
Effectiveness of omalizumab in reducing corticosteroid burden in patients with moderate to severe persistent allergic asthma

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Background: Asthma guidelines advocate maintaining asthma control while minimizing corticosteroid exposure.

Objective: To assess the reduction in corticosteroid burden during long-term treatment and the corresponding impact of this reduction on asthma control, lung function, and inflammation in patients with moderate to severe allergic asthma.

Methods: We conducted a pooled analysis (N = 1,071) of 2 similarly designed, randomized, double-blind, placebo-controlled omalizumab trials and their extension phases. Each study included a 16-week steroid-stable phase, a 12-week steroid-reduction phase, and a 24-week extension phase. Patients received subcutaneous omalizumab (minimum, 0.016 mg/kg/IU (IgE/mL) every 4 weeks) or placebo every 2 or 4 weeks. Outcomes included change from baseline in inhaled corticosteroid dose, number of oral corticosteroid bursts, and other clinical measures, including asthma exacerbations and change in asthma quality-of-life score (questionnaire), lung function, and eosinophil count.

Results: The median reduction from baseline in inhaled corticosteroid dose (beclomethasone dipropionate equivalent dose) by the completion of the extension phase was greater for the omalizumab group than for the placebo group (−420.0 vs −252.0 μ g/d; $P < .001$). During that time, omalizumab-treated patients required fewer oral corticosteroid bursts overall for treatment of acute exacerbations (mean, 0.2 vs 0.3; relative risk, 0.56; 95% confidence interval, 0.41 to 0.76; $P < .001$) and demonstrated greater improvements in measures of asthma control.

Conclusion: The addition of omalizumab to baseline therapy in patients 12 years or older with moderate to severe persistent allergic asthma resulted in a durable reduction in the overall steroid burden and improvement in other clinical measures of asthma control.

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INTRODUCTION

Asthma is a chronic inflammatory disorder of the airways that affects more than 22 million people in the United States alone, creating an individual and societal health care burden that includes lost productivity at work and school, decreased quality of life, and emergency department visits, hospitalizations, and deaths.¹ On the basis of their efficacy in reducing airway inflammation and improving clinical outcomes, cor-

ticosteroids comprise the foundation of long-term treatment of persistent asthma.¹

The dose-dependent adverse events (AEs) associated with systemic exposure to corticosteroids are widely recognized.^{2,3} Patients with more severe asthma requiring higher doses of corticosteroids may be more likely to experience these complications.⁴ Therefore, maintaining asthma control while minimizing corticosteroid exposure is an important goal of therapy.

The likelihood of AEs associated with corticosteroid use varies with agent, mode of administration, dose, and duration of therapy. The use of inhaled corticosteroids (ICSs) minimizes the systemic corticosteroid exposure by targeting the delivery of active ingredient directly into the airways.^{2,4–6} Low to medium doses of high-potency ICSs have become the therapeutic mainstay of long-term asthma control and have been shown to be generally well tolerated and safe.^{1,7,8} The dose-response curve for ICSs is relatively flat, however, and administration of high doses of ICSs for more than 1 year may provide little improvement in asthma control while increasing the potential for AEs.^{1,8,9} Moreover, a recent meta-analysis of 31 studies reported significant, dose-dependent cortisol suppression associated with the use of low-, medium-, and high-dose ICSs.¹⁰

Treatment with omalizumab was incorporated into the Third Expert Panel Report from the National Heart, Lung,

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and Blood Institute asthma guidelines as adjunctive therapy for appropriate patients 12 years and older who have sensitivity to relevant allergens and are receiving step 5 or 6 care.¹ Omalizumab is approved by the US Food and Drug Administration for adults and adolescents (12 years or older) with moderate to severe persistent asthma who have a positive skin test result or in vitro reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with ICSs (based on data from 3 clinical studies).^{11–13} Omalizumab prevents the binding of IgE to receptors expressed on effector cells, such as basophils and mast cells, thereby blocking the release of cytokines and other mediators of airway inflammation.^{11,14–16} Studies have also demonstrated anti-inflammatory effects of omalizumab in bronchial biopsy specimens showing a decrease in eosinophilic inflammation and IgE-bearing cells accompanied by suppression of the early and late asthmatic responses.¹⁷ The present analysis quantifies the reduction in combined ICS and oral corticosteroid (OCS) burden during long-term treatment with omalizumab and the associated impact of this reduction on asthma control, lung function, and inflammation.

METHODS

Data from 2 randomized, double-blinded, placebo-controlled, parallel-group, multicenter omalizumab trials (studies 008 and 009; n = 525 and 546, respectively) and their respective double-blind extension phases were pooled. Study 008 included 26 centers in the United States, whereas study 009 included 42 centers in 9 countries. Similarity of design and efficacy variables allowed a pooled analysis of the studies.^{11,12,18,19} The original studies were conducted in accordance with the principles of the Declaration of Helsinki, study protocols were approved by the respective institutional review boards, and informed written consent was obtained from study participants.

Patients

Male and female patients aged 12 to 75 years who had moderate to severe, persistent, allergic asthma (asthma duration ≥ 1 year) inadequately controlled with ICSs were recruited. The inclusion criteria included the following: a positive skin prick test result in response to at least 1 perennial allergen (including *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, cockroach, dog, or cat), total serum IgE level of 30 IU/mL through 700 IU/mL, body weight of 150 kg or less, 12% or greater increase in forced expiratory volume in 1 second (FEV₁) over baseline value within 30 minutes of taking 1 to 2 puffs of albuterol (90 μ g per puff), baseline FEV₁ of 40% through 80% of the predicted normal value for the patient, mean daily total symptom score of 3.0 or higher (range, 0–9) during the 14 days before randomization, and ICS doses equivalent to beclomethasone dipropionate of 420 through 840 μ g/d (study 008) and 500 through 1,200 μ g/d (study 009) for more than 3 months before randomization. The key exclusion criteria included previous treatment with omalizumab, sensitivity to omalizumab or any of its ingredi-

ents or related medications, and acute respiratory tract infection within 4 weeks of study entry.

Study Design and Treatment

In both double-blind studies, patients were randomized to treatment with either omalizumab or placebo for 52 weeks after a 4- to 6-week ICS stabilization run-in period. The study designs and methods have been described in detail previously.^{11,12,18,19} Omalizumab was given at a dosage of at least 0.016 mg/kg/IU (IgE/mL) per 4 weeks and was administered subcutaneously every 2 or 4 weeks. Doses of ICSs were kept constant during the initial 16 weeks of omalizumab treatment (steroid-stable phase) and then were tapered during the remaining 12 weeks of the study (steroid-reduction phase).^{11,12}

During the steroid-reduction phase, doses of ICSs were reduced by 25% of the baseline value every 2 weeks until their use was discontinued. If asthma worsened (ie, lung function declined, rescue medication use increased, and/or nighttime awakenings due to asthma required rescue medication), the ICS dose was increased by 25% or more. The lowest ICS dose required to achieve asthma control was kept constant for the final 4 weeks of the steroid-reduction phase. During a 24-week, blinded extension phase, patients were maintained on randomized treatment and the lowest possible dose of ICSs established during the steroid-reduction period of the core study.^{18,19} Clinically appropriate dose adjustments of ICSs were permitted during this phase, and the use of concomitant asthma medications (including switching to other ICSs) was at the discretion of the physician.

Outcome Measures

Impact on steroid burden was analyzed separately for the steroid-stable, steroid-reduction, and extension phases and included the change from baseline in ICS dose and number of OCS bursts. Clinical outcomes were summarized for the 28-week core study period and 24-week extension phase and included the change from baseline in the number of asthma exacerbations, quality of life, change from baseline in FEV₁, and peripheral blood eosinophil counts. An asthma exacerbation was defined as a worsening of asthma treated with a course of OCSs or by doubling the baseline dose of ICSs. Quality of life was evaluated using the 32-item Asthma Quality of Life Questionnaire (AQLQ).²⁰

Safety Assessments

All safety data were pooled for studies 008 and 009.^{11,12,18,19} Serious AEs, drug-related AEs, and AEs leading to discontinuation from the study were summarized by treatment group. Serious exacerbation episodes (requiring hospitalization) were recorded.

Statistical Analyses

Comparisons between omalizumab and placebo for the change in ICS dose from baseline were performed using the van Elteren test, adjusting for study and dosing schedule.²¹ The number of exacerbations was analyzed via Poisson regression, using treatment, age, sex, baseline FEV₁ ($\geq 80\%$,

Table 1. Patient Demographics and Baseline Characteristics From the Pooled Analysis

	Omalizumab (n = 542)	Placebo (n = 529)
Age, mean (SD), y ^a	39.7 (13.84)	39.0 (13.72)
Sex, No. (%)		
Male	245 (45.2)	238 (45.0)
Female	297 (54.8)	291 (55.0)
Duration of asthma at baseline, mean (SD), y	20.5 (13.55)	20.8 (14.04)
Baseline IgE, IU/mL	198.1 (157.81)	196.2 (152.18)
Baseline FEV ₁ , No. (%)		
≥80%	137 (25.3)	121 (22.9)
60%-79%	270 (49.8)	273 (51.6)
<60%	135 (24.9)	135 (25.5)
Baseline beclomethasone dipropionate dose, mean (SD), µg/d	670.3 (222.15)	672.8 (238.31)
Use of oral steroids at baseline, No. (%)	0 (0.0)	0 (0.0)
Baseline total rescue puffs per day, mean (SD)	4.7 (2.84)	4.8 (2.75)
Baseline total asthma symptom score, mean (SD)	4.1 (1.24)	4.1 (1.28)

Abbreviation: FEV₁, forced expiratory volume in 1 second; SD, standard deviation.

^a Percentage of participants in each age category by treatment (omalizumab, placebo): 12 to 17 years (7.0%, 7.2%), 18 to 64 years (88.2%, 89.8%), and 65 years or older (4.8%, 3.0%).

60%-79%, <60%), dosing schedule, and study as explanatory variables^{21,22}; for the number of OCS bursts, the use of OCSs at baseline (yes/no) was also an explanatory variable. The relative risks (RRs) of asthma exacerbations for omalizumab vs placebo were calculated by exponentiating the treatment parameter estimate and is presented with corresponding 95% confidence intervals (CIs).

The changes from baseline in total AQLQ score and FEV₁ were analyzed using analysis of covariance models with treatment, age, sex, dosing schedule, baseline value, and study as explanatory variables; for change from baseline in peripheral blood eosinophil counts, study center was used as an explanatory variable instead of study. For these variables, least squares means (LSMs) of the change from baseline and 95% CIs were calculated.

All statistical analyses were performed using SAS statistical software, versions 8.2 or 9.1 (SAS Institute Inc, Cary, North Carolina).

RESULTS

Baseline Demographics

A total of 1,071 patients were enrolled in the 2 clinical trials (omalizumab: n = 542; placebo: n = 529). Patient demographics and baseline characteristics were similar between the omalizumab and placebo groups (Table 1).

Corticosteroid Burden

The median changes in ICS dose from baseline to the end of the steroid-reduction and extension phases are summarized in Figure 1. At the end of the steroid-stable, steroid-reduction, and extension phases, the ICS doses (mean [SD] in beclomethasone equivalent units) were 669.7 (231.41) µg/d, 210.5 (282.31) µg/d, and 263.0 (301.60) µg/d for patients in the omalizumab group and 680.0 (243.07) µg/d, 338.8 (325.70) µg/d, and 394.1 (348.87) µg/d for patients in the

placebo group, respectively. There were statistically significant differences between the omalizumab and placebo groups at the end of the steroid-reduction and extension phases (all $P < .001$).

The number of OCS bursts required was significantly lower for the omalizumab group during each of the 3 study phases compared with the placebo group (Table 2). During the steroid-stable phase, the RR of asthma exacerbation in the omalizumab group vs placebo group was 0.47 (95% CI, 0.34 to 0.65; $P < .001$) and the mean number of exacerbations was 0.3 vs 0.6. Similar differences were observed in the steroid-reduction phase (0.7 vs 1.3; RR, 0.55; 95% CI, 0.42 to 0.71; $P < .001$) and the extension phase (0.3 vs 0.5; RR, 0.63; 95% CI, 0.50 to 0.78; $P < .001$).

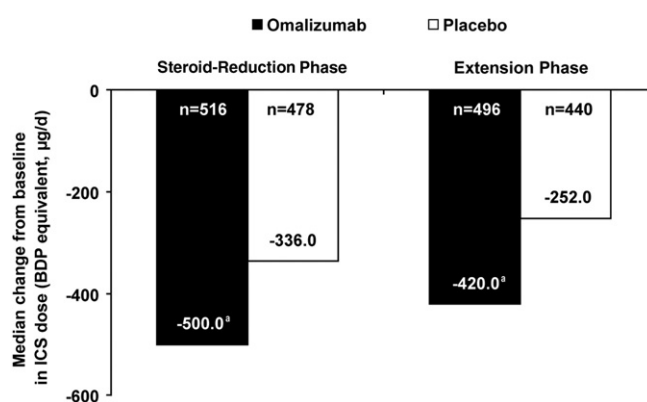


Figure 1. Median change from baseline in inhaled corticosteroid (ICS) dose at the end of the steroid-reduction and extension phases from the pooled analysis. BDP indicates beclomethasone dipropionate. ^a P value for the comparison of the 2 treatments in change from baseline was obtained from the van Elteren test adjusting for study and dosing schedule; $P < .001$ for each phase.

Table 2. Mean Number of and Relative Risk for OCS Bursts During Each Study Phase

	Steroid-stable phase (16 weeks)	Steroid-reduction phase (12 weeks)	Extension phase (24 weeks)
Mean No. of OCS bursts			
Omalizumab, n = 542	0.1	0.4	0.2
Placebo, n = 529	0.2	0.7	0.3
Omalizumab/placebo, relative risk ^a (95% CI)	0.52 (0.37 to 0.73)	0.59 (0.47 to 0.74)	0.56 (0.41 to 0.76)
P value	<.001	<.001	<.001

Abbreviations: CI, confidence interval; OCS, oral corticosteroid.

^a For a relative risk for omalizumab to placebo of 0.52, it would be expected that a patient treated with omalizumab would require 48% fewer corticosteroid bursts than a patient in the placebo group.

Clinical Outcomes

During the core 28-week study and 24-week extension phase, the addition of omalizumab significantly reduced the number of exacerbations compared with placebo. During the study periods, the change from baseline in total AQLQ also significantly favored omalizumab (Table 3). Peripheral blood eosinophil counts decreased throughout both the core and extension phases during treatment with omalizumab compared with placebo. Statistically significant improvements from baseline in FEV₁ were observed during the steroid-stable phase (LSM treatment difference vs placebo, 89.083; 95% CI, 47.16 to 131.01; *P* < .001) and were maintained in the steroid-reduction phase (LSM treatment difference vs placebo, 90.50; 95% CI, 43.95 to 137.04; *P* < .001) for the omalizumab group compared with placebo. During the extension phase, improvements from baseline in FEV₁ favored omalizumab compared with placebo but did not achieve statistical significance (LSM treatment difference vs placebo, 28.76; 95% CI, -23.94 to 81.46; *P* = .28).

Safety

The overall incidence and profile of AEs were similar in both treatment groups during the core studies (including

the steroid-stable and steroid-reduction phases) and the extension phases. There were similar numbers of serious AEs during both the core and extension phases (core: 11 omalizumab, 9 placebo; extension: 16 omalizumab, 9 placebo). None of the serious AEs were considered drug related by study investigators. Serious asthma exacerbations requiring hospitalization occurred in 1 patient receiving omalizumab and 8 patients receiving placebo during the core study and in 1 patient receiving omalizumab and 5 patients receiving placebo during the extension phase. Additional details regarding the safety profile of omalizumab have been reported previously.^{11,12,18,19}

DISCUSSION

The primary goal of guideline-based asthma management is to gain and maintain control of asthma in both the impairment and risk domains by using a stepwise approach to pharmacologic therapy. In the latest National Asthma Education and Prevention Program (NAEPP) treatment guidelines, the preferred management strategy is to minimize systemic corticosteroid exposure; however, this is especially challenging to

Table 3. Measures of Asthma Control and Peripheral Blood Eosinophil Count

	Core study (28 weeks)	Extension study (24 weeks)
Mean No. of asthma exacerbations		
Omalizumab, n = 542	0.7	0.3
Placebo, n = 529	1.3	0.5
Relative risk ^a (95% CI)	0.55 (0.42 to 0.71)	0.63 (0.50 to 0.78)
P value	<.001	<.001
Change from baseline in total AQLQ score, LSM		
Omalizumab Core: n = 466; Ext: n = 447	0.98	1.17
Placebo Core: n = 424; Ext: n = 386	0.66	0.88
LSM difference (95% CI)	0.32 (0.21 to 0.44)	0.28 (0.16 to 0.41)
P value	<.001	<.001
Change from baseline in eosinophil count, LSM		
Omalizumab Core: n = 485; Ext: n = 445	-0.078	-0.074
Placebo Core: n = 442; Ext: n = 392	-0.026	-0.025
LSM difference (95% CI)	-0.051 (-0.075 to -0.028)	-0.048 (-0.070 to -0.027)
P value	<.001	<.001

Abbreviations: AQLQ, Asthma Quality of Life Questionnaire; CI, confidence interval; LSM, least squares mean.

^a For a relative risk for omalizumab to placebo of 0.55, it would be expected that a patient treated with omalizumab would experience 45% fewer exacerbations than a patient in the placebo group.

attain in moderate and severe disease.¹ The present analysis of pooled data from 2 omalizumab pivotal clinical trials demonstrates the effectiveness of adjunctive omalizumab in both reducing the ICS dose and decreasing the number of OCS bursts, while improving asthma control and lung function in patients with persistent, moderate to severe allergic asthma. In addition, compared with placebo, significant ICS dose reductions in the omalizumab group were sustained during the 24-week extension phases of each study, demonstrating the durability of these effects. Although corticosteroids are recognized as potent suppressors of eosinophils, the addition of omalizumab in patients already receiving moderate-high doses of ICSs was associated with greater decreases from baseline in eosinophil counts compared with placebo at the end of the steroid-reduction phase and 28-week extension phase.

The results of the present pooled analysis parallel those obtained in another omalizumab clinical trial that examined the steroid-sparing effects as a primary outcome in patients with severe asthma (N = 246) using high-dose fluticasone ($\geq 1,000$ $\mu\text{g}/\text{d}$).¹³ Administration of omalizumab resulted in a median decrease of 60% in fluticasone dose compared with a median decrease of 50% in the placebo group ($P = .003$). Similar to findings of the present study, corticosteroid dose reductions were achieved while asthma symptoms and asthma-related quality of life improved and the need for rescue medication decreased.¹³

Results from another randomized, open-label, multicenter study examining the efficacy and safety of omalizumab in patients with moderate to severe poorly controlled asthma (N = 312) demonstrated that ICS doses could be reduced despite the absence of a formal protocol for steroid dose reduction.²³ Use of omalizumab led to a reduction of ICS dose by a mean of 342 $\mu\text{g}/\text{d}$ compared with a mean increase of 68 $\mu\text{g}/\text{d}$ for patients receiving standard care ($P < .001$). The real-world, clinical practice setting of this study demonstrated that a decrease in corticosteroid exposure can be achieved with the use of omalizumab.²³

A recently published pooled analysis that included results from 7 studies with omalizumab (a total of 4,308 participants) assessed asthma control and the requirement for OCS bursts,²⁴ indicating a significantly reduced number of OCS bursts (RR, 0.57; 95% CI, 0.48 to 0.66; $P < .001$) in patients receiving omalizumab compared with controls. The current study extends these findings, indicating that ICS doses and total steroid burden can be decreased while maintaining or improving asthma control and lowering eosinophil count.

The pooled results reported herein have limitations because the analyses were not prespecified. However, the overall trial designs and clinical outcomes were similar and results were consistent with the individual trials. Although our analysis was able to provide a detailed quantitative picture of ICS sparing associated with omalizumab in relation to asthma outcomes, it was not possible to evaluate the effects of omalizumab on continuous OCS use in the included studies because none of the patients was using OCS at baseline.

However, an observational study conducted in the United Kingdom, France, and Germany involving 411 patients who received omalizumab for at least 16 weeks indicated that OCS therapy could be decreased or discontinued in 55.3% of patients (mean dose reduction, 71.3%).^{25–27} Similarly, an early dose-finding study of intravenously administered omalizumab (involving 317 randomized patients) showed a median reduction in OCS dose of 50% in the high-dose omalizumab group ($P = .04$) and 65% in the low-dose omalizumab group ($P = .11$) compared with 0% in the placebo group.²⁸

To summarize, the results of the present analysis demonstrate that, compared with placebo, patients with persistent asthma symptoms at baseline who received adjunctive omalizumab, as a group, were able to reduce systemic corticosteroid burden (in terms of both ICS dose and number of OCS bursts) while maintaining or improving asthma control and lung function. Patients taking omalizumab exhibited improved clinical outcomes for both domains of asthma control described in the NAEPP guidelines (ie, reduced asthma impairment and a decreased risk of exacerbations). Omalizumab, therefore, represents an effective option for treating moderate to severe persistent allergic asthma, which can minimize the burden of systemic corticosteroids.

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