

Omalizumab: An update on efficacy and safety in moderate-to-severe allergic asthma

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ABSTRACT

Omalizumab is an anti-immunoglobulin E (anti-IgE) monoclonal antibody approved in the United States since 2003 for treatment of moderate-to-severe allergic asthma in adults and adolescents (aged ≥ 12 years) inadequately controlled with inhaled corticosteroids (ICSs). Current treatment guidelines recommend considering the addition of omalizumab if allergic asthma symptoms are not adequately controlled with high-dose ICS + long-acting beta-agonist (LABA) therapy. This study was designed to review the clinical efficacy and safety of omalizumab as established in previously published pivotal clinical trials used to support registration in the United States, i.e., primarily including patients receiving only concomitant ICS therapy, as well as results from the recently completed additional study, which specifically enrolled patients who were poorly controlled despite high-dose ICS + LABA therapy $\pm$ additional controllers (including oral corticosteroids [OCSs]). Summary of published omalizumab pivotal trials and associated extension trials, plus key results from the additional study, were used. Pediatric data (i.e., <12 years) were outside the scope of this article. Treatment with omalizumab significantly reduced asthma exacerbations versus placebo when added to ICS therapy during both steroid-stable and steroid-reduction phases of two pivotal trials. In the additional study, omalizumab significantly reduced asthma exacerbation rates versus placebo when added to high-dose ICS + LABA therapy with or without other controller medications. Results from the additional clinical study further support current asthma guideline recommendations to consider omalizumab in steps 5 or 6 for persistent allergic asthma patients whose symptoms are not adequately controlled despite high-dose ICS + LABA therapy $\pm$ additional controllers (including OCS).

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Asthma remains not well controlled in many patients despite treatment with conventional therapies.^{1,2} For example, in a 3-year retrospective observational study, 43% of patients actively taking at least one asthma medication had uncontrolled asthma in the 1st year, and 73% met the criteria for uncontrolled asthma at least once during the 3-year period.¹ This is of considerable clinical concern, because suboptimally controlled asthma places patients at greater risk for future exacerbations,² as well as impairment in daily activities and overall quality of life.^{3,4} A greater than twofold risk of limitations of outdoor or physical activities and a 66% increased risk of daily activity limitations were found with uncontrolled asthma in the Real-world Evaluation of Asthma Control and Treatment study.³

In The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR), a large observational study that included nearly 5000 patients with severe or difficult-to-control asthma, 83% of patients were found to have uncontrolled asthma and an additional 16% showed inconsistent asthma control.⁵ An analysis from this study reported that very poorly controlled asthma was associated with increased risk for hospitalization, emergency department visit, or corticosteroid burst.^{6,7} Furthermore, recent exacerbations in individuals with poorly controlled asthma were found to be a predictor of future exacerbations.⁸

Although suboptimal medication adherence is a common problem among asthma patients (with low adherence reported for 61% in a recent claims database study), ~30% of patients who had moderate or high adherence to high-dose inhaled corticosteroids (ICSs) and long-acting β -agonist (LABA) therapy in that study had indicators of poor symptom control.⁹ Furthermore, an additional analysis from The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) in adolescents aged 12–17 years revealed that despite the use of multiple long-term controllers, rates of health care use remain high (Fig. 1).¹⁰ This highlights the need for additional types of asthma therapy for patients who remain uncontrolled on their current medications.

Many asthma patients may have an allergic component to their disease.^{11,12} According to data from

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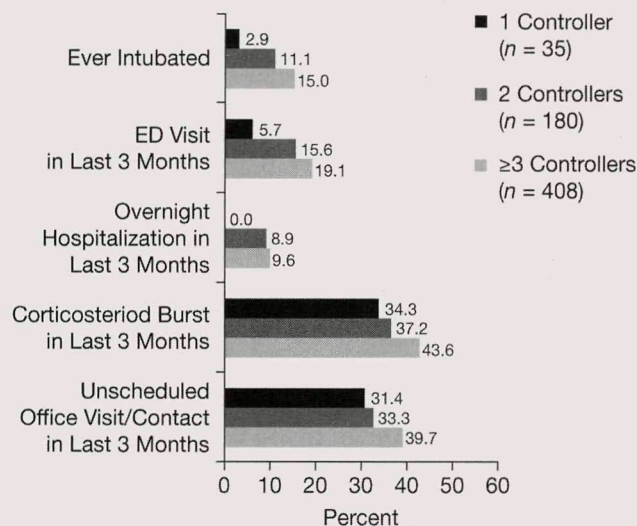


Figure 1. Health care use by number of long-term controller medications (long-term controllers included inhaled corticosteroids, long-acting β -agonists, leukotriene modifiers, methylxanthines, and cromolyn sodium or nedocromil). Differences in the rates of health care use by number of long-term controllers were not statistically significant in patients aged 12–17 years.¹⁰ (Reprinted with permission from Chipps *et al.*)¹⁰

the Third National Health and Nutrition Examination Survey, asthma is attributable to allergies in approximately one-half of patients (56%).¹³ Additional data from >1300 patients in the Asthma Clinical Research Network studies suggested that aeroallergen hypersensitivity occurs in up to 90–95% of patients with asthma, regardless of disease severity.¹⁴ Furthermore, a study conducted in an inner-city population with allergic asthma showed that targeting the allergic component in persistent asthma can provide a benefit beyond conventional treatment for asthma control.¹⁵ Omalizumab is an anti-immunoglobulin E (IgE) monoclonal antibody that inhibits binding of IgE to its high-affinity receptor (Fc ϵ RI) on the cell surface of basophils and mast cells, thus limiting the release of allergic mediators from these cells. Omalizumab treatment also has been shown to down-regulate Fc ϵ RI receptor expression on basophils.¹⁶

Omalizumab was approved by the US Food and Drug Administration (FDA) in 2003 for the treatment of moderate-to-severe allergic asthma in adults and adolescents (aged ≥ 12 years) whose symptoms are inadequately controlled with ICSs.¹⁶ This approval was based on three pivotal clinical trials: two that did not include patients using LABAs^{17,18} and one that included $\sim 45\%$ of patients taking LABAs.¹⁹ This was because the omalizumab pivotal trials were designed and implemented at a time when LABAs were not standard of care for asthma.

Over time, LABAs have become standard of care for patients with asthma inadequately controlled with ICS

therapy. The updated 2007 National Heart Lung and Blood Institute (NHLBI) asthma treatment guidelines describe a stepwise approach to asthma management that includes six steps, with the addition of an LABA to ICS therapy during steps 3 through 6. Recommendations for steps 5 and 6 include high-dose ICS + LABA therapy (with oral corticosteroids [OCS] added at step 6) and consideration of adding omalizumab therapy for patients with an allergic component to their asthma.²⁰ However, there is currently a lack of clinical evidence on which to base treatment decisions for patients continuing to exhibit poor asthma control on ICS + LABA therapy.²¹

To fill in this gap in the clinical evidence, a recent phase IIIb, randomized, controlled trial of omalizumab was conducted as part of a postmarketing commitment. This trial by Hanania *et al.*²² investigated the efficacy and safety of omalizumab versus placebo added to current therapy for patients with allergic asthma poorly controlled on high-dose ICS + LABA (with or without additional controller medication, including regular use of OCS). These data enrich the omalizumab clinical trial data currently available, extending it to patients at steps 5 and 6 of the current NHLBI treatment guidelines.

The present article is not intended to be a comprehensive review of the efficacy and safety of omalizumab, and key studies in patients ≥ 12 years of age such as the Investigation of Omalizumab in Severe Asthma Treatment trial²³ are not included within the scope of this article. Instead, this article is a detailed overview of data obtained from the original pivotal trials supporting registration in the United States (enrolling patients on ICS therapy, but no additional controller medication),^{17–19} extension trials to the pivotal trials,^{24,25} and the recently completed additional study that fulfilled part of a postmarketing commitment.²² Pediatric data (*i.e.*, from patients <12 years of age) were also beyond the scope of this article.

EFFICACY OF OMALIZUMAB IN PIVOTAL CLINICAL TRIALS

The study designs of the three pivotal clinical trials used for FDA registration in the United States (as well as the additional study described in the next section) are summarized in Table 1. All were multicenter, randomized, double-blind, placebo-controlled, parallel-group trials. Study 1 (Busse *et al.*¹⁷) and study 2 (Soler *et al.*¹⁸) were essentially identical in design; both randomized patients 1:1 to 28 weeks of treatment with omalizumab or placebo in addition to ICS therapy with no other controller medications allowed. The first 16 weeks constituted a steroid-stable phase, in which all patients continued on their baseline ICS dosage, followed by a 12-week steroid reduction phase. Both of

Table 1 Description of key omalizumab clinical trials (pivotal trials for FDA registration and additional study)

Study	Design	Patients	Treatment Arms/Duration	End Points
Study 1: Busse <i>et al.</i> ¹⁷ and Lanier <i>et al.</i> ²⁴	Randomized, double-blind, placebo-controlled, multicenter, parallel- group trial; double-blind extension	<i>n</i> = 525; aged 12–75 yr; allergic asthma symptomatic despite ICS (420–840 µg/day BDP-CFC or its equivalent); FEV ₁ ≥40% and ≤ 80% predicted; LABA use excluded	4- to 6-wk run-in phase (stable BDP-CFC dose); 16-wk steroid-stable phase (OMA or placebo added to baseline BDP-CFC dose); 12-wk steroid- reduction phase (BDP-CFC ↓ by 25% of baseline dose every 2 wk until discontinuation or worsening of asthma sx); 24-wk, double-blind extension (maintained on randomized tx, OMA or placebo, and lowest sustainable BDP-CFC dose; use of other asthma medications or different ICS was allowed)	Primary: No. of exacerbations per patient Secondary: No. of patients with ≥1 exacerbation; daily asthma sx; pulmonary function; global effectiveness
Study 2: Soler <i>et al.</i> ¹⁸ and Buhl <i>et al.</i> ²⁵	Randomized, double-blind, placebo-controlled, multicenter, parallel- group trial; double-blind extension	<i>n</i> = 546; aged 12–75 yr; allergic asthma symptomatic despite ICS (500–1200 µg/ day BDP-CFC or its equivalent); FEV ₁ ≥40% and ≤ 80% predicted; no other asthma medications allowed during the main study	4- to 6-wk run-in phase (stable BDP dose); 16-wk steroid-stable phase (OMA or placebo added to baseline BDP-CFC dose); 12-wk steroid reduction phase (BDP-CFC ↓ by 25% of baseline dose every 2 wk until discontinuation or worsening of asthma sx); 24-wk, double-blind extension (maintained on randomized tx, OMA or placebo, and lowest sustainable BDP-CFC dose; use of other asthma medications or different ICS was allowed)	Primary: No. of exacerbations per patient Secondary: No. of patients with ≥1 exacerbation; daily asthma sx; pulmonary function

Table 1 Continued

Study	Design	Patients	Treatment Arms/Duration	End Points
Study 3: Holgate <i>et al.</i> ¹⁹	Randomized, double-blind, placebo-controlled, multicenter, parallel-group trial	<i>n</i> = 246; aged 12–75 yr; allergic asthma requiring high-dose ICS (≥ 1000 $\mu\text{g}/\text{day}$ of fluticasone) for sx control, with or without LABA use; no exclusions based on FEV ₁ at baseline	6- to 10-wk run-in phase (fluticasone optimization); 16-wk steroid-stable phase (OMA or placebo added to optimized fluticasone dose); 16-wk steroid reduction phase (fluticasone dose $\downarrow$ by 250 $\mu\text{g}/\text{day}$ every 2 wk for 12 wk, until discontinuation or worsening of asthma sx; final 4 weeks assessed whether ICS dose reduction could be maintained)	Primary: % $\downarrow$ from baseline in fluticasone dose after 32 wk Secondary: Asthma exacerbations; asthma sx score; pulmonary function
Additional study: Hanania <i>et al.</i> ²²	Randomized, double-blind, placebo-controlled, multicenter, parallel-group trial	<i>n</i> = 850; aged 12–75 yr; allergic asthma uncontrolled on high-dose ICS + LABA (fluticasone, 1000 $\mu\text{g}/\text{day}$ or equivalent, salmeterol, 50 μg bid, or formoterol 12 μg bid) with or without other controller medications; FEV ₁ $\geq 40\%$ and $\leq 80\%$ predicted	2- to 4-wk run-in phase; randomized 1:1 to 48-wk treatment period with OMA or placebo added to ICS/LABA	Primary: No. of exacerbations per patient over the 48-wk treatment period Secondary: change from baseline in total asthma sx score, asthma-related quality of life (AQLQ)

AQLQ = Asthma Quality of Life Questionnaire; BDP = beclomethasone dipropionate; CFC = chlorofluorocarbon; FDA = Food and Drug Administration; FEV₁ = forced expiratory volume in 1 s; ICS = inhaled corticosteroid; LABA = long-acting β -agonist; OMA = omalizumab; sx = symptoms; tx = treatment.

these core studies were followed by 24-week, double-blind extension studies that maintained patients on their randomized treatment (omalizumab or placebo) and the lowest sustainable ICS dose but allowed use of other asthma medications if needed.^{24,25}

As shown in Table 2, both of these trials showed significant reductions in the number of exacerbations per patient, even as the steroid dose was lowered (study 1, steroid-stable phase, omalizumab 0.28, placebo 0.54 [$p = 0.006$]; steroid-reduction phase, omalizumab 0.39, placebo 0.66 [$p = 0.003$]; study 2, steroid-stable phase, omalizumab 0.28, placebo 0.66 [$p < 0.001$], steroid-reduction phase, omalizumab 0.36, placebo 0.75 [$p < 0.001$]) and percentages of patients with one or more exacerbation with omalizumab treatment versus placebo during both steroid-stable and steroid-reduction phases.^{17,18} Further supporting efficacy measures for omalizumab versus placebo in study 1 included significantly improved daily asthma symptom scores after week 4 (Fig. 2; $p < 0.05$) and increased mean forced expiratory volume in 1 second (FEV₁) from baseline to week 16 (from 68.2 to 72.53% of predicted in the omalizumab group, versus 67.7 to 69.1% of predicted in the placebo group).¹⁷ The clinical relevance of the treatment-associated differences in FEV₁ and asthma symptoms is unknown. The 24-week, double-blind extension studies of each of these trials both indicated that omalizumab continued to reduce the number of exacerbations and percentages of patients experiencing exacerbations versus placebo at 1 year of treatment (Table 2).^{24,25}

The third pivotal study by Holgate *et al.*¹⁹ had a few key differences in design from studies 1 and 2 (Table 1). This study enrolled fewer total patients ($n = 246$), used fluticasone rather than beclomethasone dipropionate (chlorofluorocarbon) as the concomitant ICS therapy, used a longer run-in phase (6–10 weeks) to optimize the fluticasone dose (1000–2000 $\mu\text{g}/\text{day}$) to maintain symptom control before randomization, had no exclusions based on FEV₁ at baseline, and had a treatment phase (with patients randomized to the addition of omalizumab or placebo) that spanned 32 weeks rather than 28 weeks (16 weeks of steroid-stable phase and 16 weeks of steroid-reduction phase). Finally, patients using LABA therapy at baseline were included in this study (49.2% of patients in the omalizumab group and 43.3% of patients in the placebo group) and were allowed to continue LABA use during the treatment period.¹⁹ This study was designed to evaluate a reduction in ICS use with a secondary end point to evaluate reduction in exacerbations. Patients treated with omalizumab had a lower number of asthma exacerbation episodes per patient compared with placebo, although these differences were not statistically significant (Table 2). The absence of an effect to significantly reduce exacerbations was not unex-

pected given the anticipated low rate of asthma exacerbations in patients optimized on high doses of inhaled fluticasone and that the study was powered to detect a reduction in ICS use and not to detect a reduction in exacerbations.

In all three of the studies described previously, a reduction in asthma exacerbations was not observed in patients treated with omalizumab who had FEV₁ > 80% at time of randomization. Reductions in exacerbations were not seen in patients who required OCS as maintenance therapy.¹⁶

EFFICACY OF OMALIZUMAB IN ADDITION TO HIGH-DOSE ICS + LABA THERAPY: ADDITIONAL STUDY

The recently completed additional²² study was a large ($n = 848$), randomized, double-blind, placebo-controlled, multicenter, clinical trial undertaken to evaluate the efficacy and safety of adding omalizumab to high-dose ICS + LABA therapy (with or without other controller medications) in patients with moderate-to-severe allergic asthma (Table 1). The treatment period was 48 weeks, spanning the entire viral/allergen season, and the primary end point was the rate of exacerbations per patient over this 48-week period. Patients were stratified into three subgroups based on concomitant asthma therapy; no dosage modifications were permitted during the study: subgroup 1 (37% of patients, $n = 310$), high-dose ICS + LABA (with no additional controller medication) + omalizumab (or placebo); subgroup 2 (46% of patients, $n = 394$), high-dose ICS + LABA + at least one additional controller medication (excluding OCS) + omalizumab (or placebo); and subgroup 3 (17% of patients, $n = 144$), high-dose ICS + LABA + chronically administered OCS + omalizumab (or placebo).

Figure 3 shows the primary end point of the additional trial, the rate of exacerbations over the 48-week treatment period. The overall result showed that omalizumab significantly reduced the rate of asthma exacerbations compared with placebo ($p = 0.006$) in patients treated with high-dose ICS + LABA therapy with or without other controller medications, for a 25% relative reduction in exacerbations associated with omalizumab treatment (exacerbation rate ratio for omalizumab/placebo: 0.75, 95% confidence interval, 0.61–0.92).

Patients treated with omalizumab in subgroups 1 and 2 experienced significantly lower exacerbation rates versus placebo, with a 34% relative reduction in exacerbations associated with omalizumab treatment in the M1 subgroup ($p = 0.033$) and a 28% relative reduction in exacerbations in the M2 subgroup ($p = 0.036$). Subgroup 3, in which patients were receiving regular stable doses of OCS in addition to high-dose

Table 2 Omalizumab pivotal clinical trials: summary of asthma exacerbations

Study	Steroid-Stable Phase		Steroid-Reduction Phase		Extension Study	
	OMA	Placebo	OMA	Placebo	OMA	Placebo
Study 1 ^{17,24}						
No. of patients	268	257	268	257	245	215
Exacerbations per patient* (p value vs placebo)	0.28 (0.006)	0.54	0.39 (0.003)	0.66	0.60 (0.023)	0.83
Patients with ≥1 exacerbation, n (%) (p value vs placebo)	39 (14.6) (0.0009)	60 (23.3)	57 (21.3) (0.0004)	83 (32.3)	78 (31.8) (0.015)	92 (42.8)
Study 2 ^{18,25}						
No. of patients	274	272	274	272	254	229
Exacerbations per patient* (p value vs placebo)	0.28 (<0.001)	0.66	0.36 (<0.001)	0.75	0.48 (<0.001)	1.14
Patients with ≥1 exacerbation, n (%) (p value vs placebo)	35 (12.8) (<0.001)	83 (30.5)	43 (15.7) (<0.001)	81 (29.8)	61 (24) (<0.001)	93 (40.6)
Study 3 ¹⁹						
No. of patients	126	120	126	120		
Exacerbations per patient (p value vs placebo)	0.15 (NS)	0.23	0.19 (NS)	0.34		
Patients with ≥1 exacerbation, n (%) (p value vs placebo)	NR	NR	NR	NR		

*Primary end point.

NR = not reported; NS = not significant; OMA = omalizumab.

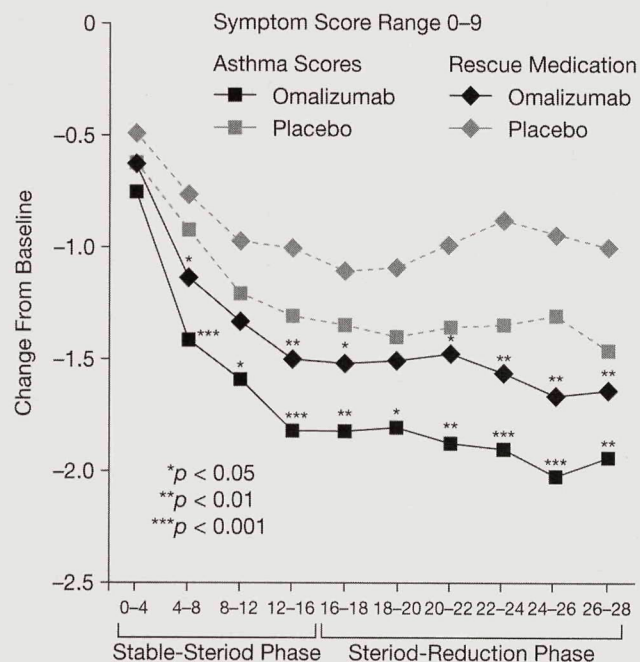


Figure 2. Mean change from baseline in total asthma symptom scores over stable-steroid (weeks 0–16) and steroid-reduction (weeks 16–28) phases in study 1.¹⁷ (Reprinted with permission from Busse et al.)¹⁵

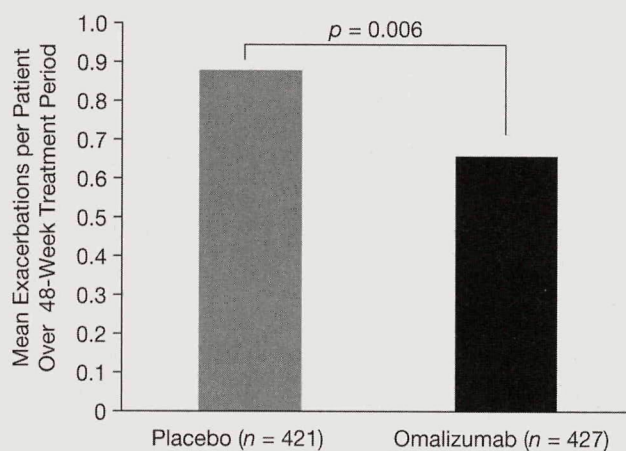


Figure 3. Asthma exacerbation rate (number of exacerbations/patient) over the 48-week treatment period of the additional randomized controlled trial.²²

ICS + LABA, did not show a significant reduction in exacerbation rate with omalizumab treatment versus placebo ($p = 0.79$). It should be noted, however, that the study was not sufficiently powered to assess efficacy in subgroup 3, which comprised only 17% of the total study population. Furthermore, the study protocol did not allow for asthma medication adjustments during the 48-week treatment period, and both patients who were on long-term corticosteroid treatment, as well as those who received frequent intermittent OCS treatment were included in this subgroup, which could have reduced the observed efficacy of omali-

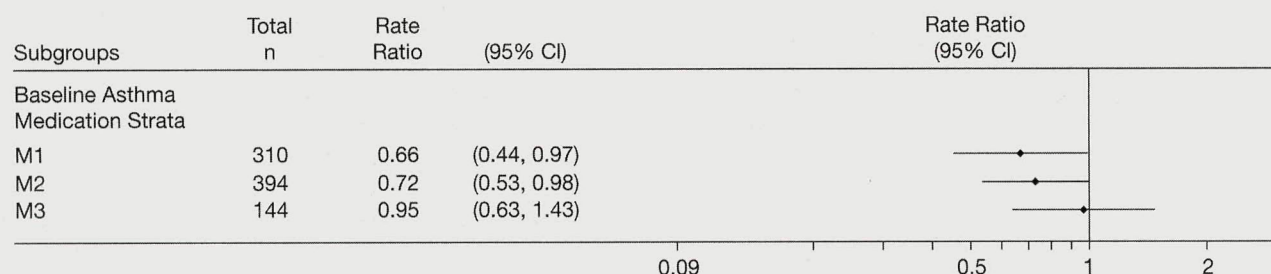


Figure 4. Subgroup analysis of exacerbation rates from the EXTRA 48-week, randomized, controlled trial, based on baseline asthma medication. M1 = inhaled corticosteroids (ICS) + long-acting β -agonists (LABA; with no additional controller medications); M2 = ICS + LABA + at least one additional controller medication (excluding oral corticosteroids [OCSs]); M3 = ICS + LABA + stable doses of OCS. Rate ratio = omalizumab/placebo exacerbation rates over the 48-week treatment period; CI = confidence interval.

zumab (Fig. 4). In a 32-week study²⁶ in which clinically appropriate changes in OCS dose were permitted, improvements in efficacy measurements were observed in omalizumab-treated patients, irrespective of changes in OCS dose over the duration of the study.

SUMMARY OF OMALIZUMAB SAFETY INFORMATION

As detailed in the omalizumab prescribing information, use of this medication is associated with the following warnings and precautions¹⁶:

- **Anaphylaxis.** In premarketing clinical trials, the frequency of anaphylaxis attributed to omalizumab was 0.1%. In postmarketing spontaneous reports, the frequency of anaphylaxis attributed to omalizumab was estimated to be at least 0.2% based on an estimated exposure of ~57,300 patients from June 2003 through December 2006. Anaphylaxis has occurred as early as after the first dose of omalizumab, but has also occurred beyond 1 year after beginning treatment. Signs and symptoms in reported cases have included bronchospasm, hypotension, syncope, urticaria, and/or angioedema of the throat or tongue; some of these events have been life-threatening. Therefore, omalizumab should only be administered in a health care setting by providers prepared to manage potentially life-threatening anaphylaxis.
- **Malignancy.** Malignant neoplasms were observed in 20 of 4127 (0.5%) omalizumab-treated patients compared with 5 of 2236 (0.2%) control patients in a previous analysis of clinical studies (2003). The observed malignancies in omalizumab-treated patients were a variety of types: breast, nonmelanoma skin, prostate, melanoma, parotid malignancies occurring more than once, and five other types occurring once each. The majority of patients were observed for <1 year. More recently, pooled data from 67 phase I-IV clinical trials were used to examine the incidence of malignancy in omalizumab-treated patients. In a prespecified primary analysis evaluating data from

32 randomized, double-blind, placebo-controlled trials, primary malignancies were identified in 14 of 4254 (0.3%) omalizumab-treated patients and 11 of 3178 (0.3%) placebo-treated patients.²⁷ Incidence rates per 1000 patient-years of observation time for omalizumab- and placebo-treated patients were 4.14 and 4.45%, respectively.²⁷ These data suggest no association between omalizumab treatment and risk of malignancy. The impact of longer exposure to omalizumab or its use in patients at higher risk for malignancy is under investigation; a long-term, ongoing, prospective study focusing primarily on the safety of omalizumab in patients with moderate-to-severe asthma (an epidemiologic study of xolair [omalizumab]: evaluating clinical effectiveness and long-term safety in patients with moderate to severe asthma [EXCELS] study) will provide further safety information when completed.²⁸

Adverse events (AEs) occurring more frequently in omalizumab-treated patients than those receiving placebo in pooled asthma studies are shown in Table 3, the most common of which were pain (7% omalizumab; 5% placebo) and arthralgia (8% omalizumab; 6% placebo).¹⁶

In study 1, the overall incidence of AEs between the omalizumab and placebo groups was similar (89.2% versus 89.1%, respectively). Seven omalizumab patients (2.6%) and six placebo patients (2.3%) experienced serious AEs (excluding asthma exacerbations). Three patients (one on omalizumab and two on placebo) had serious asthma exacerbations that required hospitalization. One death (caused by cardiac arrest) occurred in a patient receiving placebo. No serious AEs were considered drug related. Four (1.5%) patients in the omalizumab group reported urticaria compared with eight (3.1%) in the placebo group. Injection site reactions were reported in a similar percentage of injections in the omalizumab (8.6%) and placebo (6.5%) groups.¹⁷

There was a similar incidence in overall AEs between the omalizumab and placebo groups in study 2. A total

Table 3 AEs occurring in $\geq 1\%$ of patients and more frequently in those receiving omalizumab than placebo in four pooled asthma studies¹⁶

AE	Omalizumab, <i>n</i> = 738 (%)	Placebo, <i>n</i> = 717 (%)
Body as a whole		
Pain	7	5
Fatigue	3	2
Musculoskeletal system		
Arthralgia	8	6
Fracture	2	1
Leg pain	4	2
Arm pain	2	1
Nervous system		
Dizziness	3	2
Skin and appendages		
Pruritus	2	1
Dermatitis	2	1
Special senses		
Earache	2	1

AEs = adverse events.

of nine (3.3%) patients on omalizumab and three (1.1%) patients on placebo experienced serious AEs (not including asthma exacerbations). No patients in the omalizumab group experienced asthma exacerbations resulting in hospitalization, whereas six (2.2%) patients in the placebo group did. Seven patients (five on placebo) experienced urticaria that was not considered severe.¹⁸ A total of 11.8% of omalizumab injections and 7.7% of placebo injections were associated with local injection site symptoms; bruising was found to be the most frequent injection site event in both groups.¹⁸

In study 3, the omalizumab and placebo groups had similar incidence of overall AEs (76.2% versus 82.5%, respectively). One patient in the omalizumab group (0.8%) and five in the placebo group (4.2%) experienced serious AEs, none of which were considered drug related. Urticaria was experienced during the study in one patient receiving omalizumab and three receiving placebo. Local bruising was the most common local injection site symptom with 20.4% of omalizumab injections and 10.3% of placebo injections associated with injection site reactions.¹⁹

In the additional trial, the incidence of AEs was similar in the omalizumab and placebo groups (80.4% versus 79.5%, respectively). In addition, serious AEs were similar between the two groups (9.3% versus 10.5%). Three deaths occurred during this study, all in the placebo group, with one death considered treatment emergent because it occurred during the study. The rate of urticaria was similar between the omalizumab and placebo groups (9 patients [2.1%] versus 13

patients [3.1%]). Injection site reactions occurred with 5 (1.2%) omalizumab injections and 13 (3.1%) placebo injections.²²

Across studies, the incidence of AEs and serious AEs were similar for omalizumab-treated and placebo groups.^{17–19,22} However, patients taking placebo were more likely to experience serious asthma exacerbations requiring hospitalization.^{17,18} Urticaria was experienced by fewer patients treated with omalizumab than placebo.^{17–19,22} Injection site reactions were more common with omalizumab than placebo in some studies.^{17–19,22}

Recently, concerns over cardiovascular safety have arisen based on an interim analysis of the EXCELS long-term, observational, safety study with omalizumab.^{8,29} After an increased number of cardiovascular and cerebrovascular events in asthmatic patients on omalizumab treatment compared with asthmatic patients on control treatment, the FDA posted an early communication informing the public about this finding. Changes to the United States prescribing information were not recommended and patients were not advised to stop taking omalizumab. The full extent of any proposed risk of cardiovascular and cerebrovascular events with omalizumab treatment will be further elucidated once the full results of the EXCELS long-term safety study are available, later in 2012.

CONCLUSIONS

As an anti-immunoglobulin E monoclonal antibody, omalizumab acts by a unique mechanism of action and is currently the only anti-immunoglobulin E therapy approved by the FDA for treatment of moderate-to-severe allergic asthma in patients aged ≥ 12 years. Unlike other asthma controller medications that must be taken daily, omalizumab is administered as a subcutaneous injection given once every 2 or 4 weeks depending on required dosing based on bodyweight and pretreatment total IgE levels. Although the appropriate omalizumab dose is determined from a dosing table based on bodyweight and initial IgE level, continuous IgE testing during therapy is unnecessary. Total IgE levels (which include IgE bound to omalizumab) remain elevated during and up to 1 year after discontinuation of treatment with omalizumab, such that retesting IgE levels during omalizumab therapy can not be used as a guide for dose determination. Doses can be adjusted based on significant changes in bodyweight.¹⁶

Based on the three pivotal trials reviewed in this article,^{17–19} the approved indication for omalizumab is for the treatment of moderate-to-severe allergic asthma inadequately controlled with ICS therapy.¹⁶ Omalizumab is not indicated for the treatment of other allergic conditions, the relief of acute bronchospasm or status asthmaticus, or for use in pediatric patients < 12

years of age. The current NHLBI 2007 guidelines recommend considering the addition of omalizumab therapy in patients at the more severe end of the spectrum, requiring treatment at steps 5 and 6 (high-dose ICS + LABA $\pm$ additional controller medications),²⁰ and this is mostly where omalizumab is preferred as a treatment option in clinical practice today. Thus, the recently completed additional study provides important efficacy and safety information in patients with more severe asthma to supplement existing omalizumab clinical trial data. This study showed that omalizumab significantly reduces the rate of asthma exacerbations versus placebo over a 48-week treatment period when added to high-dose ICS + LABA therapy (with or without additional controller medications, including OCS), confirming the NHLBI guideline recommendation to consider omalizumab as an additional therapy for asthma patients (aged ≥ 12 years) requiring steps 5 or 6 therapy.

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