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Adding Omalizumab to the Therapy of Adolescents With Persistent Uncontrolled Moderate–Severe Allergic Asthma

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Objective. This study aimed to evaluate the effectiveness of omalizumab among adolescents with moderate–severe allergic asthma inadequately controlled with inhaled corticosteroids. **Patients and methods.** Data from patients 12 to 17 years of age were pooled from 5 placebo-controlled registration trials of omalizumab. Impact on asthma control was assessed by need for rescue bursts of oral corticosteroids, lung function, symptom scores, and unscheduled office visits. **Results.** In adolescents ($n = 146$), addition of omalizumab decreased mean number of rescue bursts (0.3 vs 0.9) versus placebo; relative risk 0.47 (95% confidence interval [CI], 0.22-0.99;

$P = .047$). At study conclusion, mean forced expiratory volume in 1 second increased 268 mL (13.8%) in omalizumab-treated subjects versus 98 mL (5.5%) for placebo (least squares mean treatment difference 146 mL [95% CI, 19.4-272.6; $P = .024$]). Omalizumab significantly improved asthma symptom scores and reduced unscheduled office visits. **Conclusion.** Omalizumab added to baseline therapy improves measures of asthma control in adolescents with persistent moderate–severe allergic asthma.

Keywords: asthma; adolescent; corticosteroids; omalizumab; inflammation

The prevalence of childhood asthma has increased considerably over the last 2 decades. Family history of atopic disease and environmental factors are associated with a greater likelihood of developing asthma.¹ Childhood asthma, particularly when not well controlled, can have long-term effects on lung function, with impairment frequently persisting into adulthood.² The main

principles of asthma management for adolescents are the same as for adults: to maintain asthma control by reducing impairment and risk with the lowest possible doses of medications, according to stepwise therapy as described in the National Heart, Lung and Blood Institute National Asthma Education and Prevention Program 3rd Expert Panel Report (NHLBI NAEPP EPR3).²

In the Children and Asthma in America survey of children and adolescents aged 4 to 18 years with asthma, 78% of respondents indicated that their asthma was well or completely controlled; however, asthma control in many of these individuals failed to meet asthma management goals established by existing national guidelines.^{3,4} More than half of the participants (54%) had at least 1 sudden, severe asthma attack within the previous 12 months and 19% had a severe attack at least twice within the past year.³

Suboptimal asthma control is associated with increased health care utilization and adversely impacts

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a patient's quality of life. A total of 42% of children in the Children and Asthma in America survey had some form of urgent or emergency care visit for their asthma in the past year, and more than half (53%) experienced an asthma attack that required a visit to the emergency room at some point in their lives.³ In addition to limitations on daily activities in nearly two-thirds of respondents (62%), children in the survey missed an average of 3.7 days of school in the past year and 9% of children missed more than 2 weeks of school. Consistent with these data, The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens study of 1261 pediatric and adolescent patients (aged 6-17 years) with difficult-to-treat asthma, showed that most (62%) were using 3 or more long-term controller medications.⁵ In this subset of patients, 53% of the children and 44% of the adolescents reported oral corticosteroid (OCS) burst therapy in the 3 months prior to enrollment in the study.

According to the recently released NHLBI NAEPP EPR3 asthma guidelines, patients with persistent uncontrolled asthma should be evaluated by an asthma specialist and specific attention focused on the role of allergies as a contributing factor.² Allergic asthma is especially prevalent among children and adolescents. Immunoglobulin E (IgE) plays a central role in the inflammatory asthma cascade, which leads to airway constriction, mucus production, wheezing, and shortness of breath.⁶ More than half of asthma cases in the United States are IgE-mediated.⁷

Omalizumab is a humanized monoclonal antibody that binds to free circulating IgE, removing it from circulation and reducing its ligand, the high-affinity IgE receptor (FC ϵ RI), on tissue resident mast cells and circulating basophils. Reduction of FC ϵ RI is associated with decreased activation of these effector cells, and subsequent release of inflammatory mediators and cytokines that lead to airway inflammation,^{8,9} thus inhibiting both early-phase and late-phase asthmatic responses. Updated treatment guidelines in the United States recognize the role of IgE and recommend omalizumab as adjunctive therapy in adolescents and adults aged ≥ 12 years with allergic asthma and persistent symptoms that are inadequately controlled by high-dose inhaled corticosteroids (ICSs) plus long-acting β_2 -agonists (LABAs).² This recommendation is based on evidence from several randomized, controlled

clinical trials, showing improved asthma symptoms and fewer exacerbations with add-on omalizumab versus placebo,¹⁰⁻¹⁴ even when concomitant doses of ICSs are reduced.

This article reports the results of a pooled analysis of data from the subpopulation of adolescent patients in these clinical trials, which evaluated the effect on asthma-related outcome measures of adding omalizumab to current treatment in patients with poorly controlled allergic asthma despite use of at least medium-dose ICSs.

Methods

Study Design and Patient Characteristics

Adolescent patients (12-17 years old) were identified from a pooled analysis of data from 5 randomized, double-blind, placebo-controlled studies of similar design.¹⁰⁻¹⁴ Omalizumab or placebo was administered for 28 weeks^{10,12-14} or 32 weeks¹¹ to patients aged 12 to 75 years with a diagnosis of moderate to severe^{10,12-14} or severe¹¹ persistent, allergic asthma (for ≥ 1 year), which was inadequately controlled despite at least medium-dose ICS therapy. Three of the studies¹⁰⁻¹² included an inhaled steroid reduction phase as part of the study design. The doses of ICSs were held constant over the initial 16 weeks of omalizumab treatment (steroid stable phase), and then were tapered during the remaining 12 weeks^{10,12} or the remaining 16 weeks of the study.¹¹ Beclomethasone dipropionate (BDP) equivalent doses were reduced by 25% of the baseline dose^{10,12} or fluticasone doses were reduced by 250 μ g/day¹¹ every 2 weeks until discontinuation or worsening of asthma symptoms. Although each of the pooled studies enrolled patients who had been treated with at least moderate doses of ICSs at baseline (NHLBI NAEPP EPR3 guidelines step 3 and above), 2 of the studies included patients receiving additional long-term controller medications (step 4),^{11,13} and 1 study required patients be treated with high-dose ICSs and LABAs (step 5).¹⁴ Further details of the study designs can be found in the individual trial publications.

Additional key inclusion criteria comprised a positive (+3 reaction) skin-prick test result to at least 1 perennial aeroallergen; total serum IgE level ≥ 30 to ≤ 700 IU/mL and body weight ≤ 150 kg; $\geq 12\%$ increase in forced expiratory volume in 1 second

(FEV₁) over baseline value within 30 minutes of taking 1 to 2 puffs of albuterol (90 µg per puff); baseline FEV₁ ≥40% to ≤80% of the predicted normal value for the patient; treatment with ICSs at doses ranging from BDP ≥400 to 1200 µg/day^{10,12-14} or fluticasone ≥1000 µg/day¹¹; and mean daily total asthma symptom score of ≥3.0 on a 9-point scale during the 14 days prior to randomization. Patients used a 4-point scale to rate their asthma symptoms during the day and at night (from 0 = no symptoms to 4 = breathing problems at rest with major discomfort that limited normal daily activity, or provoked nighttime symptoms despite the use of rescue medication). A morning score was also given for symptoms on awakening (yes = 1, no = 0), giving a maximum total score of 9. Key exclusion criteria were previous treatment with omalizumab, or known sensitivity to omalizumab, any of its ingredients, or related medications; an acute respiratory tract infection within 4 weeks of study entry; active lung disease other than allergic asthma; elevated IgE for reasons other than atopy; aspirin or other anti-inflammatory drug-related asthma; and change in ICS dose within the previous month.

Study Treatment

Omalizumab or placebo was added to current asthma treatment consisting of at least medium-dose ICS and administered subcutaneously every 2 or 4 weeks for 7 months (8 months for Holgate et al¹¹). Omalizumab doses were determined from the patient's baseline serum IgE and body weight; a minimum dose of at least 0.016 mg/kg per IgE IU/mL per month was administered every 2 to 4 weeks based on an established dosing algorithm.

Efficacy Assessments

The efficacy of omalizumab versus placebo on improving asthma control was assessed by the number of OCS bursts required to treat acute exacerbations of asthma, change from baseline in lung function (FEV₁), and change from baseline in mean total asthma symptom scores. Patients rated their asthma symptoms using the 9-point scale described in the study design. In addition, investigators assessed the effectiveness of treatment utilizing the Global Evaluation of Treatment Effectiveness (GETE) tool.^{15,16} Effectiveness was rated as excellent

(complete control of asthma)/good (marked improvement of asthma), moderate (discernible but limited improvement of asthma), or poor (no appreciable change)/worse (3 categories).

The total numbers of emergency room visits, hospital admissions, unscheduled office visits, and days lost from school due to asthma were also documented. As a marker of systemic inflammatory activity, peripheral blood eosinophil counts were measured at baseline and posttreatment.

Safety Assessments

All adverse events (AEs) occurring among the adolescent subpopulation during each study were pooled and summarized by treatment group.

Statistical Analyses

The number of OCS bursts required to treat acute exacerbations of asthma and number of school days missed were analyzed using Poisson regression with treatment, gender, baseline FEV₁ (≥80%, 60%-79%, <60%), and study as explanatory variables^{17,18}; the relative risk (RR) for omalizumab versus placebo was calculated, and presented with corresponding 95% confidence intervals (CIs). Change from baseline in FEV₁ was analyzed using analysis of covariance (ANCOVA) with treatment, gender, baseline FEV₁, and study as explanatory variables; least squares means (LSMs) of the change from baseline and 95% CIs were calculated. Changes from baseline in mean total asthma symptom scores were analyzed using ANCOVA with treatment, dosing schedule, baseline value, and study as explanatory variables; LSMs of the change from baseline and 95% CIs were calculated. Investigator-determined GETE was analyzed using a Cochran–Mantel–Haenszel mean score test.¹⁷ Health care resource use and AEs were summarized using descriptive statistics.

Absolute eosinophil counts at baseline and at the postbaseline time points were summarized descriptively for the omalizumab and placebo groups and the mean change from baseline calculated. *t* Tests were applied to determine whether the mean changes were significantly different from zero. The 2-tailed null hypothesis was that the mean change in peripheral blood eosinophil counts from baseline to the postbaseline time point was not different from zero.

Table 1. Demographics and Baseline Characteristics

	Omalizumab (n = 76) ^a	Placebo (n = 70) ^a	All Patients (n = 146) ^a
Age in years (mean ± SD)	14.2 ± 1.72	14.2 ± 1.64	14.2 ± 1.68
Gender			
Male, n (%)	47 (61.8)	44 (62.9)	91 (62.3)
Female, n (%)	29 (38.2)	26 (37.1)	55 (37.7)
Baseline FEV ₁			
≥80%, n (%)	18 (23.7)	15 (21.4)	33 (22.6)
60%-79%, n (%)	36 (47.4)	38 (54.3)	74 (50.7)
<60%, n (%)	22 (28.9)	17 (24.3)	39 (26.7)
Baseline FP equivalent dose (μg/day), mean (min, max) ± SD	514.5 (250, 1750) ± 375.82	473.9 (200, 1250) ± 303.11	495.0 (200, 1750) ± 342.32
Baseline IgE in IU/mL (mean ± SD)	353.0 ± 233.44	291.6 ± 190.60	323.6 ± 215.45
Baseline percent eosinophils (mean ± SD)	6.6 ± 3.86	6.4 ± 3.55	6.5 ± 3.71
Duration of asthma at baseline in years (mean ± SD)	9.9 ± 3.83	10.3 ± 3.84	10.1 ± 3.83

Abbreviations: SD, standard deviation; FEV₁, forced expiratory volume in 1 second; FP, fluticasone propionate; IgE, immunoglobulin E.

^aSlight variations in n (≤2 in each arm) based on availability of data.

Results are presented for the pooled intent-to-treat (ITT) population, which was defined as all randomized patients. All statistical analyses were performed using SAS software, Version 8.2 or higher. Safety was summarized using descriptive statistics.

Results

Patient Baseline Characteristics

Of the 2236 patients in the pooled population from the 5 omalizumab clinical trials, 146 were adolescents aged 12 to 17 years (the ITT population, defined as all randomized patients). The adolescent subjects had evidence of significant disease. While receiving approximately 500 μg/day of fluticasone propionate or equivalent, FEV₁ percentage predicted was <80% in more than 75% of patients and <60% predicted in more than 25% of patients (Table 1). In addition to at least medium-dose ICSs, 18.5% of the pooled population was also being treated with LABAs and 6.2% received anti-leukotrienes at baseline. Less than 1% of the pooled population was treated with OCSs at baseline. The mean serum IgE was elevated at baseline (mean 323.6 IU/mL). Overall, the omalizumab (n = 76) and placebo (n = 70) groups were well matched.

Asthma Control Measures

Asthma control measures were evaluated at the end of each study (28 weeks for Busse et al,¹⁰ Soler

et al,¹² Vignola et al,¹³ and Humbert et al¹⁴ or 32 weeks for Holgate et al¹¹). The mean number of bursts of systemic corticosteroids required for treatment of acute exacerbations of asthma was lower in the omalizumab group (0.3) than in the placebo group (0.9). The RR of corticosteroid bursts was significantly reduced with omalizumab versus placebo (0.47; 95% CI, 0.22-0.99; *P* = .047).

Clinically relevant improvements in lung function were noted in patients receiving omalizumab compared with placebo (Figure 1). Compared with baseline values, the end of study mean FEV₁ increased by 268 mL (13.8%) in the omalizumab group versus 98 mL (5.5%) in the placebo group (LSM treatment difference 146 mL; 95% CI, 19.4-272.6; *P* = .024). The mean improvement from baseline to end of study in percent predicted FEV₁ was 6.9% for the omalizumab group and 2.5% for the placebo group (LSM treatment difference 4.088%; 95% CI, 0.987-7.189; *P* = .0101). Likewise, symptom scores significantly improved in omalizumab-treated patients (LSM, -0.72; 95% CI, -1.23 to -0.22; *P* = .005).

Using the GETE, investigators rated the effectiveness of omalizumab treatment as being significantly better than placebo (*P* < .001). More omalizumab-treated patients had treatment effectiveness ratings of excellent/good versus placebo (76% vs 54%). Conversely, more patients receiving placebo had treatment effectiveness ratings of poor/worse versus omalizumab (20.0% vs 1.3%).

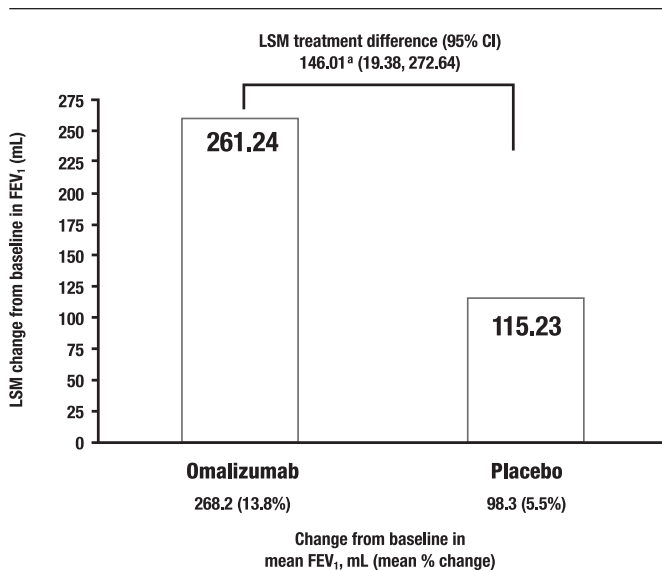


Figure 1. Improvement in lung function from baseline to end of study by LSM treatment difference.

Abbreviations: CI, confidence interval; FEV₁, forced expiratory volume in 1 second; LSM, least squares mean.

^a*P* = .024.

Impact on Health Care Utilization and School Attendance

During the clinical trial period, 3 patients (omalizumab *n* = 1; placebo *n* = 2) were admitted to the hospital for treatment of acute asthma. In addition, 8 patients (omalizumab *n* = 0; placebo *n* = 8) had at least 1 unscheduled office visit associated with worsening asthma, and 2 patients visited the emergency room (omalizumab group).

Based on pooled data from Busse et al,¹⁰ Soler et al,¹² and Holgate et al,¹¹ where the information was captured, the mean number of school days missed in the omalizumab group was 0.7, compared with 1.7 days in the placebo group. The RR for number of school days missed was significantly lower with omalizumab versus placebo (0.41; 95% CI, 0.17-0.96; *P* = .040). Data were not collected for the number of school days missed in Vignola et al¹³ and Humbert et al.¹⁴

Impact on Markers of Inflammation

The LSM for the percentage change from baseline in peripheral blood eosinophil counts (10⁹/L) at the postbaseline time point was −52.05% for omalizumab and −27.45% for placebo; treatment difference = −24.6% (95% CI, −45.22% to −3.97%; *P* = .0198).

Safety

Adverse events were similar between treatment groups with injection-site reaction, viral infection, upper respiratory infection, sinusitis, headache, and pharyngitis among the most commonly observed. Adverse events deemed related to study drug occurred in approximately 4.0% of the adolescent patients (3.8% with omalizumab and 4.2% with placebo). Serious AEs occurred in 4 patients in the omalizumab group and included infectious mononucleosis, forearm fracture, bipolar disorder, and asthma exacerbation, none of which were suspected to be related to the study medication. In the placebo group, 1 patient experienced a serious AE (asthma exacerbation), which was not believed to be due to the study medication. No study discontinuations due to AEs occurred in the omalizumab group; 1 patient from the placebo group discontinued from study participation.

Discussion

Current guidelines for the management of asthma (in adults, adolescents, and children) recommend the following as key to achieving and maintaining long-term control of asthma: reducing impairment (preventing coughing and breathlessness; reducing short-acting β_2 -agonist use; and maintaining pulmonary function, physical activity, and satisfaction with asthma care) and reducing risk (of exacerbations, AEs of therapy, loss of lung function, and reduced lung growth [in youths]).² This pooled, subgroup analysis of adolescents from 5 controlled clinical studies demonstrated that addition of omalizumab in adolescent patients with longstanding, uncontrolled asthma despite treatment with one or more controller medications (including at least medium-dose ICSs) can help achieve these therapeutic goals.

Patients with moderate or severe asthma exacerbations may be managed with short-term treatment with OCSs.² However, frequent use of OCSs is associated with the risk of immune and systemic AEs,^{2,19,20} including thrush, weight gain, mood disturbances, cardiovascular events, and growth retardation (in children).^{19,21,22} Results of the current analysis showed that, compared with placebo, adding omalizumab to baseline treatment in adolescents resulted in a significant reduction in the

number of OCS bursts required to treat exacerbations of asthma. These findings are consistent with those of previous reports that included adults.^{23,24} Notably, reduced need for OCS bursts appears to support patient and investigator evaluations of treatment effectiveness as a measure of improved asthma control.²⁴

In this pooled analysis, add-on omalizumab improved lung function (FEV₁) in adolescent patients, despite a mean duration of asthma in these patients of nearly 10 years. At study end, a clinically significant LSM treatment difference of 146 mL was observed for omalizumab compared with placebo. The observed increase from baseline to end of study in mean percentage predicted FEV₁ for adolescents treated with omalizumab was greater than improvements in FEV₁ seen in adult patients (data not shown). Omalizumab add-on therapy also improved mean symptom scores. These results are promising, especially given that effective management of asthma is particularly challenging in adolescents who may not recognize the seriousness of poor asthma control, deny their condition, or refuse to follow a treatment management plan because they feel it compromises their independence.²

Since the late 1990s, hospitalization rates for children aged 0 to 17 years have remained at historically high levels despite the availability of multiple long-term control medications.²⁵ This plateau in asthma hospitalizations for children has occurred during times of reduced overall admissions for children. Consequently, the threshold of attack severity for an admission has likely increased and hospitalizations for asthma in this decade may represent more severe exacerbations compared with past decades. Three of the studies¹⁰⁻¹² in this analysis collected data on time lost from school and health care utilization. The pooled analysis of adolescents from these studies shows that the improved clinical outcomes with omalizumab therapy versus placebo were accompanied by less frequent school absence. The reduced burden of disease for adolescent patients may also translate into a reduced burden of asthma for their parents in terms of time lost from work.

Inflammation in asthma is characterized by an increase in eosinophil numbers and their activation. Despite maintenance of other anti-inflammatory therapies, peripheral blood eosinophils number

decreased in the omalizumab treatment group indicating that binding of serum IgE leads to further improvements in underlying inflammation. These findings are consistent with earlier reports of reduction in bronchial and sputum eosinophils in adult patients.²⁶

The retrospective nature of pooled analyses is an inherent limitation; however, all outcome measures in the current analysis were prespecified in the original study protocols and the 5 studies were of similar design. Although this analysis was based on data from a sample of 146 patients, the results are consistent with the results from the total patient population (based on 2236 patients aged 12-75 years),¹⁰⁻¹⁴ which demonstrated improved asthma control while reducing corticosteroid burden.

The impact of asthma has been noted to be greatest for patients with inadequately controlled disease.^{2,27} In the current analysis there were too few hospital admissions and unscheduled physician or emergency room visits to draw comparisons between the omalizumab and placebo groups; further research is necessary to fully evaluate the impact of adding omalizumab on medical resource use in the adolescent population. However, economic modeling has suggested that adding omalizumab to current treatment is cost-effective in patients with severe allergic asthma who require treatment with high-dose ICSs plus LABAs.²⁸

Conclusion

The updated guidelines for the management of asthma identify control of asthma as the goal of therapy, regardless of disease severity. The data from this pooled analysis of adolescent patients with persistent poorly controlled allergic asthma despite treatment with at least medium-dose ICSs demonstrate that addition of omalizumab can significantly improve control of asthma both in terms of impairment and risk.

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