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## An open-label study of high-dose intravenous immunoglobulin in severe childhood asthma

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*Eight pediatric patients with severe steroid-dependent asthma were enrolled in an open-label trial of high-dose intravenous immunoglobulin (IVIG) in an attempt to decrease their steroid requirements. Monthly therapy with high-dose IVIG resulted in a threefold decrease in both maintenance oral corticosteroid dose and in extra oral corticosteroids needed for control of exacerbations of asthma. This was accompanied by significant improvements in peak expiratory flow rates and in symptom-score rating. An immunomodulatory effect of IVIG was suggested by the changes in immediate skin test reactivity. Seven of the eight patients demonstrated one or more reactions to a panel of allergens before therapy. During the course of the trial, there was a progressive diminution in skin test reactivity with a 100-fold reduction in sensitivity at the completion of 6 months of therapy. In this preliminary study, the reduction in steroid requirements, improvement in symptoms and peak flow measurements, and diminution in immediate skin test reactivity support a potential role for IVIG in the treatment of severe steroid-dependent asthma. A larger, randomized trial now appears warranted. (J ALLERGY CLIN IMMUNOL 1991;87:976-83.)*

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Received for publication June 29, 1990.

Revised Dec. 21, 1990.

Accepted for publication Dec. 21, 1990.

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\*\*Dr. Erwin W. Gelfand was supported in part by National Institutes of Health Grant AI-26490, and is a Scholar of the Raymond and Beverly Sackler Foundation.

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### Abbreviations used

|                    |                                                                  |
|--------------------|------------------------------------------------------------------|
| IVIG:              | Intravenous immunoglobulin                                       |
| PEFR:              | Peak expiratory flow rate                                        |
| ANOVA:             | Analysis of variance                                             |
| LD:                | Low dose                                                         |
| HD:                | High dose                                                        |
| IT:                | Immunotherapy                                                    |
| PC <sub>20</sub> : | Provocative concentration causing a 20% fall in FEV <sub>1</sub> |
| Ag:                | Antigen                                                          |
| Ab:                | Antibody                                                         |
| PLSD:              | Protected least-significant difference                           |
| CI:                | Confidence interval                                              |
| SPT:               | Skin prick test                                                  |

Asthma is a common childhood disorder, affecting 2% to 13% of the pediatric population.<sup>1</sup> Although most patients with asthma have a self-limited or easily manageable disease, there is a subset of patients who suffer chronic, intractable respiratory difficulties.

For those pediatric patients who, by necessity, are receiving long-term systemic corticosteroids, the disease control achieved is weighed against severe side effects. Obesity, hirsutism, and cushingoid features are often observed, and more worrisome side effects, such as growth suppression, osteoporosis, raised intraocular pressure, and posterior subcapsular cataracts are not uncommon.<sup>2</sup> Inhaled steroids may also be associated with severe side effects.<sup>3</sup> The importance, therefore, of minimizing steroid therapy cannot be overemphasized.

The lack of remittive agents for childhood asthma makes steroid reduction in the most severely affected group of patients very difficult. Agents such as gold<sup>4</sup> and methotrexate<sup>5</sup> have been used primarily in adults, and their potential in steroid-dependent subjects with asthma requires confirmation. In addition, both of these medications have hematologic suppression as a major side effect, and LD methotrexate, although it is relatively well tolerated, can still cause alopecia, mouth ulceration, and hepatic dysfunction.<sup>6</sup>

IVIg has been used effectively in the treatment of humoral immune deficiencies.<sup>7</sup> It is a safe preparation with well-defined, short-term adverse reactions and no known long-term side effects. Its use in HDs in autoimmune disorders began in the early 1980s with the treatment of immune thrombocytopenic purpura<sup>8</sup>; it remains an important mode of therapy in this disease, although its mode of action is unclear.<sup>9</sup> Since that time, HD IVIg has been successfully used in the treatment of Kawasaki syndrome,<sup>10</sup> myasthenia gravis,<sup>11</sup> autoimmune-mediated production of antifactor VIII Abs,<sup>12</sup> polymyositis,<sup>13</sup> and pure red cell aplasia.<sup>14</sup> The mechanism of action of IVIg in these disorders is also unknown. Theories of its action include Fc receptor blockade of macrophages and other reticuloendothelial system cells,<sup>15</sup> provision of anti-idiotypic Ab,<sup>12</sup> or induction of CD8<sup>+</sup> suppressor T cells that act as immunoregulatory cells.<sup>16</sup>

Active IT in asthma has been attempted to modulate patients' immune responses to allergens and therefore decrease the IgE responses to inciting agents. IVIg may be viewed as another approach to altering a patient's immune response to allergen, constituting a passive form of IT. We present data on eight patients treated with HD IVIg for severe steroid-dependent asthma. The study was performed not only to detect changes in clinical outcome but also to determine if an immunomodulatory effect of IVIg could be demonstrated in these patients.

## MATERIAL AND METHODS

### Subject selection

The study population consisted of eight children ranging in age from 6 to 17 years. All patients had severe asthma (as defined by the American Thoracic Society) and had suffered symptoms from 3 to 12 years. Although seven of eight patients had positive skin tests, their symptoms were perennial and not characterized by discernable seasonal exacerbations. All patients had optimal investigation and management of medical problems that may secondarily affect reactive airway disease, including gastroesophageal reflux and sinusitis. Their asthma therapy consisted of inhaled corticosteroids, oral corticosteroids (specifically, oral prednisone or methylprednisolone), inhaled bronchodilators, theophylline, and cromolyn sodium. These patients had been receiving oral steroid therapy from 1 to 8 years. Patients averaged more than one exacerbation of their asthma per month during the preceding year, often necessitating an additional short course of HD oral corticosteroids. All patients enrolled in the trial had, in the year before the initiation of IVIg therapy, multiple systematic attempts to decrease their steroid dose without success. The protocol was reviewed and approved by the Institutional Review Board of the National Jewish Center (protocol HS 517).

Excluded from this study were patients with a second, complicating respiratory disease, subjects actively receiving allergen IT, and those patients with abnormal humoral immune systems as defined by hypogammaglobulinemia and low responses to immunization with specific Ags.

### Evaluations

**Symptom Scores.** Patients were instructed in symptom-score rating from 0 to 4 (0, no symptoms; 1, mild symptoms but no discomfort; 2, moderate symptoms with no change in daily routine; 3, severe symptoms interfering with sleep or activity but not incapacitating; 4, very severe, incapacitating symptoms). Patients recorded their daily symptoms of cough, shortness of breath, chest discomfort, wheezing episodes, as well as medication changes, and numbers of extra inhaled treatments with albuterol or metaproteranol.

**Pulmonary function testing.** PEFs were measured with a hand-held mini-Wright peak flow meter twice daily, before and after inhaled medication was taken. Body plethysmography was performed to obtain values of lung volumes (thoracic gas volume, total lung capacity, and residual capacity) and flow rates, such as FVC and FEV<sub>1</sub>.

**Methacholine challenge.** Bronchial provocation with increasing concentrations of inhaled methacholine was performed according to the method of Chai et al.<sup>17</sup> Provocation was stopped when the patient's FEV<sub>1</sub> value fell  $\geq 20\%$  of baseline. The PC<sub>20</sub> value was then calculated, and a rating of severe (PC<sub>20</sub> < 0.13 mg/ml), moderate (PC<sub>20</sub> > 0.13 mg/ml but < 2.5 mg/ml), or mild (PC<sub>20</sub> > 2.5 mg/ml) was assigned.

**Skin testing.** SPTs were performed with commercial Ags (obtained from Greer Laboratories, Port Hyannis, N.Y., and Hollister-Stier Laboratories, Spokane, Wash.) and smallpox needles. A standard panel of common Colorado Ags were initially used to screen each patient, and the five Ags eliciting the most positive reactions were chosen for each patient.

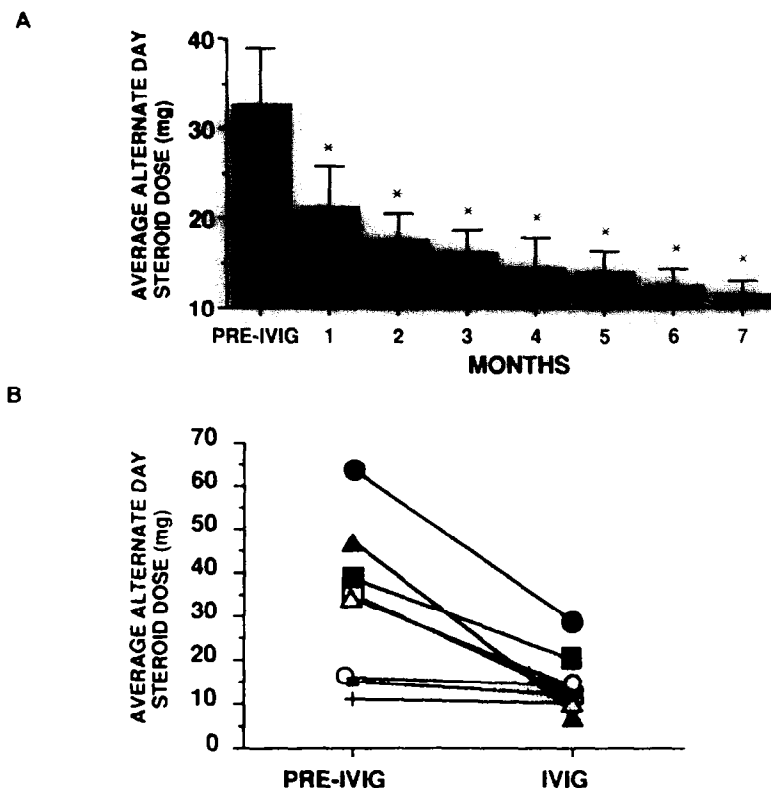


**FIG. 1.** Average alternate-day steroid dose. **A**, Subjects began the study taking an average alternate-day dose of oral corticosteroid of 32.6 mg. Indicated are the average steroid doses for the entire group of subjects after each monthly IVIG infusion. All points after the first infusion indicate a statistically significant decrease in corticosteroid dose. Values presented are mean  $\pm$  SEM; \*95% CIs, Fisher's test of PLSD;  $p < 0.005$ , Dunnett's  $t$  test. **B**, Average monthly alternate-day steroid dose of each subject before and during IVIG therapy. The average alternate-day steroid dose before IVIG therapy was  $32.6 \pm 6.4$ ; during the trial, it was reduced by  $59\% \pm 5\%$ . Each symbol represents a single patient.

for repeated SPTs and end point titration. Before each infusion, serial titrations of each of the five Ags (e.g., 1:10, 1:100, 1:1000, and 1:10,000 wt/vol) were applied to the patients' backs, and SPTs were performed. Histamine, 1 and 10 mg/ml, was used as positive controls, and glycerosaline diluent was used as a negative control. Reactions were outlined by felt pen and tape transferred to score sheets. Wheal surface areas were calculated with McTablet (Summagraphics, Fairfield, Conn.) to outline and measure the tape-transferred wheal tracings.

**Laboratory examinations.** IgG, IgA, and IgM were assayed by laser nephelometry. IgE assay was performed by PRIST (Pharmacia, Uppsala, Sweden).

**Immunoglobulin infusion.** IVIG (Sandoglobulin; Sandoz AG, Basel, Switzerland) was infused as a 6% solution. An intravenous line was started, and the infusion was initiated at a rate of 30 ml/hr, increasing every 15 minutes to the maximum rate tolerated. Each patient received 2 gm/kg of IVIG administered during 2 consecutive days (1 gm/kg/day). Infusion records were kept, and the incidence of reactions, such as temperature elevation, headache, chest pain, malaise, nausea, chills, and rash, were recorded. In-

fusions were well tolerated, and all patients completed the trial.

**Study design.** The trial was open labeled and conducted during a period of 9 months. During the 6 months of therapy, IVIG was administered every 4 weeks for a total of seven infusions. Patient enrollment was staggered to avoid a seasonal bias.

During the initial 2 months (pre-IVIG), each patient underwent full pulmonary function testing, including body plethysmography and methacholine challenge. A panel of SPTs to common Colorado allergens was performed. Blood was drawn for baseline biochemical and hematologic values, as well as IgG, IgA, IgM, IgE, and IgG subclasses, diphtheria and tetanus antibody titers, erythrocyte sedimentation rate, and total eosinophil counts. The patients were instructed in keeping symptom diaries and PEFRs, which were examined at monthly intervals by the investigators.

Before each infusion, and 4 weeks after the final infusion, symptom scores and peak flows were recorded and reviewed with each patient, and serial SPTs were repeated. Four weeks after the final infusion, body plethysmography and methacholine challenges were also repeated.

Medication adjustments and routine follow-up were performed by the patients' primary physicians, and corticosteroids were reduced based on their interpretation of the patient's clinical status.

### Statistical analysis

Statistics were performed with Statview 512+ software (BrainPower, Inc., Calabasas, Calif.). The Student's *t* test was used for comparison of before and after measures. ANOVA was used for any multiple comparisons with a repeated measures analysis. The significance level of  $>95\%$  CI was accepted, as defined by Fisher's PLSD test, and Dunnett's *t* test, which specifically tests the significance of the baseline versus the means of experimental periods over multiple sample periods.

## RESULTS

### Baseline laboratory values

No patient had any biochemical or hematologic abnormality before or after therapy. All patients had intact humoral immunity documented by normal Ab levels, normal IgG subclass distribution, and normal responses to vaccination with specific Ags, such as tetanus and diphtheria. The average serum IgG level was  $585 \pm 69.6$  mg/dl before IVIG therapy. The levels significantly increased to an average of  $1240 \pm 112.6$  mg/dl 1 month after completion of IVIG therapy ( $p < 0.001$ ). Serum IgE levels averaged  $324 \pm 110$  IU before IVIG therapy and significantly decreased to  $133 \pm 57$  IU after 6 months of infusions ( $p < 0.04$ ). Serum IgA and IgM levels were not altered.

### Steroid requirements

Three of the eight subjects began the trial receiving daily oral corticosteroids, and the remaining subjects were receiving alternate-day doses of oral corticosteroids. Because all subjects completed the trial receiving alternate-day corticosteroid therapy, all data have been converted to the equivalent average alternate daily dose. The average alternate-day oral steroid dose during the 2-month observation period for all eight patients before IVIG therapy was 32.5 mg. At the conclusion of 6 months of IVIG therapy, the average alternate-day dose was significantly reduced almost threefold to 11.5 mg ( $p < 0.005$ ). The mean steroid dose for the entire group was analyzed on a monthly basis by repeated measures ANOVA. All time points after the first infusion demonstrated a statistically significant decrease in alternate-day steroid usage (Fig. 1). Furthermore, to correct for multiple comparisons, each average monthly steroid dose administered during IVIG therapy was compared to the doses before therapy with the Tukey's multiple-comparison procedure. This analysis also indicated a high de-

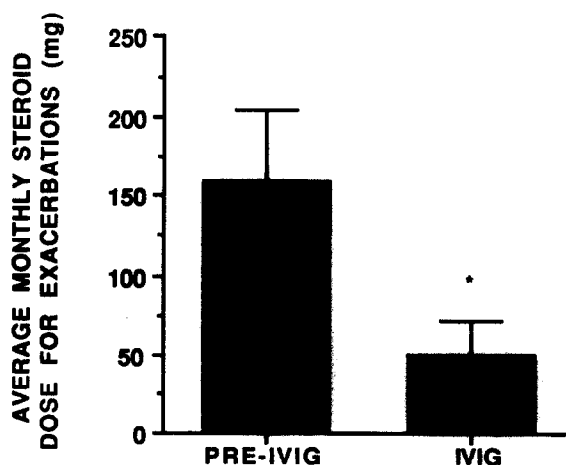


FIG. 2. Average steroid requirement for exacerbations. Subjects began the trial with an average of 158 mg/mo of extra corticosteroids for the treatment of exacerbations of asthma. The average monthly requirement for steroids for exacerbations decreased while subjects received IVIG, to 49.2 mg/mo. This difference is statistically significant ( $*p < 0.001$ , Student's *t* test). Values indicated are mean  $\pm$  SEM.

gree of significance for steroid reduction ( $p < 0.0001$ ).

The individual values for steroid reduction are illustrated in Fig. 1, *B*. All eight patients had a reduction in steroid use. We identified two groups of patients: patients beginning the trial with LD oral alternate-day steroid therapy (three patients; mean, 12 mg on alternate days) and patients receiving HD alternate-day steroid therapy (five patients; mean, 46.5 mg). In comparing the groups receiving LD and HD, we identified significant differences in pulmonary function as measured by twice-daily PEFs. Those patients who began the trial receiving HDs of oral corticosteroids had high PEF values at the onset of IVIG therapy and maintained these flow rates despite a significant decrease in corticosteroids ( $p = 0.01$ ). A second group (three patients) had been maintained with LD corticosteroids despite low PEF. Although the reduction in steroid dosage was less dramatic, this group, nonetheless, demonstrated a  $>15\%$  improvement in PEF ( $p < 0.03$ ) during IVIG therapy.

In addition to their regular daily or alternate-day dosage of systemic corticosteroids, the eight subjects generally required frequent and lengthy pulses of extra steroids for exacerbations of their asthma before enrollment in the trial. Analysis of the requirement for extra steroids, while they were receiving IVIG, further emphasized the beneficial effects of IVIG therapy. During the evaluation period before IVIG therapy, the group of patients required a monthly average of 158

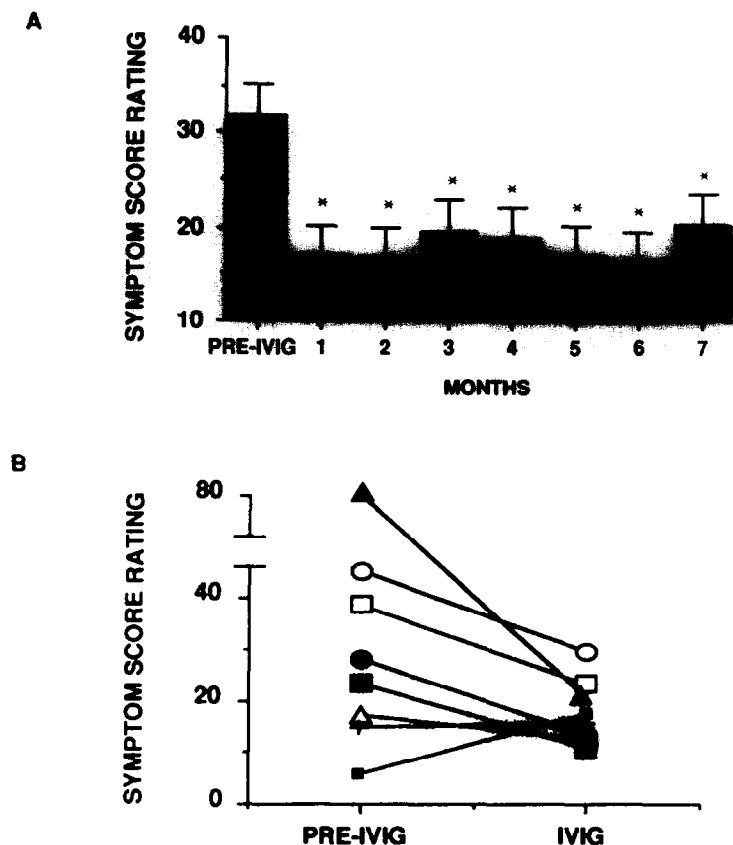


**FIG. 3.** Average monthly symptom score. Subjects were instructed in a symptom-score rating scale for six items: cough, shortness of breath, chest discomfort, morning wheezing, nocturnal wheezing, wheezing during daytime activities, as well as the number of extra doses of  $\beta$ -agonist (albuterol or metaproteranol) taken during a 24-hour period. The scale consisted of measures from 0 to 4: 0, no symptoms; 1, mild symptoms but no discomfort; 2, moderate symptoms with no change in daily routine; 3, severe symptoms, interfering with sleep or activity but not incapacitating; 4, very severe, incapacitating symptoms. **A**, The average monthly symptom-score rating decreased significantly after the first infusion and was maintained throughout the trial (\*95% CI, Fisher PLSD;  $p < 0.005$ , Dunnett's  $t$  test). Values indicated are mean  $\pm$  SEM. **B**, Average monthly symptom score for each individual before and during IVIG therapy. During IVIG therapy, there was little variability from month to month as evidenced by SEM ranging from only 1 to 3.6. Each symbol represents a single patient.

mg of oral corticosteroids for asthma exacerbations. While patients were receiving IVIG, this value decreased threefold to 49.2 mg/month (Fig. 2). ANOVA for each monthly period after initiation of IVIG therapy also indicated a clinically and statistically significant decrease in need for extra oral corticosteroids.

### Pulmonary function tests

All but two patients began the trial with pulmonary function within normal limits as indicated by body plethysmography. The six patients with normal pulmonary function at initiation of IVIG therapy demonstrated no deterioration of pulmonary function on

repeat body plethysmography, despite the large average decrease in corticosteroid dose. The two individuals who began the trial with abnormal pulmonary function demonstrated significant improvement in lung volumes, FEV<sub>1</sub>, and FVC on conclusion of IVIG therapy (data not presented).

Two measures of bronchial hyperreactivity, methacholine challenge and exercise-induced bronchospasm, did not change significantly after 6 months of IVIG therapy.

### Symptom scores

All subjects completed daily symptom diaries, rating their symptoms from 0 (no symptoms) to 4 (severe,

incapacitating symptoms). For analysis, individual daily symptom scores were added for each 4-week period. The sums were converted to categorical values for statistical comparison: 0, no symptoms (0); 1 to 7, mild (1); 8 to 14, moderate (2); 15 to 21, severe (3); and 21 to 28, incapacitating (4). Overall, there was a significant improvement in total symptom scores with a 100% to 200% improvement in total symptom score values during each month of the trial compared to baseline values (Fig. 3, A). The individual symptom scores (cough, shortness of breath, etc.) were also improved, again with a range of 100% to 200% improvement from baseline for each month of the trial. When symptom scores of each individual patient were evaluated (Fig. 3, B), 6/8 patients demonstrated a significant reduction ( $p < 0.001$ ). For the two patients who exhibited the lowest symptom scores before IVIG therapy, one exhibited no change, and the other patient's symptom scores marginally increased. There was an average 150% decrease in the monthly need for extra treatments of inhaled  $\beta$ -agonists during IVIG therapy. This was statistically significant for all time points during the trial.

### Skin testing

Of the eight patients enrolled in the trial, seven had positive SPTs to at least one or more Ags. During the course of IVIG therapy, there was a progressive reduction in skin test reactivity in all subjects. By the completion of IVIG therapy, all seven patients had a significant decrease in skin test reactivity, averaging 2.05 logs per Ag (Fig. 4). (One log decrease is equivalent to a decrease in skin test reactivity of a tenfold dilution, for example, from 1:10,000 to 1:1000.) Of the 30 initially positive reactions measured, a single response in one patient worsened during IVIG therapy, whereas 27 improved in the seven patients; two skin test reactions in separate patients were unchanged.

The differences for each individual's skin reactivity from the beginning to the completion of the trial were statistically significant ( $>99\%$  CI, Fisher's PLSD). The skin tests were performed with histamine controls at all times. The average wheal value in square millimeters for 1 mg/ml of histamine solution was 13.7 before therapy and 14.7 at completion. The differences between these values were not statistically significant. The average change in Ag skin test reactivity compared to the change in histamine during the course of therapy was highly significant ( $p < 0.005$ ). In two patients, skin testing with compound 48/80 (5 mg/ml) as a second positive control was performed, and patients demonstrated no change in reactivity to this compound during the course of the trial.

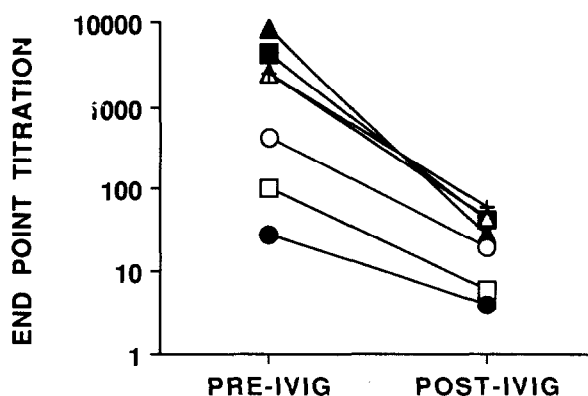


**FIG. 4.** Changes in SPT reactivity. Subjects enrolled in the trial were skin tested monthly with a panel of up to five Ags to which they were sensitive. These Ags were titrated to end point in tenfold dilutions. Indicated are the average end point titrations of all Ags for each of seven subjects who had positive skin tests. The pre-IVIG values are the end point titrations for all subjects before therapy, and the IVIG values are those end point titrations done 1 month after the final infusion. All patients had a significant decrease in end point titration (95% CI, Fisher's PLSD), and the group average decrease in end point concentration was 2.05 logs.

To determine if a patient who had increased sensitivity at baseline (e.g., end point  $10^{-4}$ ) was more likely to have a decrease in skin test reactivity than patients with moderate reactivity (e.g., end point  $10^{-2}$ ), ANOVA was performed and indicated that all end point titration values had a statistically significant chance of decreasing (95% CIs, Fisher's PLSD). The decrease in skin test reactivity was observed for all patients who exhibited positive skin test reactions. There was no correlation between change in end point titration and ability to taper steroid dose ( $r^2 = 0.3$ ).

### DISCUSSION

There is widespread agreement that corticosteroids are of value in the treatment of asthma refractory to bronchodilator therapy.<sup>18</sup> Corticosteroids act primarily by suppressing the inflammatory process that appears to play an important part in the bronchial reactivity that characterizes asthma.<sup>19</sup> However, despite the proven efficacy of oral corticosteroids in the treatment of severe asthma, the associated drug-induced morbidity has promoted the search for other, less toxic, anti-inflammatory agents or alternative approaches. In recent years some initial successes have been reported with LD oral methotrexate<sup>5</sup> or gold.<sup>20</sup> In both cases, administration of these drugs permitted some reduc-

tion in the use of corticosteroids without deterioration of pulmonary function.

This trial with IVIG in severe, steroid-dependent asthma was initiated to reduce corticosteroid dependency and corticosteroid morbidity in children without the toxicity observed with the use of methotrexate or gold. A pattern of response clearly emerged during the course of therapy. Overall, there was a significant decrease to one third of original requirements for corticosteroids, both on a daily basis and amount needed to control exacerbations. This steroid-sparing effect of IVIG was accompanied by a significant improvement in PEFs, measured on a twice-daily basis. These changes were most striking in the group of patients who began the trial with LD of corticosteroids. In the group of patients initially receiving HD corticosteroids, the rapid tapering of drug was not associated with any deterioration in PEF.

In association with these effects of IVIG therapy, there was a significant improvement in subjective ratings of six separate symptoms comprising the symptom-score rating and a decrease in the reported need for extra inhaled bronchodilators. The onset of action of IVIG was surprisingly rapid. The ability to taper steroids, the improvement in symptom scores, and the increase in PEF were observed as early as after the first infusion. These positive effects were sustained throughout the trial period. Data are currently being accumulated in patients followed after IVIG demonstrating a deterioration in these parameters as well as an increase in skin test reactivity 8 to 12 weeks after cessation of therapy.

HD IVIG (2 gm/kg/mo) was used following a regimen reported to be successful in immune thrombocytopenic purpura,<sup>8</sup> Kawasaki syndrome,<sup>10</sup> and polymyositis.<sup>13</sup> This dosing regimen was chosen to optimize the chances of observing an effect. It is uncertain whether the beneficial effects of HD IVIG are secondary to an anti-inflammatory action or are mediated through a different mechanism. An anti-inflammatory effect has been attributed to IVIG in several diseases, including Kawasaki<sup>21</sup> syndrome and polymyositis.<sup>13</sup> Since we could not demonstrate any changes during the trial in nonspecific bronchial reactivity to methacholine or reactivity induced by exercise, other mechanisms need consideration.

Investigation of patients treated with HD IVIG has demonstrated "immunomodulatory" changes in *in vitro* testing. Among these are decreases in pokeweed mitogen-stimulated immunoglobulin production.<sup>16, 22, 23</sup> Although we have demonstrated an overall reduction in serum IgE levels in our patients, the relationship to IVIG therapy remains to be demonstrated. The best support for an immunomodulatory

effect, perhaps not unlike that observed after "active" IT, is the diminution in skin test reactivity observed in all patients who began with positive skin test reactions to one or more Ags. The reductions in skin test reactivity were progressive during the 6-month period of therapy with IVIG, but decreases were observed even after the initial infusion. Moreover, this finding appeared to be specific for Ag-induced skin test responses because there were no associated changes in reactivity to histamine or compound 48/80, a nonspecific inducer of mast cell degranulation. Initial laboratory data suggest this is more than a simple provision of blocking Ab, since mixing of patient's serum to serum of untreated allergic patients did not diminish RAST titers. Although initial studies suggested a fall in specific IgE titer measured by RAST,<sup>24</sup> subsequent evaluation of the patients in studies currently in progress have not demonstrated a consistent correlation in clinical improvement, skin test response, and specific IgE titer. The mechanism whereby IVIG influences skin test reactivity and whether this has any bearing on the steroid-sparing effects or overall clinical benefit are currently under study.

This preliminary trial was carried out with a small group of patients. It, nevertheless, provides support for the future investigation of HD IVIG therapy in severe, steroid-dependent asthma. Although the mechanism of action and optimal dosing schedules are presently not defined, passive therapy with IVIG appears to provide an approach to refractory asthma that is associated with clinical improvement, steroid-sparing, and an absence of drug-induced morbidity. Confirmation of these findings in a larger randomized trial is now necessary, as is delineation of the mechanism of action to define better the benefits and minimal effective concentrations of IVIG required for therapy in severe, steroid-dependent asthma.

We thank Dan Atkins, MD, Allen Adinoff, MD, and Patsy Giclas, PhD, for their valuable advice; Beth Esterl, RN, for coordinating the infusions; Alan Bock, MD, Ross Westley, MD, Jerry Koepke, MD, Manon Brenner, MD, Robert Strunk, MD, and Ian Mitchell, MD, for referral of study patients; David Ikle, PhD, for help with statistical analyses; and Jane Watkins for preparation of this manuscript.

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