Statistical comparison of baseline values in the IVIG- and placebo-treated groups was performed by using the Mann-Whitney *U* test. Two-tailed *P* values are given, with *P* values less than .05 being indicative for a statistically significant difference.

RESULTS

Twenty-eight patients (10 males and 18 females) completed the study. Their mean age was 17.3 years (range, 5 to 35 years). Twenty-two of the patients were white, 4 were Hispanic, 1 was African American, and 1 was Asian (Table I). Baseline median oral steroid doses and mean spirometry values were similar between the 2 groups. The majority of patients in both groups were atopic, as determined by positive skin prick test responses to at least 1 allergen (Table I). Immunologic screening studies showed normal humoral immune status in all patients, as assessed by total IgG and IgG subclasses levels and normal response to tetanus and *Hemophilus influenza* type b antigens.

Oral steroid use (mg/day) was recorded daily in the patients' diaries. Fig 1 shows the average values for each patient for the first 3 months of the study (baseline phase) and for the last 3 months of the study (treatment phase). Triweekly medical assessment of oral steroid dosage was recorded in parallel, with essentially the same results. In one patient in the IVIG group and one patient in the placebo group, daily running records from the treatment phase were incomplete, and the average values from the triweekly medical assessment during this period were used instead. When the data from all enrolled patients were analyzed, a significant decrease in the prednisone requirement was observed in both the active and the placebo-treated patients. In the IVIG group oral steroid use decreased from a median daily dose of 10.05 mg/day (baseline) to 3.5 mg/day (treatment) (*P* = .0273; Fig 1). In the placebo group median oral steroid dosage was 9.3 mg/day in the baseline phase compared with 8.8 mg/day during the treatment phase (*P* = .0068; Fig 1). No significant difference was observed between IVIG and placebo treatment in the percent reduction in oral steroid requirement.

Further exploration of the results revealed that IVIG treatment, but not placebo, has the capacity to significantly decrease oral steroid consumption in a subgroup of patients that require larger doses of steroids (ie, >2000 mg of oral steroids in the year [5.5 mg/day]) preceding the study. Seventeen of the 28 patients who completed the study belonged to this subgroup (9 in the IVIG group

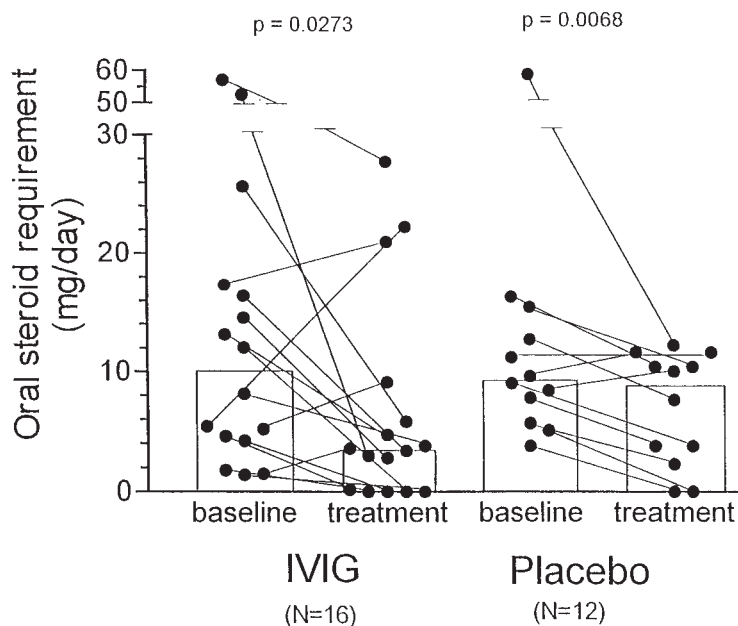


FIG 2. Oral steroid requirements (mg/day) in patients who required more than 2000 mg/year oral steroid therapy in the preceding year. Filled circles indicate average values in each patient during phases I (baseline) and IV (treatment). Median values for each group are indicated by open bars.

and 8 in the placebo group). Within this subgroup, IVIG treatment led to a significant decrease in oral steroid dosage from a median of 16.4 mg/day during the baseline phase (phase I) to 3 mg/day during the treatment phase (phase IV) ($P = .0078$; Fig 2). In contrast, no significant lowering of the oral steroid dose was observed in patients from this subgroup receiving placebo; median oral steroid use in phase I of 10.4 mg/day changed to 10.2 mg/day in phase IV ($P > .1$; Fig 2). In addition, there was a statistically significant IVIG-induced reduction in oral steroid consumption during the treatment phase relative to baseline. The mean percent reduction in oral steroid consumption observed in the IVIG group was $73.1\% \pm 12.8\%$ compared with a reduction of $33.3\% \pm 15.9\%$ in the placebo group ($P = .04$). No significant difference in baseline values was observed between IVIG- and placebo-treated patients in this subgroup.

The decrease in the oral steroid requirements in the IVIG-treated group was observed notwithstanding the lack of significant differences between the IVIG- and placebo-treated groups when comparing phase I versus phase IV in the following measures: pulmonary function testing, inhaled allergen hypersensitivity (measured both by skin testing and RAST), inhaled steroid consumption, β_2 -agonist use, symptoms scores, and days missed from school or work.

DISCUSSION

This study indicates that in a subgroup of steroid-requiring asthmatic subjects, namely those who require more than 2000 mg (5.5 mg/day) of prednisone per year, IVIG appears to have a steroid-sparing effect. This effect

was noted without an increase in the use of other asthma medications or changes in pulmonary function tests.

Previous reports of open-label trials of IVIG in patients with severe steroid-dependent asthma^{8,9,12} were promising. Nonetheless, in the treatment of a chronic disease, the placebo effect may be considerable. A significant placebo effect was observed in this study; several patients requiring chronic use of oral steroids improved with placebo therapy. This improvement with placebo therapy was likely related to the frequent medical visits and careful asthma monitoring necessitated by participating in a controlled clinical trial. However, further exploration of the results revealed that in a subgroup of patients, namely those who chronically required larger doses of steroid, IVIG treatment appears to play a significant role as a steroid-sparing agent independent of a placebo effect, as demonstrated by the significant decrease in steroid dose ($P = .0078$) compared with the placebo group ($P > .1$). Of particular interest is the finding that this reduction in oral steroid dose was not accompanied by an increase in the number of hospitalizations, days missed from school or work, or β -agonist use, indicating a true steroid-sparing effect of IVIG treatment with a stable clinical symptomatology.

Mazer and Gelfand⁹ observed a decrease in the inhalant allergen hypersensitivity in their patients, which this study did not detect. This may have been because skin test endpoint titration was not done in our study and because a lower dose of IVIG was used in comparison with the high dose of 2 g/kg in their study. Jakobsson et al¹³ evaluated the use of a different dosage regimen of IVIG, 0.8 g/kg monthly for 5 months, in an open-label study of a group of children who required high-dose

inhaled (but not oral) steroids. They found a slight steroid-sparing effect from IVIG. The higher dose 2 g/kg of IVIG may be more effective, although it will be more costly. Further studies are needed to evaluate the optimal dosing regimen of IVIG in patients with asthma.

Although IVIG was well tolerated in our patients, minor adverse reactions, such as headache and nausea, can occur with IVIG. Currently licensed IVIG preparations should have no risk of transmission of hepatitis viruses; however, there remains the remote possibility of IVIG transmission of a yet-undefined viral illness. IVIG is also expensive and time-consuming therapy and as such may be appropriate only for patients with the most severe asthma. The current shortages of IVIG products also preclude its use except in clinical trials and in rare situations when it may be life-saving or cost-effective.

During the past few years there has been substantial progress in our understanding of the pathophysiology of asthma. Studies have provided insight into the critical role that airway inflammation plays in this disease.^{14,15} In the past, use of anti-inflammatory medications was reserved mostly for patients with severe asthma during acute exacerbations of their disease.¹⁶ Currently, there is greater emphasis on the early introduction of medications that will reduce airway inflammation.¹⁷ The pathophysiology of airway inflammation in asthma is multifactorial. There is mounting evidence that lymphocytes, as well as eosinophils, are of critical importance in this inflammatory process.¹⁵⁻²⁰ Studies by Corrigan and collaborators^{21,22} showed an increase in the levels of activated T lymphocytes (expressing IL-2R and HLA-DR) in the peripheral blood of patients with acute, severe asthma. An increase in levels of IL-2R (CD25) was also observed in bronchial biopsy specimens obtained in patients with allergic asthma.²³ In a recent study Robinson et al²⁴ observed an increase in the number of cells expressing mRNA for the cytokines IL-2, IL-3, IL-4, IL-5, and GM-CSF in the bronchoalveolar lavage fluid of atopic patients with asthma. The same authors²⁵ found that a 2-week course of prednisolone resulted in a reduction in the number of bronchoalveolar lavage cells expressing IL-4 and IL-5 mRNA and an increase in the number of cells expressing IFN- γ mRNA in asthmatic patients. Studies have also shown an increase in the expression of intercellular adhesion molecule-1^{26,27} and HLA-DR²⁷ in the airway epithelium of asthmatic subjects.

IVIG is known to have immunomodulatory properties. It has been successfully used in the treatment of several diseases with immunoregulatory abnormalities. In Kawasaki Disease, IVIG treatment reduces vascular inflammation and cytokine production by immune effector cells.^{28,29} Leung et al³⁰ observed that PBMCs from patients with acute Kawasaki Disease spontaneously secrete high levels of IL-1 and that secretion normalizes in patients who respond to IVIG therapy. These patients also had a decrease in the expression of endothelial cell leukocyte adhesion molecule-1 in their skin biopsy specimens after therapy with IVIG. Dalakas et al³¹ conducted a dou-

ble-blind, placebo-controlled study of IVIG treatment in dermatomyositis. They observed a significant clinical improvement in the treated group. The expression of intercellular adhesion molecule-1, which had been increased on the endothelial cells and lymphocytic infiltrates, was markedly reduced after treatment with IVIG. Use of IVIG has also been associated with remission of thrombocytopenia in patients with idiopathic thrombocytopenic purpura, even in steroid-resistant and steroid-dependent patients.^{32,33} Potential mechanisms of action of IVIG that have been studied include Fc receptor blockade, idiotype-anti-idiotypic antibody interaction, enhancement of T-cell suppressor function, inhibition of cytokine production, and the presence of sCD4, sCD8, and sHLA class II in IVIG preparations.⁴

This study shows that IVIG may be a useful steroid-sparing agent in patients with severe steroid-requiring asthma. A larger double-blind, placebo-controlled study of this subgroup of patients is required to confirm our findings.

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