

Open-Label Trial of High-Dose Intravenous Immunoglobulin in Patients with Severe Asthma

SANDRA J. DOWNES, M.D., M.P.H., JON E. STAHLMAN, M.D., IRENE M. BORRAS, C.C.R.C., LUIS M. SALMUN, M.D., and LYNDY C. SCHNEIDER, M.D.

ABSTRACT

Anti-inflammatory corticosteroid therapy is highly effective, however, the long term adverse effects may be devastating for patients with severe asthma. Intravenous immunoglobulin (IVIG) is known to have immunomodulatory effects, and in a few clinical trials has been shown to have potential benefit as a steroid-sparing agent in asthma patients requiring high doses of corticosteroids. This study assessed the efficacy of high-dose IVIG in reducing the steroid requirement and subsequently improving the pulmonary function, symptomatology, and quality of life in patients with severe steroid-dependent asthma. Six immunocompetent, steroid-dependent patients were enrolled in an open-label trial of IVIG given as six monthly infusions of 2 g/kg per dose. Five patients completed the study. Of these, four showed a significant reduction in oral corticosteroid requirement while being treated with IVIG. The mean reduction was 10.1 mg/d ($p = 0.02$), which was an almost 50% decrease in corticosteroid requirement. Two patients were able to completely discontinue oral corticosteroids by the end of the study. The remaining subjects were maintained on the same dose of inhaled corticosteroid throughout the study, as well as any other comedication. The forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), and peak expiratory flow rate (PEFR) showed improvement in all but one patient, but these did not reach statistical significance. Patients reported an overall improvement in quality of life. There were no significant adverse effects noted during the treatment period. High-dose IVIG may be beneficial as a steroid-sparing agent in the population of patients with severe steroid-dependent asthma. (*Pediatr Asthma Allergy Immunol* 2002; 15[4]:187–194.)

INTRODUCTION

ASTHMA is a chronic inflammatory disorder of the bronchial airways characterized by airway hyperresponsiveness, airflow obstruction, and inflammation. Asthma disproportionately affects the pediatric population and it is the most common chronic lung disorder of childhood in the United States.⁽¹⁾ Therapy and management of asthma has improved but substantial morbidity and mortality from asthma persist.⁽¹⁾ Until further research can clarify the genetics of asthma, thus bringing the possibility of a cure close to re-

Division of Immunology, Children's Hospital, Department of Medicine, Harvard Medical School, Boston, Massachusetts.
Presented at the American Academy of Allergy, Asthma and Immunology 56th Annual Meeting, March 2000, San Diego, California.

ality, the treatment of asthma remains symptomatic. There is a broad spectrum of asthma severity, from patients with mild intermittent symptoms, to those with chronic, severe respiratory symptoms requiring high daily doses of multiple medications including systemic corticosteroids. These patients have frequent hospitalizations and sometimes near-death experiences. The patients at the extreme of this spectrum are most often steroid-dependent and at high risk for severe side effects from the chronic use of this medication. These side effects include growth retardation for the pediatric population, cataracts and glaucoma, hypertension, diabetes, suppression of the pituitary-adrenal axis, gastrointestinal distress, weight gain and cushingoid appearance, osteopenia, and psychosis.

Airway inflammation is known to play a significant role in asthma, and new modalities seeking to modulate the pathways leading to the immunologic inflammatory response. Intravenous immunoglobulin (IVIG) has been used successfully in the treatment of several diseases with immunoregulatory abnormalities because it has been shown to have immunomodulatory effects.^(2-5,14-22) There have been previous reports on the possible usefulness of IVIG in the treatment of asthma. Page and collaborators⁽⁵⁾ treated patients with asthma with concomitant IgG subclass deficiency with IVIG. They demonstrated a decrease in the severity of these patients' asthma symptoms and medication requirements. Mazer and colleagues⁽⁷⁾ first reported a case study of a 14-year-old patient with severe steroid-dependent asthma who showed improvement of her disease while receiving IVIG. Mazer and Gelfand⁽⁷⁾ later reported the open-label treatment of eight patients with steroid-dependent asthma with IVIG and showed a reduction in steroid requirement and improvement in pulmonary function. Landwehr and collaborators⁽⁸⁾ showed a similar reduction in steroid requirement in their group of 14 adolescent and adult patients with severe asthma receiving IVIG. Our recent randomized, double blind, placebo-controlled trial of 28 patients reported by Salmun et al.,⁽⁹⁾ showed a steroid-sparing effect of IVIG in a subset of patients requiring high doses of oral steroids (>5.5 mg/d average dose over 1 year). This study used a high-dose of IVIG (2 g/kg) as a loading dose, then a lower dose (400 mg/kg) for their remaining infusions. Page and colleagues⁽⁵⁾ also used a lower dose of IVIG while both the Mazer and Landwehr studies used high-dose IVIG in their studies.

The primary objective of this study was to assess the efficacy of high-dose IVIG in reducing the steroid requirement of patients with severe steroid-dependent asthma. In addition, we attempted to determine whether therapy with IVIG is associated with improvement of clinical symptoms and pulmonary function in this population, and to assess the effect of IVIG therapy on the patients' quality of life.

METHODS

Subjects

Six immunocompetent patients, ages 4 to 32 years, with a clinical diagnosis of severe steroid-dependent asthma were enrolled. Steroid-dependent patients were defined as those patients using oral steroids on a daily or alternate day basis for at least 6 months prior to study entry. An immunocompetent subject was defined in this study as a patient with a normal immunologic evaluation and lack of significant medical history of recurrent infections in multiple sites. The immunologic laboratory evaluation included serum immunoglobulin (Ig)G, IgA, IgM, IgG subclasses, and specific antibody titers to tetanus toxoid, and to polyribosylribitol phosphate (PRP) polysaccharide antigens of *Hemophilus influenza* type b. In addition, patients older than 6 years old who were able to perform pulmonary function tests adequately were required to show documentation of a 15% variation in FEV₁ within the past year.

Patients using comedications such as inhaled cromolyn or ipratropium, long-acting bronchodilators, theophylline, antileukotrienes or inhaled steroids, were required to have been on these agents for a minimum of 3 months preceding enrollment, and were maintained on the same dose throughout the study. Female patients of child-bearing potential were required to have a negative urine pregnancy test and to have been practicing effective birth control for at least 30 days prior to entry into the study. They were continued on the same method of birth control until completion of the study. With the exception of allergic disorders, the patients were required to be in good health without other pulmonary disease. Cigarette smokers, those enrolled in other experimental studies, and those who had received IVIG in the previous 6 months were not eligible for enrollment. Informed consent was voluntarily signed by the patients or their parents or guardians

if the patients were younger than age 18. The study protocol was reviewed and approved by the Committee on Clinical Investigation at Children's Hospital, Boston, Massachusetts.

Study design

This is an open-label trial of six monthly infusions of high-dose IVIG given to patients severe steroid-dependent asthma. Patients who met eligibility criteria were enrolled in a 2-month run-in period to confirm their need for long-term corticosteroid therapy. During this time period, an effort was made to taper each patient's corticosteroid dose by 5–7.5 mg (of prednisone or equivalent steroid) every other week if PEFR remained above 60% predicted and symptom scores were stable.

Patients who failed to wean off corticosteroid during this 2-month period then entered the active treatment phase. They received high-dose IVIG infusions at 2 g/kg body weight every 4 weeks for a total of six infusions. Interim history and physical examinations were performed at 4-week intervals, with an emphasis on steroid requirement, days of wheezing, and other pertinent asthma symptoms. Pulmonary function was measured using spirometry. The patients were eligible to have their doses of oral steroids reduced every 2 weeks as long as their peak expiratory flow rate (PEFR) remained above 60% predicted, they were clinically stable and their symptom scores remained at or above baseline. Dose reductions were similar to those in the run-in period, with increments of 5–7.5 mg of prednisone or equivalent steroid. The level of comedication was monitored closely and kept stable if possible. However, if patients were able to discontinue oral steroids during the active treatment phase, an attempt was then made to reduce the dose of inhaled steroid used by the patient.

Follow-up evaluations were performed at 1, 6, and 12 months after active treatment was completed. The asthma quality-of-life questionnaire developed by Juniper et al.⁽¹⁰⁾ was administered at the baseline visit, at the end of the active treatment period and at the 12-month follow-up visit.

Study drug

Gammagard® S/D Immune Globulin Intravenous (Human) was supplied by Baxter Healthcare Corporation, Hyland Division (Glendale, CA). IVIG was administered as a 10% solution. Infusion rates began at 1 mL/kg per hour and were doubled every 30 minutes to 8 mL/kg per hour, then maintained at this rate for the duration of the infusion. Patients who developed side effects after the first infusion were pretreated with antipyretic, anti-inflammatory, or antihistamine medications for subsequent infusions.

Patient evaluation

Clinical assessment by a physician was performed at study entry, every 4 weeks throughout the active treatment period, and at subsequent follow-up visits. The physical examination graded wheezing, rhonchi, intercostal retractions, and decreased breath sounds as present or absent. Pulmonary function testing was performed at each visit by a trained technician. The asthma quality-of-life questionnaire was administered by a trained research assistant.

Each patient was given a symptom diary for documentation of PEFR, asthma symptom scores, medication use, days missed from school or work, and hospital visits. The Assess Home Peak Flow Meter⁽¹¹⁾ was provided to each patient who was adequately and consistently able to perform PEFR. Measurements were taken twice per day at home and recorded in the diary. Patients were also instructed by a physician on how to assess disease activity by completing a symptom score card daily. Symptoms of coughing, shortness of breath, wheezing or chest tightness, exercise tolerance, and sleep disturbance caused by asthma were rated on a scale between 1 and 5. Grade 1 was characterized by no asthma symptoms. Grade 2 was mild symptoms without interference with daily activities. Grade 3 was mild symptoms with some impact on daily activities. Grade 4 was moderate symptoms with some limitation of daily activities and sleep disturbance. Grade 5 was characterized by severe and constant asthma symptoms, significant sleep disturbance, and inability to perform daily activities. When pertinent, other allergic symptoms such as rhinitis and allergic conjunctivitis were scored similarly.

Humoral immunity was evaluated at study entry. Serum IgG, IgA, IgM, and IgG subclasses were measured by radial immunodiffusion and IgE by enzyme-linked immunosorbent assay (ELISA). Specific antibody titers

to *Hemophilus influenza* type b and tetanus toxoid were measured by ELISA. Serum IgE and radioallergosorbent testing (RAST) to mites, ragweed, and grasses were measured at baseline, and repeated at week 24 and at study completion. To evaluate possible adverse effects of the study drug, complete blood count with differential, alanine-aminotransferase (ALT) and hepatitis C antibody were performed at entry, at month 3, and at end of the active treatment phase. Hepatitis B surface antibody was also obtained at study entry. Adrenal suppression was determined by Cortrosyn® (Organon, Inc., West Orange, NJ)-stimulation test for those on less than physiologic replacement doses of hydrocortisone at the end of the active treatment phase.

Skin prick testing of a panel of 30 inhalant allergens (Hollister-Stier Laboratories LLC, Spokane, WA) was performed at study entry and at end of the active treatment phase using the Multi-Test Device (Lincoln Diagnostics, Decatur, IL). Saline and glycerol was used as a negative control, and histamine, 1:10,000 dilution was used as the positive control. For skin test titration, quantitative dilutions were performed to at least four allergens to which patients had positive reactions.

Statistical analysis

The sample size was based on the ability to detect a 40% decrease in the median oral steroid requirement during the 2-month run in period compared with the last 2 months in the study. The power achieved with this sample size was calculated to be 90%. Statistical comparisons were made using the paired Student's t-test. *p* Values less than 0.05 were considered statistically significant.

RESULTS

Five patients, two males and three females ages 4–32 years, completed the study (Table 1). One patient was withdrawn from the study after enrollment but prior to any IVIG infusions because of the diagnosis of an underlying pulmonary disease, Wilson-Mikity syndrome. The study patients had associated disorders that included allergic rhinitis, food allergies, and a history of sinusitis and gastroesophageal reflux. There were four Caucasians and one African American patient. On average, the subjects required 32.9 mg/d of oral steroids in the previous year prior to study entry. There was no significant change in dosing of oral corticosteroids during the run-in phase. The range of steroid use was 2–60 mg/d. There was a mean of three hospitalizations in the previous year with a range of one to five hospitalizations per patient. In addition to oral corticosteroids, all patients were similar in their use of comedication. These included inhaled corticosteroids, leukotriene modifiers, theophylline, long-acting bronchodilators, and short-acting β -agonists. In addition, four of five patients used antihistamines and topical intranasal corticosteroids for allergic rhinitis. Antireflux therapy was prescribed to two patients.

TABLE 1. PATIENT DEMOGRAPHICS

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Gender	M	M	F	F	F
Age (years)	16	13	32	6	4
Ethnicity	C	C	C	AA	C
Number of hospitalizations in the previous year	3	4	2	5	1
Average daily oral steroid (mg) requirement for the previous year	60	60	16	6	22.5
Average daily inhaled steroid (μ g) in the previous year	2640	2640	1320	880	1320
Average daily dose of oral steroid (mg/day) in the run-in period	37.6	27.3	18.8	12.8	16.3
Average daily dose of oral steroid (mg/day) in the active period	20.5	27.5	6.4	1.0	6.9
Number of positive skin test (30 total tested)	26	13	0	23	7
IgE level (U/mL) at baseline	34	131	57	835	614
IgE level (U/mL) during active treatment	26	189	128	695	457

C, Caucasian; AA, African American; IgE, immunoglobulin E.

Table 1 also shows the average daily dose of oral steroid used by each patient. The doses are the average daily dose during the 2-month run-in period and the average of the last 2 months of the active treatment period. As seen in Figure 1, four of five patients showed a significant reduction in oral steroid requirement, with a mean decrease of almost 50%, 22.6 versus 12.5 mg/d, after treatment with IVIG. This mean reduction of 10.1 mg/d was statistically significant at $p = 0.02$. In addition, one patient was able to decrease her use of inhaled corticosteroids by the end of the treatment period from 1320 $\mu\text{g}/\text{d}$ to 880 $\mu\text{g}/\text{d}$. Table 2 shows pulmonary function test results before and after IVIG treatment. Three of the four patients able to adequately perform PFT measurements using spirometry demonstrated an increase in measurements of forced vital capacity (FVC), forced expiratory volume in 1 second (FEV₁, and PEFR. However, the difference in these mean values did not reach statistical significance. Patient 5 was 4 years old at study entry and unable to perform spirometry. Asthma symptom scores were improved in three of five patients but did not reach statistical significance, and four of five patients reported an overall improvement in quality of life.

Baseline serum IgE levels ranged from 34–835 U/mL. Three of five patients demonstrated a decrease in IgE during the active treatment period (Table 1). Absolute eosinophil count was elevated in all patients at baseline, and showed some decreased in four of five patients after active treatment. This decrease was not statistically significant. All but one patient showed skin test reactivity to multiple common inhalants. Results of end-point titration for at least four antigens to which the subjects had initial positive skin test reactions were inconsistent. One patient showed evidence of adrenal suppression at study entry and remained suppressed at study completion despite a reduction in oral corticosteroid use.

All patients had negative hepatitis C antibodies before study entry and after all IVIG infusions. In addition, ALT levels remained stable. There were no adverse side effects noted during the treatment period. Nausea, vomiting, and headache were most often reported approximately 24 hours after infusions, which resolved without complication. All patients subsequently received antipyretics, such as acetaminophen or ibuprofen, and Benadryl® (Pfizer, Inc., New York, NY) as pretreatment for infusions 2 through 6. Two patients, in addition, received hydrocortisone as pretreatment.

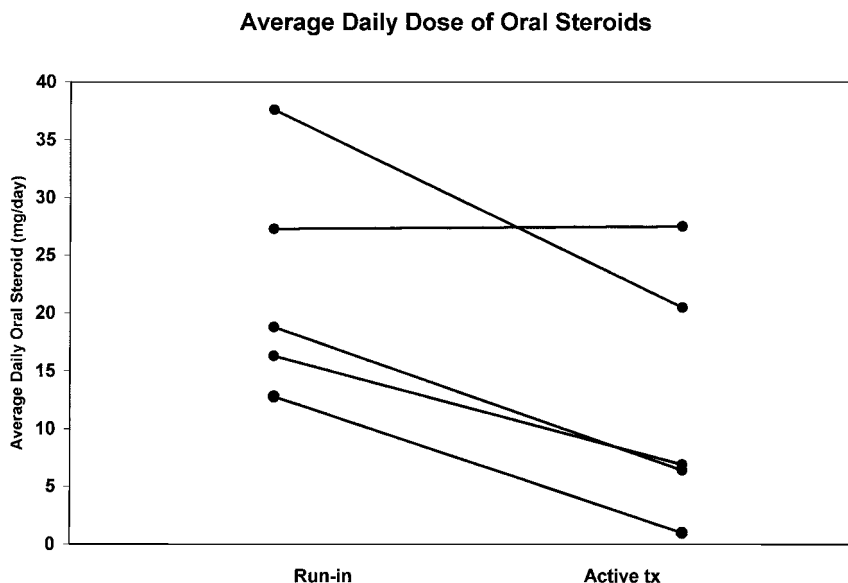


FIG. 1. Average daily dose of steroids. Doses were the average daily dose during the 2-month run-in period compared to the last 2 months of the active treatment period. Four of five patients showed a significant reduction in oral steroid requirement, with a mean decrease of almost 50%, 22.6 versus 12.5 mg/d, with intravenous immunoglobulin (IVIG) treatment. The mean reduction of 10.1 mg/day (standard deviation [SD] 6.4) was statistically significant at $p = 0.02$ using the paired Student's t test.

TABLE 2. PULMONARY FUNCTION TESTS

	<i>Patient</i>	<i>FVC (L)</i>	<i>FEV₁ (L)</i>	<i>PEFR (L/s)</i>
Run-in	1	3.07	2.11	197
Active tx		3.37	2.43	297
Run-in	2	3.42	1.75	265
Active tx		3.76	2.15	259
Run-in	3	3.70	2.32	325
Active tx		2.95	1.92	279
Run-in	4	2.22	1.09	102
Active tx		2.73	1.21	128
Mean run-in		3.1	1.82	222
Mean active tx		3.2	1.93	241
Mean difference		0.10	0.11	18.5
Standard deviation		0.57	0.36	61.8

Three of the four patients able to adequately perform PFT measurements using spirometry demonstrated an improvement in measurements of FVC and FEV₁. However, the difference in these mean values did not reach statistical significance ($p = 0.75$ and 0.58 , respectively). Two of the four patients demonstrated an overall improvement in PEFR but this did not reach statistical significance ($p = 0.59$).

FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; PEFR, peak expiratory flow rate; PFT, pulmonary function tests; tx, treatment.

DISCUSSION

The results of this study suggest that high-dose IVIG may be beneficial as a steroid-sparing agent in the population of patients with severe steroid-dependent asthma. The study shows a statistically significant reduction in the requirement of daily oral steroids by almost 50%. Despite this reduction, there was no significant deterioration in measurements of asthma control, and patients reported an overall improvement in quality of life. The patient who did not show a reduction in oral corticosteroid use had more severe asthma and required higher doses of oral corticosteroid before enrollment in the study. He had several asthma exacerbations while enrolled in the study, requiring additional bursts of prednisone, and was therefore tapered more slowly than the other patients. However, this patient demonstrated an improvement in pulmonary function test, and reported an overall improvement in his asthma during the study period. Although not statistically significant, there were trends toward improvement in pulmonary function tests, asthma symptom scores, and atopic parameters such as IgE and eosinophil levels. The IVIG infusions were well tolerated.

The steroid-sparing effect of high-dose IVIG in asthma reported in our study has been reported previously in other small trials⁽⁵⁻⁸⁾ and in the randomized, double-blind, placebo-controlled trial by Salmun et al.⁽⁹⁾ These studies have used various Ig preparations and dosing regimens. However, reductions in steroid requirements have consistently been demonstrated, although it appears that higher doses of IVIG are more effective. In their multicenter, randomized, double-blind, placebo-controlled trial of IVIG in asthma, Kishiyama and colleagues⁽¹²⁾ did not demonstrate a significant difference between IVIG and placebo. They enrolled 16 patients to receive IVIG, 2 g/kg, 9 patients to receive 1 g/kg, and 15 patients to receive albumin, 2 g as placebo. They noted a reduction in average daily steroid dose of 33%, 39%, and 33% for the respective groups. The authors reported premature termination of the study because of adverse experiences, notably symptoms consistent with aseptic meningitis in 3 patients randomly assigned to the higher dose IVIG treatment arm. They reported an overall rate of headaches of 27% in the 2 g/kg IVIG-treated group, 33% in the 1 g/kg group, and 16% in the placebo group. This study used an IVIG preparation containing

mannitol not found in other preparations that may have contributed to the severity of these symptoms. Although headaches are common, such severe adverse effects as those experienced by the Kishiyama group have not been previously reported in the studies of IVIG use in asthma. In our study, the patients complained of nausea, vomiting or headache approximately 24 hours after the infusion of varying intensity but responded to antipyretics or antihistamines, and these side effects resolved over a short period of time. All of our patients received antihistamine, antipyretic, and/or hydrocortisone medication as pretreatment before subsequent infusions if they complained of symptoms after the first infusion. This lessened the severity of the side effects, and enabled the patients to continue in the study. Other larger randomized, double-blind, placebo-controlled studies are needed to confirm either the results of our study or the results of the Kishiyama study.

Despite the widespread use of IVIG use in asthma, and other diseases such as Ig-subclass deficiency^(14,15), Kawasaki disease,^(16,17) thrombocytopenia,⁽¹⁹⁾ and atopic dermatitis and hyper-IgE syndrome,⁽²¹⁾ the mechanisms of action in this disease are not yet entirely elucidated. Proposed immunomodulatory effects of IVIG include the binding of the Fc receptor on B cells by IVIG leading to inhibition of immune cell proliferation and immunoglobulin production.⁽²²⁾ Other mechanisms include alteration of lymphocyte populations or inhibition of their activation through binding to cytokines or cell surface proteins. IVIG also has antigen-specific activity via neutralization of viruses and toxins, and opsonization of bacteria. Spahn and colleagues⁽²³⁾ recently proposed a mechanism for the steroid-sparing effects of IVIG seen when used in asthma by demonstrating that IVIG-enhanced glucocorticoid receptor binding affinity despite a reduction in corticosteroid use in their study population. They propose that this improvement in binding affinity may be responsible for the steroid-sparing effects of IVIG. In addition, they showed that IVIG and glucocorticoids act in synergy to suppress mitogen induced lymphocyte activation.

Clearly additional research is needed to further elucidate the mechanisms of action of IVIG, in particular as it relates to the suppression of the inflammatory response in asthma. IVIG is an expensive and time consuming therapy. However, for patients who have reached the limit of traditional methods of asthma treatment, who rely on high daily doses of oral corticosteroids, or who are steroid-resistant, high dose IVIG may be a viable option.

ACKNOWLEDGMENTS

We thank James Dicanzio in the Clinical Research Core Programs Office for help with the statistical analysis; Evan Bailey and Jeanne Testa for administrative assistance; and Patricia Pratt, R.N. and the staff of the Center for Ambulatory Treatment and Clinical Research for their assistance with patient care.

The study was supported by the Children's Hospital General Clinical Research Center M01 RR02172 from the General Clinical Research Centers Program, National Center for Research Resources, and the National Research Service Award T32 AI07512-14, National Institutes of Health, and by Baxter Healthcare Corporation, Hyland Immuno Division, Glendale, CA.

REFERENCES

1. Surveillance for asthma, United States 1960–1995. *MMWR Morb Mortal Wkly Rep* 1998; 47(SS-1):1–27.
2. Ballou M. Mechanisms of action of intravenous immune serum globulin treatment. *Pediatr Infec Dis J* 1994; 13:806–811.
3. Debre M, Bonnet MC, Fridman WH, Carosella E, Philippe N, Reinert P, Vimer E, Kaplan C, Teillaud JL, Griscelli C. Infusion of Fc gamma fragments for treatment of children with acute immune thrombocytopenic purpura. *Lancet* 1993; 342:945–949.
4. Imbach P, Barandun S, d'Apuzzi V, Baumgartner C, Hirt A, Morell A, Rossi E, Schoni MM, Vest M, Wagner HP. High-dose intravenous gammaglobulin for idiopathic thrombocytopenic purpura in childhood. *Lancet* 1981; 1:1228–1231.
5. Page R, Friday G, Stillwagon P, Skoner D, Caliguiri L, Fireman P. Asthma and selective immunoglobulin subclass deficiency: Improvement of asthma after immunoglobulin replacement therapy. *J Pediatr* 1988; 112:127–131.

6. Mazer B, Giclas P, Gelfand E. Immunomodulatory effects of intravenous immunoglobulin in severe steroid-dependent asthma. *Clin Immunol Immunopathol* 1989; 53:S156–S163.
7. Mazer B, Gelfand E. An open-label study of high-dose intravenous immunoglobulin in severe childhood asthma. *J Allergy Clin Immunol* 1991; 87:976–983.
8. Landwehr LP, Jeppson JD, Katian MG, Esterl B, McCormick D, Hamilos DL, Gelfand EW. Benefits of high-dose IV Immunoglobulin in patients with severe steroid-dependent asthma. *Chest* 1998; 114:1349–1356.
9. Salmun L, Barlan I, Wolf H, Eibl M, Twarog F, Geha RS, Schneider LC. Effects of intravenous immunoglobulin on steroid consumption in patients with severe asthma: A double-blind, placebo-controlled randomized trial. *J Allergy Clin Immunol* 1999; 103:810–815.
10. Juniper EF, Guyatt GH, Ferrie PJ, Griffith LE. Measuring quality of life in asthma. *Am Rev Respir Dis* 1993; 147(4):832–838.
11. Cross D, Nelson H. The role of the peak flow meter in the diagnosis and management of asthma. *J Allergy Clin Immunol* 1991; 87:120–128.
12. Kishiyama JL, et al. A multicenter, randomized, double-blind, placebo-controlled trial of high-dose intravenous immunoglobulin for oral corticosteroid-dependent asthma. *Clin Immunol* 1999; 91:123–125.
13. Ballou M. Is steroid-dependent asthma treatable with intravenous immunoglobulin? *Clin Immunol* 1999; 91:126–133.
14. Bernatowska-Matuszewska E, Pac M, Skopcynska H, Pum M, Eibl MM. Clinical efficacy of intravenous immunoglobulin in patients with severe inflammatory chest disease and IgG3 subclass deficiency. *Clin Exp Immunol* 1991; 85:193–197.
15. Jakobsson T, Croner S, Kjellman NI, Pettersson A, Vassella C, Bjorksten B. Slight steroid-sparing effect of intravenous immunoglobulin in children and adolescents with moderately severe bronchial asthma. *Allergy* 1994; 49:413–420.
16. Newburger J, Takahashi M, Beiser A, Burns JC, Bastian J, Chung KJ, Colan SD, Duffy CE, Fulton DR, Glode MP. A single intravenous infusion of gammaglobulin as compared with four infusions in the treatment of acute Kawasaki Syndrome. *N Engl J Med* 1991; 324:1633–1639.
17. Leung D. The immunoregulatory effects of IVIG in Kawasaki disease and other auto-immune diseases. *Clin Rev Allergy* 1992; 10(1–2):93–104.
18. Leung D, Cotran R, Kurt-Jones E, Burns J, Newburger J, Pober J. Endothelial cell activation and high interleukin-1 secretion in the pathogenesis of acute Kawasaki Disease. *Lancet* 1989; ii:1298–1302.
19. Mori P, Mancuso G, Del Principe D, Duse M, Miniero R, Tovo R, Berdare M, Carnelli V, de Mattia D. Chronic idiopathic thrombocytopenia treated with immunoglobulin. *Arch Dis Child* 1983; 58:851–855.
20. Dalakas MC, Illa I, Dambrosia JM, Soueidan SA, Stein DP, Otero C, Dinsmore ST, McCroskey S. A controlled trial of high-dose intravenous immune globulin infusions as the treatment for dermatomyositis. *N Engl J Med* 1993; 329:1993–2000.
21. Wakim M, Alazard M, Yajima A, Speights D, Saxon A, Stiehm ER. High dose intravenous immunoglobulin in atopic dermatitis and hyper-IgE syndrome. *Ann Allergy Asthma Immunol* 1998; 81:153–158.
22. Ashman R, Peckham D, Stuntz L. Fc receptor off-signal in the B-cell involves apoptosis. *J Immunol* 1996; 157:5–11.
23. Spahn JD, Leung D, Chan MT, Szeffler SJ, Gelfand EW. Mechanisms of glucocorticoid reduction in asthmatic subjects treated with intravenous immunoglobulin. *J Allergy Clin Immunol* 1999; 103:421–426.

Address reprint requests to:
 Lynda C. Schneider, M.D.
 Children's Hospital
 Division of Immunology
 300 Longwood Avenue
 Boston, MA 02115

E-mail: schneider@tch.harvard.edu