

Efficacy of omalizumab in cat-allergic patients with moderate-to-severe persistent asthma

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ABSTRACT

Cat allergen (Fel d 1) is a pervasive and common trigger of exacerbations in sensitized patients with IgE-mediated asthma. This study was designed to evaluate the effect on asthma-related outcome measures of adding omalizumab to current treatment in patients with moderate-to-severe persistent asthma and cat allergen sensitivity. A pooled analysis was conducted of two double-blind, placebo-controlled, 28-week pivotal U.S. registration trials. In all patients, asthma was inadequately controlled with moderate-high dose inhaled corticosteroids. Patients were randomized to receive subcutaneous omalizumab (minimum, 0.016 mg/kg per IgE IU/mL every 4 weeks) or matched placebo. The effects of omalizumab on asthma-related outcomes were assessed for patients with cat allergen sensitivity ($n = 811$), identified by positive skin-prick test. The mean number of asthma exacerbations requiring treatment with systemic steroid bursts in cat allergen-sensitive patients was lower in those receiving omalizumab versus placebo (0.6 versus 1.3, respectively; relative risk = 0.50, $p < 0.001$). Compared with placebo, omalizumab treatment led to significantly lower asthma symptom scores (least squares means (LSMs) treatment difference [95% confidence interval {CI}]: $-0.57 [-0.77, -0.37]$; $p < 0.001$), less rescue medication use (LSMs treatment difference [95% CI]: -0.75 puffs of rescue beta-agonist per day $[-1.04, -0.46]$; $p < 0.001$), and improvement in forced expiratory volume in 1 second (LSMs treatment difference [95% CI]: $100.84 \text{ mL} [51.86, 149.81]$; $p < 0.001$). Patient and investigator global evaluations of treatment effectiveness paralleled these outcomes. Omalizumab improved asthma control by reducing exacerbations and decreasing symptoms in cat-allergic patients with moderate-to-severe persistent IgE-mediated asthma.

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Key words: Allergic asthma, asthma, cat allergen, exacerbations, IgE, lung function, omalizumab, steroid bursts, symptom scores

According to the most recent National Health and Nutrition Examination Survey, atopy is very common among patients with asthma (78.9%). More than one-half of all asthma is attributable to atopy.¹ Exposure to airborne allergens can trigger asthma exacerbations and reduce treatment effectiveness, worsening disease control.² Allergen avoidance is key to effective asthma management and is recommended in treatment guidelines.³ However, limiting exposure is often difficult. Animal allergens in particular are hard to avoid, not only because of the high prevalence of pet ownership, but also because of inadvertent exposure to allergen in homes without pets, in the workplace, schools, and child-care centers.^{4–6} The National Survey of Lead and Allergens in Housing showed that al-

though cats or dogs lived in ~50% of U.S. households, their principal allergens, Fel d 1 and Can f 1, were detected in 99.9 and 100% of homes, respectively.⁴ In addition, asthma was attributed to cat allergen in 29.3% of subjects, the highest percentage among 10 allergens tested in the National Health and Nutrition Examination Survey.¹ Fel d 1 is readily airborne and easily spread, adhering to surfaces such as clothing and transferring from building to building *via* normal human contact.^{4–7} Nearly all surveyed homes with a cat and more than one-half of homes without a cat had allergen levels that exceeded the $1\text{-}\mu\text{g/g}$ level associated with allergic sensitization.⁴ Even levels of $<100 \text{ ng/m}^3$ can trigger asthma symptoms in sensitized individuals, and this is often exceeded in environments where the patient may not suspect a presence of cat allergen.^{8,9} Studies have also suggested that sensitization to cat allergen predicts more severe asthma, which may be more difficult to treat.¹⁰

Fel d 1 has a more complex structure than other aeroallergens.¹¹ It is a noncovalently linked dimer with a molecular mass of ~38 kDa, consisting of two subunits of ~18 kDa that are each composed of covalently bound α -polypeptide and β -polypeptide chains encoded by different genes.^{12,13} Exposure to Fel d 1 is strongly associ-

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ated with development of cat allergen-specific IgE.¹⁴ IgE mediates the allergic response by activating effector cells of the immune system, leading to histamine release, eicosanoid synthesis, and cytokine gene expression.^{11,15} IgE also plays a central role in the pathophysiology of allergic asthma, initiating a cascade of inflammatory events leading to airway constriction, mucus production, wheezing, and shortness of breath.^{16,17}

Omalizumab is a humanized antibody that attaches to the receptor-binding region of circulating IgE, leading to a marked reduction in high-affinity IgE receptor density and a decrease in mast cell degranulation.^{18,19} Several randomized, controlled clinical trials have shown that adding omalizumab to an inhaled corticosteroid (ICS) significantly reduced exacerbations and decreased asthma symptom scores in patients with moderate-to-severe persistent asthma who are allergic to perennial aeroallergens.^{1,20–23} Here, the authors present the results of a pooled analysis conducted to investigate the effect on asthma-related outcomes of adding omalizumab to the treatment regimen of patients with moderate-to-severe persistent asthma and cat allergen sensitivity.

METHODS

Study Design and Patient Characteristics

Patients with cat allergen sensitivity were identified in two large randomized, double-blind, 28-week, placebo-controlled pivotal trials (CIGE025A 008 and 009), which supported approval of omalizumab in the United States.^{20,21} The studies had similar design and efficacy variables that permitted pooling of data. Omalizumab was given at a dosage of at least 0.016 mg/kg per IgE IU/mL per 4 weeks, administered subcutaneously every 2 or 4 weeks. All patients were using ICSs at baseline. Rescue albuterol and bursts of systemic corticosteroids were limited to use for acute exacerbations; otherwise, other asthma medications were not permitted. Patients receiving omalizumab and ICS were compared with those receiving matched placebo and ICS. The individual studies included in the pooled analysis were performed in accordance with the principles of the Declaration of Helsinki and its amendments. Each subject provided written informed consent before enrollment. The studies were approved by the Institutional Review Board at each center.

The studies recruited male and female patients aged 12–75 years with a diagnosis of moderate-to-severe persistent asthma (≥ 1 year in duration) who were inadequately controlled with ICS. The inclusion criteria included a positive (at least 3+) skin-prick test result in response to at least one perennial aeroallergen; total serum IgE level of ≥ 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 1–2 puffs of albuterol (90 μ g/puff); baseline FEV₁ of ≥ 40 to $\leq 80\%$ of the predicted normal value for the patient; mean daily total symptom score of ≥ 3.0 (total score = nocturnal [0–4] + daytime [0–4] + morning score [0–1]); maximum total of 9 being the worst during the 14 days before randomization; and treatment with ICS at doses equivalent to beclomethasone dipropionate, ≥ 420 –840 μ g/day (study 008) or 500–1200 μ g/day (study 009). In the present analysis, patients with cat allergen sensitivity were defined as those with a positive (at least 3+) skin-prick test result in response to Fel d 1.

Patients were excluded for the following reasons: previous treatment with omalizumab or known sensitivity to omalizumab, any of its ingredients, or related medications; 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. Details of the study designs can be found in the individual trial publications.^{20,21}

Assessments

Efficacy was evaluated using the following variables: the number of acute, clinically significant exacerbation episodes (defined as a worsening of asthma requiring treatment with systemic corticosteroids) during the 28-week double-blind period; change from baseline in mean asthma symptom scores; change from baseline in lung function (FEV₁); mean number of puffs of rescue medication taken in the day/night; and patient-determined and investigator-determined Global Evaluation of Treatment Effectiveness (GETE). 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 (three categories). All adverse events (AEs) occurring during the double-blind treatment phase were summarized by treatment group.

Statistical Analyses

The number of acute exacerbations requiring treatment with a steroid burst among patients with cat allergen sensitivity was analyzed using Poisson regression with treatment, age, gender, baseline FEV₁ ($\geq 80\%$, 60–79%, and $< 60\%$), and study as explanatory variables.^{24,25} The relative risk for omalizumab versus placebo was calculated, and was presented with corresponding 95% confidence intervals (CIs). Change from baseline in FEV₁ was assessed 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

Table 1 Demographics and baseline characteristics of patients with cat allergen sensitivity from studies 008 and 009

	Omalizumab (<i>n</i> = 415)	Placebo (<i>n</i> = 396)	All Patients (<i>n</i> = 811)
Age, mean $\pm$ SD (yr)	39.0 $\pm$ 12.95	39.2 $\pm$ 13.53	39.1 $\pm$ 13.22
Sex, <i>n</i> (%)			
Male	179 (43.1)	172 (43.4)	351 (43.3)
Female	236 (56.9)	224 (56.6)	460 (56.7)
Baseline total serum IgE, median (IU/mL)	159	167	162
Baseline FEV ₁ , <i>n</i> (%)			
$\geq$ 80%	106 (25.5)	92 (23.2)	198 (24.4)
60–79%	210 (50.6)	204 (51.5)	414 (51.0)
<60%	99 (23.9)	100 (25.3)	199 (24.5)
Baseline ICS dose (beclomethasone equivalent), mean $\pm$ SD (μ g/day)	723.1 $\pm$ 208.73	717.7 $\pm$ 234.37	720.5 $\pm$ 221.50
Duration of asthma, mean $\pm$ SD (yr)	21.2 $\pm$ 13.02	21.6 $\pm$ 14.35	21.4 $\pm$ 13.68

Source: Refs. 21 and 22.

FEV₁ = forced expiratory volume in 1 s; ICS = inhaled corticosteroid; IgE = immunoglobulin E; SD = standard deviation.

were calculated. Changes from baseline in mean total rescue puffs of β -agonist and mean total asthma symptom score 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 and patient-determined GETE were analyzed using a Cochran-Mantel-Haenszel mean score test.²⁵ Results are presented for the pooled intention-to-treat population, which was defined as all randomized patients. All statistical analyses were performed using SAS software, Version 8.2. Safety was summarized using descriptive statistics and the detailed results are reported elsewhere.^{20,21}

RESULTS

Demographics

Of the 1071 patients in the pooled population, 811 were sensitive to Fel d 1. Overall, omalizumab and placebo groups were similar in terms of lung function (FEV₁), total serum IgE level, and dose of ICS at baseline (Table 1). Patients who were sensitive to Fel d 1 alone (single-allergen allergic, *n* = 38) exhibited baseline characteristics similar to those who were sensitive to Fel d 1 in addition to other aeroallergens (multiple-allergen allergic, *n* = 773).

Asthma Outcome Measures in Cat Allergen-Sensitive Patients

In the cat allergen-sensitive population, the number of acute asthma exacerbations requiring a steroid burst was significantly lower in the group treated with omalizumab compared with the placebo group (0.6 versus

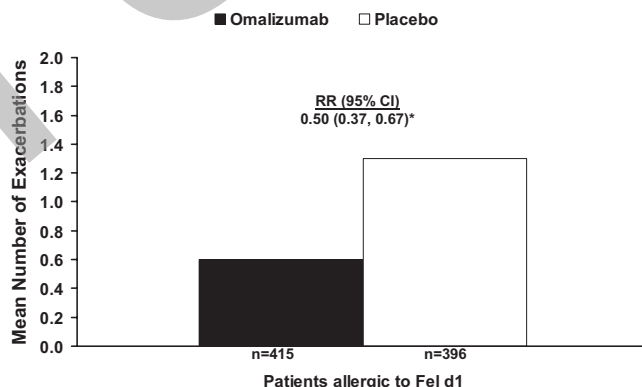


Figure 1. Asthma exacerbations with add-on omalizumab or placebo in patients with cat allergen sensitivity.**p* < 0.001 versus placebo. RR = relative risk.

1.3), with a relative risk of 0.50 (*p* < 0.001; Fig. 1). Patients with single-allergen sensitivity to cat also experienced a significant reduction in the use of steroid bursts during treatment with omalizumab versus placebo (0.1 versus 0.6), with a relative risk of 0.16 (95% CI, 0.03–0.78; *p* < 0.023). Compared with placebo, adding omalizumab significantly improved mean asthma symptom scores from baseline (LSM treatment difference [95% CI]: –0.57 [–0.77, –0.37]; *p* < 0.001; Table 2).

In regard to the effect on lung function, omalizumab significantly improved FEV₁, compared with placebo (LSM treatment difference [95% CI]: 100.84 mL [51.86, 149.81]; *p* < 0.001; Table 2). Patients who received omalizumab showed greater reduction from baseline in mean number of puffs of rescue β -agonist, compared with patients on placebo (LSM treatment difference [95% CI]: –0.75 [–1.04, –0.46], *p* < 0.001; Table 2). Moreover, investigator assessment of treatment effec-

Table 2 Symptoms, rescue medication use, and lung function with add-on omalizumab or placebo

	Omalizumab (<i>n</i> = 415)	Placebo (<i>n</i> = 396)	All Patients (<i>n</i> = 811)
Change from baseline to end of study			
Mean asthma symptom score	−1.6	−1.0	−1.3
LSM	−1.62	−1.05	
LSM treatment difference (95% CI)	−0.57 (−0.77, −0.37)		
<i>p</i> Value	<0.001		
Mean total rescue puffs of β -agonist	−1.5	−0.8	−1.1
LSM	−1.49	−0.74	
LSM treatment difference (95% CI)	−0.75 (−1.04, −0.46)		
<i>p</i> Value	<0.001		
FEV ₁ , mL, mean (% change, mean)	130.8 (6.7%)	30.9 (2.4%)	82.2 (4.6%)
LSM	138.81	37.98	
LSM treatment difference (95% CI)	100.84 (51.86, 149.81)		
<i>p</i> Value	<0.001		

CI = confidence interval; FEV₁ = forced expiratory volume in 1 s; LSM = least squares means.

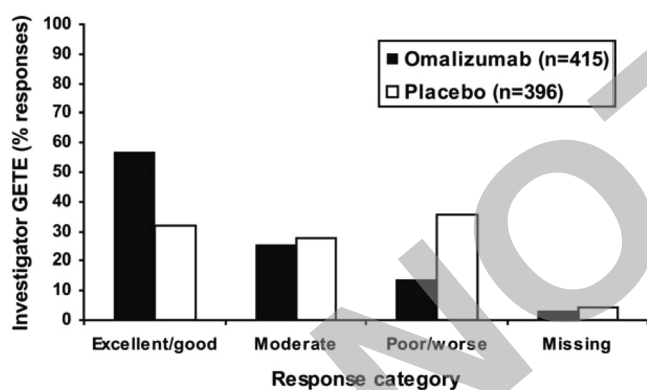


Figure 2. Investigators' global evaluations of treatment effectiveness for patients with cat allergen sensitivity. GETE = Global Evaluation of Treatment Effectiveness. *p* < 0.001 versus placebo.

tiveness was good/excellent for 57.1% of patients treated with omalizumab compared with 32.1% of those on placebo (Fig. 2). Similarly, 62.9% of patients who received omalizumab rated the treatment effectiveness good/excellent in contrast to 36.4% of patients on placebo (Fig. 3).

Safety. Safety data from the two trials are reported in detail elsewhere.^{20,21} The frequency of AEs was similar in the omalizumab and placebo groups, with injection-site reaction, viral infections, upper respiratory infection, sinusitis, headache, and pharyngitis being the most commonly observed. The percentage of cat dander-sensitive patients with an AE thought to be related to study drug was 6.3% for the omalizumab group and 5.3% for the placebo group. Serious AEs occurred in 2.2% of omalizumab-treated patients and 1.8% of placebo-receiving patients. Investigators considered none of these reactions to be drug related. There were no

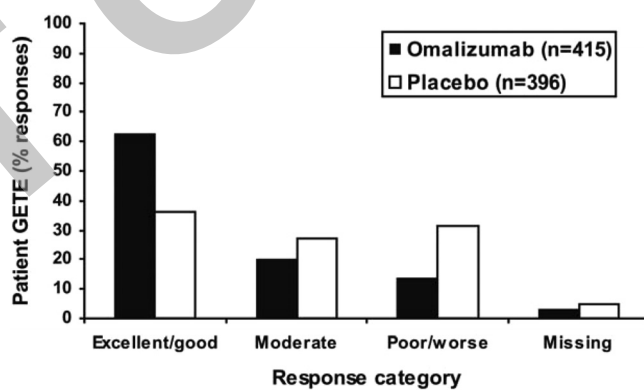


Figure 3. Patients' global evaluations of treatment effectiveness for patients with cat allergen sensitivity. GETE = Global Evaluation of Treatment Effectiveness. *p* < 0.001 versus placebo.

clinically meaningful changes in laboratory variables or vital signs associated with omalizumab therapy.

DISCUSSION

The efficacy and safety of adding omalizumab to moderate-high doses of ICS is supported by several large-scale clinical trials of patients with moderate-to-severe IgE-mediated asthma.^{20–23} A closer analysis of the response data from clinical studies may help identify subpopulations most likely to respond to therapy and may provide important information for clinicians who care for patients with particular clinical characteristics.

In cat allergen-sensitive patients with asthma, the addition of omalizumab to ICS therapy improved asthma outcomes across all prespecified measures. Compared with placebo, subjects receiving omalizumab experienced significantly improved asthma symptom scores, significant increases in FEV₁, and

there was nearly a doubling in the proportion of investigators or patients assessing treatment effectiveness as good or excellent. This analysis also evaluated the number of acute asthma exacerbations requiring steroid bursts as a measure of asthma control^{26–29} and showed a clinically significant reduction for patients treated with omalizumab compared with placebo. Studies have indicated that the AEs related to systemic corticosteroids may be related to the cumulative dose and frequency of bursts.^{27,28}

Conducting an analysis that was not prespecified in the original protocol has inherent limitations; however, a strength of this approach is that this pooled analysis was based on two trials of similar design and variables allowing for the precise assessment of treatment effects based on patient-level data. In addition, the consistency of response across multiple outcome measures shows the internal validity of the trials.

The ability to assess treatment effectiveness in individual patients is important to prevent extended patient exposure to ineffective medications or premature termination of beneficial therapy that does not have effects that are immediately recognizable. A recent study suggested that it may be preferable to assess the clinical efficacy of omalizumab after an initial course of add-on therapy (16 weeks) by using the investigator's GETE rather than by predicting response based on baseline patient characteristics.³⁰ In the cat allergen-sensitive population, investigator ratings of treatment effectiveness were significantly more favorable for omalizumab than for placebo and were similar to results seen for the overall population studied. This is especially important, because, historically, cat allergen-sensitive asthma has been considered especially difficult to treat.

Another interesting finding of this analysis is that patients with asthma and a single allergen sensitivity to cat do not appear to differ from those with multiple-allergen sensitivity that includes cat. Previous observations have suggested that multiple-allergen sensitivity predicts worse outcomes in asthma.³¹ Although the sizes of other single-allergen groups were too small to perform a robust comparison with patients who have single-allergen sensitivity to cat, this observation suggests that cat allergen sensitivity may be the main driver of asthma severity in patients with asthma sensitive to perennial aeroallergens. Omalizumab is an important treatment option for patients with cat allergen sensitivity and moderate-to-severe persistent IgE-mediated asthma inadequately controlled with ICSs.

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