

Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma

William Busse, MD,^a Jonathan Corren, MD,^b Bobby Quentin Lanier, MD,^c
Margaret McAlary, MS,^d Angel Fowler-Taylor, RPh,^d Giovanni Della Cioppa, MD,^e
Andre van As, MD, PhD,^d and Niroo Gupta, MD, PhD^d *Madison, Wis, Los Angeles, Calif,
Fort Worth, Tex, East Hanover, NJ, and Horsham, United Kingdom*

Background: A recombinant humanized anti-IgE mAb, omalizumab, forms complexes with free IgE, blocking its interaction with mast cells and basophils; as a consequence, it might be effective in the treatment of asthma.

Objective: The purpose of this study was to evaluate the efficacy and safety of omalizumab in the treatment of inhaled corticosteroid-dependent asthma.

Methods: In this phase III, double-blinded, placebo-controlled trial, 525 subjects with severe allergic asthma requiring daily inhaled corticosteroids were randomized to receive placebo or omalizumab subcutaneously every 2 or 4 weeks, depending on baseline IgE level and body weight. Inhaled corticosteroid doses were kept stable over the initial 16 weeks of treatment and tapered during a further 12-week treatment period.

Results: Omalizumab treatment resulted in significantly fewer asthma exacerbations per subject and in lower percentages of subjects experiencing an exacerbation than placebo treatment during the stable steroid phase (0.28 vs 0.54 [$P = .006$] and 14.6% vs 23.3% [$P = .009$], respectively) and during the steroid reduction phase (0.39 vs 0.66 [$P = .003$] and 21.3% vs 32.3% [$P = .004$], respectively). Beclomethasone dipropionate reduction was significantly greater with omalizumab treatment than with placebo (median 75% vs 50% [$P < .001$]), and beclomethasone dipropionate discontinuation was more likely with omalizumab (39.6% vs 19.1% [$P < .001$]). Improvements in asthma symptoms and pulmonary function occurred along with a reduction in rescue β -agonist use. Omalizumab was well tolerated, with an adverse-events profile similar to that of placebo.

Conclusion: The addition of omalizumab to standard asthma therapy reduces asthma exacerbations and decreases inhaled corticosteroid and rescue medication use. (*J Allergy Clin Immunol* 2001;108:184-90.)

Key words: Asthma, allergy, IgE, monoclonal antibody, anti-IgE, omalizumab, rhuMAB-E25

IgE plays a central role in the pathogenesis of allergic diseases. After sensitization, atopic patients respond to allergen exposure through a number of IgE-dependent mechanisms. By forming complexes with free IgE, mAbs against IgE block the interaction between IgE and mast cells and basophils. Thus the use of anti-IgE mAbs is considered to be a promising approach for the treatment of allergic conditions such as asthma.

Omalizumab (rhuMAB-E25) is a recombinant humanized mAb that recognizes IgE at the same site as the high-affinity IgE receptor (Fc ϵ RI binding site).¹ Single doses of omalizumab rapidly reduce free IgE concentrations by >95% in patients with allergic asthma.²⁻⁴ Omalizumab was shown to attenuate both the early-phase and the late-phase reactions in patients with mild asthma.^{2,4}

The objective of this study was to assess the efficacy and tolerability of subcutaneous omalizumab in adolescents and adults with severe allergic asthma whose disease was not adequately controlled with inhaled corticosteroids (ICSs).

METHODS

Subjects

Male or female allergic asthmatics aged 12 to 75 years who were symptomatic despite treatment with ICSs were eligible if they met the following criteria: duration of asthma, ≥ 1 year; positive immediate responses on skin prick testing to at least 1 common allergen, including *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, cockroach (whole body), dog, or cat; total serum IgE ≥ 30 IU/mL to ≤ 700 IU/mL; FEV₁ reversibility of $\geq 12\%$ within 30 minutes after administration of albuterol (90-180 μ g); baseline FEV₁ $\geq 40\%$ and $\leq 80\%$ of predicted; and treatment with 420 to 840 μ g/day of beclomethasone dipropionate (BDP) or its equivalent ICS for ≥ 3 months prior to randomization. Exclusion criteria included the following: prior exposure or sensitivity to omalizumab; acute upper respiratory tract infection within 1 month; < 3 months of stable immunotherapy; elevated IgE levels for reasons other than atopy; regular treatment with β -adrenergic antagonists; and requirement of omalizumab doses of > 750 mg per 4 weeks on the basis of serum IgE and body weight.

The study was performed in accordance with the Declaration of Helsinki and its amendments. Each subject provided written informed consent before enrollment. The study was approved by the institutional review board at each center.

From ^athe University of Wisconsin; ^bthe Allergy Research Foundation, Inc, Los Angeles; ^cthe Lanier Education and Research Network, Fort Worth; ^dNovartis Pharmaceuticals, East Hanover; and ^eNovartis Horsham Research Centre, Horsham.

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Reprint requests: William Busse, MD, Department of Medicine, Section of Allergy and Clinical Immunology, University of Wisconsin Hospital & Clinics, Madison, WI 53792.

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Abbreviations used

BDP: Beclomethasone dipropionate
FVC: Forced vital capacity
ICS: Inhaled corticosteroid
PEF: Peak expiratory flow

Study design

This was a double-blinded, placebo-controlled, multicenter, parallel-group trial. On entry into the study, each patient was switched from his or her currently prescribed ICS to an equivalent dose of BDP. At the end of the second week of the 4- to 6-week run-in period, the dose of BDP was adjusted upward or downward to maintain previous asthma control. The patients were monitored to ensure both the presence of asthma symptoms at levels acceptable to the patients and investigators and patient safety. A stable BDP dose (baseline dose) was maintained for 4 weeks prior to randomization. A mean total symptom score over the last 2 weeks of run-in of 3 or more (range, 0-9) was required for the patient to be eligible for randomization to omalizumab or placebo administered subcutaneously at baseline (week 0). The dose and dosing intervals were based on the serum half-life of omalizumab, efficacy results from previous studies, and the subject's body weight and baseline serum IgE. This ensured for each patient a dosage approximately equal to 0.016 mg/kg IgE (IU/mL) per 4 weeks. Subjects thus received 150 mg or 300 mg every 4 weeks or 225 mg, 300 mg, or 375 mg every 2 weeks.

The baseline BDP dose was maintained unchanged during the 4-month stable steroid phase (weeks 1-16). During the subsequent 3-month steroid reduction phase (weeks 16-28), the dose of BDP was reduced by approximately 25% of the baseline dose every 2 weeks for 8 weeks until discontinuation or worsening of asthma symptoms, defined by any one of the following criteria: requirement of an unscheduled physician visit; peak expiratory flow (PEF) <50% of personal best; decrease in morning PEF $\geq 20\%$ on ≥ 2 of 3 consecutive days in comparison with the week before the steroid reduction phase; decrease in FEV₁ of $\geq 20\%$ from the value at the beginning of the steroid reduction phase; 50% increase in 24-hour albuterol usage on ≥ 2 of 3 consecutive days (exceeding 8 puffs/day); or ≥ 2 of 3 consecutive nights with awakening due to asthma symptoms requiring rescue medication. If worsening occurred, BDP was increased by $\geq 25\%$ and the patient was reevaluated for tapering after a week of improvement. For the final 4 weeks of the steroid reduction phase, each subject was maintained on the lowest effective dose of BDP that did not result in worsening of symptoms.

Concomitant medication

Rescue albuterol, 2 puffs (90 μ g/puff) as needed, (maximum, 8 puffs daily) was allowed for symptomatic episodes of wheezing. Patients exceeding this albuterol dosage limitation were instructed to contact the investigator immediately for further evaluation. Treatment with stable doses of immunotherapy and other nonasthma medication was continued at maintenance doses. All other asthma medications, except those used in the treatment of asthma exacerbations, were prohibited during the study.

Study assessments

The primary endpoint was the number of exacerbation episodes experienced by a patient during the steroid reduction period and during the stable steroid phase. Secondary efficacy variables measured throughout the study were as follows: number of patients experiencing at least 1 exacerbation; daily asthma symptoms; rescue medication use; pulmonary function; and global evaluation of

treatment effectiveness. The BDP dose reduction achieved without worsening of asthma symptoms determined the steroid-sparing effect. Other evaluations included safety and tolerability and free and total serum IgE concentrations.

Asthma exacerbations

An asthma exacerbation was defined as a worsening of asthma symptoms, as determined by 1 or more of the criteria listed above, that was severe enough to require treatment with oral or intravenous corticosteroids or a doubling of the subject's baseline inhaled BDP dose. Only episodes defined according to the protocol described above were recorded and analyzed as asthma exacerbations.

Asthma symptoms, rescue medication use, and pulmonary function

Asthma symptoms were recorded in a diary twice daily; nocturnal symptom assessment included the use of rescue medication, and daytime symptom assessment incorporated limitations in physical activity. Both were assessed through use of a 0- to 4-point scale, whereas asthma symptoms on awakening were assessed on a 2-point scale (0 = no and 1 = yes). Daily rescue medication and morning and evening PEF (Mini-Wright peak flow meter; best of 3 efforts) were also recorded. Spirometry was performed every 2 or 4 weeks prior to dosing and 1 hour after each dose.

Global assessment of efficacy

At the end of the study (week 28), subjects and physicians rated global treatment effectiveness as excellent (complete control of asthma), good (marked improvement of asthma), moderate (discernible but limited improvement in asthma), poor (no appreciable change in asthma), or worsening.

Serum IgE levels

Serum samples were taken at baseline and before dosing at weeks 16 and 24 to determine IgE concentrations. In omalizumab-treated subjects, serum IgE comprised free IgE and IgE bound to omalizumab. Serum IgE at baseline (prior to omalizumab treatment) represented free IgE. Serum concentrations of both free and total IgE (free IgE and bound IgE) were measured by an enzyme-linked immunoassay.^{5,6} Samples were screened for anti-omalizumab antibodies through use of an antibody assay.⁵ Values of free IgE >62 IU/mL in the presence of omalizumab could not be quantified by the assay and were reported as >62 IU/mL.

Safety and tolerability

Adverse events were recorded and categorized according to seriousness, severity, relationship to study drug, and time of onset. Clinically significant changes from baseline in laboratory parameters and vital signs and local reactions at the injection site were recorded.

Statistical analysis

The following variables were analyzed through use of the generalized Cochran-Mantel-Haenszel (van Elteren) test, stratified by treatment schedule: number of asthma exacerbations per subject; percent reduction in, and proportion of subjects reducing, the dose of BDP; change from baseline in rescue albuterol use; total and individual asthma symptom scores; and the subject's and the investigator's global evaluation of the treatment effectiveness. The number of subjects experiencing 1 or more asthma exacerbations in each phase and the number of subjects experiencing at least 1 adverse event (whether study drug-related or not) were analyzed through use of the Cochran-Mantel-Haenszel test, stratified by treatment schedule. The Breslow-Day test was used to determine the homogeneity of proportions across the strata. The mean number of days

TABLE I. Baseline demographic characteristics of intent-to-treat population

	Omalizumab (n = 268)	Placebo (n = 257)
Sex (no. of subjects [%])		
Male	104 (38.8)	111 (43.2)
Female	164 (61.2)	146 (56.8)
Race (no. of subjects [%])		
Caucasian	238 (88.8)	229 (89.1)
Black	21 (7.8)	16 (6.2)
Other	9 (3.4)	12 (4.7)
Age (mean [range]) (y)	39.3 (12-73)	39.0 (12-74)
Age group (no. of subjects [%])		
12-17 y	20 (7.5)	21 (8.2)
18-64 y	241 (89.9)	229 (89.1)
≥65 y	7 (2.6)	7 (2.7)
Duration of asthma (mean [range]) (y)	20.6 (1-61)	22.7 (2-60)
Smoking status (no. of subjects [%])		
Never smoked	204 (76.1)	181 (70.4)
Ex-smoker	64 (23.9)	76 (29.6)
Beclomethasone dipropionate dose (mean [range]) (μg/day)	570 (420-1008)	568 (336-840)
Serum total IgE (mean [range]) (IU/mL)	172.5 (20-860)	186.3 (21-702)
FEV ₁ percent of predicted (screening) (mean [SD])	64.6 (12.5)	64.1 (11.6)
FEV ₁ percent of predicted (randomization) (mean [SD])	68.2 (14.9)	67.7 (14.3)
FEV ₁ (mean [SD]) (L/s)	2.3 (0.67)	2.4 (0.69)
Qualifying FEV ₁ reversibility (mean) (%)	26.9	25.9
Morning PEF during run-in (mean [SD]) (L/min)	321 (88.0)	328 (90.2)
Puffs of rescue medication per day during run-in (mean [SD])	4.9 (2.65)	4.8 (2.51)
Total asthma symptom score during run-in* (mean [SD])	4.31 (1.17)	4.24 (1.17)

*Sum of nocturnal, morning, and daytime scores.

per exacerbation was analyzed through use of the Wilcoxon rank sum test. To account for the potential bias introduced by subjects who discontinued the study, the number of exacerbations during a phase for these subjects was for the purpose of analysis imputed as number observed + (number of days between discontinuation and planned end of phase)/14, rounded up to the next integer. Subjects who permanently discontinued treatment during the double-blinded stable steroid phase were included in the analysis of the double-blinded steroid reduction phase. The number of exacerbations assigned to these subjects was the maximum number of exacerbations calculated during the steroid reduction phase plus 1. Subjects who did not enter the steroid reduction phase were included in the analysis of the steroid reduction variables with 0% BDP reduction. Percent of predicted FEV₁ and changes from baseline in morning PEF were analyzed through use of analysis of covariance in which treatment, center, treatment schedule, and gender were included as factors in the model and the baseline value was the covariate. All *P* values are 2-sided.

RESULTS

Demographics

With respect to demographic characteristics, the 2 groups were not statistically different (Table I). At the visit after screening, the distribution of ICS use was as follows: fluticasone propionate, 36.6%; BDP, 30.0%; triamcinolone acetonide, 21.0%; flunisolide, 8.8%; budesonide, 3.6%. After switching from these ICSs and dose titration, the BDP dose achieved in the last 4 weeks of the run-in period was 570 μg/day for the omalizumab group and 560 μg/day for the placebo group. The mean duration of asthma was at least 20

years, and the mean symptom score (on a scale of 0 to 9) was 4.31 and 4.24 for the omalizumab and placebo treatment groups, respectively. Mean FEV₁ was slightly higher for both groups at visit 3 randomization after ICS dose adjustment than at visit 1 screening. The asthma severity, based on National Heart, Lung, and Blood Institute (NHLBI) criteria,⁷ for the entire population in the study is shown in Table II. The data for this analysis were collected at the end of the run-in period. Most (99.3%) of the patients fell into the category of severe persistent asthma.

Nineteen (7.1%) of the omalizumab recipients and 34 (13.2%) of the placebo recipients withdrew prematurely. Thirteen (5%) of the omalizumab subjects and 23 (9%) of the placebo subjects discontinued during the stable steroid phase; 6 (2%) of the omalizumab subjects and 11 (4%) of the placebo subjects discontinued during the steroid reduction phase. Unsatisfactory therapeutic effect (1 vs 14), consent withdrawal (7 vs 11), administrative problem (4 vs 2), and lost to follow-up (4 vs 4) were common reasons for early termination in the omalizumab and placebo groups, respectively.

Asthma exacerbations

During the stable steroid phase, fewer omalizumab recipients than placebo recipients experienced 1 or more exacerbations (14.6% vs 23.3%; *P* = .009; Table III). In addition, the mean number of exacerbations per subject (0.28 vs 0.54; *P* = .006) and the mean duration of exacerbations (7.8 vs 12.7 days; *P* < .001) were lower with

TABLE II. Summary of asthma severity based on NHLBI guidelines by treatment (all randomized patients)

NHLBI severity and criteria ⁷	No. of subjects (%)		
	Omalizumab (n = 268)*	Placebo (n = 257)	All subjects (N = 525)
Severe persistent asthma (≥ 1 criterion)	266 (99.3)	256 (99.6)	522 (99.4)
FEV ₁ $\leq 60\%$ of predicted	79 (29.5)	76 (29.6)	155 (29.5)
Frequent nocturnal symptoms	174 (64.9)	167 (65.0)	341 (65.0)
Limited physical activity	243 (90.7)	239 (93.0)	482 (91.8)

Presence of a single feature is sufficient to place the patient in that category. Each patient is assigned to the most severe grade in which any feature occurs.

*Two patients, 1 moderate and 1 mild persistent, were not included.

TABLE III. Summary of asthma exacerbations by treatment phase

Asthma exacerbations	Stable steroid phase		Steroid reduction phase	
	Omalizumab (n = 268)	Placebo (n = 257)	Omalizumab (n = 268)	Placebo (n = 257)
No. of subjects with exacerbation (%)	39 (14.6)	60 (23.3)	57 (21.3)	83 (32.3)
P value	.0009	—	.0004	—
Mean no. of exacerbations per subject	0.28	0.54	0.39	0.66
P value	.006	—	.003	—
Mean no. of days per exacerbation	7.8	12.7	9.4	12.6
P value	<.001	—	.021	—

omalizumab than with placebo. A smaller proportion of subjects in the omalizumab group than in the placebo group experienced exacerbations that required urgent, unscheduled physician visits (3.0% vs 7.4%) or were associated with a reduction in PEF to $\leq 50\%$ of personal best value (0.4% vs 3.5%).

The decrease in asthma exacerbations produced by omalizumab during the stable steroid phase was maintained during the steroid reduction phase. During the steroid reduction phase, the omalizumab group had fewer subjects with exacerbations (21.3% vs 32.3%; $P = .004$), fewer exacerbations per subject (0.39 vs 0.66; $P = .003$), and a shorter mean duration of exacerbations (9.4 vs 12.6 days; $P = .021$) than placebo-treated subjects. As in the stable steroid phase, fewer omalizumab subjects than placebo subjects (0.8% vs 3.0%) had exacerbations associated with a decline in PEF of $\geq 50\%$.

Steroid dose reduction

The median reduction in ICS dose was significantly greater in the omalizumab group than in the placebo group (75% vs 50%; $P < .001$; Fig 1). Significantly more omalizumab recipients than placebo recipients achieved a $\geq 50\%$ reduction in BDP dose (72.4% vs 54.9%; $P < .001$). Overall, more omalizumab subjects than placebo subjects reduced their BDP dose. BDP was discontinued in 106 (39.6%) of the 268 omalizumab-treated recipients and 49 (19.1%) of the 257 placebo recipients ($P < .001$).

Asthma symptoms, rescue medication use, and pulmonary function

Omalizumab significantly improved daily asthma scores in comparison with placebo after week 4, and rescue medication use was significantly reduced in comparison with placebo for most weekly intervals (Fig 2).

TABLE IV. Summary of adverse events reported in at least 5% of subjects in either treatment group

Adverse event	No. of subjects (%)	
	Omalizumab (n = 268)	Placebo (n = 257)
Any adverse event	239 (89.2)	229 (89.1)
Upper respiratory tract infection	84 (31.3)	76 (29.6)
Viral infection	71 (26.5)	80 (31.1)
Headache	60 (22.4)	70 (27.2)
Sinusitis	52 (19.4)	56 (21.8)
Pharyngitis	39 (14.6)	35 (13.6)
Pain (back)	38 (14.2)	39 (15.2)
Arthralgia	26 (9.7)	9 (3.5)
Rhinitis	22 (8.2)	8 (3.1)
Coughing	20 (7.5)	23 (8.9)
Sprains and strains	20 (7.5)	14 (5.4)
Myalgia	19 (7.1)	17 (6.6)
Bronchitis	18 (6.7)	25 (9.7)
Nausea	18 (6.7)	16 (6.2)
Pain	18 (6.7)	14 (5.4)
Dyspepsia	17 (6.3)	31 (12.1)
Diarrhea	14 (5.2)	15 (5.8)
Insomnia	11 (4.1)	13 (5.1)
Sinus headache	4 (1.5)	13 (5.1)

Increases in morning PEF were greater on omalizumab (from 320 to 335 L/min) than on placebo, which remained at approximately 300 L/min, from baseline to the end of the study. At week 16, the mean change from baseline in PEF was 18.5 L/min with omalizumab and 6.9 L/min with placebo. Mean FEV₁ increased from 68.2% to 72.53% of predicted in the omalizumab group and from 67.7% to 69.1% of predicted in the placebo group. Statistically significant improvements for FEV₁ in comparison with placebo were maintained for the entire study (P values ranged from $<.001$ to .019).

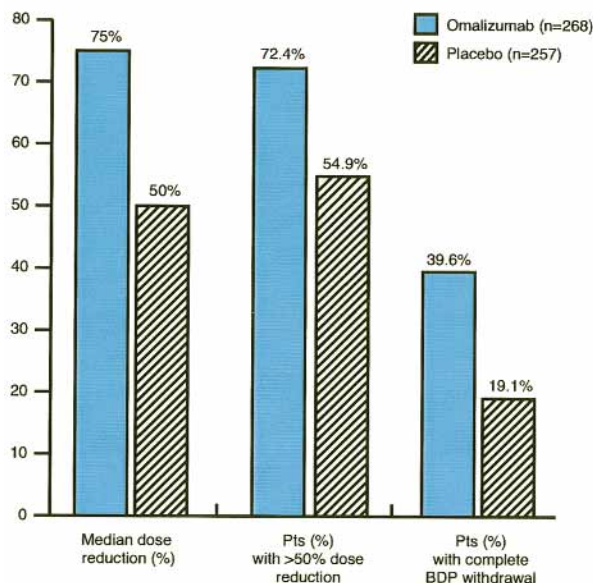


FIG 1. Effect of treatment on ICS use.

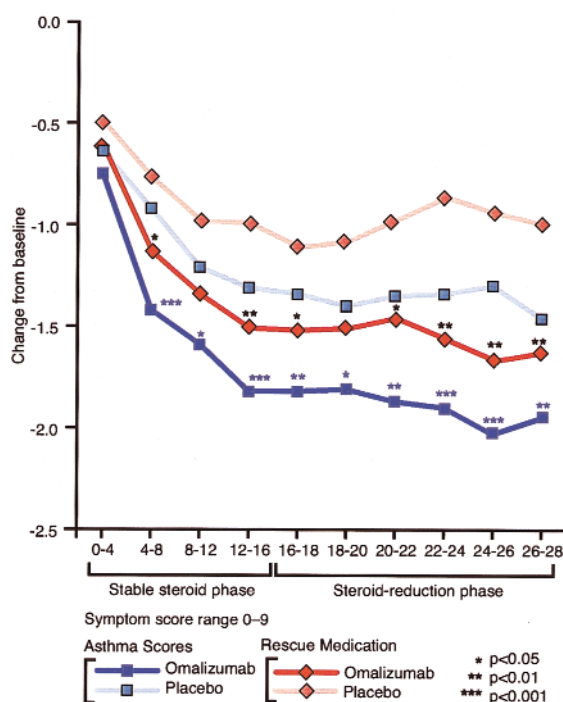


FIG 2. Mean change from baseline in total asthma symptom scores and numbers of puffs of rescue medication (albuterol) per day.

Global evaluation of therapy effectiveness

After 28 weeks of therapy, 60.6% of omalizumab recipients and 38.1% of placebo recipients rated treatment effectiveness as good (marked improvement of asthma) or excellent (complete control of asthma). The corresponding values for physicians' ratings of treatment effectiveness were 53.1% and 33.3%. The overall difference between the groups was significant in favor of omalizumab (both $P < .001$).

Serum IgE levels

Across the omalizumab dosing regimens, median free IgE was reduced by between 89% and 98%. At weeks 16 to 24, free IgE concentrations ranged from 6 to 8 IU/mL for the omalizumab group; this compared with >62 IU/mL for the placebo group. Total IgE increased in the omalizumab-treated subjects and did not change appreciably in the placebo subjects.

Adverse effects

Overall, the frequency of adverse events in the omalizumab and placebo groups was identical (89.2% vs 89.1%; Table IV). The majority of adverse events were mild or moderate in severity; 14.9% and 11.7% of adverse events in the omalizumab and placebo groups, respectively, were considered severe. There were 7 omalizumab patients (2.6%) and 6 placebo patients (2.3%) who experienced serious adverse events (not including asthma exacerbations); these included 1 death due to cardiac arrest in a subject receiving placebo. No serious adverse events were considered drug-related. Serious asthma exacerbations requiring hospitalization occurred in 3 subjects, 1 receiving omalizumab and 2 receiving placebo. Urticaria was reported in 4 (1.5%) of the omalizumab subjects and 8 (3.1%) of the placebo subjects. The percents of injections associated with local reactions were similar in the omalizumab (8.6%) and placebo (6.5%) groups. Two omalizumab subjects were discontinued because of adverse events; neither event was drug-related. No clinically relevant laboratory test abnormalities were observed. ELISA-reactive antibodies to the Fab fragment of omalizumab were not detected.

DISCUSSION

Allergic asthmatic patients enrolled in this study were not well controlled before randomization while being treated with a significant dose of BDP (400-800 µg per day). This, in conjunction with a long history of asthma, low FEV₁ on entry into the study, or significant symptoms as judged from daily diary card recordings, classified 99.3% of these patients as severe persistent asthmatics. In this often problematic patient population, omalizumab therapy was associated with significantly fewer asthma exacerbations than placebo. The mean number of asthma exacerbations per subject was 48% lower during the stable steroid phase and 41% lower during the steroid reduction phase in the omalizumab group than in the placebo group. In addition, more than one third fewer subjects in the omalizumab group experienced asthma exacerbations. The exacerbations that did occur had a significantly shorter mean duration in the omalizumab-treated patients. The analysis of exacerbations was restricted to those episodes severe enough to require a doubling of baseline BDP dose or a course of systemic corticosteroid. This conservative approach considerably strengthens the clinical relevance of the results.

Omalizumab was associated with a significant ICS-sparing effect. After 16 weeks of treatment, a significantly greater reduction in BDP was achieved with omalizumab treatment than with placebo. ICSs were completely withdrawn in twice as many subjects in the omalizumab group as in the placebo group. The reduction in BDP dose was achieved without precipitating asthma exacerbations, worsening symptoms and lung function, or increasing the use of rescue medication. This is an important outcome, given the fact that the patients enrolled in this study could be classified as severe persistent asthmatics, who in the scope of daily clinical practice are responsible for the a significant portion of the health care burden associated with asthma.⁸

The safety profile of omalizumab was no different from that of placebo, and adverse events were similar in the omalizumab and placebo groups. Arthralgia, reported more frequently in the omalizumab-treated patients, was generally mild and of short duration. In no instance was arthralgia associated with other symptoms suggestive of serum sickness. There was no evidence of hypersensitivity-type or immune complex-related adverse events. Taken altogether, these results further confirm the efficacy and safety of omalizumab treatment in patients with moderate to severe allergic asthma observed in an early study.⁹

A large reduction in serum free IgE concentration after omalizumab treatment is believed to be the basis of its therapeutic action.⁵ The increase in total IgE levels is expected in patients receiving omalizumab⁵ because omalizumab-bound IgE has a slower clearance than free IgE.¹⁰

Omalizumab suppresses free IgE and inhibits indices of allergen-induced inflammation, including mast cell degranulation and histamine release, late-phase asthmatic responses, pulmonary eosinophil infiltration,^{2,4,9,11,12} and nitric oxide concentration in exhaled air.¹³ IgE antibodies are crucial immune mediators of allergic reactions thought to be responsible for the induction and maintenance of chronic airway inflammation and asthma-related symptoms in genetically predisposed patients with asthma.¹⁴ Epidemiologic data demonstrate that elevated serum IgE levels and the presence of atopy are the strongest predictors of the development of asthma.¹⁵

Anti-inflammatory agents such as ICSs are currently the most effective drugs for the treatment of asthma.⁷ While suppressing inflammation, they are also associated with pharmacologically predictable side effects of steroid expression. Because IgE is an early and central mediator responsible for the induction and progression of allergic reactions, it is a promising therapeutic target in asthma treatment. A clear advantage of blocking IgE is that the allergic cascade is interrupted at its initiation before mediator release. Thus the expression of inflammation can be prevented rather than suppressed.

This study has shown that omalizumab is effective and safe in patients with severe allergic asthma who experience poor disease control or exacerbations despite recommended therapy. Omalizumab has steroid-sparing

effects in allergic asthma, is efficacious in seasonal allergic rhinitis,^{5,16} and is administered infrequently. Thus it might be useful for those allergic asthmatic patients who do not tolerate and/or are at risk of side effects of ICS, for those with concomitant occurrence of seasonal allergic rhinitis, and for those who have problems in adhering to the recommended treatment regimens.

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APPENDIX

In addition to the authors, the members of the Omalizumab (rhuMAB-E25) Study Group are William Berger, Southern California Research Center; Jonathan Bernstein, Bernstein Clinical Research Center, Inc; Edwin Bronsky,

Intermountain Clinical Research; B. Lauren Charous, Milwaukee Medical Clinic; Paul Chervinsky, New England Research Center; Albert Finn, Allergy & Asthma Centers of Charleston, Pa; James Grady, Boulder Medical Center; Gary Gross, Pharmaceutical Research and Consulting, Inc; Jeff Kishiyama, UCSF Clinical Trials Center; Theodore Lee, Peachtree Allergy and Asthma Clinic; Edward Lisberg, Asthma & Allergy Center of Chicago; William Lumry, Asthma and Allergy Research Associates; Andrew Martin, Asthma and Allergy Clinical Research Center;

James Metzger, East Carolina University; Anjuli Nayak, Asthma, Allergy & Immunology; Harold Nelson, National Jewish Center for Immunology and Respiratory Medicine; Warren Pleskow, El Camino Real; Stuart Simon, Southeast Research Associates; William Schoenwetter, Asthma and Allergy Research Center; M. Ross Thomas, Midwest Allergy and Asthma Clinic; Alkis Togias, Johns Hopkins Asthma and Allergy Center; Jay H. van Bavel, Allergy and Asthma Associates Research Center; and Hugh Windom, Asthma and Allergy Research Center.