

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial of High-Dose Intravenous Immunoglobulin for Oral Corticosteroid-Dependent Asthma¹

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To determine the efficacy of high doses of intravenous gammaglobulin (IVIG) for the treatment of severe, steroid-dependent asthma in patients between 6 and 68 years of age, a randomized, double-blind, placebo-controlled multicenter clinical trial was conducted in private and university hospitals in the United States. Patients were randomized to one of three treatment arms: 2 g IVIG/kg/month (16 patients); 1 g IVIG/kg/month (9 patients); or 2 g iv albumin (placebo)/kg/month (15 patients). The treatment consisted of seven monthly infusions followed by a posttreatment observation period. The primary outcome measurement was mean daily prednisone-equivalent dose requirements, determined during the observation month preceding initiation of treatment and compared to the month preceding the seventh infusion. Secondary clinical endpoints measured were pulmonary function, frequency of emergency room visits or hospitalizations, and number of days absent from school or work. When adjusted for body weight, the mean dose requirements fell by 33, 39, and 33% in the placebo, IVIG (1 g/kg), and IVIG (2 g/kg) treatment arms, respectively. The differences between therapies were not statistically different ($P = 0.9728$). The mean percentage-of-predicted FEV1 fell in all three treatment groups during the treatment period but there was no significant difference between treatment groups ($P = 0.8291$). There was also no significant difference in the percentage of subjects requiring emergency room visits or hospitalizations or missing days of work/school, among the three treatment groups. The trial was terminated prematurely after interim analysis determined the adverse experience rate was different between the three groups. Three patients, all randomized to the 2-g/kg IVIG dose group, were hospitalized with symptoms consistent with aseptic meningitis. In summary, in this randomized, double-blind,

placebo-controlled multicenter study, high doses of IVIG did not demonstrate a clinically or statistically significant advantage over placebo (albumin) infusions for the treatment of corticosteroid-dependent asthma. Subgroup analysis failed to identify markers predicting responsiveness. High-dose IVIG can also be associated with a significant incidence of serious adverse events. © 1999 Academic Press

Key Words: intravenous immunoglobulin; asthma; placebo-controlled trial.

Asthma is a disease characterized by reversible airways obstruction, which affects about 10 million people in the United States (1). The airways demonstrate bronchial hyperreactivity to specific antigens and non-specific stimuli such as cold air, histamine, and methacholine. Although the immunopathogenesis of asthma is incompletely understood, chronic airway inflammation is characterized by bronchial edema, excess mucus production, eosinophil, and mononuclear cell infiltration.

The recognition that asthma is an inflammatory disease of the airways has led to the recommendation that patients with persistent asthma are most effectively treated with daily antiinflammatory medications (2). Inhaled corticosteroids are the mainstay of therapy but the most severely affected patients frequently require systemic glucocorticoids for long-term prevention of symptoms and control of inflammation. Patients with severe corticosteroid-dependent asthma are at risk for associated complications of therapy, including growth failure, hypothalamic-pituitary-adrenal axis suppression, mood alterations, weight gain, hypertension, diabetes, osteoporosis, aseptic necrosis of long bones, cataracts, muscle weakness, and impaired cellular immunity. The cumulative morbidity of these complications is high and has led to investigation of alternative therapies with steroid-sparing potential (3–5).

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Intravenous gammaglobulin (IVIG) has immunomodulatory and antiinflammatory activities. In addition to replacement therapy for humoral immunodeficiency disorders, IVIG is the standard of care for immunologically mediated disorders, including Kawasaki syndrome and refractory idiopathic thrombocytopenic purpura (6–8). Additionally, IVIG has also been shown to be as effective as plasmapheresis in the treatment of acute Guillain–Barre syndrome (9). These applications of IVIG have all been demonstrated to be safe and effective in randomized, placebo-controlled trials.

Numerous other immunologically mediated disorders have been treated with IVIG on an empirical basis often supported by case reports or open-labeled pilot studies linked to a disease with a suggested immunopathogenesis (10–14). Furthermore, the immunomodulatory and antiinflammatory activities of IVIG are currently undergoing characterization but the primary mechanism of action is incompletely understood for most immune-mediated disorders.

IVIG is produced from plasma and contains millions of antibody specificities, reflecting the humoral immune repertoire of the thousands of normal blood donors. The interaction of IVIG with functional molecules of the immune system, such as intracellular proteins, cellular surface markers, membrane receptors, and antibodies, may underlay its immunomodulatory activities. Suggested immunomodulatory activities of IVIG include suppression of autoantibody formation, suppression of T cell activation/proliferation, modulation of NK cell activity, Fc receptor blockage or down-regulated expression, antiidiotypic interactions, generation or stimulation of T suppressor cells, alteration of monocyte/phagocyte function, inhibition of superantigen-induced T cell activation, and modulation of cytokine production/activity (10, 13, 15–25).

In 1991, Mazer and Gelfand reported a 6-month open-labeled trial of IVIG in eight pediatric patients with severe steroid-dependent asthma and noted a threefold decrease in corticosteroid requirements, symptom scores, and skin test reactivity (26). The quantity of both maintenance and rescue corticosteroids was decreased significantly, despite stable asthma, as documented by symptom scores and twice daily peak-flow measurements (27–30). The substantial improvement seen in these open-labeled studies was compelling enough to warrant the design of a controlled clinical trial to extend and confirm the findings. This trial was designed to be a randomized, double-blinded, placebo-controlled trial to determine the efficacy of high doses of IVIG for the treatment of severe, steroid-dependent asthma in patients between 6 and 68 years of age.

METHODS

Study Overview

During a 2-month observation/run-in period, each patient's medications were optimized by the study physicians, and baseline corticosteroid requirements were determined. After the observation period, patients were randomized to one of three treatment arms: 2 g IVIG/kg/month, 1 g IVIG/kg/month, or 2 g IV albumin (placebo)/kg/month. Overall, the treatment would consist of seven monthly infusions followed by a posttreatment observation period. Because it was postulated that IVIG was a potential corticosteroid-sparing therapeutic modality, the primary outcome measurement was systemic corticosteroid usage. Secondary clinical endpoints measured were pulmonary function, frequency of emergency room visits or hospitalizations, and number of days absent from school or work. Patients were seen at the study center on a monthly basis for interval histories, physical examinations, and scheduled testing. The investigators were blinded to the treatment and results of the serum immunoglobulin levels until completion of the trial. They continued to be followed by their primary physician throughout the study period, and corticosteroid dosages were adjusted based on their interpretation of the patient's clinical status. During the treatment period, steroid reductions of 10–20% every 28 days were attempted providing spirometry values and clinical status remained stable.

Subject Selection

All patients were between 6 and 66 years of age and had been previously diagnosed with asthma, defined by the American Thoracic Society criteria. All patients had been unable to decrease their steroid dosage to less than 0.1 mg/kg/day prednisone (or the equivalent) during the prior 3 months of optimizing therapy or failed to maintain peak flows of greater than 80% of predicted values on their current dose of prednisone. Patients were excluded if they had been diagnosed with additional, complicating lower respiratory disorders, concurrent renal, cardiac, or neoplastic disease, extensive sinusitis determined by sinus coronal CT or undergone sinus surgery, recent smoking, escalating immunotherapy, or steroid-sparing drugs (methotrexate, cyclosporine, or oral gold) within 2 months prior to enrollment. Subjects weighing more than 120 kg or who were pregnant or nursing were also excluded.

EVALUATIONS

Radiographic. Chest X rays and sinus coronal CT scans were obtained at baseline and at the end of the treatment period.

TABLE 1
Patient Demographics^a

	IVIG (2 gm/kg)	IVIG (1 gm/kg)	Placebo
<i>n</i>	16	9	15
Mean age (years)	38.8 ± 16.4	45.9 ± 16.0	37.0 ± 19.6
Mean weight (kg)	68.0 ± 20.5	77.9 ± 11.3	68.8 ± 21.1
Sex (M:F)	3:6	8:8	7:8
Ethnicity ^b	12W, 2B, 2O	7W, 1B, 1O	11W, 4B
Mean baseline IgE (IU/ml)	234 ± 439	32.3 ± 25.8	162.0 ± 351.5
Atopic by skin-prick testing	10	7	12
Mean FEV1 %	87.3	70.2	86.0
Mean initial prednisone dose (mg/day)	16.2 ± 19.6	15.8 ± 5.9	17.9 ± 9.5
Mean initial prednisone dose, adjusted for weight (mg/kg/day)	0.23	0.19	0.27

^a Plus-minus values are means ± SD.

^b Caucasian (W), African-American (B), other (O).

Pulmonary functions. Full pulmonary function tests were completed at enrollment, including lung volumes by body plethysmography, diffusion capacity, and flow rates before and after bronchodilator. Spirometry with forced expiratory volume during the first second of exhalation (FEV1), forced vital capacity, and forced expiratory flow during the middle portion of FVC was performed every other month during the treatment phase and during month 1, 3, and 6 of the posttreatment observation period. Peak expiratory flows were measured by mini-Wright hand-held peak-flow meter during the observation period and every other month throughout the treatment phase.

Skin prick testing. Immediate hypersensitivity skin testing was performed by skin prick method, using a standard panel of regional environmental aeroallergens with appropriate histamine positive- and glycerosaline diluent-negative controls.

Laboratory examinations. Serum for quantification of immunoglobulins and IgG subclasses was obtained at enrollment, the end of treatment, and follow-up periods. Complete blood counts with differential and chemistry panels were followed serially. Hepatitis C viral serologies, HBcAb, and circulating HBsAg measurements were obtained at enrollment and study completion.

Immunoglobulin infusions. Intravenous immunoglobulin (Venoglobulin-I, lyophilized IVIG reconstituted to 10% with 4% D-mannitol, Alpha Therapeutic Corp., Los Angeles, CA) or albumin (Albutein, Alpha Therapeutic Corp.) was given as a 10% solution. The rate of infusion was initially 0.01 ml/kg/min and, if tolerated, the rate increased by 0.02 to 0.03 ml/kg/min, every 30 min to a maximum of 0.08 ml/kg/min. Maximum tolerated infusion rates were determined on an individual basis, as patients were monitored for infu-

sion-related back pain, chills, headache, myalgias, malaise, arthralgias, fever, nausea, flushing, tightness of chest, dyspnea, and hypotension.

Statistical analysis. Certain assumptions were used for calculation of prednisone daily equivalents. One milligram of methylprednisolone was assumed to be equivalent to 1.25 mg of prednisone. The average daily equivalent was calculated for the second observation month and the month following the sixth infusion, based on a 31-day month, assuming physician prescriptions/tapering regimes were followed exactly and compliance was good.

The study was designed to have an 80% likelihood ($\beta = 0.20$) of detecting a 40% decrease in mean daily prednisone dose, with a false-positive Type I or α error of 0.05. Power calculations determined that a study of 63 evaluable patients, divided equally between the three treatment arms, would detect a clinically significant difference in corticosteroid requirements. Analysis of variance and analysis of covariance methods were used to evaluate the effects of the three treatment arms on primary outcome parameters. Secondary outcomes and safety data were tested for normality, log transformed if appropriate and analyzed by either paired *t* test or the χ^2 test.

RESULTS

Fifty-four patients were enrolled and received at least one dose of IVIG but only 30 completed the entire study, including the follow-up period. Forty patients were deemed evaluable, having completed six or seven infusions prior to study termination. There were 18 males and 22 females, mean age 40 years, with a range of 7–66 years, and a range of daily steroids from 2.5–80 mg prednisone equivalents per day (Table 1).

TABLE 2
Change in Average Daily Steroid Dose Adjusted for Body Weight^a

Study group	Initial dose (mg/kg)	Final dose (mg/kg)	Change ^b ± S.D.	Percentage reduction
Placebo (1 g/kg albumin)	0.27	0.18	-0.09 ± 0.21	33
1 g/kg IVIG	0.19	0.12	-0.08 ± 0.09	39
2 g/kg IVIG	0.23	0.16	-0.08 ± 0.20	33

^a Oral prednisone equivalents in mg/kg.

^b ANOVA of change; *P* value = 0.973.

Corticosteroid Requirements

The mean daily oral corticosteroid requirements decreased in all three treatment groups, when comparing observation month 2 and infusion 7. The mean changes in milligrams of prednisone equivalents and the percentage reduction, adjusted for body weight, were not statistically different (*P* = 0.97) (Table 2, Fig. 1). When adjusted for body weight, the mean dose requirements fell by 33, 39, and 33% in the placebo, IVIG (1 g/kg), and IVIG (2 g/kg) treatment arms, respectively (Table 2, Fig. 1). Furthermore, utilizing the starting dose (observation month 2) as a covariate, there was still no difference in the overall dose reductions (*P* = 0.87).

The mean absolute changes in prednisone equivalents, unadjusted for body weight, also failed to demonstrate differences between treatment groups (Table 3). The mean prednisone dose requirements (milligrams per day) fell by 5.4 ± 13.2 , 6.3 ± 6.6 , and 6.7 ± 16.9 mg, respectively (*P* = 0.97).

Pulmonary Functions

The mean percentage predicted (% predicted) FEV1 fell in all three treatment groups during the treatment period. The subjects treated with IVIG experienced a mean decrease of 0.7 and 4.4% predicted, respectively, in the 2 and 1 g/kg treatment groups. The placebo group experienced a 2.1% decrease in % predicted FEV1. Overall, there was no significant difference in the changes seen in pulmonary functions between treatment groups (*P* = 0.83).

Clinical Outcomes

While there was a broad range of missed work/school days for individual subjects, the median number of school/work days missed per subject was less than 2 days in all three groups. The percentage of subjects who missed at least 1 day of work or school, during the treatment period, was 53% in the placebo-treated group and 56% in both IVIG-treated groups. There was also no significant difference in the percentage of sub-

jects requiring emergency room visits or hospitalizations among the three treatment groups (Table 4), nor was the incidence of acute infection different.

Immunological Parameters

Total serum IgG levels were statistically different among the three treatment groups (Table 5). The serum IgE levels were not significantly different at enrollment, nor did the mean IgE levels for the treatment groups change before and after therapy.

Adverse Experiences

While there were no significant differences in corticosteroid requirements, pulmonary function, and clinical outcomes, the adverse experience rate was different between the three groups. Table 6 lists the adverse experience rate stratified by severity. Three patients,

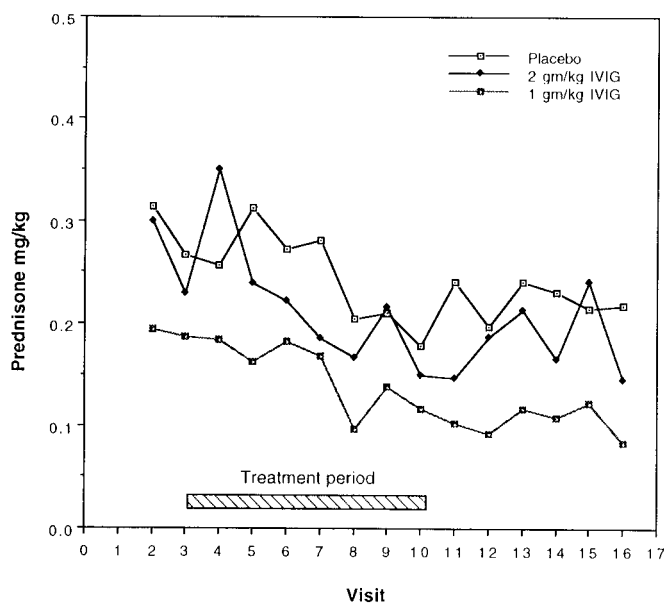


FIG. 1. Mean daily prednisone equivalents for each treatment group adjusted for body weight.

TABLE 3
Absolute Change in Average Oral Daily Steroid Dose Unadjusted for Body Weight^a

Study group	Initial dose (mg/day)	Final dose (mg/day)	Change ^b ± S.D.	Percentage reduction
Placebo (1 g/kg albumin)	17.9	12.4	−5.4 ± 13.2	30
1 g/kg IVIG	15.2	8.9	−6.3 ± 6.6	41
2 g/kg IVIG	16.2	9.5	−6.7 ± 16.9	41

^a Oral prednisone equivalents in mg/kg.
^b ANOVA of change; *P* value = 0.970.

all randomized to the 2 g/kg IVIG dose group, were hospitalized with symptoms of headache, nausea, vomiting, photophobia, and meningismus. Cerebral spinal fluid analysis, negative cultures and clinical presentation were consistent with aseptic meningitis syndrome. Other patients suffered from severe headaches, lasting over 24 h and sometimes requiring treatment with narcotic analgesics. The overall rate of headaches was 16% in the placebo group but 33 and 27% in the 1 and 2 g/kg IVIG-treated groups, respectively; these differences were statistically significant (*P* = 0.02) (Table 5).

DISCUSSION

Intravenous immunoglobulin was originally introduced to supplement or replace the antibodies lacking in humoral immune deficiency states but has been shown to exert a number of additional activities on the immune system. In patients afflicted by a selected group of inflammatory or autoimmune disorders, it can lead to amelioration of disease and clinical improvement. The biological effects of IVIG in these cases are poorly understood. Despite the number of conditions for which it has been tried, the list of proven clinical indications remains short. Because the complications of long-term systemic corticosteroid use are many, several open-labeled studies have evaluated the use of IVIG in children with corticosteroid-dependent asthma, demonstrating clinical and physiologic improvement. Mazer and Gelfand have reported de-

creases of 64% in mean daily prednisone requirements after 6 months of treatment with high-dose IVIG therapy (26). To assess the potential role of high-dose IVIG in adults and children with severe, corticosteroid-dependent asthma, we conducted a double-blinded, placebo-controlled multicenter trial evaluating the effects of IVIG on corticosteroid-requirements, pulmonary function and clinical endpoints including lost days of work or school, emergency room visits, and hospitalizations.

Corticosteroid requirements were decreased over the treatment period in all three groups but the difference in responses between the three treatments was not statistically significant. The large variance seen in the oral corticosteroid reductions may reflect differences in disease severity/labability, natural variability in these patients' systemic corticosteroid requirements, and/or the lack of standardized approaches to steroid dose reduction in this trial design. Because these subjects had known severe asthma, heightened underlying bronchial reactivity may have led to exaggerated clinical responses to allergens, nonspecific stimuli, inhaled irritants, and respiratory viruses. A significant number of these subjects demonstrated large fluctuations in oral corticosteroid doses, which were determined through clinical assessment by the patients' primary physicians. Consideration was given in the study to reduce the variability of corticosteroid dosing by having all doses prescribed by the small number of principal investigators at each site, utilizing symptom score and peak-flow parameters to determine medication changes based on a prespecified dosage schedule.

TABLE 4
Emergency Room Visits and Hospitalizations during the Treatment Period (*n* = 40)

Treatment group	<i>n</i>	Percentage of subjects with emergency room visits ^a	Percentage of subjects hospitalized ^b
Placebo	15	27	13
1 g/kg IVIG	9	33	22
2 g/kg IVIG	16	19	19

^a *P* value = 0.73.
^b *P* value = 0.82.

TABLE 5
Total Serum Immunoglobulin Levels^a

Treatment group	<i>n</i>	IgG at enrollment	IgG at infusion 7
Placebo	15	815 (257)	754 (228)
1 g/kg IVIG	9	747 (75)	1046 (102) ^b
2 g/kg IVIG	16	829 (229)	1400 (237) ^b

^a Milligram/deciliter; standard deviations are in parentheses.
^b The two means for the treatment group are significantly different from each other.

TABLE 6Adverse Experience Rate (%) by Severity for Each Treatment Group ($n = 49$)

Treatment group	<i>n</i>	Mild	Moderate	Severe	Serious ^a
Placebo	16	4.7	17.0	5.7	0.0
1 g/kg IVIG	12	15.3	23.6	5.6	0.0
2 g/kg IVIG	21	13.2	17.4	6.6	2.5

^a Three subjects required hospitalization with symptoms of aseptic meningitis syndrome.

Nevertheless, while the observed standard deviations of the oral corticosteroid dose reductions were higher than anticipated, the magnitude of the observed treatment effects was not significant compared to the magnitude of the placebo effect.

The mean daily oral corticosteroid doses were not significantly different between the three treatment arms; there were individual subjects, in all three groups, who experienced dramatic reductions in their daily corticosteroid requirements. Because our cohort of patients was significantly older than those studied by Mazer and Gelfand (26), exploratory statistical analyses were performed to identify subgroups of patients that might respond to IVIG. Age, sex, baseline serum IgE, atopic status determined by allergy skin-prick testing, and paranasal sinus disease were evaluated as possible covariates or markers associated with responsiveness to IVIG. Analysis of mean daily prednisone doses, stratified by these parameters, failed to identify trends or predictors of responsiveness. Further analysis, using starting oral corticosteroid dose as a covariate, also failed to demonstrate significant differences in the changes seen in each treatment arm.

The mean total serum IgG levels increased significantly, in a dose-related response, to the IVIG infusions. There were no differences seen in the incidence of acute infection between the treatment groups. Pulmonary function, assessed by percentage-of-predicted FEV1, fell slightly in all three treatment groups. There were no significant differences between groups in the observed changes in FEV1 signifying differences in severity of clinical asthma at the time prednisone requirements were determined.

The strength of this trial is its double-blinded, placebo-controlled design. In trials of asthma surveillance and therapy, considerable placebo effects are not unprecedented. Enrollment and participation in clinical trials does not guarantee compliance; however, subjects appear to be more highly motivated during periods of more frequent medical attention and close monitoring. Had this trial not contained a placebo-control group, the decrease in corticosteroid requirements during the treatment period may have been interpreted differently. In 1979, Benson and McCallie described

the potent responses to the giving and receiving of treatment (i.e., the "placebo effect") after reviewing published trials of xanthines, vitamin E, and surgical ligation of the internal mammary artery for the treatment of angina (31). Studies relying on historical comparisons frequently suffer from limitations and biases, on the part of both patient and physician.

This study highlights the inherent difficulty studying patients with severe, corticosteroid-dependent asthma. Asthma can be associated with comorbidities, such as sinusitis, gastroesophageal reflux disease, laryngeal dysfunction, and psychological/psychiatric overlay. The enrollment criteria were established to eliminate those with excessive sinus disease before randomization, but some subjects with minor sinus abnormalities were allowed to participate after receiving appropriate therapy. Patients were not screened for gastroesophageal reflux disease by 24-h esophageal pH monitoring or laryngeal dysfunction by fiberoptic nasopharyngoscopy. Last, a few of the participants in this trial were observed to have significant psychological issues associated with their health and medical status. Accurate assessment of these patients' true oral corticosteroid requirements proved difficult for the managing physicians.

Although this study was prematurely terminated due to the significant incidence of adverse effects in the high-dose IVIG group, it is highly unlikely that full enrollment would have changed the clinical outcomes. This study was designed to detect a statistically significant and clinically relevant steroid-sparing effect of IVIG. Because IVIG therapy might be considered both drastic and cost-prohibitive in all but the most severely affected patients, clinical efficacy would need to be dramatic to justify such therapy. Furthermore, power calculations and sensitivity analysis demonstrated that a study powered to detect smaller effect sizes would have been untenably large and infeasible.

This trial was terminated early due to the unexpected high incidence of adverse experiences. Although aseptic meningitis syndrome was a previously reported complication of IVIG, the rate in this trial, 3 cases in 40 subjects, exceeds previous experiences (32, 33). One patient with aseptic meningitis syndrome was hospitalized for 6 days after suffering from severe headache, rash, nuchal rigidity, photophobia, and culture-negative, cerebral spinal fluid pleocytosis. Less serious but clinically severe headaches occurred in 24.7% of all infusions, possibly related to a number of factors, including large volumes and fluid shifts, protein loads, and infusion rates. Unlike many headaches seen with other IVIG infusions, some of these were delayed, not infusion rate-related or preventable with usual premedications. The etiology of the aseptic meningitis syndrome is unknown; however, IVIG products contain significant quantities of sugars and solutes that may

potentially lead to osmotic diuresis, fluid shifts, and electrolyte imbalances within the central nervous system or meninges. IVIG preparations contain sugars such as sucrose, maltose, glucose, or D-sorbitol to stabilize the monomeric immunoglobulin molecules. The study preparation contained mannitol, which is not found in other IVIG products and has subsequently been replaced by other stabilizers.

These adverse events highlight some of the risks associated with infusions of IVIG. Other complications attributed to IVIG but not seen in this trial include transmission of infectious disease, generalized or hypersensitivity reactions, and renal and hematologic complications (34–38).

In summary, in this controlled study, high doses of IVIG did not demonstrate a clinically or statistically significant advantage over placebo (albumin) infusions for the treatment of corticosteroid-dependent asthma. Subgroup analysis failed to identify markers predicting responsiveness, but the sensitivity of these analyses can be limited in small studies. For clinical applications with preliminary evidence suggesting efficacy, we support well-designed, randomized, placebo-controlled trials to demonstrate proof of concept. Beyond health and economic considerations, the potential complications of therapy must be outweighed by demonstration of clinical efficacy.

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