

Mechanisms of glucocorticoid reduction in asthmatic subjects treated with intravenous immunoglobulin

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Background: Intravenous immunoglobulin (IVIG) has been used as an oral glucocorticoid (GC)-sparing agent in patients with steroid-dependent asthma. Despite its use, little is known regarding its mechanism of action.

Objective: We sought to determine whether the GC-sparing effects of IVIG in severe asthma are related to improved GC receptor (GCR)-binding affinity and subsequent enhanced GC sensitivity.

Methods: In an open-label study, 11 steroid-dependent asthmatic subjects (6 GC-insensitive, 5 GC-sensitive) received monthly infusions of IVIG (2 g/kg) for 6 months. Peak expiratory flow rates and oral GC dose were recorded daily, and spirometry was performed monthly. Blood was drawn for lymphocyte stimulation assays and GCR assays at baseline and after 3 and 6 months of therapy. Lymphocytes were stimulated ex vivo with PHA in the presence and absence of IVIG and increasing concentrations of dexamethasone (DEX).

Results: IVIG resulted in significant reductions in oral GC dose ($P < .02$), number of GC bursts ($P = .033$), and hospitalizations ($P = .001$) after 6 months of IVIG. Those with GC-insensitive asthma responded equally well to IVIG as those with GC-sensitive asthma. Associated with the improved clinical efficacy, IVIG acted synergistically with DEX in suppressing lymphocyte activation as measured by a shift in the DEX dose-response curve by 1 log-fold ($P = .03$). IVIG therapy was also associated with significantly improved GCR-binding affinity ($P = .01$).

Conclusions: IVIG resulted in significant reductions in oral GC requirements and hospitalizations in a group of patients with severe asthma, with IVIG being as effective in patients with GC-insensitive asthma as in patients with GC-sensitive asthma. IVIG therapy acted synergistically with DEX in suppressing lymphocyte activation and significantly improved GCR-binding affinity after 3 and 6 months of therapy.

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Key words: Glucocorticoids, inflammation, intravenous immunoglobulin, glucocorticoid-insensitive asthma, steroid-resistant asthma

Patients with severe asthma often require chronically administered oral glucocorticoid (GC) therapy to only marginally control their disease. Unfortunately, long-term oral GC therapy is associated with multiple debilitating effects, such as growth delay, osteoporosis, and adrenal suppression.¹ As a result, GC-sparing agents are often attempted in these patients. Intravenous immunoglobulin (IVIG) has been used over the past several years as a GC-sparing agent in asthma.²⁻⁴ The mechanisms involved in its GC-sparing effects are largely unknown but may involve immunomodulation. In this regard IVIG has been shown to reduce immediate skin test reactivity to allergen, inhibit lymphocyte activation in vivo, and suppress cytokine-dependent lymphocyte proliferation in vitro.^{2,5,6} Amran et al⁵ have demonstrated IVIG to inhibit both IL-2 and IL-4 production by T lymphocytes.

At the extreme end of asthma severity are individuals who fail to derive optimal benefit from GC therapy. These patients often have histories of having severe steroid-dependent asthma and have become less responsive to GC therapy over time.^{7,8} These subjects have historically been classified as having "GC-resistant" asthma, but a recent symposium on the subject has suggested using the term "GC-insensitive" asthma because these patients rarely have an absolute resistance to GCs.⁹ Although much is known regarding the immunologic abnormalities associated with GC-insensitive asthma, the diagnosis of this condition is based on clinical criteria. These individuals will have significant airflow obstruction and fail to respond to a short course of high-dose oral GC therapy (at least 40 mg daily for 7 to 14 days) as reflected by a less than 15% improvement in their morning prebronchodilator FEV₁ values.^{9,10}

A spectrum of GC receptor (GCR) abnormalities have recently been described in asthma, with GC-insensitive asthmatic subjects displaying the most significant abnormalities.¹¹⁻¹⁴ GC-insensitive asthmatic subjects have been noted to display both ligand- and DNA-binding abnormalities.^{11,13,14} Diminished GCR-binding affinity can be induced in vitro by the coincubation of lymphocytes with the combination of IL-2 and IL-4.¹² In addition, BAL cells obtained from patients with GC-insensitive asthma express significantly higher levels of IL-2 and IL-4 mRNA than patients with GC-sensitive asthma.¹⁵ Of greater importance, GC therapy failed to signif-

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Abbreviations used

DEX:	Dexamethasone
GC:	Glucocorticoid
GCR:	Glucocorticoid receptor
IC ₅₀ :	Inhibitory concentration that results in a 50% reduction in proliferation
IVIG:	Intravenous immunoglobulin

icantly suppress cytokine expression from the GC-insensitive asthmatic subjects, whereas it significantly suppressed cytokine expression in GC-sensitive asthmatic subjects.

Because IVIG may act in suppressing T-lymphocyte activation by inhibiting IL-2 and IL-4 production, we hypothesized that IVIG therapy would render asthmatic subjects more sensitive to GCs as a consequence of diminution of the inflammatory response and improvement in GCR-binding affinity. In this study we thus sought to examine the mechanisms responsible for IVIG's GC-sparing effects in a group of subjects with severe, steroid-dependent asthma. In addition, we evaluated the effectiveness of IVIG therapy in subjects with documented GC-insensitive asthma.

METHODS**Study design**

This was an open-label, 6-month study. To be eligible for participation, subjects had to have steroid-dependent asthma requiring at least 20 mg of prednisone or its equivalent on alternate days and to have no other respiratory conditions. Informed consent was obtained from all subjects, and the study was approved by the National Jewish Medical and Research Center's Institutional Review Board. All subjects had optimal management of other medical conditions that can negatively influence asthma control, such as gastroesophageal reflux and sinus disease. In fact, 9 of the 11 subjects were invited to participate in the study after extensive inpatient evaluation of their asthma in the Day Hospital Program at National Jewish because of persistence of symptoms, an unacceptably high oral GC requirement despite optimal management, or both. All subjects received 6 monthly infusions of IVIG (Gamimmune N; Bayer Laboratories, Elkhart, Ind) at a dose of 1 g/kg administered over 3 to 6 hours on 2 consecutive days for a total of 2 g/kg/mo. All subjects completed diary cards on which they described the severity of asthma symptoms and recorded their asthma medications and oral GC dose. The daily prednisone requirement per month of the study was calculated by adding the total amount of prednisone administered during the entire month and dividing that amount by the number of days in the month. All doses of prednisone were added when calculating the daily dose for the month. This included the subject's maintenance dose plus any supplemental prednisone used during exacerbations of asthma. The subjects also performed peak expiratory flow measurements twice daily. Before receiving their monthly IVIG infusion, an interval history was obtained, a physical examination was performed, diary cards were reviewed, and spirometry was performed before and after inhalation of 2 puffs of albuterol. Heparinized blood was obtained at baseline, after 3 months, and after 6 months of IVIG therapy for lymphocyte stimulation assays and determination of GCR-binding affinity.

In vitro assays

Lymphocyte proliferation assay. Blood samples were obtained between 7 AM and 9 AM, before the administration of the subject's oral GC dose and immediately before IVIG infusion. PBMCs were isolated by density centrifugation with Ficoll-Paque (Pharmacia LKB Biotechnology, Inc, Piscataway, NJ). The cells were then resuspended at a concentration of 1×10^6 cells/mL in RPMI 1640 (Bioproducts, Walkersville, Md) supplemented with 10% heat-inactivated FCS (HyClone Labs, Logan, Utah), L-glutamine (4 mmol), penicillin (100 U/mL), streptomycin (100 µg/mL), and HEPES (20 mmol/L solution) in the presence and absence of PHA (5 µg/mL; Sigma Chemical Co, St Louis, Mo), increasing concentrations of dexamethasone (DEX) from 10^{-6} to 10^{-10} mol/L, and IVIG (1, 5, or 10 mg/mL). The cells were then incubated for 72 hours at 37°C in 5% CO₂ before pulse labeling with tritiated (³H) thymidine for 6 hours and harvesting onto glass-fiber filter disks to assess [³H]-thymidine incorporation. Cell viability was 95% or greater as measured by trypan blue exclusion. Diluent controls were used, with no effect on proliferation noted.

GCR-binding assay. [³H]-DEX radioligand binding assays and Scatchard analysis were performed to determine PBMC GCR-binding affinity as previously described.^{11,12,16} After isolation, the cells were incubated with increasing concentrations of [³H]-DEX from 0.8 nmol/L to 400 nmol/L for 60 minutes at 37°C. For measurement of nonsaturable binding, a solution of 20 nmol/L [³H]-DEX and 2 µmol/L unlabeled DEX was added to the respective tubes. After incubation, 20 µL of supernatant was counted in a β-spectrometer to measure free DEX concentrations. The cell pellet, which measures whole cell DEX concentration, was rinsed, dried, and counted in a β-spectrometer. All values obtained were corrected for nonsaturable binding for each respective concentration.

Saturation binding analysis was performed, assuming a linear binding plot of the bound divided by the free [³H]-DEX concentration versus the amount bound and extrapolating to the amount bound at an infinite free hormone concentration. A linear regression fit was used to define both GCR sites per cell and binding affinity. When repeated on several different patients who maintained similar disease activity, the GCR-binding affinity was found to be highly reproducible, with interclass correlation coefficients of 0.95 for the GCR number and 0.999 for the GCR K_d, with 1.00 indicating an excellent agreement between assays.

Data analysis

For studies comparing the effectiveness of IVIG on GC dose reduction and change in GCR-binding affinity over time, ANOVA with repeated measures was used. ANOVA with repeated measures was also used in determining the differences in dose-response curves for DEX in the absence and presence of increasing concentrations of IVIG. For studies comparing the number of supplemental GC bursts, hospitalizations, and the inhibitory concentration that results in a 50% reduction in proliferation (IC₅₀) for DEX in the presence and absence of IVIG before and during IVIG therapy, paired Student t tests were used. All data are expressed as means ± SEM.

RESULTS**Patient characteristics at baseline**

Twelve subjects were recruited into the study. All of the subjects completed the study, but only 11 were included in the analysis. The excluded subject was diag-

TABLE I. Patient characteristics at baseline (n = 11)

Parameter	Value*
Age at entry	15.5 ± 0.7 years
Race	
White	6
African American	4
Hispanic	1
Asthma duration	10.7 ± 1.4 years
Subjects with GC-insensitive asthma	6
Duration of chronic oral GC therapy	2.1 ± 0.5 years
Medications at entry	
Oral GC (prednisone or equivalent)	26.1 ± 4.9 mg/day
Inhaled GC	2125 ± 219 µg/day
Atopic (≥3 positive skin prick test responses)	11/11
Laboratory data	
Serum IgE (nl 10-180)	470 ± 120 IU/mL
Circulating eosinophil count (nl 0-400)	238 ± 67
Lung function	
FVC (% predicted)	86 ± 4
FEV ₁ (% predicted)	67 ± 4
FEV ₁ /FVC	0.69 ± 0.03

*Values are listed as means ± SEM where applicable.

FVC, Forced vital capacity; nl, normal range.

nosed with a neutrophil defect after her second infusion. Her history was significant for having recurrent skin infections and pneumonias complicating her asthma. The mean age of the study subjects was 15.5 years, with an almost equal sex distribution (5 males and 6 females; Table I). Four subjects were African American, 1 was Hispanic, and the remainder were white. The subjects had long-standing asthma and had required chronic oral GC therapy for at least 2 years. All subjects were receiving high-dose inhaled GC therapy, with a mean daily dose of 2125 ± 219 µg, and their average oral GC dose (prednisone or its equivalent) was 26 ± 5 mg/d. All subjects were atopic as defined by at least 3 positive skin prick test responses to major regional aeroallergens and had elevated mean serum IgE levels. The subjects also had evidence of moderately severe airflow obstruction as evidenced by a baseline FEV₁ of 67% of predicted value and an FEV₁/forced vital capacity ratio of 69%. Six of the 11 study subjects (55%) had documented GC-insensitive asthma as defined by less than 15% improvement in their morning prebronchodilator FEV₁ value after a 10-day course of 40 mg/d or greater prednisone or its equivalent.

Clinical efficacy parameters

IVIG therapy was associated with a statistically significant reduction in the mean daily prednisone requirement after 2 months of therapy. As can be seen in Fig 1, the mean daily dose of oral GC for the 6 months preceding entry into the study was 5 mg higher than that of the baseline dose (26 vs 21 mg/d). This difference was the result of optimization of asthma therapy during the subjects' inpatient evaluation at National Jewish before enrollment into the study. Within 2 months of therapy, the mean oral GC requirement had declined from 21 mg

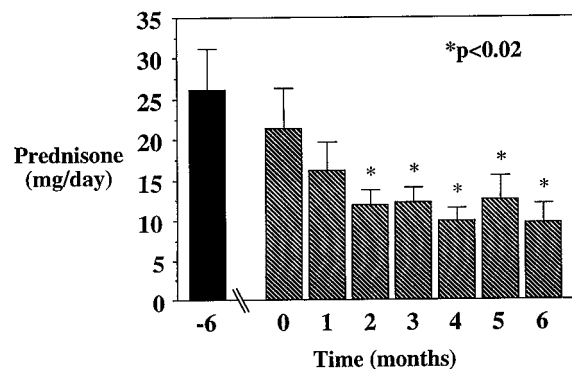


FIG 1. Effect of IVIG on oral GC requirement. IVIG therapy was associated with a statistically significant reduction in mean daily prednisone requirement after 2 months of therapy. The difference in mean dose for the preceding 6 months (5 mg higher than baseline dose) was the result of optimization of asthma therapy before enrollment into the study. Values represent the mean daily dose for each month and include supplemental GC if required.

to 12 mg daily. This reduction was sustained for the remainder of the study, with the dose after 6 months of therapy being 9.6 mg per day. Of note, the oral GC values represent the mean daily dose for each month and include any supplemental GC, if required, during each month of the study. After 6 months of IVIG therapy, all 11 patients demonstrated a reduction in their prednisone requirement, with a mean reduction in dose of 47.5% ± 6.2%. The dose reduction ranged from 25% to 96.5%. Eight of 11 (73%) subjects had a 40% or greater reduction in oral steroid requirement. No patient was completely tapered off oral GCs during the study. Those subjects with GC-insensitive asthma had a greater prednisone requirement at baseline (30.8 ± 7.4 mg/d vs 11.5 ± 1.5 mg/d; *P* = .09) and after 6 months of IVIG therapy (14.6 ± 3.4 mg/d vs 5.4 ± 0.8 mg/d; *P* = .12) compared with those with GC-sensitive asthma. However, the magnitude of oral GC dose reduction in each group was similar and statistically significant within both groups.

Associated with the reduction in daily oral GC requirement were significant reductions in the need for supplemental GC therapy and numbers of hospitalizations for acute severe asthma exacerbations. As can be seen in Fig 2, during the 6 months preceding entry into the study, the subjects averaged 2.6 GC bursts for acute asthma exacerbations. During the 6 months of IVIG therapy, the number of supplemental GC bursts declined significantly to only 1.0 during the study. Similar results were noted for hospitalizations. Before the study, subjects averaged 3 hospitalizations for severe asthma exacerbations. This value declined significantly to 0.5 hospitalizations during the 6 months of the study. Similar reductions in need for supplemental GC bursts and hospitalizations were seen in the GC-insensitive and GC-sensitive groups. Lung function, as measured by both daily peak expiratory flow and monthly spirometry, remained stable despite significant reductions in oral GC dose.

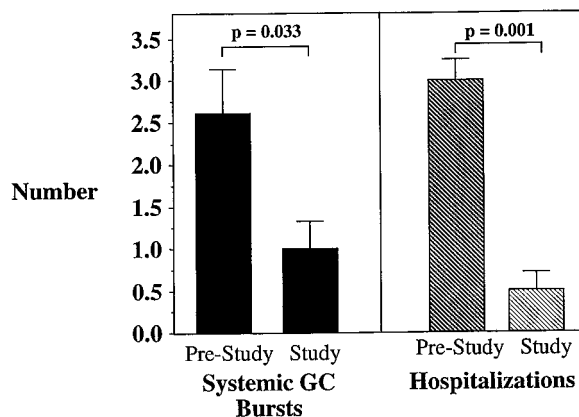


FIG 2. Effect of IVIG on need for supplemental GC and hospitalizations. IVIG was associated with reductions in need for supplemental GC bursts and number of hospitalizations for poor asthma control. During the 6 months before entry into the study, the subjects averaged 2.6 GC bursts, which decreased to only 1.0 burst during the study. Similar results were noted for hospitalizations. Before the study, the subjects averaged 3 hospitalizations, which decreased to 0.5 hospitalizations during the study.

In vitro effects

IVIG alone resulted in a dose-dependent inhibition of PHA-induced lymphocyte stimulation (Fig 3). Maximal suppression was noted at the highest concentration studied (ie, 10 mg/mL with 40% suppression noted). Of greater interest, the combination of IVIG and DEX acted synergistically in suppressing lymphocyte activation (ie, the combination of the 2 agents resulted in much greater suppression than that achieved by either alone). This synergism between IVIG and DEX was assessed by measuring the IC_{50} for DEX in the presence and absence of IVIG (10 mg/mL). The IC_{50} is the inhibitory concentration of DEX that results in a 50% reduction in lymphocyte proliferation. As can be seen in Fig 4, the log-transformed mean IC_{50} for DEX alone was 1.0 nmol/L, whereas the IC_{50} for DEX in the presence of IVIG was 14 times less at 0.07 nmol/L. In other words, IVIG shifted the dose-response curve for DEX to the left (ie, to the more sensitive range) by greater than 1 log-fold. These values remained essentially unchanged from baseline to those obtained after 6 months of therapy despite a significant reduction in the subjects' oral GC requirement. Also, there was no difference in IC_{50} values between the GC-insensitive and GC-sensitive groups.

Associated with a shift in the DEX dose-response curve to the more sensitive range were improvements in GCR-binding affinity during IVIG administration (Fig 5). The baseline PBMC GCR dissociation constant (Kd) of the study subjects was elevated at 37.5 nmol/L, a value similar to that previously reported for GC-insensitive asthmatic subjects.¹¹ Of note, the Kd is inversely proportional to the binding affinity, and thus the higher the Kd, the poorer the binding affinity. After 3 months of IVIG therapy, the mean Kd had significantly fallen to 23 nmol/L and remained essentially unchanged at 21 nmol/L after 6 months ($P = .011$). The

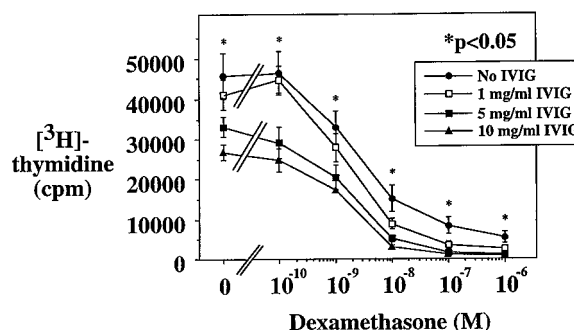


FIG 3. Effect of IVIG and DEX on inhibition of lymphocyte stimulation. On the Y axis is $[^3H]$ -thymidine incorporation as a measure of cell proliferation, and the X axis reflects increasing concentrations of DEX from 10^{-10} to 10^{-6} mol/L. IVIG alone results in a dose-dependent suppression of proliferation. The combination of IVIG and DEX resulted in much greater suppression of proliferation than either agent alone.

Kd values at baseline and after 3 and 6 months of IVIG therapy were similar in the GC-insensitive and GC-sensitive groups.

DISCUSSION

Airway inflammation plays a significant role in the pathogenesis of asthma.¹⁷ As a result, GCs have become an important modality of treatment. Various mechanisms of GC actions include inhibition of inflammatory cell influx, as well as inhibition of cytokine and mediator production by T cells and macrophages, which are important in the initiation and persistence of the inflammatory response.^{18,19} Although the majority of asthmatic subjects respond favorably to GCs, a subpopulation of patients with severe asthma show a poor response.²⁰⁻²² These asthmatic subjects have been termed steroid-resistant or more recently GC-insensitive.⁹

Because long-term oral GC use is associated with many debilitating adverse effects, several alternative GC-sparing agents have been used in this group of subjects with severe asthma.¹ Many of these alternative treatments, such as cyclosporine, also have potentially harmful adverse effects, which make them unacceptable for use in all but patients with the most severe asthma. IVIG therapy has been reported to have GC-sparing effects in severe asthma.² Because there are relatively few adverse effects associated with IVIG therapy, it has the potential to be safely administered in all groups of asthmatic subjects, including children. The mechanisms involved in IVIG's steroid-sparing effects are unknown but may involve immunomodulation.^{2,5}

This study provides novel insight into the potential mechanisms involved in IVIG's steroid-sparing effects. IVIG had immunomodulatory effects, with a dose-dependent suppression of PHA-induced lymphocyte proliferation similar in magnitude to values previously reported.⁵ Of interest, we also demonstrated that IVIG acts synergistically with GCs to suppress mitogen-induced lymphocyte activation. The addition of IVIG to

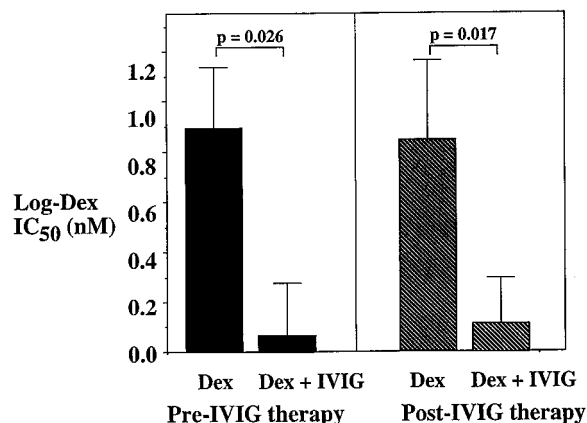


FIG 4. IVIG increases sensitivity of lymphocytes to DEX. The synergism between IVIG and DEX was measured by analyzing the IC₅₀ for DEX in the presence and absence of IVIG (10 mg/mL). The log-transformed mean IC₅₀ for DEX alone was 1.0 nmol/L whereas the IC₅₀ for DEX in the presence of IVIG was 14 times less at 0.07 nmol/L. These values remained essentially unchanged from baseline to those obtained after 6 months of therapy despite a significant reduction in the subject's oral GC requirement.

PHA-stimulated lymphocytes significantly shifted the DEX dose-response curve to the left, rendering the cells much more sensitive to the suppressive effects of DEX.

This observation has important clinical ramifications. First, by using combinations of agents with different anti-inflammatory actions, the inflammatory cycle may be more effectively interrupted. Second, with interruption of the inflammatory cycle there is downregulation of proinflammatory cytokines, such as IL-2, IL-4, and IL-13, which have been demonstrated to induce diminished GC sensitivity.^{12,23} Third, with improved GC sensitivity, less GC may be required to inhibit residual inflammation. Consistent with our current results, Vrugt et al²⁴ recently reported on the clinical efficacy of IVIG in 2 patients with GC-insensitive asthma and found IVIG therapy to result in reductions in airway inflammatory cell influx despite significant reductions in the need for oral GC therapy. Specifically, they performed bronchoscopy with endobronchial biopsies and analyzed peripheral blood for T-lymphocyte activation before and after IVIG in one of the subjects and found significant reductions in all inflammatory cells, including CD3+, CD4+, and CD25+ T cells within the airway and peripheral blood.

Of interest, IVIG was as effective in the subgroup of patients with GC-insensitive asthma as those with GC-sensitive asthma. That IVIG was effective in both GC-insensitive and GC-sensitive asthmatic subjects supports the concept that these 2 forms of asthma are part of the spectrum of asthma severity rather than 2 distinct types of asthma. To our knowledge, this is the only study that has evaluated the effectiveness of an alternative asthma therapy in subjects with documented GC-insensitive asthma and the only study that suggests that alternative asthma therapies can be effective in those with GC-insensitive asthma. In addition, it suggests that IVIG therapy

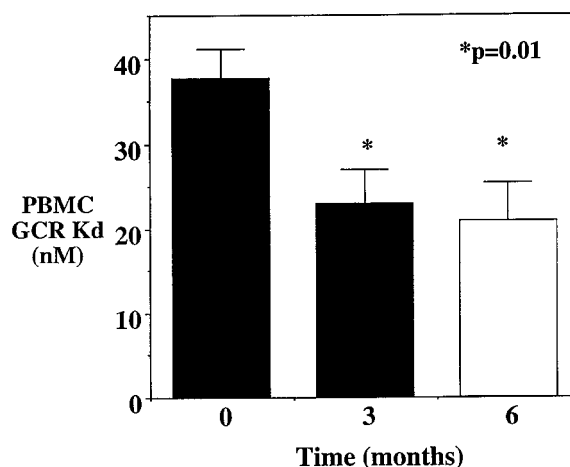


FIG 5. IVIG increases GCR-binding affinity. The baseline PBMC GCR Kd was elevated at 37.5 nmol/L, which fell significantly to 23 nmol/L after 3 months and to 21 nmol/L after 6 months of therapy. Note that the Kd is inversely proportional to the binding affinity, and thus the higher the Kd, the poorer the binding affinity.

can improve GCR-binding affinity in individuals in whom oral GC therapy may be unable to do so.

In addition to demonstrating that the combination of IVIG and DEX act to synergistically suppress lymphocyte activation, we have demonstrated IVIG's ability to significantly improve GCR-binding affinity. The mean Kd of the study group fell significantly from 38 nmol/L at baseline, a value similar to that reported for GC-insensitive and poorly controlled asthmatic subjects, to 23 nmol/L after 3 months and to 21 nmol/L after 6 months of therapy, respectively. Of significance, the Kd values obtained after IVIG therapy are similar to those previously reported in individuals with GC-sensitive asthma¹¹ and similar to values obtained in a group of poorly controlled asthmatic subjects after a 7- to 10-day course of high-dose oral GC therapy.²⁵ This improvement in GCR-binding affinity was seen despite a significant reduction in the subjects' oral GC requirement.

Associated with the improvements in lymphocyte sensitivity to DEX and GCR-binding affinity were significant improvements in all efficacy parameters studied. IVIG therapy resulted in a significant reduction in the oral GC requirement in this group of patients who continued to require high-dose oral GC therapy after all other confounding illnesses, educational deficits, and compliance issues were addressed as a result of inpatient stays at National Jewish before entry into the study. Despite significant reductions in their oral GC requirements, the subjects also required fewer oral GC bursts and fewer hospitalizations during the 6 months of IVIG therapy secondary to asthma exacerbations compared with the 6 months before entry into the study. It is possible that some of the reduction in need for supplemental steroid bursts and hospitalizations could be attributed to the optimization of asthma control that the study patients underwent during their inpatient evaluation at National Jewish before entry into the study. Arguing against this

possibility is the fact that these subjects were enrolled into this study because they continued to be symptomatic and required unacceptably high oral steroid doses despite the aggressive management they received while inpatients.

A potential limitation to this study was its small size and lack of a placebo arm. This study was designed primarily to evaluate efficacy in GC-insensitive asthma and the mechanisms responsible for GC dose reduction. Even after extensive evaluation and treatment under supervised conditions, the study subjects continued to require high-dose oral GC therapy for control of their asthma. Although the majority of studies evaluating IVIG in asthma have not been placebo controlled, a controlled study by Salmun et al²⁶ reported that IVIG was significantly better than placebo in GC dose reduction in a subset of patients with the highest oral GC requirements.

The data presented here are compatible with the concept that IVIG, by virtue of its immunosuppressive or anti-inflammatory effects, results in improved GCR-binding affinity, and this improvement in GCR-binding affinity is responsible for its steroid-sparing effects. This hypothesis is supported by the significant increase in steroid sensitivity noted when IVIG was cocultured with DEX in lymphocytes stimulated with PHA and the significant reductions in oral GC requirement associated with improved asthma control in our study population. These findings warrant further evaluation of this novel and important mechanism of action for improving GC responsiveness.

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