

TREATMENT OF ALLERGIC ASTHMA WITH MONOCLONAL ANTI-IgE ANTIBODY

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ABSTRACT

Background Immune responses mediated by IgE are important in the pathogenesis of allergic asthma. A recombinant humanized monoclonal antibody (rhuMAB-E25) forms complexes with free IgE and blocks its interaction with mast cells and basophils. We studied the efficacy of rhuMAB-E25 as a treatment for moderate-to-severe allergic asthma.

Methods After a 4-week run-in period, we randomly assigned 317 subjects (age range, 11 to 50 years) who required inhaled or oral corticosteroids (or both) to receive either placebo or one of two regimens of rhuMAB-E25: high-dose rhuMAB-E25 (5.8 μ g per kilogram of body weight per nanogram of IgE per milliliter) or low-dose rhuMAB-E25 (2.5 μ g per kilogram per nanogram of IgE per milliliter) intravenously on days 0 (half a dose), 4 (half a dose), and 7 (full dose) and then once every 2 weeks thereafter for 20 weeks. For the first 12 weeks of the study, the subjects continued the regimen of corticosteroids they had received before enrollment. During the following eight weeks, the doses of corticosteroids were tapered in an effort to discontinue this therapy. The primary outcome measure was an improvement in the asthma symptom score at 12 weeks, according to a 7-point scale, in which a score of 1 indicated no symptoms and a score of 7 the most severe symptoms.

Results A total of 106 subjects were assigned to receive a high dose of rhuMAB-E25, 106 were assigned to receive a low dose, and 105 were assigned to receive placebo. At base line, the mean asthma symptom score was 4.0. After 12 weeks of therapy, the mean (\pm SE) scores were 2.8 ± 0.1 in the high-dose group ($P=0.008$) and 2.8 ± 0.1 in the low-dose group ($P=0.005$), as compared with 3.1 ± 0.1 in the placebo group. At 20 weeks, the mean scores were 2.7 ± 0.1 in both the high-dose group ($P=0.048$) and the low-dose group ($P=0.14$), as compared with 2.9 ± 0.1 in the placebo group. More subjects in the two rhuMAB-E25 groups were able to decrease or discontinue their use of corticosteroids than in the placebo group, but only some of the differences were significant. After 20 weeks, serum free IgE concentrations decreased by a mean of more than 95 percent in both rhuMAB-E25 groups. The therapy was well tolerated. After 20 weeks, none of the subjects had antibodies against rhuMAB-E25.

Conclusions A recombinant humanized monoclonal antibody directed against IgE has potential as a treatment for subjects with moderate or severe allergic asthma. (N Engl J Med 1999;341:1966-73.)

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RECOMBINANT humanized monoclonal antibody (rhuMAB-E25) was developed by immunizing mice with human IgE. A monoclonal antibody was selected that recognizes IgE at the same site as the high-affinity receptor for IgE (Fc ϵ RI).¹ This antibody forms complexes with free (unbound) IgE but not with IgG or IgA. It blocks the binding of IgE to cell-membrane receptors, thereby inhibiting the release of mediators, but it does not bind to cell-bound IgE.² For clinical use, the amino acid residues of the variable immunoglobulin region of mouse origin that were implicated in binding to IgE were grafted onto the constant region of human IgG1, resulting in an immunoglobulin protein that is more than 95 percent human.³

The use of rhuMAB-E25 dramatically reduces serum concentrations of free IgE immediately after the first injection⁴ and, after a course of therapy, attenuates both early- and late-phase reactions to inhaled allergens.^{5,6} The ability of rhuMAB-E25 to suppress the late-phase reaction, which is associated with bronchial inflammation followed by bronchoconstriction, has been postulated to have a beneficial effect on the pathogenesis of asthma.⁷ We examined the efficacy of rhuMAB-E25 as a treatment for allergic asthma.

METHODS

Subjects

The protocol was approved by the institutional review board at each study site, and all subjects or, when appropriate, their parents or guardians provided written informed consent. We screened 569 subjects and enrolled 317. The subjects ranged from 11 to 50 years of age, and all had moderate-to-severe perennial allergic asthma, classified as "moderate persistent" to "severe persistent,"⁸ on the basis of a base-line value for mean forced expiratory volume in one second (FEV₁) that was 71 percent of the predicted value, a mean daily symptom score of 4.0 on a 7-point scale (with a score of 1 indicating no symptoms and a score of 7 the most severe symptoms), and the daily use of a β -agonist bronchodilator as a rescue medication.

Thirty-four subjects did not complete the study. At enrollment all subjects had to have been taking inhaled triamcinolone (Azmacort, Rhone-Poulenc Rorer, Collegeville, Pa.) at a dose of at least 200 μ g twice daily or equivalent amounts of flunisolide (Aerobid, Forest Pharmaceuticals, St. Louis) or beclomethasone (Beclovent, Glaxo Wellcome, Research Triangle Park, N.C., or Vanceril, Key

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Pharmaceuticals, Kenilworth, N.J.) for at least two months. Thirty-five subjects were taking oral prednisone at a dose of no more than 20 mg daily or 40 mg every other day in addition to the inhaled corticosteroids. Criteria for eligibility included positive responses on skin-prick testing to two or more perennial allergens to which the subjects would be exposed and documented reversibility of the airway abnormalities (an increase of 12 percent or more after the administration of albuterol). In the week before randomization the subjects also had to have an FEV₁ that was 50 to 90 percent of the predicted value and a mean symptom score of at least 2.5 on each of the seven days.

The most common reasons for exclusion were a daily symptom score of less than 2.5 (26 percent of those excluded), airway obstruction that was not reversible (13 percent), a dose of rhuMAB-E25 that was projected to be less than 1 ml (11 percent), scheduling problems (10 percent), a serum IgE concentration of more than 1785 IU per milliliter (9 percent), negative skin-prick tests (8 percent), an FEV₁ that was outside the specified range (7 percent), active disease other than asthma (7 percent), and lack of compliance (5 percent).

Study Design

This randomized, placebo-controlled, double-blind, multicenter trial comprised four phases: a 4-week enrollment and run-in period; 12 weeks of adjunctive treatment in which placebo or rhuMAB-E25 was administered intravenously on days 0 (half a dose), 4 (half a dose), and 7 (full dose) and then once every 2 weeks thereafter, in addition to established corticosteroid therapy; an 8-week phase in which rhuMAB-E25 or placebo was continued but the doses of corticosteroids were tapered; and a 10-week follow-up phase. Subjects who were randomly assigned to receive rhuMAB-E25 were given either a high dose (5.8 μ g per kilogram of body weight per nanogram of IgE per milliliter) or a low dose (2.5 μ g per kilogram per nanogram of IgE per milliliter).

Outcome Measures

The primary outcomes were daytime and nocturnal asthma symptom scores at 12 weeks. The secondary outcomes were changes in the extent of use of a β -agonist bronchodilator as a rescue medication, the doses of oral and inhaled corticosteroids, peak expiratory flow rate, and asthma-specific quality of life. The safety and tolerability of rhuMAB-E25 were evaluated.

Serum concentrations of free and total IgE were measured by an enzyme-linked immunoassay^{9,10} with the use of Fc-receptor-IgG chimeric antibody and monoclonal anti-IgE.

Asthma Symptom Scores

Symptoms of asthma were recorded twice daily with use of an electronic diary¹¹ (MiniDoc Electronic Patient System, MiniDoc, Northbrook, Ill.). Separate scales were used for adults and adolescents (age, 11 to 17 years). Adults used the following scale to rate their symptoms in the preceding 24 hours: none, a score of 1; very little, a score of 2; some, a score of 3; a moderate amount, a score of 4; a good deal, a score of 5; a great deal, a score of 6; and a very great deal, a score of 7. The frequency of symptoms in the preceding 24 hours was scored with use of the following scale: none of the time, a score of 1; hardly any of the time, a score of 2; a little of the time, a score of 3; some of the time, a score of 4; a good bit of the time, a score of 5; most of the time, a score of 6; and all of the time, a score of 7. The total symptom score for adults was the average score for 9 questions regarding magnitude and 7 regarding frequency on a given day (3 questions in the morning and 13 in the evening).

The scale used by adolescents to assess the magnitude of their symptoms was similar to that used by adults, but it used simplified language: a score of 1 indicated that they were not bothered by symptoms, a score of 2 hardly bothered, a score of 3 bothered slightly, a score of 4 somewhat bothered, a score of 5 quite bothered, a score of 6 very bothered, and a score of 7 extremely both-

ered. Adolescents used essentially the same scale as adults to assess the frequency of symptoms. The total symptom score for adolescents was the average score for 9 questions regarding magnitude and 8 regarding frequency on a given day (3 questions in the morning and 14 in the evening).

The percent reduction in the symptom score was calculated according to the following formula: (base-line score - follow-up score) \div (base-line score - 1), where the base-line score is the mean symptom score for the week before day 0 and the follow-up score is the mean symptom score on week 12 or week 20.

Use of Inhaled β -Agonists and Withdrawal of Corticosteroids

The extent of use of inhaled β -agonists was recorded in the electronic diary twice daily. A total of 315 subjects used β -agonists as rescue therapy, and 202 used metered-dose inhalers exclusively. Results are presented only for the 202 subjects who used metered-dose inhalers exclusively. After 12 weeks of treatment with rhuMAB-E25 or placebo, subjects began the third phase (withdrawal of corticosteroids). Treatment with rhuMAB-E25 or placebo was continued during this phase. Every two weeks during this eight-week period, the subjects underwent a physical examination and had their FEV₁ and peak expiratory flow rate measured, their diary cards assessed, and their total use of rescue medication and corticosteroids evaluated. For subjects who required high daily doses of inhaled triamcinolone (≥ 600 μ g per day), an attempt was made to reduce the dose by 200 μ g every two weeks; for subjects who were taking less than 600 μ g per day, the target reduction in the dose was 25 percent of the base-line value every two weeks. Weekly decreases were not permitted. For subjects who were taking no more than 20 mg of oral corticosteroids daily or 40 mg every other day, the dose was reduced by no more than 20 percent at one-week intervals. For subjects who were taking both oral and inhaled corticosteroids, only the dose of the oral agent was tapered.

Measurements of Lung Function

FEV₁ was measured every two weeks.¹² Peak expiratory flow rates were measured in the morning and evening by the subjects with a portable peak flowmeter (Mini-Wright flowmeter, Armstrong Industries, Northbrook, Ill.).

Assessment of the Quality of Life

A total of 263 adults completed the Asthma Quality-of-Life Questionnaire¹³ and 45 adolescents completed the Pediatric Asthma Quality-of-Life Questionnaire¹⁴ at base line, week 12, and week 20. The adult questionnaire that we used is a validated, asthma-specific instrument.¹³ Subjects rate the degree of impairment caused by asthma during the preceding 14 days and respond to each of the 32 items using a 7-point scale on which a score of 1 indicates maximal impairment and a score of 7 no impairment. Changes in the score of 0.5, 1.0, and 1.5 correspond to small, moderate, and large differences, respectively.¹⁵ The questionnaire can be used to provide an overall score and scores in four areas: limitation of activities, asthma symptoms, emotional functioning, and symptoms arising from environmental exposures.

The pediatric questionnaire was designed and validated for use in children with asthma who are 7 to 17 years of age.¹⁴ It has 23 items covering three areas (symptoms, limitation of activities, and emotional functioning). The scoring system is identical to that of the adult questionnaire.

Exacerbations of Asthma

If an exacerbation of asthma occurred during the withdrawal of corticosteroids, the tapering was interrupted and the exacerbation was treated with prednisone for five to seven days. An exacerbation was defined by any of the following: a decrease in morning peak expiratory flow rate of at least 20 percent during three of the seven days preceding a visit, a decrease in FEV₁ of at least 20 percent, an urgent or unscheduled visit for asthma symptoms, or

TABLE 1. BASE-LINE CHARACTERISTICS OF THE 317 SUBJECTS.*

| CHARACTERISTIC | HIGH-DOSE rhuMAB-E25 (N=106) | LOW-DOSE rhuMAB-E25 (N=106) | PLACEBO (N=105) | ALL SUBJECTS (N=317) |
|--|------------------------------------|-----------------------------------|--------------------|-------------------------|
| Age (yr) | | | | |
| Mean | 29 | 30 | 30 | 30 |
| Range | 12–50 | 12–47 | 11–48 | 11–50 |
| No. of adolescents (11–17 yr of age) | 21 | 16 | 17 | 54 |
| Male sex (%) | 38 | 43 | 45 | 42 |
| Serum IgE (ng/ml)† | | | | |
| Mean | 898 | 826 | 660 | 794 |
| Range | 65–4697 | 41–3950 | 46–3336 | 41–4697 |
| Overall asthma symptom score | | | | |
| Mean | 4.1 | 4.0 | 4.0 | 4.0 |
| Range | 2.4–6.5 | 2.0–6.5 | 1.5–6.5 | 1.5–6.5 |
| Morning PEFr (liters/min) | | | | |
| Mean | 378.0 | 380.0 | 384.1 | 380.7 |
| Range | 143–599 | 151–626 | 150–620 | 143–626 |
| FEV ₁ (percentage of predicted value) | | | | |
| Mean | 73 | 71 | 70 | 71 |
| Range | 34–129 | 29–115 | 32–101 | 29–129 |
| Dose of inhaled corticosteroids in adults | | | | |
| Median (μ g/day) | 800 | 800 | 800 | 800 |
| Range (μ g/day) | 200–2400 | 400–3200 | 200–4000 | 200–4000 |
| No. of subjects | 78 | 78 | 76 | 232 |
| Dose of inhaled corticosteroids in adolescents | | | | |
| Median (μ g/day) | 800 | 600 | 800 | 800 |
| Range (μ g/day) | 400–2600 | 600–2000 | 400–1600 | 400–2600 |
| No. of subjects | 19 | 14 | 17 | 50 |
| Dose of oral corticosteroids‡ | | | | |
| Median (mg/day) | 10.0 | 10.0 | 10.0 | 10.0 |
| Range (mg/day) | 5.0–10.0 | 5.0–20.0 | 2.5–40.0 | 2.5–40.0 |
| No. of subjects | 9 | 14 | 12 | 35 |
| Use of β -agonists | | | | |
| Mean (puffs/day) | 8.8 | 8.8 | 8.2 | 8.6 |
| Range (puffs/day) | 2.0–37.7 | 2.0–22.7 | 2.0–16.8 | 2.0–37.7 |
| No. of subjects | 73 | 66 | 63 | 202 |

*There were no significant differences among the three groups. PEFr denotes peak expiratory flow rate, and FEV₁ forced expiratory volume in one second.

†To convert values to international units per milliliter, divide by 2.4.

‡Doses are shown as prednisone.

an increase in β -agonist use of at least 50 percent for at least two consecutive days.

Statistical Analysis

The base-line characteristics of the three groups were compared with use of the Kruskal–Wallis and chi-square tests.¹⁶ Data from subjects who discontinued treatment after less than four weeks were excluded from efficacy analyses but included in safety analyses, whereas subjects who discontinued treatment after at least four weeks had their last value carried forward in efficacy analyses. The primary efficacy end point was a change in the weekly symptom score between base line and week 12. The efficacy of treatment was compared in a pairwise fashion between each of the two rhuMAB-E25 groups and the placebo group.¹⁷ The weekly symptom scores and quality-of-life results were compared with the use of least-squares means, the Wilcoxon rank-sum test was used for other continuous variables, and the chi-square test was used for binary end points.¹⁶ All efficacy analyses were prospectively defined except those involving exacerbations of asthma. All P values are two-sided.

RESULTS

Base-Line Characteristics

The base-line characteristics of the subjects are shown in Table 1. The average age of the subjects was 30 years, and they had had asthma for a median

of 19 years. There were 106 subjects in the group given a high dose of rhuMAB-E25, 106 subjects in the low-dose group, and 105 in the placebo group.

Serum IgE Concentration

Serum concentrations of free IgE dropped rapidly after the first dose of rhuMAB-E25 (Fig. 1). In the high-dose group, serum free IgE concentrations fell from 1000 ng per milliliter to 7.3 ng per milliliter (416.7 to 3.0 IU per milliliter) within one hour after the dose on day 0. In the low-dose group, the concentrations decreased from 1060 ng per milliliter to 13.9 ng per milliliter (441.7 to 5.8 IU per milliliter). After 20 weeks of treatment, serum free IgE concentrations averaged 10.2 ng per milliliter (4.3 IU per milliliter) in the high-dose group and 18.0 ng per milliliter (7.5 IU per milliliter) in the low-dose group, for a mean decrease of 97.1 and 95.5 percent, respectively. Mean serum total IgE concentrations (the total of free and small complexes) increased significantly over time in both groups and appeared to plateau by day 21 (Fig. 1).

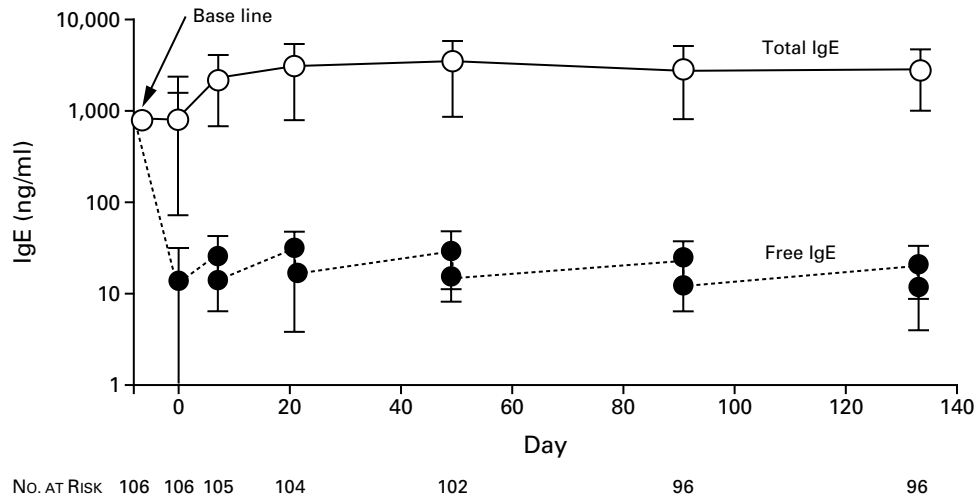


Figure 1. Mean (\pm SD) Serum Concentrations of Total and Free IgE in Subjects Given a Low Dose of rhuMAb-E25 for 20 Weeks. Serum free IgE concentrations decreased rapidly by more than 95 percent (base-line level, 1060 ng per milliliter [441.7 IU per milliliter]). To convert values to international units per milliliter, divide by 2.4. A log (base 10) scale is shown.

Asthma Symptom Scores

The mean asthma symptom score at enrollment was 4.0. After 12 weeks of treatment, the mean (\pm SE) score was 2.8 ± 0.1 for subjects in the high-dose group ($P=0.008$ for the comparison with the placebo group) and 2.8 ± 0.1 for those in the low-dose group ($P=0.005$), as compared with 3.1 ± 0.1 for those in the placebo group. The scores improved by a mean of 42 percent in the high-dose group and 40 percent in the low-dose group, as compared with 30 percent in the placebo group. Forty-seven percent of the subjects in the low-dose group ($P<0.001$) and 49 percent of those in the high-dose group ($P<0.001$) had a reduction in weekly symptom scores of more than 50 percent at week 12, as compared with 24 percent of subjects in the placebo group. The improvement in symptoms continued until week 20, notwithstanding the reduction in the dose of corticosteroids in both groups treated with rhuMAb-E25. At 20 weeks, the mean scores were 2.7 ± 0.1 in the high-dose group ($P=0.048$), 2.7 ± 0.1 in the low-dose group ($P=0.14$), and 2.9 ± 0.1 in the placebo group (Table 2).

β -Agonist Use

The mean number of puffs of albuterol per day at base line was 8.8 for subjects in both the high-dose group and the low-dose group and 8.2 for subjects in the placebo group (Table 1). After 12 weeks of treatment, the subjects in the high-dose group had reduced their use of albuterol by 1.8 puffs per day ($P=0.02$) and those in the low-dose group had reduced their use by 1.2 puffs per day ($P=0.24$), as compared with a reduction of 0.8 puff per day among subjects in the placebo group. These decreases

TABLE 2. REDUCTIONS IN OVERALL ASTHMA SYMPTOM SCORES.*

| SCORE | HIGH-DOSE rhuMAb-E25 (N=103) | LOW-DOSE rhuMAb-E25 (N=103) | PLACEBO (N=100) |
|---|------------------------------------|-----------------------------------|--------------------|
| Base line | | | |
| Mean | 4.1 ± 0.1 | 4.0 ± 0.1 | 4.0 ± 0.1 |
| Median | 3.8 | 4.0 | 3.8 |
| Week 12 | | | |
| Mean | 2.8 ± 0.1 | 2.8 ± 0.1 | 3.1 ± 0.1 |
| P value | 0.008 | 0.005 | |
| >50% Reduction in scores — no. of subjects (%) | 50 (49) | 48 (47) | 24 (24) |
| P value | <0.001 | <0.001 | |
| Week 20 | | | |
| Mean | 2.7 ± 0.1 | 2.7 ± 0.1 | 2.9 ± 0.1 |
| P value | 0.048 | 0.14 | |
| >50% Reduction in scores — no. of subjects (%) | 51 (50) | 48 (47) | 34 (34) |
| P value | 0.03 | 0.07 | |

*Plus-minus values are means \pm SE. Data are presented for the 306 subjects with at least four weeks of treatment. Subjects who left the study after at least four weeks of treatment had their last value carried forward. Asthma symptoms are scored on a 7-point scale, with a score of 1 indicating no symptoms and a score of 7 indicating maximal symptoms. The P values are for the comparison with placebo.

in the use of rescue medication in the groups given rhuMAb-E25 were maintained at 20 weeks (data not shown).

Withdrawal of Oral Corticosteroids

For the 35 subjects who required oral corticosteroids at base line, the median reduction in the dose of prednisone over the eight-week tapering phase

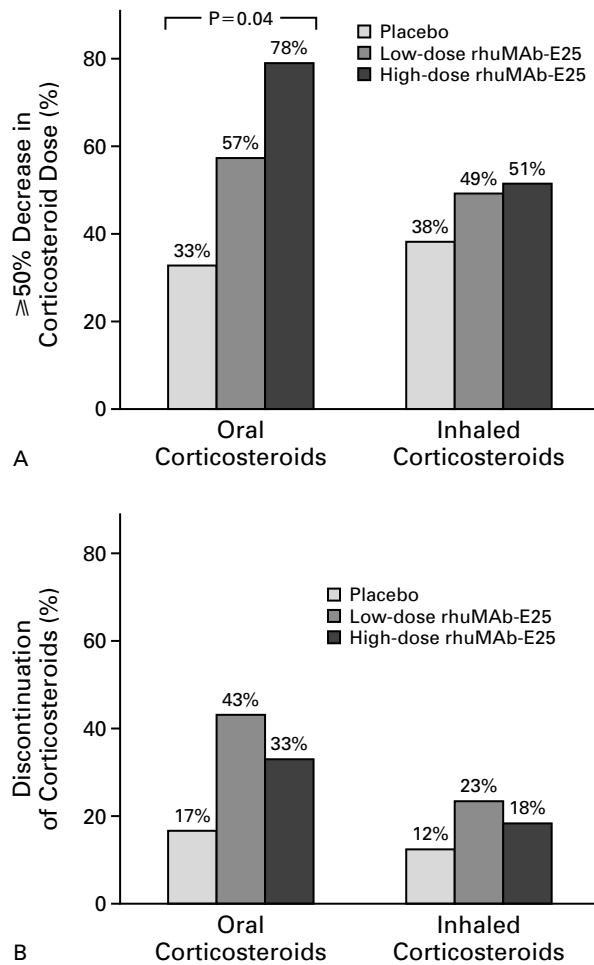


Figure 2. Results of Efforts to Taper the Dose of Corticosteroids. Panel A shows the percentage of subjects in each group who were able to reduce their daily corticosteroid dose by at least 50 percent at 20 weeks. Panel B shows the percentage of subjects in each group who were able to discontinue corticosteroid therapy. In the placebo, low-dose, and high-dose groups, 12, 14, and 9 subjects, respectively, were taking oral corticosteroids and 93, 92, and 97 subjects were taking inhaled corticosteroids. Subjects who left the study had their last recorded dose carried forward.

was 50 percent in the high-dose group ($P=0.045$) and 65 percent in the low-dose group ($P=0.11$), as compared with 0 percent in the placebo group. Seventy-eight percent of the subjects in the high-dose group ($P=0.04$) and 57 percent of those in the low-dose group ($P=0.23$) had a reduction in the dose of oral corticosteroids of at least 50 percent, as compared with 33 percent of subjects in the placebo group (Fig. 2A). Thirty-three percent of the subjects in the high-dose group ($P=0.38$) and 43 percent of those in the low-dose group ($P=0.15$) were able to stop taking oral corticosteroids, as compared with 17 percent of those in the placebo group (Fig. 2B).

Withdrawal of Inhaled Corticosteroids

Fifty-one percent of the subjects in the high-dose group ($P=0.07$) and 49 percent of those in the low-dose group ($P=0.12$) had a reduction in their dose of inhaled corticosteroids of at least 50 percent, as compared with 38 percent of subjects in the placebo group (Fig. 2A). Eighteen percent of the subjects in the high-dose group ($P=0.27$) and 23 percent of those in the low-dose group ($P=0.048$) stopped taking inhaled corticosteroids, as compared with 12 percent of those in the placebo group (Fig. 2B).

FEV₁

The mean FEV₁ of the subjects at base line was 71 percent of the predicted value (Table 1). The absolute improvement in FEV₁ at 12 weeks was 1.9 percent in the high-dose group ($P=0.81$), 2.1 percent in the low-dose group ($P=0.49$), and 1.0 percent in the placebo group.

Peak Expiratory Flow Rates

The increase in the morning peak expiratory flow rate from base line to week 12 was 30.7 liters per minute in the high-dose group ($P=0.007$), 18.6 liters per minute in the low-dose group ($P=0.10$), and 11.3 liters per minute in the placebo group. At week 20, the difference from the base-line value was 29.9 liters per minute in the high-dose group ($P=0.02$), 20.8 liters per minute in the low-dose group ($P=0.046$), and 10.2 liters per minute in the placebo group.

Quality of Life

After 12 weeks of treatment, the overall score for adults on the asthma-specific quality-of-life questionnaire had increased by a mean of 1.4 in the high-dose group ($P<0.001$), 1.2 in the low-dose group ($P=0.007$), and 0.8 in the placebo group. The results were similar for each of the four areas covered by the questionnaire (Table 3) and were maintained during the corticosteroid-tapering phase. The results were also similar among the adolescents (data not shown).

Exacerbations of Asthma

During the 20 weeks of treatment, 32 subjects in the high-dose group (30 percent, $P=0.03$) and 30 subjects in the low-dose group (28 percent, $P=0.01$) had exacerbations of asthma, as compared with 47 subjects in the placebo group (45 percent). Treatment with oral corticosteroids for exacerbations of asthma was required in 13 percent of subjects in the high-dose group ($P=0.01$), 16 percent of those in the low-dose group ($P=0.06$), and 28 percent of those in the placebo group.

Adverse Effects

There were no significant differences in the incidence of adverse events among the three groups. There were 17 reports of mild-to-moderate urticaria

TABLE 3. MEAN SCORES ON THE ASTHMA-SPECIFIC QUALITY-OF-LIFE QUESTIONNAIRE FOR 263 ADULT SUBJECTS.*

| SCORE | HIGH-DOSE rhuMAB-E25 (N=85) | P VALUE | LOW-DOSE rhuMAB-E25 (N=90) | P VALUE | PLACEBO (N=88) |
|----------------------------------|-----------------------------------|---------|----------------------------------|---------|-------------------|
| Overall | | | | | |
| Base line | 3.7±0.8 | | 3.7±0.9 | | 3.9±0.8 |
| Increase at week 12 | 1.4 | <0.001 | 1.2 | 0.007 | 0.8 |
| Increase at week 20 | 1.5 | <0.001 | 1.2 | 0.007 | 0.8 |
| Limitation of activities | | | | | |
| Base line | 4.0±0.9 | | 4.0±1.0 | | 4.3±1.0 |
| Increase at week 12 | 1.4 | <0.001 | 1.2 | 0.02 | 0.8 |
| Increase at week 20 | 1.4 | <0.001 | 1.3 | 0.003 | 0.8 |
| Asthma symptoms | | | | | |
| Base line | 3.5±0.8 | | 3.5±0.9 | | 3.5±0.9 |
| Increase at week 12 | 1.3 | 0.002 | 1.2 | 0.02 | 0.8 |
| Increase at week 20 | 1.5 | <0.001 | 1.2 | 0.02 | 0.8 |
| Emotional functioning | | | | | |
| Base line | 3.4±1.3 | | 3.5±1.4 | | 3.6±1.2 |
| Increase at week 12 | 1.5 | <0.001 | 1.2 | 0.09 | 0.9 |
| Increase at week 20 | 1.6 | <0.001 | 1.2 | 0.049 | 0.9 |
| Environmentally induced symptoms | | | | | |
| Base line | 3.9±1.2 | | 3.8±1.3 | | 4.0±1.1 |
| Increase at week 12 | 1.2 | <0.001 | 1.1 | <0.001 | 0.6 |
| Increase at week 20 | 1.3 | 0.002 | 1.2 | 0.02 | 0.9 |

*Plus-minus values are means ±SD. All other values are means. The scores can range from 1 to 7, with lower scores indicating greater impairment in asthma-specific quality of life. P values are for the comparison with placebo.

(8 in the high-dose group, 6 in the low-dose group, and 3 in the placebo group). Ten cases occurred within 60 minutes after the infusion on the first day of treatment (three in the low-dose group and seven in the high-dose group), and all subsided promptly after treatment with antihistamines. Seven subjects in the high-dose group withdrew, 3 because of adverse effects; the respective numbers were 11 and 3 in the low-dose group and 16 and 5 in the placebo group. After 20 weeks of treatment, none of the subjects in the rhuMAB-E25 groups had antibodies against rhuMAB-E25.

DISCUSSION

Allergic diseases are characterized by biphasic reactions mediated by IgE.¹⁸ The immediate reaction appears within minutes after exposure to an antigen, and the late-phase reaction may occur two to eight hours afterward. The latter process is the model for allergic disease.^{19,20} Lung biopsy^{21,22} and bronchoalveolar lavage²³ in subjects with stable asthma show the presence of inflammation consistent with a late-phase reaction, whereas pulmonary-function tests show hyperresponsiveness of the airway that is proportional to the magnitude of the late-phase reaction.²⁴ IgE binds to high-affinity receptors on tissue mast cells and circulating basophils.^{10,25} In subjects with asthma, there is a correlation between serum IgE concentrations and both airway responsiveness²⁶ and the number of high-affinity receptors.²⁵

Effective allergen immunotherapy attenuates the

late-phase reaction.²⁷ However, immunotherapy as currently practiced has not been uniformly effective in the treatment of allergic disease.^{28,29} Consequently, the basis of therapy remains the consistent use of antiinflammatory medication, most often in the form of inhaled corticosteroids, to block the late-phase reaction and reduce airway hyperresponsiveness.^{8,30} Successful antiinflammatory therapy leads to long-term prevention of the symptoms of asthma by suppressing, controlling, and reversing inflammation.^{8,30} The clinical efficacy of rhuMAB-E25 may be the result of similar effects on the pathogenesis of the allergic response.

Although immunotherapy is effective only in a narrow, antigen-specific range,⁹ rhuMAB-E25 removes IgE from the circulation, basophils,¹⁰ and mast cells regardless of its antigen specificity.^{31,32} In this study and in earlier work,^{5,6} a single dose of rhuMAB-E25 rapidly reduced serum free IgE serum concentrations by more than 95 percent. Although serum free IgE concentrations declined precipitously, mean serum total IgE concentrations, consisting mostly of immunoglobulin complexes, increased over time and appeared to reach a plateau.⁴ Analytic ultracentrifugation and size-exclusion chromatography identified the largest complexes of rhuMAB-E25 and IgE as heterohexamers with a molecular mass of 1,000,000 or less.³³ Because these complexes cannot bind IgE receptors, they lack the biologic activity of IgE. The complexes are cleared by low-avidity interaction with the Fcγ receptors of leukocytes and the reticuloendothelial system.⁴ These low-molecular-weight complexes, which

do not fix complement or accumulate in renal glomeruli, do not pose a risk of immunopathogenicity.⁴

The subjects we studied, all of whom had documented allergic disease, tolerated rhuMAb-E25 therapy well. After 20 weeks of treatment, none had antibodies against rhuMAb-E25. The absence of immunogenicity may be attributed to the humanization of the antibody³⁴ and to protein engineering that resulted in a non-complement-fixing molecule with a human IgG1- κ framework distinguished from that of the natural immunoglobulin by only three amino acids.^{3,35}

With respect to the primary measure of efficacy — the daily asthma symptom score — we found that subjects treated with rhuMAb-E25 had greater improvements than those who received placebo. This decrease in symptoms occurred in the context of a low number of withdrawals from treatment in the high-dose group. Furthermore, treatment with rhuMAb-E25 was associated with an improvement in the asthma-specific quality of life.

In our study, all subjects received care in accordance with the recommendations of international consensus groups.^{8,30,36} The subjects received oral or inhaled corticosteroids, or both, at doses that optimized pulmonary function. Their status was assessed by a physician every two weeks, and they were regularly encouraged to adhere to their therapeutic regimens. The effectiveness of the clinical protocol is evidenced by the improvement in symptoms among the subjects in the placebo group. Nonetheless, the improvement was significantly greater in the other two groups.

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APPENDIX

In addition to the authors, other members of the study group were as follows: T. Casale, Nebraska Medical Research Institute, Papillion; S. Chodosh, Veterans Affairs Out-Patient Clinic, Boston; J. Corren, Allergy Research Foundation, Los Angeles; L. Cosmo, Tampa Medical Research Associates, Tampa, Fla.; J. Fahy, University of California at San Francisco, San Francisco; J. Fine, Norwalk Hospital, Norwalk, Conn.; D. Geller, Nemours Children's Clinic, Orlando, Fla.; J. Georgitis, Bowman Gray-Baptist Hospital Medical Center, Winston-Salem, N.C.; S. Gillman, Cummins, Kozak, Gillman and Ellis, Orange, Calif.; A.B. Goldsobel, Allergy and Asthma Associates of the Santa Clara Valley, San Jose, Calif.; J. Grossman, Allergy Care Consultants, Tucson, Ariz.; R. Laughlin, Mitchell-Pappas Associates, Bakersfield, Calif.; B.E. Levine, Pulmonary Associates, Phoenix, Ariz.; M. Liu, Johns Hopkins Asthma and Allergy Center, Baltimore; M. Massanari, All Children's Hospital, St. Petersburg, Fla.; E. Meltzer, Allergy and Asthma Medical Group and Research Center, San Diego, Calif.; S.D. Miller, New England Research Center, North Dartmouth, Mass.; O. Schwartz, Bellevue West Medical Building, St. Louis; G. Shapiro, Associated Scientists to Help Minimize Allergies, Seattle; S.J. Simon, Georgia Lung Associates, Austell; J.O. Stewart, Pulmonary Consultants of Orange County, Orange, Calif.; D. Valacer, Cornell University Medical College, New York; M.M. Weinberger, University of Iowa Hospital, Iowa City; R.S. Zeiger, Kaiser Permanente Medical Group, San Diego, Calif.

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