

Efficacy of soluble IL-4 receptor for the treatment of adults with asthma

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Background: IL-4 mediates important proinflammatory functions in asthma, including induction of the IgE isotype switch, increased expression of vascular cell adhesion molecule 1 and promotion of eosinophil transmigration across the endothelium, stimulation of mucus production, and T_H2 lymphocyte differentiation, leading to release of IL-4, IL-5, IL-9, and IL-13.

Objective: The current study evaluated the therapeutic potential of inhaled recombinant human soluble interleukin-4 receptor (IL-4R) as an IL-4 antagonist.

Methods: This study was a randomized, double-blind, placebo-controlled study in 62 subjects involving 12 once weekly nebulizations of 0.75, 1.5, or 3.0 mg of IL-4R or placebo. During screening, subjects documented dependence on inhaled corticosteroids by an exacerbation in asthma induced by one or two 50% dose reductions at 2-week intervals. After restabilization for 2 weeks on the dose above which their asthma flared, inhaled steroids were discontinued, patients were randomized, and study medication was started on day 0.

Results: IL-4R was well tolerated. Efficacy was demonstrated by a decline in FEV₁ observed in the placebo group (−0.4 L and −13% predicted), which did not occur in the group receiving 3.0 mg of IL-4R (−0.1 L and −2% predicted; $P = .05$ over the 3-month treatment period). Daily patient-measured morning FEV₁ also demonstrated a significant decline in the placebo group (−0.5 L and −18% predicted), which did not occur in the group receiving 3.0 mg of IL-4R (−0.1 L and −4% predicted; $P = .02$ over the 3-month treatment period). The efficacy of IL-4R was further confirmed by the absence of increase in asthma symptom scores in the group receiving 3.0 mg of IL-4R ($\Delta 0.1$) compared with that seen in the placebo group ($\Delta 1.4$ over 1 month; $P = .07$). Study discontinuation for asthma exacerbation was not significantly different between groups (placebo, 56%; 3.0 mg of IL-4R, 47%; $P =$ not significant).

Conclusion: These promising data suggest that IL-4R is safe and effective in the treatment of moderate persistent asthma. (J Allergy Clin Immunol 2001;107:963-70.)

Key words: IL-4, IL-4 receptor, soluble receptor, clinical trials, asthma, therapy, cytokines, T_H2

IL-4 is critical to the development of allergic inflammation. It is associated with the isotype switch to IgE production.¹⁻⁴ IgE-mediated immune responses are further enhanced by IL-4 by means of the upregulation of both the high-affinity IgE receptor (FcεRI) on mast cells and basophils⁵ and of low-affinity IgE receptors (FcεRII and CD23) on B lymphocytes⁶ and monocytes.⁷ One of the most important activities of IL-4 in promoting allergic inflammation is its ability to induce expression of vascular cell adhesion molecule 1 (VCAM-1), which directs the migration of T lymphocytes, monocytes, basophils, and especially eosinophils to the site of allergic inflammation. IL-4 also prolongs eosinophil survival by inhibiting apoptosis.⁸⁻¹¹ An additional mechanism by which IL-4 contributes to asthma is induction of mucin gene expression, leading to increased mucus production.¹² A unique biologic activity of IL-4 is its ability to drive the differentiation of naive T_H0 lymphocytes into the T_H2-like phenotype.¹³⁻²⁰ In the presence of IL-4, T_H0 lymphocytes differentiate into T_H2-like cells capable of secreting IL-4, IL-5, IL-9, and IL-13, but not IFN-γ. An agent that blocks T_H2-like differentiation could therefore inhibit production of further IL-4 and other type 2 cytokines.

Neutralizing the biologic activities of excess IL-4 specifically targets the underlying cause of asthma by blocking multiple pathways of inflammation at the key central point of T_H2 differentiation, thereby preventing the allergic response. Studies with IL-4 knockout mice have demonstrated that IL-4 is critical for the development of allergen-specific IgE, airway eosinophilia, and hyperresponsiveness.²¹⁻²³ Recombinant murine soluble IL-4 receptor, which inhibits IL-4, has blocked allergen-specific IgE production, airway hyperresponsiveness, allergen-specific skin test responses, VCAM-1 expression, eosinophil infiltration, and mucus hypersecretion in murine asthma models.²⁴⁻²⁶ Soluble receptors have already been used successfully; soluble TNF receptor (Enbrel) is highly effective for the long-term treatment of rheumatoid arthritis.

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Abbreviations used

FVC: Forced vital capacity
IL-4R: Recombinant human soluble IL-4 receptor
PEF: Peak expiratory flow
VCAM-1: Vascular cell adhesion molecule 1

The current study uses recombinant human soluble IL-4 receptor (IL-4R), a selective cytokine inhibitor, to neutralize endogenously produced IL-4. IL-4R consists of the soluble extracellular portion of the human IL-4 receptor α chain, which has been cloned and produced in a mammalian expression system. In human trials IL-4R has been safe and well-tolerated, with an estimated serum half-life of an inhaled dose of approximately 5 days (unpublished data).²⁷ This prolonged half-life supports the feasibility of once weekly inhaled therapy with IL-4R.

In a previous double-blind, placebo-controlled phase I safety and dose-finding trial,²⁷ 25 patients with moderate asthma receiving inhaled corticosteroids were randomly assigned to receive a single nebulized dose of IL-4R at 0.5 mg or 1.5 mg or placebo after abruptly stopping inhaled corticosteroids. In contrast to the placebo group, treatment with IL-4R significantly maintained FEV₁ and forced expiratory flow, midexpiratory phase and stabilized asthma symptom scores and β_2 -agonist rescue use among patients treated with 1.5 mg of IL-4R despite withdrawal of corticosteroids. The objective of the current study of 12 once weekly doses of IL-4R in patients with moderate and persistent asthma was to demonstrate the safety and efficacy of long-term administration of IL-4R as a single anti-inflammatory agent for the treatment of asthma without the use of corticosteroids.

METHODS**Subjects**

Subjects were identified from the population of 4 university- or community-based asthma clinics between May 1998 and September 1998. Approximately 150 subjects were screened, and 62 subjects were enrolled. Two subjects were previously enrolled in a study of IL-4R. Enrolled subjects were nonsmoking adults who met National Institutes of Health guidelines for moderate persistent asthma that was present for more than 1 year.²⁸ Patients were required to have used inhaled corticosteroids for more than 6 months and were taking stable moderate doses for at least 1 month. Inclusion criteria included an FEV₁ of greater than 65% of predicted normal values, reversibility of at least 12% within 30 minutes of inhalation of albuterol, positive skin prick test responses to at least 2 allergens, and reactivity to methacholine with a provocative concentration of 20% of 8 mg/mL or less. During screening, subjects underwent one or two 50% reductions in inhaled corticosteroid dose at 2-week intervals, during which they were required to have a 10% or greater decrease in FEV₁ and one of the following: (1) nocturnal awakening; (2) increased symptoms; (3) increased β_2 -agonist use; or (4) a 15% or greater decrease in peak expiratory flow (PEF). Washout of other asthma therapy was required for at least 4 weeks. Subjects were allowed to continue using an albuterol inhaler as needed at up to 12 puffs daily. Exclusion criteria included allergen immunother-

apy within 3 months, oral or parenteral steroids continuously for more than 1 year, emergency department treatment within 6 weeks, hospitalization within 1 year, or intubation for asthma. The protocol was approved by the local institutional review boards, and all subjects gave written informed consent.

At the time of initiation of study drug, the subjects had poorly controlled asthma, as summarized in Table I. They had abnormal spirometry results at baseline, with a reduced FEV₁ (76% $\pm$ 12% predicted) and forced vital capacity (FVC; 88% $\pm$ 17% predicted), active symptoms (2.8 $\pm$ 2.2), and use of inhaled β_2 -agonists (4.1 $\pm$ 3.0 puffs/d) despite the ongoing use of inhaled corticosteroids (10.0 $\pm$ 6.6 puffs/d beclomethasone [42 μ g/puff] equivalents). The median baseline reactivity to methacholine with a provocative concentration of 20% was 0.54 mg/mL in methacholine challenge testing. There was no significant difference in baseline characteristics between groups; however, there was a trend toward less severe asthma in the placebo group (Table I).

Study design

This was a randomized, double-blind, dose-finding study of IL-4R (Immunex Corporation, Seattle, Wash) at 0.75, 1.5, or 3.0 mg or placebo given by means of inhalation once weekly for 12 weeks. During screening, patients documented dependence on inhaled corticosteroids by an exacerbation in asthma induced by one or two 50% dose reductions at 2-week intervals. Patients then reinstituted inhaled corticosteroids for 2 weeks at the dose above which their asthma symptoms flared. Inhaled corticosteroids were discontinued, patients were randomized, and study medication was started on day 0. This study was performed on inhaled corticosteroid-dependent asthmatic subjects to evaluate the efficacy of IL-4R in this group. Withdrawal of the steroids was also performed to improve the sensitivity to detect a clinical response.

The study drug was administered in the clinic at a final volume of 2.5 mL in sterile normal saline solution with a breath-assisted Pari LC Star nebulizer powered by a Proneb Turbo portable compressor (Pari Respiratory Equipment, Inc, Richmond, Va). The placebo consisted of identically prepared excipient in the same volume. To maintain blinding, medication was dispensed by an individual who was not responsible for patient care or assessment. Treatment assignment was blinded to all personnel involved in direct conduct or monitoring of the study. In a separate study this nebulizer was demonstrated to generate a particle with a mass median aerodynamic diameter of 3.5 μ m.²⁹ The efficiency of pulmonary delivery was 26.5% $\pm$ 2.9% of the dose placed in the nebulizer.

Efficacy was primarily assessed by FEV₁ change from baseline, as measured by spirometry. Safety was assessed by incidence of adverse events, vital signs, physical examinations, hematologies, chemistry panels, urinalyses, and electrocardiograms. Anti-IL-4R antibodies were measured with ELISA before the study, at study completion, and 4 weeks after study completion (Immunex Corporation). Tetanus toxoid immunization was performed at day 28, and antitetanus antibodies were measured before vaccination and 4 weeks after vaccination with ELISA (Scripps Reference Laboratory, San Diego, Calif) to evaluate immunocompetence.

Spirometry was performed in triplicate at each time point by using a Koko spirometer with the largest FEV₁ recorded.³⁰ In-clinic spirometry data were collected before nebulization and therefore represented the response when drug levels were at trough. Before spirometry, inhaled β_2 -agonists were withheld for 8 hours, and loratidine, chlorpheniramine, and salmeterol were withheld for 48 hours (salmeterol was not allowed once randomized). Patient-measured PEF values and FEV₁ were collected at home twice daily, on awakening before β_2 -agonist use, and at bedtime. Subjects were provided with a portable spirometer (Air Watch; Enact Health Management Systems, Mountain View, Calif), which recorded 3 determinations

TABLE I. Demographics and baseline characteristics

Characteristic	Placebo (n = 16)	IL-4R, 0.75 mg (n = 15)	IL-4R, 1.5 mg (n = 16)	IL-4R, 3.0 mg (n = 15)
Age (y), median (range)	41 (22-60)	46 (28-59)	40 (24-72)	36 (20-64)
Sex (% female)	63	73	75	67
Asthma duration ≥ 15 y (%)	69	73	31	87
FEV ₁ (% predicted), mean $\pm$ SD	76 $\pm$ 11	76 $\pm$ 12	76 $\pm$ 13	75 $\pm$ 14
FVC (% predicted), mean $\pm$ SD	88 $\pm$ 12	87 $\pm$ 19	91 $\pm$ 22	85 $\pm$ 14
Morning FEV ₁ (L),* median (IQR)	2.5 (2.4)	2.3 (1.2)	2.2 (1.0)	2.4 (0.8)
Evening FEV ₁ (L),* median (IQR)	2.7 (2.4)	2.3 (1.3)	2.1 (1.3)	2.7 (1.0)
Morning PEF (L/min),* median (IQR)	433 (176)	388 (136)	358 (73)	369 (201)
Symptom score,* median (IQR)	1.9 (3)	2.6 (2)	2.9 (3)	2.3 (3)
β_2 -Agonist use (puffs/d),* median (IQR)	1.7 (5)	5.4 (7)	4.0 (5)	5.1 (4)
Beclomethasone equivalents (42- μ g puffs/day), mean $\pm$ SD	8.7 $\pm$ 4.5	11.0 $\pm$ 8.2	11.2 $\pm$ 7.3	9.0 $\pm$ 6.2
Methacholine challenge PC ₂₀ (mg/mL), geometric mean	0.5	0.511	0.66	0.424

No significant differences between groups.

IQR, Interquartile range.

*Results are obtained before the first dose on day 0. If marked with an asterisk, results reflect the average daily value for the week before dosing.

electronically. The highest of these values was manually recorded in the patient diary. Patients were provided with albuterol metered-dose inhalers, and puffs used were recorded by the patients twice daily. Symptoms were assessed daily on a scale with a total range of 0 (best) to 15 (worst; ie, 0-3 each for wheezing, shortness of breath, cough, chest tightness, and nocturnal awakening). A standardized asthma quality-of-life questionnaire was administered at baseline, day 49, and end of study.^{31,32} Radioallergosorbent testing (FEIA, Pharmacia CAP System; Pharmacia and Upjohn Diagnostics AB, Uppsala, Sweden), total serum IgE measurement, and titrated allergen skin prick testing were also performed.

Subjects were discontinued from the study if they experienced an asthma exacerbation that was defined as (1) a decrease in FEV₁ of 20% or more from randomization, (2) a decrease in morning PEF of 20% or more, (3) an increase in daily symptom score of more than 6 points, (4) an increase in β_2 -agonist use to more than 12 puffs daily, (5) requirement for inhaled or oral corticosteroid treatment, or (6) an emergency department visit or hospitalization.

Statistical methods

A blocked randomization with equal allocation of treatments was used within each of the 4 centers. All randomized subjects received at least one dose of study medication and were included in the intent-to-treat analyses of efficacy and safety. Some subjects were expected to drop out from the study because of asthma exacerbations after withdrawal of inhaled corticosteroids. For subjects who discontinued study drug, summarization and statistical analyses at subsequent time points were made with data derived by using the last-observation-carried-forward technique.³³ This procedure replaces a missing value with the most recent previous value (ie, before discontinuation). For spirometry, the average change from baseline was analyzed; average change from baseline was determined as the area under the curve of the change from baseline by time divided by 84 (the nominal study duration in days). Clinic spirometry values were censored if albuterol had been used within 8 hours. This constituted 7.7% of observations and was not significantly different between groups (5% in the placebo group and 10%, 7%, and 8% in the 0.75-, 1.5-, and 3.0-mg treatment groups, respectively). Morning FEV₁ measurement was to be performed before albuterol use each morning and was not censored if albuterol had been used in the previous 8 hours because data on specific timing of daily albuterol use were not collected. For data collected in symptom diaries (FEV₁ and PEF, use of β_2 -agonists, and asthma symptoms), the 1-month and 3-month

average changes from baseline were analyzed; average change from baseline was determined as the average of the daily changes from baseline, and baseline was determined as the average of the 7 daily values before the first day of the study drug.

Statistical analysis was performed with the SAS computer software system, version 6.12 (SAS Institute). Differences between the treatment groups were evaluated with the Wilcoxon 2-sample test for continuous and ordinal variables, and the likelihood ratio χ^2 test was used for categorical variables. Time to study discontinuation was analyzed by using the log-rank test stratified by center. All *P* values are 2-tailed, and significance is defined as a *P* value of less than .05.

Pharmacokinetic analysis

IL-4R concentration versus time data were plotted to examine their suitability for pharmacokinetic modeling by using a multiple-dose, multiexponential equation in a nonlinear least-squares regression computer program.³⁴ The most appropriate multiexponential equation for each individual study subject was determined by means of visual inspection of the observed and model-calculated concentration-time data, correlations between the observed and model-calculated concentration-time data, evaluation of residuals plotted against concentration and time, and the Akaike's information criteria.³⁵ Half-life was calculated from the terminal elimination rate constant (β). The maximum drug concentration and the time that the maximum drug concentration occurred after the first dose were determined from the pharmacokinetic model.

RESULTS

In this study design, with subjects whose asthma was poorly controlled at the initiation, it is expected that some patients would have increased asthma symptoms and be required to discontinue from the study because of the stringent safety guidelines. Patients were required to withdraw after a single exacerbation, which may have been expected to occur once during 12 weeks in this population with moderately severe disease, even in the absence of corticosteroid withdrawal. Most study discontinuations occurred in the first month. At day 28, 50% of patients receiving placebo, 47% of patients receiving 0.75 mg of IL-4R, and 50% of patients receiving 1.5 mg of IL-4R had withdrawn, but only 33% of patients receiv-

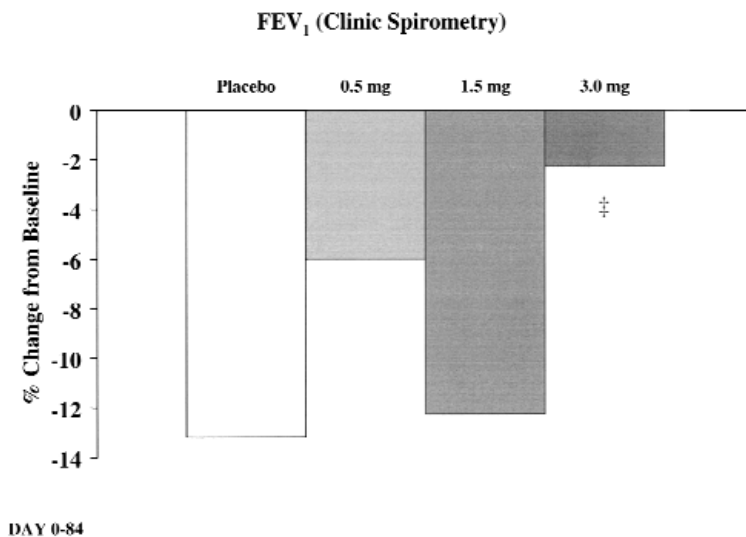


FIG 1. Mean percentage change from baseline in FEV₁. Treatment with 3.0 mg of IL-4R after discontinuation of inhaled corticosteroids prevented decline in clinic-measured FEV₁ (–2% with 3.0 mg of IL-4R vs –13% with placebo, [†]*P* = .05) over the 3-month treatment period.

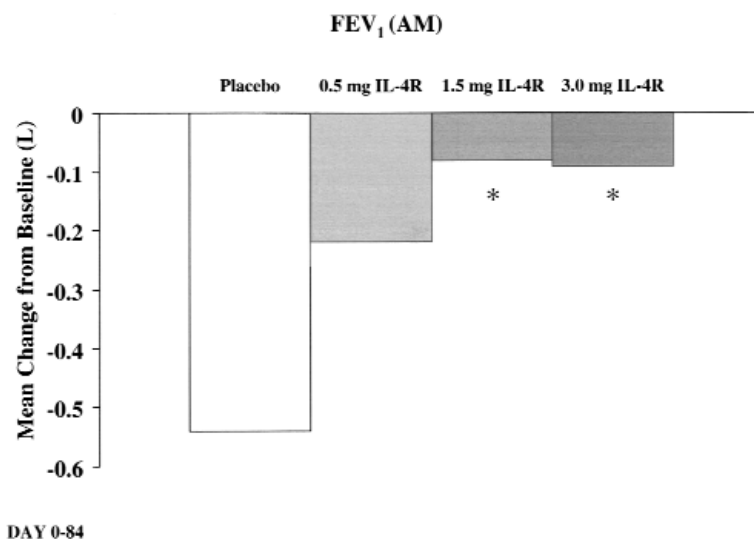


FIG 2. Mean change from baseline morning FEV₁ (in liters). Morning FEV₁ was measured daily at home by using an Air Watch meter in the morning before β_2 -agonist therapy. Treatment with 3.0 mg of IL-4R after discontinuation of inhaled corticosteroids prevented decline in FEV₁ (–0.1 L with 3.0 mg of IL-4R vs –0.5 L with placebo) over the 3-month treatment period. **P* < .05 versus placebo.

ing 3.0 mg of IL-4R had discontinued (*P* = .44, placebo vs 3.0 mg). At day 84, 56%, 67%, 69%, and 47% of the groups, respectively, had discontinued. In general, patients in the 3.0-mg group dropped out for less severe exacerbations than patients in the placebo or low-dose groups (only 3 of 6 had a 20% or greater decrease in FEV₁ compared with 9 of 9 in the placebo group).

Efficacy after corticosteroid withdrawal

Efficacy of IL-4R was determined by the ability of weekly nebulizations to preserve pulmonary function in the absence of inhaled corticosteroids. As shown in Fig 1, at the highest dose, IL-4R maintained FEV₁ after corti-

costeroid discontinuation, with a decline of only –2% averaged over the 3-month treatment period compared with the –13% decline over the 3-month treatment period observed in the placebo group (*P* = .05, placebo vs 3.0 mg). Similarly, a statistically significant difference in FVC over the 3-month treatment period was observed, with preservation of FVC in the 3.0-mg cohort (+1%) compared with that found in the placebo group (–8%; *P* = .05, placebo vs 3.0 mg). Because of the severity of their symptoms, many of the subjects were unable to withhold β_2 -agonists for 8 hours before being evaluated in the clinic. Because spirometry data from these subjects would reflect transient improvement as a result of the use of β_2 -

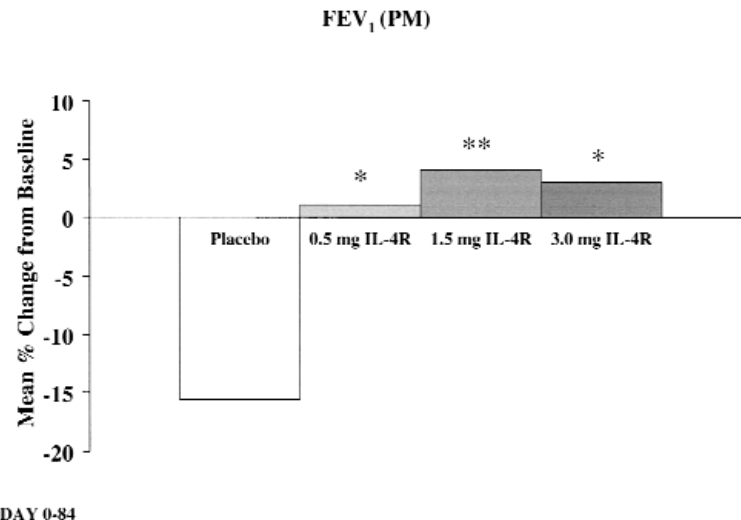


FIG 3. Mean percentage change from baseline in evening FEV₁. Evening FEV₁ was measured daily at home by using an Air Watch meter at bedtime. Treatment with 3.0 mg of IL-4R after discontinuation of inhaled corticosteroids prevented decline in evening FEV₁ (+3% with 3.0 mg of IL-4R vs -16% with placebo) over the 3-month treatment period. **P* < .05 versus placebo, ***P* < .01 versus placebo.

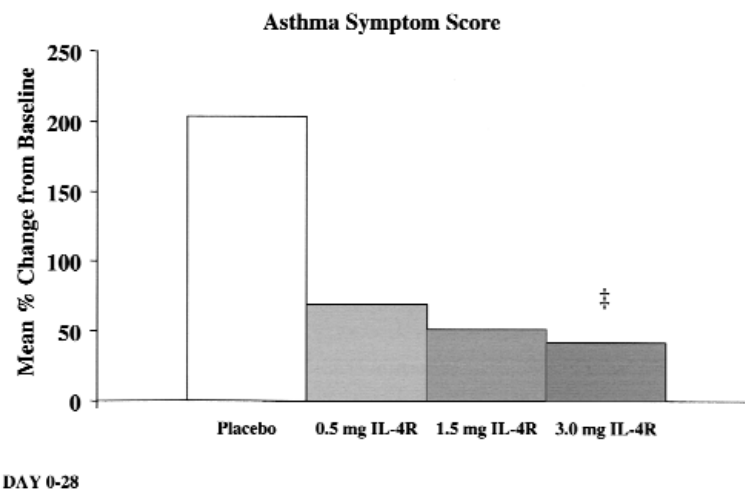


FIG 4. Mean percentage change from baseline in asthma symptom score. Patients treated with 3.0 mg of IL-4R at the time of discontinuation of inhaled corticosteroids had mean asthma score increases of 0.1 (42% change from baseline) versus an increase of 1.4 (204% change from baseline) in patients with placebo over the first month of observation (0-15 possible). †*P* = .07 versus placebo for percentage change.

agonists, these data were censored because they would not reflect the true decline in FEV₁ that developed after inhaled corticosteroid withdrawal. To compensate for this limitation of spirometry data, subjects were provided with an Air Watch device for home monitoring of peak flow and FEV₁ to accurately measure the decline in lung function associated with the inhaled corticosteroid cessation. As shown in Fig 2, there was a minimal decline in morning FEV₁ observed with 3.0 mg of IL-4R (-0.1 L [-4% predicted] mean change from baseline) compared with the marked decline observed in subjects randomized to the placebo group (-0.5 L [-18% predicted] mean change from baseline; *P* = .02, placebo vs 3.0 mg) over the 3-month treatment period. The differences in evening

FEV₁ were even more marked, with the 3.0-mg IL-4R group increasing by a mean of +3% (+0.1 L), and the placebo group decreasing by -16% (-0.5 L; Fig 3; *P* = .01, placebo vs 3.0 mg) over the 3-month treatment period, suggesting the possibility that IL-4R therapy may have improved lung function response to β_2 -agonist. The other dose groups (0.75 and 1.5 mg) did not have responses for FEV₁ (Fig 1) or FVC, as determined by mean of clinic spirometry, that were significantly different than those with placebo. Results for home-measured morning and evening FEV₁ that were significantly different are labeled in Figs 2 and 3.

Over the first month of the study, asthma symptom scores tended to increase in the placebo group (Δ 1.4)

TABLE II. Adverse events by decreasing frequency*

	Placebo (n = 16)	IL-4R (n = 46)
Headache, n (%)	1 (6)	6 (13)
Nausea, n (%)†	0 (0)	6 (13)
Upper respiratory tract infection, n (%)‡	1 (6)	5 (11)
Pain, n (%)	1 (6)	5 (11)
Sinusitis, n (%)	2 (13)	4 (9)
Flu syndrome, n (%)	2 (13)	2 (4)
Pharyngitis, n (%)	3 (19)	2 (4)
Asthenia, n (%)	2 (13)	1 (2)

*Events occurring in at least 6% of patients in either group; no significant differences were observed between groups.

†All grade 1, transient.

‡Mild "colds."

versus continued symptom control in the 3.0-mg IL-4R group (Δ 0.1; Fig 5; $P = .07$, placebo vs. 3.0 mg). Importantly, the decline of lung function in the placebo cohort occurred in the presence of a trend toward increased asthma symptom scores (Δ 1.8 ± 0.8) despite their increased use of rescue β_2 -agonists (Δ 1.1 ± 0.6 puffs/d) over the 3-month treatment period. In contrast, subjects who received the highest dose of IL-4R did not have noticeably worsening asthma symptom scores (Δ 0.8 ± 0.8) while increasing their rescue β_2 -agonist use by 0.8 ± 1.0 puffs/d. No apparent differences in asthma quality-of-life scores were noted between treatment groups over the relatively short duration of this study.

Two patients receiving IL-4R, but no patients receiving placebo, had a one-log reduction in RAST titer to one of the 2 antigens tested. Five patients receiving IL-4R, but no patients receiving placebo, had negative titrated allergen skin prick test responses for both allergens to which they had previously had positive test reactions. There was no significant difference between groups in circulating eosinophils or total serum IgE over the duration of this study. Patients receiving IL-4R did not have an impairment in the ability to respond to tetanus immunization, as determined by antitetanus antibody response, indicating that normal immune function was not compromised by IL-4R inhibition.

Pharmacokinetic and safety analysis

The time to maximum serum concentration of IL-4R was 2.5 ± 1.5 days, and the maximum serum concentration increased in a linear fashion with dose. The serum elimination half-life was 5.3 ± 2.4 days. The drug was safe and well tolerated (Table II). There were no significant differences in adverse events between IL-4R and placebo. One patient in the 0.75-mg dose group had antibodies to IL-4R, which were nonneutralizing and not associated with symptoms. The doses evaluated in this study are not directly comparable with the doses used in the earlier study of IL-4R because a different aerosol delivery system was used.²⁷

DISCUSSION

This is the first study to demonstrate the potential clinical efficacy of a T_H2 inhibitor for the treatment of asthma. In this study we demonstrate that 3.0 mg of IL-4R nebulized weekly was significantly better than placebo in maintaining FEV₁ after corticosteroid discontinuation whether measured by means of clinic spirometry or with a portable spirometer twice daily. IL-4R also showed a trend to maintaining asthma symptom scores compared with placebo. The demonstrated ability to maintain lung function was achieved in the absence of adverse side effects. This lack of side effects might be anticipated with a molecule-like soluble IL-4 receptor that occurs naturally in human subjects. Targeting treatment to the lungs and targeting the underlying cause of asthma offers the potential to prevent the allergic cascade at a key central regulatory point. These data suggest that in some patients with moderate and persistent asthma who discontinue inhaled corticosteroids, IL-4R may prevent significant decline in lung function or asthma symptoms.

Some theoretical concerns can be raised regarding the long-term sequelae of blocking the biologic activity of IL-4, even though long-term preclinical and clinical studies to date have not demonstrated adverse effects. IL-4 and IL-4R knock-out mice, as well as IL-4R transgenic mice, have normal reproduction and life span without evidence of disease.³⁶ T_H2 -mediated eosinophilic responses may be important in immunity to parasites; however, knockout mice deficient in IL-4 are able to expel *Nippostrongylus brasiliensis* normally.^{36,37} Although IL-4 was originally cloned as a B-cell growth factor, IL-4-deficient mice do not demonstrate any impairment in their humoral immunity. In this study subjects had normal antibody responses to tetanus toxoid immunization, and thus IL-4R inhibited the allergic response but not the immune response.

IL-4 antagonism does not have the corticosteroid side effects of growth inhibition and osteoporosis. In contrast, IL-4 overproduction is associated with the development of osteoporosis in transgenic mice.³⁸ Osteoporosis frequently develops in asthma and hyper-IgE syndrome, and both osteoporosis and diminished serum osteocalcin concentrations can be demonstrated, even in the absence of systemic or inhaled corticosteroid use.^{39,40} Thus IL-4R could theoretically provide some degree of protection against the development of osteoporosis in asthma.

In addition to having an improved safety profile in comparison with that of corticosteroids, an important advantage of IL-4R is the enhanced potential for improved patient compliance. IL-4R will potentially eliminate noncompliance that is due to patients' concerns regarding the use of corticosteroids. More important will be the improved compliance associated with the possible substitution of a once weekly regimen for once or twice daily dosing.

Many of the biologic activities of IL-4, including IgE production and VCAM-1 expression, are shared with IL-13.⁴¹⁻⁴³ The key central regulatory point of promotion of

the T_H2 phenotype is, however, unique to IL-4. Blocking IL-13 has also been shown to attenuate the asthma phenotype in murine models.^{44,45} Blocking IL-4 will likely decrease production of IL-13 and additional IL-4 by decreasing T_H2 differentiation.

Future studies will be essential to demonstrate the anti-inflammatory effects of IL-4R on the asthmatic airway and its ability to protect the airway against remodeling. By reducing VCAM-1 expression, IL-4R should inhibit the endothelial transmigration of eosinophils into the airway.⁸⁻¹⁰ In addition, through inhibition of T_H2 -like lymphocyte differentiation, inhibition of IL-4 has been shown to reduce in vitro expression of the eosinophilopoietic, activating, and antiapoptotic cytokines IL-5, IL-3, and GM-CSF.¹³⁻²⁰ IL-4R may reduce these eosinophil growth and differentiation factors. Finally, soluble IL-4R treatment would block the survival-enhancing effect of IL-4 on eosinophils.¹¹ Thus IL-4R may indirectly promote eosinophil death in the airways. Further support for the anti-inflammatory efficacy of IL-4R is supported by our previous observations demonstrating reduced exhaled nitric oxide after a single dose of this agent.²⁷ An anti-inflammatory agent that is not a corticosteroid and that selectively inhibits allergic mechanisms will be a significant advance in the treatment of asthma.

Future studies will provide insight into the role of this novel anti-inflammatory treatment. These data demonstrate the critical role of IL-4 in the pathogenesis of asthma and the potential benefit of this approach to therapy.

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Correction

In the supplement to the February issue of the Journal (Volume 107, Number 2), the name of an author was spelled incorrectly in one of the published abstracts. With respect to abstract 180 (2001;107:S52), the authors of "Idiopathic Angioedema Is a Distinct Clinical Syndrome" are *Raj Kumar, Edmond Chan, and Richard Warrington*, University of Manitoba, Winnipeg, Canada.