Omalizumab for the treatment of exacerbations in children with inadequately controlled allergic (IgE-mediated) asthma

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Background: Many children with asthma continue to experience symptoms despite available therapies.
Objective: This study evaluated the efficacy and safety of omalizumab, a humanized anti-IgE mAb, in children with moderate-to-severe persistent allergic (IgE-mediated) asthma that was inadequately controlled despite treatment with medium-dose or high-dose inhaled corticosteroids (ICSs) with or without other controller medications.
Methods: A randomized, double-blind, placebo-controlled trial enrolled children age 6 to <12 years with perennial allergen sensitivity and history of exacerbations and asthma symptoms despite at least medium-dose ICSs. Patients were randomized 2:1 to receive omalizumab (75-375 mg sc, q2 or q4 wk) or placebo over a period of 52 weeks (24-week fixed-steroid phase followed by a 28-week adjustable-steroid phase).
Results: A total of 627 patients (omalizumab, n = 421; placebo, n = 206) were randomized, with efficacy analyzed in 576 (omalizumab, n = 384; placebo, n = 192). Over the 24-week fixed-steroid phase, omalizumab reduced the rate of clinically significant asthma exacerbations (worsening symptoms requiring doubling of baseline ICS dose and/or systemic steroids) by 31% versus placebo (0.45 vs 0.64; rate ratio, 0.69; $P = .007$). Over a period of 52 weeks, the exacerbation rate was reduced by 43% versus placebo ($P < .001$). Omalizumab significantly reduced severe exacerbations. Over a period of 52 weeks, omalizumab had an acceptable safety profile, with no difference in overall incidence of adverse events compared with placebo.
Conclusion: Add-on omalizumab is effective and well tolerated as maintenance therapy in children (6 to <12 years) with moderate-to-severe persistent allergic (IgE-mediated) asthma whose symptoms are inadequately controlled despite medium to high doses of ICSs. (J Allergy Clin Immunol 2009;124:1210-6.)

Key words: *Asthma, omalizumab, IgE, allergic, anti-IgE, exacerbation, child, pediatric*

Asthma is the most common chronic disease in children.[1] In the United States, it is estimated that 6.8 million children have asthma, accounting for 7 million physician visits and nearly 200,000 hospitalizations each year.[2] Children with asthma frequently have poorly controlled disease, often as a result of undertreatment with controller medications[3]; however, many have poor asthma control despite intensive treatment.[4] The need for controller medications in addition to those currently available is illustrated by a US survey of children with asthma (6 to 11 years old) in which 53% had an oral corticosteroid (OCS) burst and 25% had an emergency department visit in the previous 3 months (National Heart, Lung, and Blood Institute guidelines consider asthma to be inadequately controlled if patients require ≥2 OCS bursts per year[5]), despite receiving ≥3 long-term controller medications.[6]

Inhaled corticosteroids (ICSs) are an effective controller therapy and recommended for the treatment of asthma in children. However, it is recognized that a plateau in efficacy is seen with increasing doses of ICS,[7,8] and dose increases may be associated with an increased risk of adrenal suppression.[9] Physicians should also be mindful of the cumulative steroid burden in children with asthma who are receiving steroids by other routes (eg, topically or intranasally) for other allergic conditions.[10,11]

Although the prevalence of pediatric asthma is high, most research into therapeutic interventions has focused on adults.[1,12] There are, however, important differences between pediatric and adult disease.[13] Children are more likely to be atopic, have concomitant rhinitis, and generally have lower airway resistance than adults.[13] Most children with inadequately controlled asthma have near-normal FEV_1 values,[14,15] in contrast with adult asthma, in which FEV_1 declines with increasing disease severity.[16] These differences, coupled with the need to improve asthma control, provide a strong rationale for conducting further research in children.

Omalizumab is a humanized anti-IgE mAb approved for the treatment of adults and adolescents (≥12 years) with inadequately controlled moderate-to-severe (United States) or severe (Europe) allergic (IgE-mediated) asthma.[17,18] The addition of omalizumab to current asthma therapy has been shown to be effective and well tolerated in these patient populations.[19-25] Moreover, in a randomized, double-blind, placebo-controlled study in 334 children (6 to 12 years) with moderate-to-severe allergic asthma, omalizumab significantly reduced asthma exacerbations compared with placebo and enabled greater reductions in ICS dose and a higher frequency of ICS discontinuation.[26] The aim of the current study was to evaluate the efficacy and safety of omalizumab in children age 6 to <12 years with inadequately controlled moderate-to-severe persistent allergic (IgE-mediated) asthma.

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Abbreviations used
AE: Adverse event
GCP: Good Clinical Practice
GETE: Global evaluation of treatment effectiveness
ICS: Inhaled corticosteroid
ITT: Intent-to-treat
LABA: Long-acting β_2-agonist
mITT: Modified intent-to-treat
OCS: Oral corticosteroid
PAQLQ: Pediatric Asthma Quality of Life Questionnaire
QOL: Quality of life
RR: Rate ratio
SAE: Serious adverse event

METHODS

Patients

Patients were boys or girls age 6 to <12 years with moderate-to-severe allergic (IgE-mediated) asthma.[27] Patients had inadequately controlled asthma despite receiving at least medium doses of ICS (≥200 μg/d fluticasone propionate via dry powder inhaler or equivalent).[27] They had daytime or nighttime symptoms, demonstrated an increase of ≥12% in FEV_1 after 4 puffs (4 × 100 μg) or up to 5 mg nebulized albuterol, and had a history of exacerbations (≥2 within 1 year, ≥3 within 2 years, or ≥1 severe exacerbation requiring hospitalization within 1 year before study entry). Patients were required to weigh between 20 and 150 kg, have a positive skin prick test result to at least 1 perennial allergen and/or a positive radioallergosorbent test, and have a total serum IgE level of 30 to 1300 IU/mL.

Exclusion criteria were use of systemic corticosteroids (for reasons other than asthma), β-adrenergic antagonists, anticholinergics, and immunosuppressants (those not indicated in asthma). Patients receiving desensitization therapy with <3 months of stable maintenance doses before the first visit were excluded. Other exclusion criteria were a history of food-related or drug-related severe anaphylaxis, allergy to mAbs, and asthma associated with aspirin or other nonsteroidal anti-inflammatory drugs. Finally, patients were excluded if they had active lung disease, elevated IgE levels for reasons other than allergic asthma, cancer, abnormal electrocardiogram results in the previous month, or clinically significant laboratory abnormalities at the first visit.

Study design

This was an international, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. The study was designed, implemented, and reported in accordance with Good Clinical Practice (GCP), local regulations, and the Declaration of Helsinki. The protocol and informed consent form were reviewed and approved by institutional review boards and/or ethics committees. Written, informed consent was provided by parents or a legally acceptable representative.

Eligibility was evaluated during a 1-week screening phase. Patients then entered an 8-week run-in phase, during which asthma management was optimized and baseline asthma control assessed. ICSs and other asthma control medications could be adjusted during the first 4 weeks of the run-in; further dose adjustments were not permitted during the last 4 weeks of the run-in. The run-in could be extended if the patient had an asthma exacerbation during the last 4 weeks of this phase. Patients who remained symptomatic during the last 4 weeks of the run-in were then randomized (2:1) to receive omalizumab or placebo by using a randomization card system; patients who did not meet symptom score criteria were excluded from the study. Omalizumab 75 to 375 mg was administered once or twice a month by subcutaneous injection as determined from dosing tables, based on baseline serum total IgE and body weight. The double-blind treatment period consisted of a 24-week fixed-steroid phase (constant ICS dose unless adjustment was required for an exacerbation) and a 28-week adjustable-steroid phase. During the adjustable-steroid phase, doses could be adjusted downward (by 25% to 50% no more than once every 8 weeks) only if patients met strict criteria for steroid reduction. To reduce the ICS dose, patients had to have an FEV_1 equal to or higher than the highest FEV_1 value obtained during the run-in and meet ≥2 of the following criteria: (1) ≤1 nighttime awakening caused by asthma symptoms requiring rescue medication within the past 7 days, (2) use of rescue medication ≤3 times/day on ≤2 days within the past 7 days, (3) mean daytime symptom score <1.5 and daytime symptom score <2 on any individual day in the past 7 days, and (4) no clinically significant exacerbation in the past 4 weeks. Inhaled and nebulized β_2-agonists were permitted throughout the study. Investigators were to be notified about any new medications after commencing the study drug.

Study assessments

The primary efficacy endpoint was the rate of clinically significant asthma exacerbations (defined as worsening of asthma symptoms requiring doubling of baseline ICS dose and/or treatment with rescue systemic corticosteroids for ≥3 days) over a period of 24 weeks (end of the fixed-steroid treatment phase).

Secondary efficacy endpoints included the rate of clinically significant asthma exacerbations over a period of 52 weeks, change from baseline at 24 weeks in nocturnal clinical symptom score (scale, 0-4, where 0 = no symptoms and 4 = breathing problems resulting in nocturnal symptoms despite use of rescue medication), rescue medication use, and quality of life (QOL) score (Pediatric Asthma Quality of Life Questionnaire [PAQLQ][28]).

Exploratory efficacy endpoints included the rate of severe asthma exacerbations (defined as clinically significant exacerbations that required treatment with systemic corticosteroids and where peak expiratory flow or FEV_1 was <60% of personal best) over periods of 24 and 52 weeks, percentage reduction in ICS dose during the steroid-adjustable phase, and investigator and patient global evaluation of treatment effectiveness (GETE) at 52 weeks.

Safety assessments consisted of the recording of all adverse events (AEs), physical examinations, medical history, vital signs, and any clinically significant changes in laboratory values.

Statistical analyses

All efficacy analyses reported are based on the modified intent-to-treat (mITT) population, consisting of all patients in the intent-to-treat (ITT) population after excluding patients from 2 sites because of noncompliance with GCP. All safety analyses are based on the safety population, which included all patients who received any study drug and had at least 1 postbaseline safety assessment.

The rates of clinically significant and severe asthma exacerbations were compared by using generalized Poisson regression (commonly used to analyze discrete count data such as asthma exacerbations; it assumes the response variable follows a Poisson distribution rather than a normal distribution) with terms for treatment, dosing schedule, country (to account for any differences in local treatment practices), and exacerbation history. The sample size for the study was determined by ensuring at least 85% power for the generalized Poisson regression; the size of the placebo group required for 85% power was estimated to be 190, with a 2:1 ratio bringing the total required sample size to 570. Rate ratios (RRs) (antilogarithmic transformation of the difference of the exacerbation rates) and 95% CIs were generated, with the rate defined as the number of exacerbations after adjusting for time at risk. Clinically significant exacerbation data were imputed for patients who discontinued early. Subgroup analyses by baseline FEV_1, and long-acting β_2-agonist (LABA) use were performed for the primary endpoint.

Nocturnal clinical symptom score, rescue medication use, and reduction in ICS dose were compared by using the van Elteren test, a nonparametric test that compares treatments in the presence of blocking (an extension of the Wilcoxon rank-sum test).[29] PAQLQ overall score was compared by using an analysis of covariance; missing data were imputed by using the last available assessments. The level of statistical significance was adjusted for secondary efficacy endpoints, based on the hierarchical Hochberg multiple testing procedure.[30]

Investigator and patient GETE were compared by using the Cochran Mantel-Haenszel test. No adjustments for multiple comparisons were made for exploratory efficacy endpoints.