ABSTRACT. Background and Objective. There seems to be a strong causal relationship between allergy and the origins of asthma. Susceptibility to both is determined by a combination of genetics and environment acting through a complex network of cytokines. Nearly 90% of affected children have positive skin tests indicating the presence of specific immunoglobulin E (IgE), with sensitivity to house dust mite, Alternaria, cockroach, cat, and dog most closely linked to the disease. Greater exposure to house dust mite during infancy leads to earlier onset of wheezing, and elevated serum IgE levels correlate with the appearance of asthma symptoms. Specific IgE binds to high-affinity (FcεRI) receptors on mast cells and basophils. The IgE-mediated reactions that follow exposure of sensitized mast cells to an allergen are designated early- and late-phase asthmatic responses (EAR and LAR). EAR is characterized by release of histamine and other preformed mediators within 1 hour of allergen exposure. It is often followed by LAR, an infiltration of the airways by inflammatory cells associated with an episode of more prolonged, and usually more severe airflow obstruction, 4 to 8 hours after antigen exposure. Chronic airway symptoms result from persistent LAR caused by continuous allergen exposure. IgE antibodies are capable of passive transfer of both EAR and LAR sensitivity. IgE-mediated mast cell activation contributes to chronic tissue eosinophilia and airway remodeling, with permanent loss in pulmonary function.

Omalizumab (rhuMAb-E25) is a recombinant, humanized, monoclonal anti-IgE antibody of mouse origin developed for the treatment of IgE-mediated diseases. Omalizumab binds to free IgE at the same site as the high-affinity receptor. Although it attaches to free IgE, it does not bind to IgA, IgG, or cell-bound IgE. It therefore does not induce cross-linking of cell-bound IgE, which would lead to the release of allergic mediators. It has been reported to decrease serum IgE levels in a dose-dependent manner, inhibit EAR and LAR, and cause a down-regulation of FcεRI receptors on basophils. Omalizumab has been reported to be safe and effective in improving asthma control and reducing the requirement for oral and inhaled corticosteroids. This double-blind, randomized, placebo-controlled study evaluated the safety, steroid-sparing effects, and impact on disease exacerbations of omalizumab in the treatment of childhood asthma.

Methods. Participants were 334 males and premenarchal females aged 6 to 12 years, with moderate to severe allergic asthma requiring treatment with inhaled corticosteroids. During a run-in phase, all children were switched to equivalent doses of beclomethasone dipropionate (BDP), and the dose was adjusted to assure maintenance of asthma control achieved with previous corticosteroid treatment. Children were randomized to subcutaneously administered placebo (N = 109) or omalizumab (N = 225) at a dose based on body weight and initial serum IgE (0.016 mg/kg/IgE [IU/mL] per 4 weeks). BDP dose (initial range 168–420 μg/d) was kept stable for 16 weeks (stable-steroid phase), reduced over 8 weeks to the minimum effective dose (steroid-reduction phase), and maintained constant for the final 4 weeks.

Results. More participants in the omalizumab group decreased their BDP dose, and their reduction was greater than that of the placebo group (median reduction 100% vs 66.7%). BDP was withdrawn completely in 55% of the omalizumab group versus 39% of the placebo group. The incidence and the frequency of asthma exacerbations requiring treatment with doubling of BDP dose or systemic corticosteroids were lower in the omalizumab group. The treatment differences were statistically significant during the steroid-reduction phase, during which fewer participants in the omalizumab group had asthma exacerbation episodes (18.2% vs 38.5%), and the mean number of episodes per patient was smaller than with placebo (0.42 vs 2.72). Five asthma exacerbations requiring hospitalization all occurred in the placebo group.

Participants’ and investigators’ global evaluations of treatment effectiveness were more favorable for omalizumab than placebo. Investigators rated effectiveness excellent for 31.5% of the omalizumab group versus 16.3% of the placebo group and good for 44.7% of the omalizumab group versus 32.7% of the placebo group.

There was little change in asthma symptom scores or spirometry measurements during either the stable-steroid or steroid dose-reduction phase, with minimal differences between the treatment groups.

The requirement for rescue medication in the omalizumab group during both the stable-steroid and steroid dose-reduction phases was consistently lower than at baseline. At week 28, the median number of puffs of rescue medication taken daily was 0 in the omalizumab group and 0.46 in the placebo group. The change from baseline was significant in favor of omalizumab.

Over the entire treatment period, patients in the omalizumab group missed a mean of 0.65 school days, com-
pared with a mean of 1.21 days in the placebo group. The mean number of unscheduled medical contacts attributable to asthma-related medical problems was significantly smaller in the omalizumab group than in the placebo group throughout the treatment period (0.15 vs 5.35).

Median reduction in serum free IgE was 95% to 99% among omalizumab patients. Median free IgE ranged from 133 to 790 IU/mL at baseline and was in the range of 6 to 9 IU/mL during the treatment period. The dosing scheme used in the trial therefore effectively reduced serum IgE in patients with initial concentrations as high as 1500 IU/mL. There was no reduction in free IgE in the placebo group.

Omalizumab treatment was well tolerated. There were no serious treatment-related adverse events. The frequency and types of all adverse events were similar in the omalizumab and placebo groups. The majority of adverse events were mild to moderate in severity. No adverse events suggestive of serum sickness or immune complex formation were observed. Study-drug–related adverse events occurred more frequently in the omalizumab group than in the placebo group (6.2% vs 0.9%). Urticaria was reported in 9 omalizumab patients (4%) compared with 1 (0.9%) placebo patient and was mild or moderate in nearly all cases.

Conclusion. Treatment with omalizumab is safe in children with asthma. It reduces the requirement for inhaled corticosteroids while protecting against disease exacerbation. 

ABBREVIATIONS. IgE, immunoglobulin E; EAR, early-phase asthmatic response; LAR, late-phase asthmatic response; FEV-1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; BDP, beclomethasone dipropionate; AE, adverse event; PEFR, peak expiratory flow rate; FVC, forced vital capacity; FEF 25%–75%, forced expiratory volume during middle half of forced vital capacity.

The prevalence of asthma, the most common chronic illness of children, has increased dramatically over the past several decades, culminating in a 75% rise between 1980 and 1994 in the United States. Despite progress in the understanding of its pathophysiology and an increase in the number of treatment modalities, the age-adjusted mortality rate of asthma has accelerated from 0.93 per 100 000 between 1979 and 1980 to 1.49 between 1993 and 1994. There seems to be a strong causal relationship between allergy and the origins of asthma. The susceptibility to both is determined by a combination of genetics and environment acting through a complex network of cytokines. Nearly 90% of affected children have positive skin tests, indicating the presence of specific immunoglobulin E (IgE), with sensitivity to the common allergens—house dust mite, Alternaria, cockroach, cat, and dog—most closely linked to the disease. Significantly, greater exposure to house dust mite during infancy leads to earlier onset of wheezing, and elevated serum IgE levels correlate with the appearance of asthma symptoms.

Specific IgE binds to high-affinity (FcεRI) receptors on mast cells and basophils. The IgE-mediated reactions that follow the exposure of the sensitized mast cells of an individual with asthma to an allergen have been designated as early- and late-phase asthmatic responses (EAR and LAR). EAR is characterized by a release of histamine and other preformed mediators from the mast cells and a short-lived fall in forced expiratory volume in 1 second (FEV-1) within 1 hour of allergen exposure. It is often followed by LAR, an infiltration of the airways by inflammatory cells associated with an episode of more prolonged, and usually more severe airflow obstruction, 4 to 8 hours after antigen exposure. Chronic airway symptoms result from persistent LAR caused by continuous allergen exposure. IgE antibodies are capable of passive transfer of both EAR and LAR sensitivity. IgE-mediated mast cell activation contributes to chronic tissue eosinophilia and airway remodeling, an irreversible change in airway architecture with permanent loss in pulmonary function.

Omalizumab (rhuMAb-E25) is a recombinant, humanized, monoclonal anti-IgE antibody of mouse origin developed for the treatment of IgE-mediated diseases. Omalizumab binds to free IgE at the same site as the high-affinity (FcεRI) receptor. Although it attaches to free IgE, it does not bind to IgA, IgG, or cell-bound IgE. It is termed nonanaphylactogenic because it does not induce cross-linking of cell-bound IgE that would lead to the release of allergic mediators. It decreases serum IgE levels in a dose-dependent manner, inhibits EAR and LAR, and causes a down-regulation of FcεRI receptors on basophils. It has been found safe and effective in improving asthma control and reducing the requirement for oral and inhaled corticosteroids.

We report here on a multicenter, randomized, double-blind, placebo-controlled, parallel-group, 28-week trial designed primarily to evaluate the safety and steroid-sparing effect and secondarily, the impact on asthma exacerbations of omalizumab in children with moderate to severe allergic asthma who require daily treatment with inhaled corticosteroids (ICSs).

METHODS

Patients

The study enrolled male and premenarchal female asthmatic patients aged 6 to 12 years, whose asthma was well controlled with ICSs equivalent to 168 to 420 μg/d of beclomethasone dipropionate (BDP) and bronchodilator therapy as needed for ≤3 months before randomization. To be included in the study, patients had to have: 1) a diagnosis of allergic asthma of at least 1 year’s duration; 2) a positive skin prick test to at least 1 of the following allergens, to which the children were exposed during the study: Dermatophagoides farinae, Dermatophagoides pteronyssinus, cockroach (whole body), dog or cat; 3) total serum IgE level between 30 and 1300 IU/mL; 4) body weight ≤90 kg; 5) baseline forced expiratory volume at 1 second (FEV-1) ≥60% of the predicted normal value; 6) at least a 12% increase in FEV-1 over baseline within 30 minutes of taking 1 or 2 puffs of albuterol (90 μg/puff); and 7) stable asthma, defined as no significant change in the regular asthma medication and no acute asthma exacerbation requiring corticosteroid rescue for at least 4 weeks before enrollment. Patients were excluded from the study if they had previously been treated with omalizumab; known hypersensitivity to any study drug; a history of acute infectious sinusitis or respira-
tory tract infection or active lung disease other than allergic asthma within 1 month or any other significant systemic disease within 3 months of visit 1; clinically significant abnormalities in electrocardiogram, chest radiograph, or laboratory values, or ele-
vated serum IgE levels for reasons other than atopy. Those chil-
dren who would have required omalizumab doses of >750 mg per 4 weeks, based on total serum IgE and body weight consideration (0.016 mg/IgE in IU/mL × body weight in kg), were excluded.

**Study Protocol**

After a 1-week enrollment and screening period, there were 3 phases: 1) run-in phase (4–6 weeks), 2) stable-steroid phase (16 weeks), and 3) steroid dose-reduction phase (12 weeks). Patients who completed the study were offered entry into an open-label extension study to assess long-term safety, which will be reported elsewhere. The study was performed in accordance with the Declaration of Helsinki and its amendments. Parents or guardians gave written informed consent, and the patients signed an assent statement before enrollment. The institutional review board at each center approved the study.

In the 4- to 6-week run-in phase, all patients not receiving BDP were switched to BDP 42 μg/puff for oral inhalation administered twice daily (168–420 μg/d). Initially, BDP was administered in doses considered to be comparable to the patient’s previous maintenance corticosteroid treatment. Subsequently, at week 2 of the run-in phase, the dose of BDP was adjusted to maintain the previous level of asthma control. Patients whose asthma was well-controlled with BDP 2 or 5 puffs twice daily (168–420 μg/d ex mouthpiece equal to 200–500 μg/d ex valve, as often reported outside the United States) were maintained on stable doses for 4 weeks before randomization. At the end of the run-in phase, patients who met the criteria were randomized to either omalizumab or placebo with a 2:1 randomization ratio. Patients and investigators were blinded to the treatment administered.

Depending on the patient’s body weight and serum IgE at visit 1, patients randomized to omalizumab were treated with subcu-
taneous administration of omalizumab 150 mg or 300 mg every 4 weeks or with omalizumab 225 mg, 300 mg, or 375 mg every 2 weeks, using a dosing chart designed to assure a minimum dose of 0.016 mg/kg/IgE (IU/mL) per 4 weeks. Patients were main-
tained on the baseline dose of BDP for the first 16 weeks of the double-blind treatment period (stable-steroid phase), and then the dose was tapered gradually (steroid dose-reduction phase). Over the first 8 weeks of steroid dose-reduction phase, BDP was reduced step-wise, approximately 25% of the baseline dose every 2 weeks, until total elimination or worsening of asthma, to establish the minimum effective dose of BDP. If the reduction in the BDP dose resulted in development of 1 or more of the criteria associated with the worsening of asthma listed below, the corticosteroid tapering was stopped and the BDP dose was increased to a previ-
ously tolerated level or higher, based on the investigator’s clini-
cal judgment. Participants were maintained on this minimum effective dose of BDP during the last 4 weeks of the steroid dose-reduction phase.

**Concomitant Medication**

Throughout the study, albuterol (salbutamol) 2 puffs (90 μg/ puff ex mouthpiece equal to 100 μg/puff ex valve, as often re-
ported outside the United States) as needed (maximum 8 puffs daily) was allowed as rescue medication for symptoms of bron-
chospasm. Except for treatment of asthma exacerbation, all other asthma medications, including β-adrenergic agonists other than albuterol, were prohibited during the study.

**Safety Assessments**

Safety and tolerability were evaluated by gauging the fre-
quency, severity, and seriousness of adverse events (AEs) and the reported relationship to the study drug; clinically significant changes in laboratory measures and vital signs; and local reactions at the injection site.

**Efficacy Assessments**

To evaluate the steroid-sparing effects, the BDP dose main-
tained constant for the last 4 weeks of the steroid dose-reduction phase was compared with the baseline dose. The percentage re-
ductions in the dose of BDP from baseline value and the propor-
tion of patients with a reduction in the dose of BDP were analyzed. Asthma symptom scores, rescue medication use, pulmonary function test results, and asthma exacerbations were recorded as follows:

- During both the run-in and stable-steroid phases, patients maintained a daily diary to record nocturnal and daytime asthma symptom score (0–4 scale), morning asthma symptoms (yes = 0, no = 1), number of puffs of rescue medication during day and night, morning peak expiratory flow rate (PEFR) using Mini-Wright peak flow meter (Clement Clarke International for Ferraris Medical Inc, Holland, NY), and number of puffs of BDP.
- Spirometry measurements (FEV1, forced vital capacity [FVC], forced expiratory volume during middle half of forced vital capacity [FEF 25%–75%]) were performed before start of the treatment and predose, and 1-hour postdosing throughout both the stable-steroid phase and the steroid dose-reduction phase.
- Any worsening of asthma that in investigator’s clinical judg-
ments required additional treatment, over and above the main-
tenance BDP dose and pro re nata β2 agonist rescue medica-
tion, was defined as an asthma exacerbation episode.

For early assessment of worsening asthma, patients were in-
structed to contact the investigator for any of the following indi-
cations:

- Worsening of asthma requiring an urgent (unscheduled) visit for medical care;
- PEFR <50% of patient’s personal best;
- A decrease in morning PEFR of ≥20% on ≥2 of 3 successive days, compared with baseline (the lowest morning PEFR in the week before visit 3 [week 0] and before start of BDP dose-
reduction provided the baseline values for the stable-steroid phase and steroid dose-reduction phase, respectively);
- A >50% increase in 24-hour rescue medication use on ≥2 of 3 successive days (≥8 puffs), compared with baseline;
- ≥2 of 3 successive nights with awakenings because of asthma symp-
toms requiring rescue medication;
- A decrease in FEV1-1 of ≥20% compared with baseline.

Patients developing any of the above manifestations were eval-
uated by the investigator and treated in accordance with the current guidelines for management of asthma exacerbation. Each asthma exacerbation episode requiring additional treatment was recorded on the case report form with the start and end date, the cause of asthma exacerbation, the asthma exacerbation criteria met, and the treatment required. Asthma exacerbations that were serious enough to require doubling of the BDP dose or systemic corticosteroids were used for the statistical analysis.

**Global Evaluation of Effectiveness**

At the end of the study both patients and investigators per-
formed global evaluations of treatment effectiveness using the following ratings: excellent (complete control of asthma), good (marked improvement), moderate (discernible but limited im-
provement), poor (no appreciable change), or worsening.

**Pharmacoeconomics**

Frequency of unscheduled medical contacts (phone consults, office visits, emergency department visits, urgent care center vis-
ts, admissions to hospital, additional lab work, additional proce-
dures) for treatment of asthma and other allergic diseases, fre-
quency of school absence because of asthma, and frequency of
missed work by the patient’s caregiver were recorded throughout double-blind treatment.

**Pharmacodynamics**

Serum samples were taken at baseline and before dosing at weeks 16 and 24 for determination of IgE concentrations. In pa-
tients treated with omalizumab, total serum IgE comprises free IgE (that not bound to omalizumab) and bound IgE (that com-
plicated to omalizumab). Serum IgE at baseline (before omalizumab treatment) consists entirely of free IgE. Serum concentrations of both free and total IgE (free IgE + bound IgE) were measured using an enzyme-linked immunoassay with the use of Fc-receptor-IgG chimeric antibody and monoclonal anti-IgE. Serum samples were screened for the presence of anti-omalizumab antibodies
using an antibody assay based on the method described by Casale et al.30

After omalizumab treatment, values of free IgE above 150 ng/mL could not be quantified by the assay and were reported as >150 ng/mL. Concentrations of free IgE in ng/mL can be converted to IU/mL by dividing by 2.42.31,32 Changes in total and free IgE levels in serum compared with baseline were calculated.

Statistical Analysis

All randomized patients who received 1 or more doses of the study medication were included in the efficacy and safety analyses.

The percentage reduction in the dose of BDP and the proportion of patients who were able to reduce the dose of BDP were analyzed using the generalized Cochran-Mantel-Haenszel (van Elteren) test stratified by treatment schedule.33 Patients who did not enter the steroid dose-reduction phase were included in the analysis of these 2 variables with 0% BDP reduction. Asthma exacerbations requiring treatment with doubling of the BDP dose or systemic corticosteroid were expressed as the number of exacerbations per patient and the number of patients experiencing one or more exacerbation in each phase and analyzed using the generalized van Elteren test stratified by treatment schedule. The Breslow-Day test was used to determine the homogeneity of proportions across the dosing frequency strata (q 2 weeks, q 4 weeks).34 To account for the potential bias introduced by patients who discontinued the study, for the purpose of analysis, the number of asthma exacerbations during a phase for these patients was imputed as \( \text{number observed} + \lfloor \text{number of days between discontinuation and planned end of phase} / 14 \rfloor \) rounded up to the nearest integer. Patients who permanently discontinued treatment during the double-blind stable-steroid phase were included in the analysis of the double-blind steroid dose-reduction phase.

In the steroid dose-reduction phase, the number of asthma exacerbations assigned to patients who discontinued during the stable-steroid phase was the maximum number of episodes calculated during the steroid dose-reduction phase + 1). Differences in the proportion of patients who had an unscheduled physician visit, experienced a decrease in morning PEFR >20% on 2 or 3 successive days, or awakenings on 2 or 3 successive nights that required rescue medication were analyzed using the Pearson \( x^2 \) test. The patients' and investigators' global evaluations of treatment effectiveness were analyzed at the last visit using the generalized Cochran-Mantel-Haenszel test, stratified by treatment schedule. Change from baseline in rescue albuterol use was analyzed using the Pearson \( x^2 \) test. The Breslow-Day test was used to determine the homogeneity of proportions across the dosing frequency strata (q 2 weeks, q 4 weeks).34 To account for the potential bias introduced by patients who discontinued the study, for the purpose of analysis, the number of asthma exacerbations during a phase for these patients was imputed as \( \text{number observed} + \lfloor \text{number of days between discontinuation and planned end of phase} / 14 \rfloor \) rounded up to the nearest integer.

RESULTS

Patient Characteristics

A total of 334 patients were randomized into the double-blind study: 225 to omalizumab (76 dosed every 2 weeks, 149 dosed every 4 weeks) and 109 to placebo (35 dosed every 2 weeks, 74 dosed every 4 weeks). Baseline characteristics of the study population are summarized in Table 1. At baseline, patients in both treatment groups had minimal asthma symptoms, with mean rescue albuterol use under 2 puffs/d. There were no statistically significant differences between the omalizumab and placebo groups with respect to any of the demographic or background variables.

Patient Disposition

Of the 501 patients screened, 6.8% were excluded because of serum IgE >1300 IU/mL, and 5.4% were excluded because of serum IgE <30 IU/mL. Sixteen (7.1%) omalizumab and 12 (11.0%) placebo participants did not complete the study. In the omalizumab group, 9 patients (4%) were discontinued during the stable-steroid phase and 7 (3.1%) during the steroid dose-reduction phase; in the placebo group, 8 patients (7.3%) were discontinued during the stable-steroid phase and 4 (3.7%) during the steroid dose-reduction phase. Withdrawal of consent was the most frequent reason for premature termination in both omalizumab (3.1%) and placebo (4.6%) groups. One patient in each treatment group was discontinued because of lack of efficacy, and 1 patient in each was discontinued because of adverse effects (urticaria in 1 omalizumab treated patient, hip fracture in 1 placebo patient).

Safety and Tolerability

There were no serious treatment-related AEs reported in this study. Serious asthma exacerbations

| TABLE 1. Summary of Demographic and Baseline Characteristics by Treatment (All Randomized Patients) |
|------------------------|------------------------|------------------------|
|                         | Omalizumab (N = 225)   | Placebo (N = 109)      |
| Gender, n (%)           | 158 (70.2)             | 73 (67.0)              |
| Male                   | 158 (70.2)             | 73 (67.0)              |
| Race, n (%)            | 168 (74.7)             | 86 (78.9)              |
| White                  | 38 (16.9)              | 14 (12.8)              |
| Black                  | 19 (8.4)               | 9 (8.3)                |
| Mean age (range, y)    | 9.4 (5–12)             | 9.5 (6–12)             |
| Mean duration of asthma (range, y) | 6.1 (1–12)       | 6.1 (1–12)             |
| Mean BDP dose (range, µg/day) | 284 (165–672)     | 267 (165–504)          |
| Mean serum total IgE (range, IU/mL) | 348 (20–1269) | 323 (29–1212)         |
| Mean FEV-1, % predicted (range) | 84 (49–129) | 85 (43–116)          |
| Mean FEV-1 reversibility, % | 20.39               | 19.59                  |
| Mean morning PEFR (range, L/min) | 261 (101–408) | 264 (140–407)         |
| Number hospitalized for asthma treatment past y, n (%) | 18 (8.0) | 9 (8.0) |
| Mean number of doctor’s office visits for urgent asthma treatment past y | 1.9 | 1.6 |
| Mean number emergency room visits for asthma past y | 0.6 | 0.6 |
| Mean daytime asthma symptom score (median) | 0.52 (0.31) | 0.57 (0.38) |
| Mean nocturnal asthma symptom score (median) | 0.21 (0) | 0.25 (0) |
| Mean morning asthma symptom score (median) | 0.17 (0) | 0.17 (0) |
| Mean albuterol use (median, puffs/day) | 1.1 (0.31) | 1.4 (0.45) |
requiring hospitalization occurred in 5 patients, all in the placebo group. The frequency and types of all AEs, judged treatment related or not, were similar in the omalizumab group and the placebo group (Table 2). The majority of AEs were mild to moderate in severity. The most commonly reported AEs were headache (36.0% vs 30.3% for placebo), pharyngitis (25.8% vs 23.9% for placebo), upper respiratory tract infection (34.7% vs 35.8% for placebo), and viral infection (24.9% vs 22.9% for placebo). No AEs suggestive of serum sickness or immune complex formation were observed. Urticaria was reported in 9 omalizumab patients (4%) compared with 1 (0.9%) placebo patient. In all except 2 patients, the urticaria was mild or moderate, resolved spontaneously or with antihistamine therapy (1 patient required corticosteroid treatment), and did not recur with subsequent treatment. The urticaria occurring 1 day after the first injection of omalizumab in 1 patient was considered severe; this resolved spontaneously in 20 minutes and did not recur with subsequent treatment. One omalizumab patient experienced mild to moderate urticaria on 2 occasions and was discontinued from the study.

Study-drug–related AEs occurred more frequently in the omalizumab group than in the placebo group (6.2% vs 0.9%; \( P = .029 \)), but these were few in either group (Table 2). The drug-related AEs in omalizumab treated patients included urticaria (1.3%), rash (0.4%), flushing (0.4%), and pruritus (0.4%). Urticaria, dyspepsia, and abnormal vision reported in 1 placebo patient were considered treatment related. Injection site pain or other local skin reactions (burning, itching, warmth, bruising, redness, hive formation, rashes) occurred in 37.5% omalizumab and 36.6% placebo-treated patients; the frequency and severity of local reaction tended to decrease over the course of the study. Four omalizumab patients (1.7%) and 2 placebo patients (1.8%) withdrew from the study because of pain and/or fear of injection. There were no clinically meaningful changes from baseline in clinical laboratory measures or vital signs in either the omalizumab or placebo group. There were no significant differences between the omalizumab and placebo group in changes in height and weight during the study.

One patient (0.4%) in the omalizumab group was withdrawn from the study because of urticaria, as described above, and 1 patient (0.9%) in the placebo group was withdrawn because of a prolonged hospitalization for hip fracture.

**BDP Dose Reduction**

The median reduction in the dose of BDP from baseline was 100% in the omalizumab group compared with that in the placebo group (Fig 1). The difference between the omalizumab group and the placebo group is statistically significant (\( P = .002 \)).

| TABLE 2. Number (%) of All Randomized Patients Reporting Most Frequent Adverse Events |
|----------------------------------------|-----------------|-----------------|
| **Adverse Event** | **Omalizumab (N = 225)** | **Placebo (N = 109)** |
| | Number (%) | Number (%) |
| **Whether or not judged study related** | | |
| Any | 201 (89.3) | 95 (87.2) |
| Headache | 81 (36.0) | 33 (30.3) |
| Pharyngitis | 58 (25.8) | 26 (23.9) |
| Upper respiratory tract infection | 78 (34.7) | 39 (35.8) |
| **Viral infection** | 56 (24.9) | 25 (22.9) |
| **Fever** | 39 (17.3) | 16 (14.7) |
| **Sinusitis** | 38 (16.9) | 22 (20.2) |
| **Coughing** | 30 (13.3) | 19 (17.4) |
| Abdominal pain | 28 (12.4) | 13 (11.9) |
| Rhinitis | 24 (10.7) | 12 (11.0) |
| Otitis media | 19 (8.4) | 7 (6.4) |
| Trauma | 17 (7.6) | 3 (2.8) |
| Vomiting | 15 (6.7) | 9 (8.3) |
| **Ear ache** | 15 (6.7) | 4 (3.7) |
| Injury | 13 (5.8) | 1 (0.9) |
| Dyspepsia | 13 (5.8) | 2 (1.8) |
| **Judged study related** | | |
| Any | 14 (6.2) | 1 (0.9) |
| Urticaria | 3 (1.3) | 0 (0.0) |
| Rash maculopapular | 1 (0.4) | 0 (0.0) |
| Flushing | 1 (0.4) | 0 (0.0) |
| Pruritus | 1 (0.4) | 0 (0.0) |
| Pain, arm | 1 (0.4) | 0 (0.0) |

http://www.pediatrics.org/cgi/content/full/108/2/e36
pared with 66.7% in the placebo group ($P = .001$). A significantly greater proportion of patients treated with omalizumab reduced the inhaled steroid dose compared with patients in the placebo group ($P = .002$; Fig 1). BDP was withdrawn completely in 55% of the omalizumab group versus 39% of the placebo group ($P = .004$).

### Asthma Exacerbations

Table 3 summarizes the asthma exacerbations reported during the stable-steroid and steroid dose-reduction phases. The majority of the asthma exacerbations required treatment with doubling of BDP dose or systemic corticosteroids. During both phases, the incidence (percentage of patients with exacerbation) and the frequency (number of episodes per patient) of asthma exacerbations requiring treatment with doubling of BDP dose or systemic corticosteroids were lower in the omalizumab group; the treatment differences were statistically significant during the steroid dose-reduction phase (18.2% vs 38.5%, $P < .001$; 0.42 vs 2.72, $P < .001$, respectively). The mean duration of asthma exacerbation episodes was similar in the 2 treatment groups during both phases (range: 10–14 days).

The most frequently reported reason for asthma exacerbation was infection, including upper respiratory tract infection, pharyngitis, bronchitis, and influenza (50% omalizumab, 41% placebo) followed by allergen exposure, including allergic rhinitis (13.2% omalizumab, 14.8% placebo). Steroid reduction was considered the cause of asthma exacerbation in only 1 patient (omalizumab group).

A markedly higher proportion of patients in the placebo group than in the omalizumab group required an urgent, unscheduled physician visit (30.3% placebo vs 12.9% omalizumab, $P = .001$), or experienced a decrease in morning PEFR ≥20% on 2 or 3 successive days (17.4% vs 6.7%, $P = .002$) or awakening on 2 or 3 successive nights that required rescue medication (21.1% vs 11.6%, $P = .002$).

### Asthma Symptom Score, Rescue Beta-Agonist Use, and Pulmonary Function

There was little change in asthma symptom scores, morning PEFR, FEV-1, FVC, or FEF 25%–75% during the course of either stable-steroid or steroid dose-reduction phase, with minimal difference between the treatment groups. Median nocturnal asthma symptom score was zero in both the omalizumab and placebo groups at week 0 and remained at or close to zero throughout the study. Mean nocturnal asthma symptom score was lower in the omalizumab group at all evaluations. No notable treatment group differences were seen in daytime asthma symptom score until week 22, when the omalizumab group had a mean symptom score of 0.36, compared with 0.54 in the placebo group. A similar difference persisted until the end of the study. Mean morning PEFR was 261.3 L/min in the omalizumab group and 264.0 L/min in the placebo group at week 0; it was 269.8 L/min vs 265.0 L/min at the end of the study (week 28). Mean FEV-1 was 1797.1 mL in the omalizumab group and 1855.2 mL in the placebo group at week 0; it was 1891.0 mL versus 1883.5 mL at week 28. Mean FVC was 2272.2 mL in the omalizumab group and 2334.4 mL in the placebo group at week 0; it was 2404.9 mL versus 2422.0 mL at week 28. Mean FEF 25%–75% was 1711.7 mL/s in the omalizumab group and 1752.5 mL/s in the placebo group at week 0; it was 1774.8 mL/s versus 1691.5 mL/s at week 28. The dosage of rescue medication (puffs of albuterol taken daily) was consistently lower than baseline during both the stable-steroid and steroid dose-reduction phases in the omalizumab group. At week 28, the median number of puffs of rescue medication taken daily was 0 in the omalizumab group and 0.46 in the placebo group. The change from baseline was statistically significant in favor of omalizumab ($P = .004$).

### Table 3. Summary of Asthma Exacerbations by Treatment Phase

<table>
<thead>
<tr>
<th>Asthma Exacerbations</th>
<th>Stable Steroid Phase</th>
<th>Steroid Reduction Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Omalizumab</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>$n = 225$</td>
<td>$n = 109$</td>
</tr>
<tr>
<td>Number (% patients with exacerbations</td>
<td>45 (20.0)</td>
<td>30 (27.5)</td>
</tr>
<tr>
<td>Treated with β-agonists or CS</td>
<td>34 (15.1)</td>
<td>21 (19.3)</td>
</tr>
<tr>
<td>Treated with systemic CS</td>
<td>28 (12.4)</td>
<td>20 (18.3)</td>
</tr>
<tr>
<td>Mean number of episodes per patient</td>
<td>0.26</td>
<td>0.36</td>
</tr>
<tr>
<td>Treated with β-agonists or CS</td>
<td>0.18</td>
<td>0.24</td>
</tr>
<tr>
<td>Treated with systemic CS</td>
<td>0.14</td>
<td>0.23</td>
</tr>
<tr>
<td>Analysis of exacerbations requiring doubling of BDP dose or systemic CS*</td>
<td>35 (15.6)</td>
<td>25 (22.9)</td>
</tr>
<tr>
<td>Number (%) patients with exacerbation (imputed value)</td>
<td>.095</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mean number of episodes per patient (imputed value)</td>
<td>0.3</td>
<td>0.4</td>
</tr>
<tr>
<td>Mean number of days per exacerbation</td>
<td>10.2</td>
<td>14.0</td>
</tr>
</tbody>
</table>

* CS indicates corticosteroids.
† Percentages based on the number of randomized patients.
Global Evaluation of Treatment Effectiveness

At the end of the study, investigators’ global evaluation of effectiveness favored the omalizumab group over the placebo group \((P < .001)\). Effectiveness was rated excellent for 31.5% of the omalizumab group versus 16.3% of the placebo group; it was rated good for 44.7% of the omalizumab group versus 32.7% of the placebo group. The patients’ global evaluation of effectiveness was virtually identical to the investigators’; it was significantly better for omalizumab as compared with placebo \((P < .001)\).

Pharmacoeconomics

Over 28 weeks of the double-blind treatment period, patients in the omalizumab group missed a mean of 0.65 school days, compared with a mean of 1.21 days in the placebo group \((P = .040)\). The mean number of missed work days by the patient’s caregiver was 0.29 days in the omalizumab group compared with 0.49 days in the placebo group, but the difference did not achieve statistical significance \((P = .097)\).

The mean number of unscheduled medical contacts attributable to asthma-related medical problems was significantly smaller in the omalizumab group than in the placebo group throughout the treatment period \((0.15\,vs\,5.35;\,P = .001)\).

Pharmacodynamics

Serum free IgE decreased in omalizumab treated patients (Fig 2). Across the 5 dosage subgroups (150 mg q 4 weeks, 300 mg q 4 weeks, 225 mg q 2 weeks, 300 mg q 2 weeks, and 375 mg q 2 weeks), median free IgE ranged from 133 to 790 IU/mL at baseline, from 6 to 9 IU/mL predose at the end of the stable-steroid phase, and from 7 to 9 IU/mL predose at week 24 of the treatment period. This corresponded to a reduction in free serum IgE ranging from 95% in the 150 mg q 4 weeks subgroup to 99% in the q 2 weeks subgroups. Greater reductions were observed during the first few days after dosing. For the placebo group during the treatment period, median free IgE was greater than 62 IU/mL (150 ng/mL, which was the upper limit of quantification of the free IgE assay during the treatment period), and it is plotted in Fig 2 as the baseline value.

Total IgE (free + bound IgE) increased in omalizumab treated patients (Fig 3). The median of the percentage increases ranged from 168% (375 mg q 2 weeks) to 431% (150 mg q 4 weeks) at week 16 and from 160% (375 mg q 2 weeks) to 372% (150 mg q 4 weeks) at week 24. For the placebo group, total IgE was close to baseline at weeks 16 and 24.

DISCUSSION

Worldwide, 5% to 10% of children suffer from asthma. Atopy, the genetic predisposition to develop IgE-mediated responses to common allergens, and elevated IgE concentrations are the strongest identifiable factors for the development of asthma in young children. The recently developed recombinant humanized monoclonal anti-IgE antibody, omalizumab, has been found to be safe and effective in adult and adolescent patients with seasonal allergic rhinitis and allergic asthma. The present study was undertaken to assess the safety and steroid-sparing effects of omalizumab in children (aged 6–12 years) with moderate to severe allergic asthma.

Omalizumab was well tolerated, with no evidence of clinically significant drug toxicity or serious treatment-related AEs. It is noteworthy that serious asthma exacerbations requiring hospitalization occurred in 5 (4.6%) of 109 placebo patients but in none of the omalizumab group. No immunologic or immune complex-related AEs were noted except for several generally mild or moderate cases of urticaria.

The adverse events reported in the omalizumab group were similar to those in the placebo group. The most frequently reported adverse events in both groups consisted of commonly occurring medical complaints (headache, respiratory infection). Reactions at the injection site occurred infrequently and decreased with continued therapy.

The study was conducted in children whose asthma was well controlled with ICS, and the ability of omalizumab to replace ICS was evaluated to as-

Fig 2. Serum free IgE during the study by dosage subgroups. The free IgE measured at baseline is plotted as a reference value. Values >62 IU/mL could only be determined at baseline, not after omalizumab treatment.
assess the drug efficacy. After 16 weeks of treatment with omalizumab, BDP dose was gradually reduced to the lowest effective dose level. The reduction in BDP dose was significantly greater in the omalizumab group than the placebo group, and a significantly greater percentage of omalizumab treated patients could reduce their BDP dose. BDP could be withdrawn completely in 55% of omalizumab patients. Daily asthma symptom scores, rescue β-agonist requirement, and pulmonary function assessment showed that asthma control was well maintained despite significant reduction in BDP dose. During the steroid dose-reduction phase, asthma exacerbations requiring doubling of the ICS dose or addition of oral corticosteroid therapy occurred 42% less frequently among omalizumab patients, and 53% fewer patients had 1 or more asthma exacerbations.

Acute asthma exacerbations requiring additional β-agonist and/or corticosteroid treatment occurred more frequently during the steroid dose-reduction phase compared with stable-steroid phase; the difference in exacerbation rates between the 2 phases was much greater for the placebo group. The increase in exacerbation rate during the steroid dose-reduction phase is related to the loss of anti-inflammatory effects of ICS. The lower exacerbation rate in omalizumab-treated patients reflects its ability to provide similar protection.

Treatment with omalizumab resulted in a reduction from baseline in mean serum free IgE that ranged from 95% to over 99% across all dosing regimens, indicating that the dosing scheme used in the trial effectively reduces serum IgE in patients with initial concentrations as high as 1300 IU/mL. At the same time there was an increase in total IgE, ranging from 167% to 431% of baseline serum IgE level, depending on baseline IgE and omalizumab dose. This increase in total IgE represents the persistence in circulation of biologically inactive omalizumab-IgE complexes.38,39 These low molecular weight complexes lack the biological activity of IgE because the Fc portion of the molecule is blocked. They are cleared by low-avidity interaction with the Fc-γ receptors of leukocytes and the reticuloendothelial system.38 They do not fix complement or accumulate in renal glomeruli and do not pose a risk for immunopathogenicity.38

Overall, the outcome among omalizumab-treated patients was better than the placebo group as evaluated by reduction in BDP dosage, percentage of patients who discontinued BDP, incidence and frequency of asthma exacerbations, participants’ and investigators’ global evaluations of treatment effectiveness, dosage of rescue medication, missed school days, and unscheduled medical contacts attributable to asthma-related medical problems. The frequency and types of all adverse events, judged treatment related or not, were similar in the omalizumab group and the placebo group. The majority of adverse events were mild to moderate in severity. Study-drug–related adverse events occurred more frequently in the omalizumab group than in the placebo group, but were relatively infrequent in both groups. The several cases of urticaria were nearly all mild or moderate.

Early aggressive therapy is needed to maximize control of asthma in all age groups.40–43 Despite the effectiveness of ICS, there is a continuing reluctance to use these agents, especially in younger patients.44,45 Anti-IgE therapy is a promising alternative treatment for those children who fail to respond to corticosteroid therapy, require unacceptably high doses of ICS or systemic corticosteroids, have frequent exacerbations, or suffer unacceptable side effects of corticosteroid therapy. Because of serious limitations in the adherence to daily ICS therapy, a long-acting treatment is especially desirable. Because imperfect effort or technique limit efficacy of inhaled medication, the introduction of an effective agent that can be administered parenterally at long intervals is a propitious development.

Omalizumab is a novel monoclonal antibody that binds to IgE and may interfere with the pathogenesis

Fig 3. Serum total IgE during the study by dosage subgroups.
of atopic disease. Additional studies are needed to realize its full potential, which may include not merely effective symptom control but also favorable modification of IgE-mediated disorders.

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