

Omalizumab in Asthma

Approval and Postapproval Experience

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Abstract

Omalizumab is a humanized mouse monoclonal antibody that binds specifically to the constant region of the immunoglobulin (Ig)E heavy chain. Omalizumab exerts its effects by reducing free serum IgE levels and FcεRI expression on several cell types. These effects have been shown to result in decreased airway inflammation and clinical improvement. In multiple studies, omalizumab has been shown to be efficacious in the treatment of moderate-to-severe persistent asthma and is currently approved by the US Food and Drug Administration for the treatment of moderate-to-severe allergic asthma in patients age 12 yr and older. Moreover, omalizumab has been demonstrated to be effective in the treatment of children and adults with seasonal and perennial allergic rhinitis. Postmarketing surveillance has shown omalizumab to be a relatively safe and well-tolerated medication.

Index Entries

Omalizumab; anti-IgE; asthma; rhinitis; allergies.

Introduction

The development of a selective humanized monoclonal antibody (omalizumab) that binds to immunoglobulin (Ig)E and interferes with its association with both high- and low-affinity IgE receptors has been a major breakthrough in the treatment of allergic diseases. Omalizumab interrupts the allergic cascade by preventing

allergen from activating mast cells or basophils, as well as FcεRI-bearing antigen-presenting cells. Omalizumab has been shown to be effective in multiple clinical trials both in children and adults for chronic asthma and rhinitis. A summary of the results of these trials and a discussion of the mechanisms whereby omalizumab influences the pathophysiological responses in the airways will be discussed in this article.

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Immunoglobulin E and the Allergic Response

Since IgE was characterized by Ishizaka in 1967 (1), its central role in allergic disorders has become well-established. IgE is believed to have evolved as a mechanism of defense against parasitic organisms. The sites most affected by the many manifestations of allergic diseases, including the skin, lungs, and gastrointestinal tract, are also the areas most commonly involved in parasitic infections (2). An elevated serum IgE is a feature common to all atopic disorders.

Susceptible individuals produce IgE that recognizes unique allergen epitopes. The Fc portion of IgE binds to its high-affinity receptor (FcεRI) and is subsequently expressed on the surface of several cell types, including mast cells, basophils, dendritic cells (DCs), and, to a lesser extent, other cell types. An antigen that expresses the unique epitopes recognized by a particular IgE molecule bind to the Fab portion of the IgE molecule. On the cell surface, when two adjacent IgE molecules are crosslinked by an antigen, an intracellular signaling process begins that culminates in the release of mediators from mast cells and basophils. It is these mediators (including histamine, prostaglandins, and leukotrienes), as well as cytokines (e.g., interleukin [IL]-4, IL-13, and, in the case of mast cells, IL-5) that are responsible for the clinical manifestations of atopic disorders, such as asthma, allergic rhinitis, and food allergy.

Relative to IgG, IgM, and IgA, the amount of IgE in the circulation is very small. The half-life of IgE in the serum is approx 2 d. The half-life of cell-surface-expressed IgE in the tissues is weeks (3). Recent work has confirmed that IgE appears to upregulate the expression of FcεRI on human basophils, and it seems likely that this is mediated by IgE interacting through FcεRIα itself (4). IgE also upregulates FcεRII, the "low-affinity" IgE receptor (CD23), whose role is less certain (5). It appears that soluble

FcεRII upregulates IgE production via interaction with CD21 in the B-cell coreceptor complex. However, ligation of cell surface-expressed FcεRII appears to inhibit synthesis of IgE (6).

Characteristics of Omalizumab

Omalizumab is a humanized mouse monoclonal antibody. A murine anti-IgE antibody was produced by the immunization of mice with human IgE (7). To facilitate its use in humans, the critical sequences responsible for IgE binding were engrafted onto a human IgG1κ framework. The resulting antibody is composed of approx 95% human and 5% murine sequences (7,8).

Omalizumab binds to the third constant domain of the IgE heavy chain (Cε3), which is conserved among all IgE molecules (9). Omalizumab thus binds to all IgE, regardless of allergen specificity. This is also the binding site of FcεRI. Binding of omalizumab to its target site prevents the association of free IgE with FcεRI and its subsequent expression on the cell surface of mast cells and basophils. As a result of its binding characteristics, omalizumab does not bind to cell surface-expressed IgE and does not lead to the crosslinking of cell surface IgE and the subsequent release of mast cell or basophil products (10). Omalizumab binds to free IgE, predominantly forming trimeric and hexameric complexes that are subsequently cleared from the body by the reticular endothelial system without activation of complement.

After subcutaneous administration, peak serum concentration is reached in 7 to 8 d (11). The elimination half-life is 1 to 4 wk after subcutaneous or intravenous administration.

Effects of IgE and Omalizumab on IgE Receptor Expression and In Vivo Responses

Omalizumab exerts its effects through two important mechanisms: omalizumab reduces free serum IgE levels, and consequently, omalizumab reduces the expression of FcεRI on several cell types. MacGlashan et al. (12) found an

early and dramatic reduction (99%) in free IgE levels in 15 patients sensitive to dust mites. The FcεRI expression on circulating basophils was reduced by 97% in the presence of low serum levels of IgE during the 90 d of treatment with omalizumab. This lends support to the role of IgE in controlling the expression of FcεRI. Basophil histamine release in response to dust-mite allergen challenge was reduced by approx 90%.

More recently, Casale and colleagues (13) examined the kinetics of reduction in free serum IgE and basophil FcεRI expression in 24 patients with allergic rhinitis who were also sensitive to ragweed. Mean serum IgE levels showed a 96% reduction within 3 d of treatment in the omalizumab group ($p < 0.001$). Additionally, the expression of FcεRI on blood basophils was reduced by 73% ($p < 0.001$) within 7 d of treatment in the group treated with omalizumab. Furthermore, the decreased FcεRI expression on basophils correlated with the time at which patients treated with omalizumab experienced a reduction in nasal allergen challenge responses. In addition to examining omalizumab's effect on basophil FcεRI expression, these investigators explored the role of omalizumab on the expression of FcεRI on DCs in the same patients (14). Expression of FcεRI by DCs greatly facilitates antigen presentation to T-cells (15). Two subsets of DCs have been identified: type I DCs (DC1) and type II DCs (DC2). DC1 cells appear to shift T-cells toward a T-helper (Th)1 cytokine profile, whereas the DC2 subset appears to be important for T-cell cytokine production toward a Th2 phenotype (16). The expression of FcεRI by both the DC1 and DC2 subsets has been shown to correlate with serum IgE. Allergic asthmatic patients exhibit greater DC FcεRI expression than non-atopic controls, likely resulting from higher IgE levels (17). Prussin and colleagues (14) examined the effect of omalizumab on DC FcεRI expression in 24 patients with ragweed-sensitive seasonal allergic rhinitis (out of season). Omalizumab downregulated FcεRI expression on

both the DC1 and DC2 subsets. This effect became significant when compared with placebo on day 7 and remained significant throughout the remainder of the study (days 14, 21, 28, 35, 42). The change in DC FcεRI expression correlated with the change in serum free IgE levels, as well as with basophil FcεRI expression. Therefore, in addition to its well-established effects on the effector phase of the allergen-specific immune response, omalizumab may induce an effect on the sensitization phase of allergic responses by regulating the expression of FcεRI on antigen-presenting cells.

In contrast to the rapid reduction of FcεRI on basophil and DCs, the decrease in FcεRI observed on cutaneous mast cells appears to occur in a much slower fashion after omalizumab treatment. A recently published small study evaluated intradermal skin test titration and skin biopsy specimens in eight subjects with allergic rhinitis sensitive to dust mites (3 omalizumab, 5 placebo) (18). Subjects underwent skin test titration to dust-mite allergen and biopsy at the skin test site at days 0, 7, 70, and 196. The expression of FcεRI in the biopsy specimens remained unchanged at 7 d. By day 70, however, there was a 90% reduction in the expression of FcεRI in the biopsy specimens in the treatment group. This reduction in FcεRI did not result from a reduction in skin mast cells, because the number of tryptase-positive cells remained unchanged. The delay in reduction of cutaneous mast cell FcεRI expression was associated with a longer time to measure inhibition of cutaneous skin test responses after treatment with omalizumab (18–20). The late-phase reaction was significantly reduced at 2 wk, whereas the early phase reaction was not inhibited until 8 wk after treatment with omalizumab (19).

The reduction of FcεRI is as significant as the omalizumab-induced reduction in serum IgE. Without FcεRI downregulation, near-total removal of free IgE must occur to elicit the same functional consequence in mast cells and basophils (12).

Omalizumab and Airway Hyperresponsiveness

The effect of omalizumab on nonspecific airway hyperresponsiveness (an important component of asthma) is currently unclear. Several authors have explored airway reactivity as a secondary endpoint (21–24), but the studies have provided conflicting results. Boulet et al. (22) examined allergen and methacholine responsiveness in a multicenter, randomized, double-blind, parallel-group study ($N = 10$). Subjects were adults with mild asthma who required only an inhaled β_2 -agonist on demand for symptom control. Methacholine PC20 was determined on days 2, 42, and 76. A small improvement in methacholine PC20 became statistically significant on day 76 (average 0.9 doubling dose; $p < 0.05$).

Fahy and colleagues (21) determined methacholine responsiveness in a similar group of patients with mild allergic asthma. Again, these patients were on no controller medications at the time of study enrollment. The authors showed a small improvement in methacholine responsiveness, which was not statistically significant. In another multicenter, randomized, placebo-controlled, parallel-group trial, Noga et al. (23) examined the effect of omalizumab on acetylcholine PC20 in patients with moderate-to-severe asthma, all of whom required daily inhaled corticosteroids. The results were reported as percentage change from baseline. The group treated with omalizumab ($n = 18$) showed a significant increase in acetylcholine PC20 compared with the group given placebo ($n = 17$). After discontinuation of the therapy, no difference between treatment groups was observed. The most recent and largest trial to date examined methacholine responsiveness in 45 mild-to-moderate asthmatics (omalizumab group, $n = 22$; placebo group, $n = 23$) at 2-wk intervals for 16 wk (24). All subjects had discontinued the use of inhaled corticosteroids at least 6 wk prior to enrollment. There was no significant change in metha-

choline responsiveness over baseline in the treatment or placebo group. Additionally, there was no improvement in the group treated with omalizumab compared to the group given placebo. The authors speculated that airway responsiveness may partly reflect the complex remodeling process of the asthmatic airway, and, therefore, a longer treatment time might be necessary to achieve improvement in methacholine responsiveness. However, these investigators did find a significant decrease in lung inflammation in the same patients treated with omalizumab.

Perhaps another important distinction regarding airway responsiveness is direct vs indirect bronchoprovocation challenges. Direct challenges, such as methacholine, involve the interaction of a pharmacological agent with a specific receptor on the airway smooth muscle, resulting in smooth muscle contraction and airway obstruction. Conversely, indirect challenges with various physical and pharmacological agents (exercise, cold air, hypertonic saline, adenosine, and others) induce the release of several mediators from a variety of cell types, which, in turn, results in airway obstruction. Many investigators have suggested that indirect challenges better reflect the pathophysiology of the asthmatic airway. In particular, indirect challenges may correlate better with markers of inflammation, such as exhaled nitric oxide and sputum eosinophils (25). To date, no published data exist regarding the effect of omalizumab on indirect airway challenges. Research in this area is ongoing and will hopefully provide additional insight regarding the effects of omalizumab on airway hyperresponsiveness.

Omalizumab and Airway Inflammation

Nitric oxide (NO) is a highly reactive central mediator in biological systems. NO is produced from L-arginine by the action of NO synthase (NOS), which exists as three isoforms: two are constitutively expressed (types I and

III) and one is inducible (type II). Type II NOS is expressed in pathological states in response to pro-inflammatory cytokines. Immunohistochemical studies have demonstrated increased expression of type II NOS in asthmatic airway epithelial cells, and studies have demonstrated that the fractional concentration of exhaled NO (FENO) is increased in patients with asthma (26). FENO has been proposed as a noninvasive marker of airway inflammation (27).

In a small preliminary study, Silkoff and colleagues (28) conducted a randomized, double-blinded, placebo-controlled trial assessing the effects of omalizumab on FENO in 29 children with moderate-to-severe allergic asthma before and during inhaled corticosteroid withdrawal. After randomization, the patients entered a 16-wk steroid-stable phase of treatment with either omalizumab or placebo. After treatment, the patients entered a 12-wk steroid reduction phase, during which patients' inhaled corticosteroid dose was reduced by 25% every 2 wk. In a 24-wk open-label extension, all patients previously receiving placebo were switched to treatment with omalizumab. During the steroid reduction phase, FENO was increased in the placebo group compared to the omalizumab group. FENO fell significantly after 1 yr of continuous treatment with omalizumab, despite a reduction in corticosteroid therapy. The effects on FENO were similar to those observed for inhaled corticosteroids alone, suggesting an anti-inflammatory action for omalizumab in allergic asthma (28).

Djukanovic et al. (24) conducted a 16-wk placebo-controlled trial in 45 mild-to-moderate asthmatics with at least 2% sputum eosinophilia to more directly evaluate the anti-inflammatory effects of omalizumab in the asthmatic airways. Markers of airway inflammation were assessed in induced sputum and bronchial biopsies obtained by fiberoptic bronchoscopy before and after 16 wk of subcutaneous treatment with omalizumab. Compared with patients given placebo, patients treated with omalizumab showed significant reduc-

tions in sputum eosinophil counts (6.6 to 1.7%), as well as eosinophil counts in the epithelial and submucosal compartments. These data confirmed an earlier pilot study showing a reduction in sputum eosinophils after treatment with omalizumab (21). IgE⁺ cells in the airway mucosa were reduced 10-fold. Additionally, CD3⁺, CD4⁺, CD8⁺ T-lymphocytes, B-lymphocytes, and cells staining for IL-4 also decreased with omalizumab treatment.

Overall, these data suggest an anti-inflammatory effect of omalizumab for asthma.

Omalizumab in Asthma

Omalizumab has been approved by the US Food and Drug Administration for the treatment of moderate-to-severe persistent allergic asthma in patients age 12 yr and older. An extensive body of literature exists regarding the clinical efficacy of omalizumab in patients with asthma. The results of two early studies suggested that omalizumab inhibits both the early and late-phase asthmatic response, as assessed by allergen bronchoprovocation challenge (21,22).

Milgrom and colleagues (29) conducted a phase II study using an intravenous formulation of omalizumab in 317 patients with moderate-to-severe allergic asthma requiring either inhaled or oral corticosteroids. Two dosing protocols were used: low-dose (2.5 µg/kg of body weight per nanogram of IgE per milliliter) and high-dose (5.8 µg/kg of body weight per nanogram of IgE per milliliter). During the first 12 wk of the study, the subjects continued the same corticosteroid regimen they had received prior to enrollment. Over the following 8 wk, the corticosteroid dose was tapered. The primary outcome measure was an improvement in the asthma symptom score at 12 wk. At 12 wk, symptom scores were improved in both the high-dose ($p = 0.008$) and the low-dose ($p = 0.005$) groups compared with the group given placebo. Additionally, more subjects in both treatment groups were able to reduce or

Table 1
Demographics of Subjects in Three Phase III Pivotal Omalizumab Trials in Asthma

Characteristic	Busse et al. (adults and adolescents)		Soler et al. (adults and adolescents)		Milgrom et al. (children)	
	Omalizumab	Placebo	Omalizumab	Placebo	Omalizumab	Placebo
Number treated	268	257	274	272	225	109
Mean age (yr)	39	39	40	39	9	10
Mean duration of asthma (yr)	21	23	20	19	6	6
Mean serum total IgE level (IU/mL)	172	186	223	206	348	323
Mean FEV ₁ (% predicted)	68	68	70	70	84	85
Mean BDP dosage (mg/d)	679	676	769	772	338	318
Severe asthma (%)	22	21	22	22	9	6

BDP, beclomethasone dipropionate; FEV₁, forced expiratory volume in 1 s. (Adapted from ref. 35.)

discontinue use of corticosteroids than in the placebo group, and fewer subjects in the two treatment groups had asthma exacerbations (29).

Three phase III trials were later conducted in a total of 1405 patients (Table 1) with moderate-to-severe allergic asthma; two trials were conducted in symptomatic adolescents and adults (age >12 yr) treated with inhaled corticosteroids, and one trial was conducted in asymptomatic children (ages 6–12 yr) treated with inhaled corticosteroids (30–32). All three studies shared a similar design (Fig. 1). Subcutaneous injections of 150 to 375 mg of omalizumab were administered every 2 or 4 wk (Fig. 2). Dosing was based on the patient's baseline IgE and body weight to provide at least 0.016 mg/kg of omalizumab per IU/mL of IgE every 4 wk. Omalizumab was added to an inhaled corticosteroid regimen during the initial 16 wk. Following this period, the subjects underwent a 12-wk steroid reduction phase, during which corticosteroid doses were reduced by up to 25% every 2 wk to the lowest level required for optimal asthma control. In all three studies, the primary endpoint was a reduction in asthma exacerbations. Secondary efficacy variables measured throughout the study included daily and nocturnal asthma symptoms, reduced use of inhaled corticosteroids, quality of life, rescue medication use, and lung functions.

All three studies showed a reduction in asthma exacerbations in the subjects treated with omalizumab compared with those treated with placebo. Omalizumab demonstrated a corticosteroid-sparing effect in all three studies; patients treated with omalizumab were able to significantly reduce their inhaled corticosteroid dose and, in many cases, were able to withdraw completely from corticosteroids. Approximately twice as many patients treated with omalizumab completely withdrew from use of inhaled corticosteroids compared to patients given placebo. Patients treated with omalizumab also showed fewer asthma symptoms, less β -agonist use, and improvements in quality-of-life indices (30–32).

Corren and colleagues (36) pooled the data from these three studies to determine the effect of omalizumab on serious asthma exacerbations, defined as asthma-related urgent care visits, emergency room visits, or hospitalizations. Patients treated with omalizumab experienced significantly fewer unscheduled outpatient visits and emergency room visits (rate ratios: 0.60 and 0.47, respectively; $p \leq 0.05$) compared with patients given placebo. Furthermore, hospitalizations were significantly reduced from 3.42 events per 100 patient-years with placebo to 0.26 for patients treated with omalizumab, a rate ratio of 0.08 ($p < 0.01$).

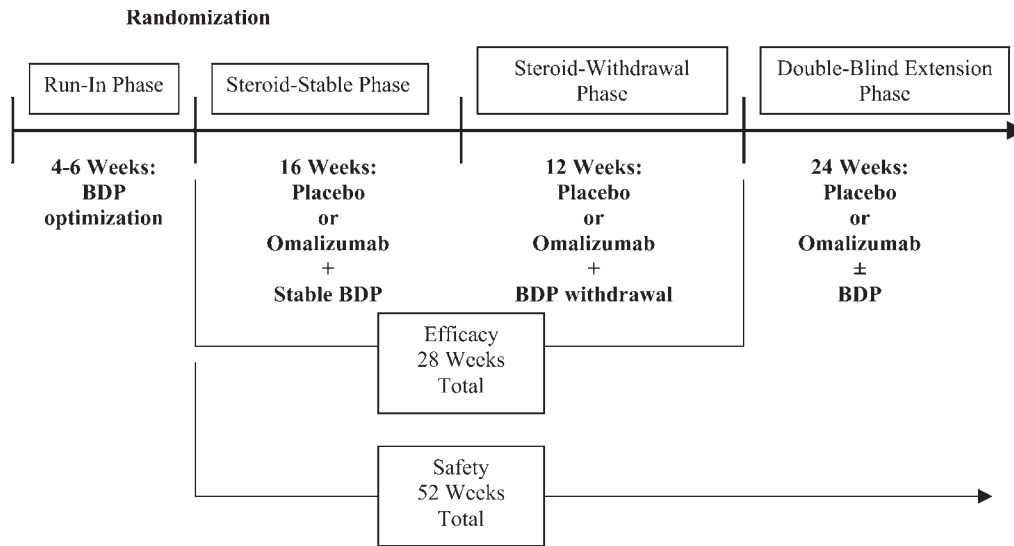


Fig. 1. Study design of three pivotal, multicenter phase III studies of omalizumab vs placebo in the treatment of allergic asthma. The trials were similar in study design and included four distinct phases: run-in, steroid-stable, steroid-withdrawal, and double-blind extension. During the 4- to 6-wk run-in phase, patients' standard therapy was switched to inhaled beclomethasone (BDP) and stabilized, which required the investigators to adjust the BDP dose so the patients entered the core study period (steroid-stable phase) symptomatic yet exacerbation-free (adult and adolescent studies only). Following the run-in phase, patients were randomized to receive omalizumab or placebo plus the stable dose of BDP for the next 16 wk. This was followed by a 12-wk steroid-withdrawal phase. A 24-wk extension phase was added. Drug efficacy was evaluated over 28 wk, and safety was assessed over 52 wk. (Adapted from ref. 30.)

Bousquet et al. (37) performed a pooled analysis of two of these phase III studies (30,32) to determine baseline patient characteristics predictive of the best response to omalizumab therapy for allergic asthma. These two studies included 1070 adults and adolescents with allergic asthma. They found that patients with a history of emergency treatment of asthma in the recent year, patients on high-dose inhaled corticosteroids ($\geq 800 \mu\text{g}$ of beclomethasone per day), and patients with poor lung function (forced expiratory volume after 1 s $\leq 65\%$ predicted) were those most likely to benefit from add-on therapy with omalizumab (Fig. 3). They also concluded that patients should be treated with omalizumab for a minimum duration of 12 wk to assess possible therapeutic benefit.

In a study by Holgate and colleagues (38), omalizumab allowed a clinically significant

reduction in high-dose corticosteroids while maintaining asthma control in patients with severe asthma. A randomized, double-blind, placebo-controlled trial was conducted in 246 patients with severe allergic asthma. All patients required at least $1000 \mu\text{g}/\text{d}$ of inhaled fluticasone for symptom control. Subcutaneous omalizumab (minimum: $0.016 \text{ mg}/\text{kg}/\text{IgE}$ [IU/mL] per 4 wk; $n = 126$) or placebo ($n = 120$) was added to the patients' optimized fluticasone therapy. After 32 wk of treatment, patients treated with omalizumab had a greater reduction in fluticasone dose than patients given placebo (mean: 57.2 vs 43.3% ; $p = 0.003$; Table 2). Patients receiving omalizumab also had reduced rescue medication use, improved asthma symptoms, and improved asthma-related quality of life compared with patients given placebo (38).

Pre-treatment Serum IgE (IU/mL)	Body Weight (kg)				Frequency of Dosing
	30-60	> 60-70	> 70-90	> 90-150	
≥30-100	150	150	150	300	Every 4 weeks
> 100-200	300	300	300	225	Every 2 weeks
> 200-300	300	225	225	300	
> 300-400	225	225	300		
> 400-500	300	300	375		
> 500-600	300	375	Not Dosed		
> 600-700	375				

Fig. 2. Omalizumab dosing table. Omalizumab doses (mg) administered by subcutaneous injection every 4 wk for adults and adolescents (age 12 yr and older) with asthma. Dosing is based on weight (kg) and pretreatment total IgE level.

Ayres et al. (39) evaluated the efficacy of omalizumab as an add-on therapy in 312 symptomatic patients with moderate-to-severe allergic asthma treated with high doses of inhaled corticosteroids and other controller medications. These patients were symptomatic, despite treatment with high doses of inhaled corticosteroids plus long-acting β_2 -agonists, antileukotrienes, or oral steroids. About 23% of patients treated with omalizumab were on oral corticosteroids, 78% were on long-acting β_2 -agonists, and 29% were on antileukotrienes. Similar use of controller medications occurred in the placebo group. After 52 wk of treatment, the group treated with omalizumab experienced a greater reduction of asthma exacerbations (60%), unscheduled physician visits, and days lost from work/school compared with the group given placebo (Fig. 4). These data suggest that the efficacy of omalizumab is not affected by the use of other controller agents and mimics more of a “real-life” situation in which omalizumab would be added to standard care in patients with symptoms (39).

A significant, practical concern regarding the administration of omalizumab is cost. Pres-

ently, the estimated annual cost of omalizumab therapy is approx \$10,000 to 20,000 per patient (40). It is well-established that a relatively small proportion of asthmatics with severe disease are responsible for the majority of health costs associated with asthma care. Emergency room visits and hospitalizations account for most of these costs. Despite the high cost of omalizumab therapy, it may be cost-effective when its use is restricted to a select population, including patients with frequent exacerbations—especially those requiring emergency room visits and/or hospitalizations.

Patients with severe persistent asthma who are inadequately controlled despite being maximally treated according to current asthma management guidelines are at high risk for serious exacerbations and asthma-related mortality. Two recently published studies offered evidence that when added to conventional therapy, omalizumab provided additional symptom control and reduction of exacerbations in patients with severe persistent asthma (41,42). Bousquet et al. (41) pooled data from seven studies to determine the effect of omalizumab on asthma exacerbations in patients with severe

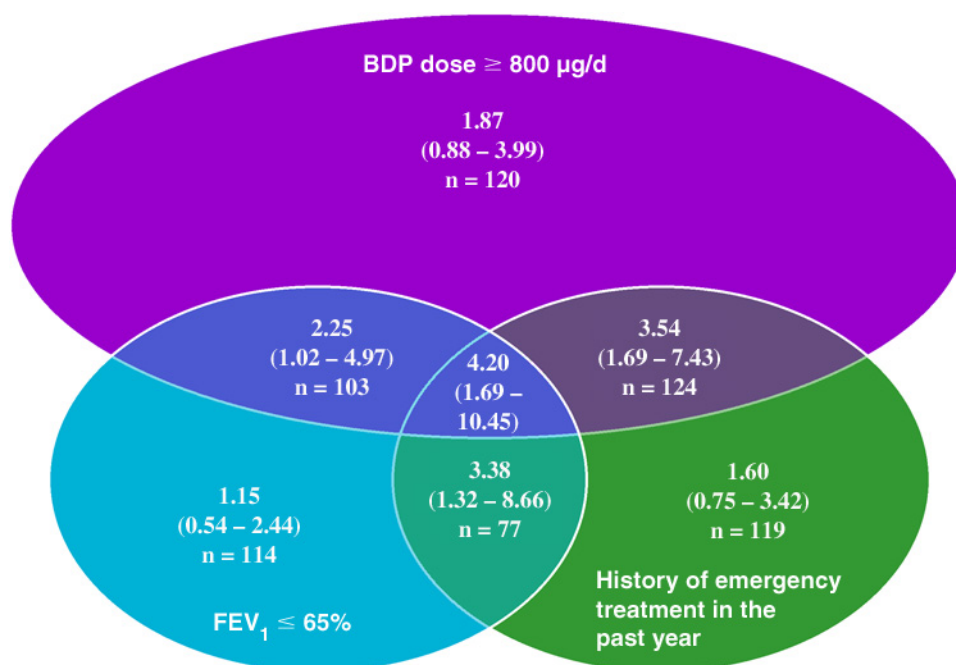


Fig. 3. Venn diagram of odds ratios and corresponding 95% confidence intervals for response on omalizumab relative to placebo according to three high-severity baseline covariates. BDP, beclomethasone dipropionate; FEV₁, forced expiratory volume in 1 s. (Adapted from ref. 37.)

persistent asthma. Omalizumab was added to current asthma therapy and compared to placebo (in five double-blind studies) or to current asthma therapy (in two open-label studies). The studies included 4308 patients (2511 treated with omalizumab). Omalizumab was found to significantly reduce the rate of asthma exacerbations by 38%, as well as the rate of total emergency visits by 47% (41). Humbert et al. (42) randomized 419 patients who were symptomatic despite therapy with high-dose inhaled corticosteroids and long-acting β_2 -agonists to receive omalizumab or placebo for 28 wk. Omalizumab was found to significantly reduce the rate of severe asthma exacerbation, as well as the rate of emergency visits (42). These studies suggest that omalizumab should be considered as add-on therapy for patients with inadequately controlled, severe, persistent asthma who are maximally treated with therapy according to current guidelines.

Omalizumab in Asthma With Co-Existing Allergic Rhinitis

Allergic rhinitis affects 20 to 40 million Americans annually, including 10 to 30% of adults and up to 40% of children (43). Symptoms can range from mild to seriously debilitating and can affect quality of life, resulting in loss of work and school days (44). The most concerning issue is that the majority of allergic asthmatics also have concomitant allergic rhinitis. In these patients, poorly controlled allergic rhinitis can have a detrimental effect on asthma (45). Moreover, several studies have reported that successful treatment of rhinosinusitis in patients with co-existent asthma and rhinosinusitis is associated with improvement of asthma (45–48).

Omalizumab has been demonstrated as safe and effective for the treatment of children and adults with seasonal and perennial allergic

Table 2
Omalizumab in Severe Asthmatics

	Placebo (<i>n</i> = 120)	Omalizumab (<i>n</i> = 126)	
Reduction in fluticasone dose (%); Median (95% CI)	50.0 (33.3-50.0)	60.0 (50.0-75.0)	<i>p</i> = 0.003
Patients with ≥50% reduction in fluticasone dose (%)			
All patients	50.8	73.8	<i>p</i> = 0.001
Patients receiving LABA	53.8 (<i>n</i> = 52)	72.6 (<i>n</i> = 62)	<i>p</i> = 0.039
Patients not receiving LABA	48.5 (<i>n</i> = 68)	75.0 (<i>n</i> = 64)	<i>p</i> = 0.002
Absolute reduction in fluticasone dose (μg/d); Median (95% CI)	500 (500-750)	750 (750-1000)	<i>p</i> = 0.003
Patients reduced to ≤500 μg/d of fluticasone (%)	45.8	60.3	<i>p</i> = 0.026

Omalizumab was evaluated in a double-blind, placebo-controlled, parallel-group trial comprising 246 patients (ages 12-75 yr) with severe allergic asthma (mean forced expiratory volume in 1 s: 64% predicted) requiring high-dose inhaled corticosteroids (mean fluticasone propionate dose approx 1369 μg/d). After 32 wk of treatment, patients receiving omalizumab had a greater reduction in fluticasone dose than patients receiving placebo. (Adapted from ref. 38.)

CI, confidence interval; LABA, long-acting β₂-agonist.

rhinitis. Ädelroth et al. (49) examined the effects of omalizumab on birch pollen-sensitive seasonal allergic rhinitis in 251 adolescents and adults. A dose of 300 mg of omalizumab or placebo was administered subcutaneously two or three times during the birch pollen season, depending on baseline IgE levels. Significant improvements over placebo were reported in average daily symptom scores, amount of rescue antihistamines used per day, proportion of days with any antihistamine usage, and all quality-of-life measures (49).

In another large, seasonal allergic rhinitis study, 536 patients with ragweed-sensitive seasonal allergic rhinitis were randomized to receive 50 (*n* = 37), 150 (*n* = 134), or 300 mg (*n* = 129) of omalizumab or placebo (*n* = 136) subcutaneously just before the ragweed season, and treatment was repeated every 3 or 4 wk throughout the pollen season (50). Nasal symptom scores were significantly lower in patients who received 300 mg of omalizumab compared with those given placebo (least squares means: 0.75 vs 0.98, respectively; *p* = 0.002). Quality-of-life scores were consistently better in those patients who received 300 mg of omalizumab than in those patients receiving lower

doses or placebo. Interestingly, a significant correlation was reported between IgE reduction and improvements in nasal symptoms and rescue antihistamine use (50).

The efficacy of omalizumab in patients with perennial allergic rhinitis was also demonstrated in a 16-wk trial of 289 patients with moderate-to-severe disease (51). Patients were randomized to omalizumab (at least 0.016 mg/kg/IgE [IU/mL] every 4 wk) or placebo. Mean daily nasal severity scores were significantly lower in the omalizumab group compared to the group given placebo (*p* < 0.001), as was use of rescue antihistamines (*p* ≤ 0.005 overall).

A randomized, double-blind, placebo-controlled trial was conducted on 23 patients with allergic rhinitis to evaluate the influence of omalizumab on the early nasal response to allergen challenge (52). Omalizumab (*n* = 12) or placebo (*n* = 11) was given at 2- or 4-wk intervals (based on a patient's body weight and IgE levels) to a total dose of at least 0.016 mg/kg/IgE every 4 wk. After 16 wk of treatment, patients treated with omalizumab showed significantly inhibited allergen challenge-induced nasal symptoms compared to patients given placebo. A significant decrease in human serum

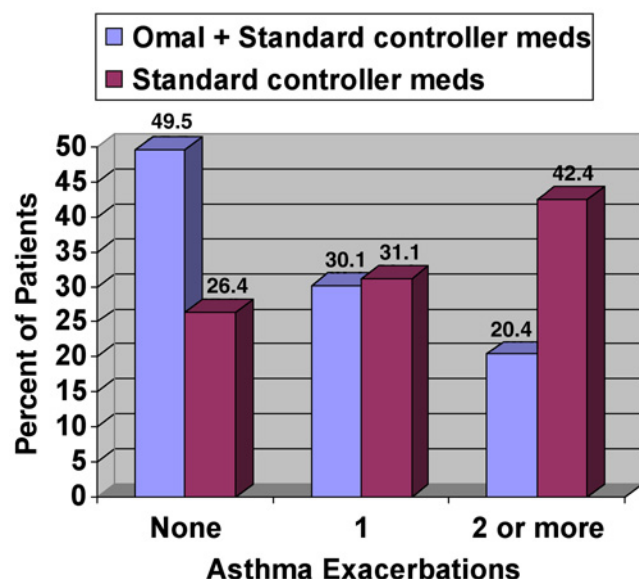


Fig. 4. Percent of patients experiencing clinically significant asthma exacerbations. A total of 312 symptomatic patients with moderate-to-severe allergic asthma treated with omalizumab or placebo were studied. Exacerbation is defined as a course of systemic corticosteroids with an associated asthma worsening adverse event. (Adapted from ref. 39.)

albumin (a marker of vascular permeability) after allergen challenge was observed in the nasal lavage fluid of patients treated with omalizumab. Basal nasal lavage tumor necrosis factor- α was significantly decreased in the patients treated with omalizumab. No significant difference in histamine release after allergen challenge was observed in patients treated with omalizumab compared to those who received placebo (52). This is in contrast to a preclinical study by MacGlashan et al. (12), which showed a 90% reduction in basophil histamine release in response to dust mite allergen challenge 3 mo after the start of omalizumab therapy. This also differs somewhat from the findings of Lin et al. (13), who showed a significant inhibition of ragweed-induced nasal responses at 7 to 14 d as well as maximal Fc ϵ RI downregulation on basophils 2 wk after starting omalizumab.

Because asthma and allergic rhinitis are both IgE-mediated diseases with similar pathophysiology and they frequently co-exist, the effect of omalizumab on both asthma and rhini-

tis control was studied. Data from the Study of Omalizumab in comorbid Asthma and Rhinitis (SOLAR) study indicated that, when treated with omalizumab, patients with both asthma and rhinitis experienced improvements in asthma and rhinitis symptoms (53). A total of 405 patients with moderate-to-severe asthma on stable treatment who also had persistent allergic rhinitis received omalizumab or placebo for 28 wk. Patients treated with omalizumab experienced fewer asthma exacerbations (20.6%) than patients given placebo (30.1%; Fig. 5A,B). A clinically significant improvement in both asthma and rhinitis quality-of-life indices occurred in 57.7% of patients treated with omalizumab compared with 40.6% of patients who received placebo. This suggests that omalizumab has beneficial effects on both upper and lower airway diseases occurring in the same individuals (53).

Safety

An extensive body of research has shown omalizumab to be a relatively safe, well-tolerated medication. Omalizumab appears to differ little from placebo regarding type and frequency of adverse events. The most common adverse effect associated with omalizumab administration is a reaction at the injection site, including bruising, redness, warmth, burning, stinging, itching, hives, pain, indurations, mass, and inflammation (33,34). An injection site reaction was observed in approx 45 and 43% of asthmatics who received omalizumab or placebo, respectively, and severe reactions occurred in 12 and 9%, respectively (33,34).

A large meta-analysis of eight phase II and III clinical trials involving 3041 patients showed the frequency of adverse events to be similar between omalizumab and placebo (54). Patients treated with omalizumab and patients given placebo experienced the following adverse events most frequently: viral infection (23 vs 28%), headaches (23 vs 24.5%), upper respiratory infections (20 vs 22%), sinusitis (11.5 vs 16%), and pharyngitis (12% for both). Of these,

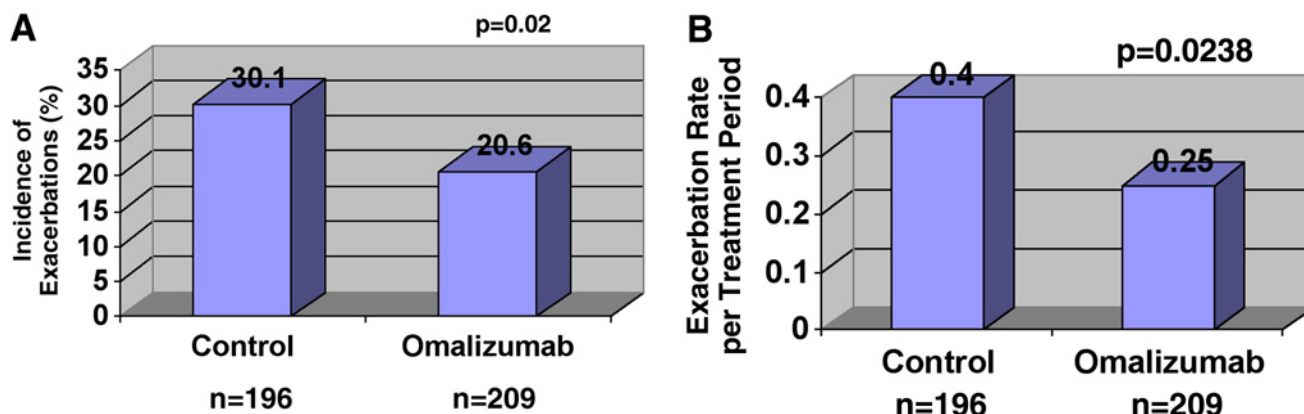


Fig. 5. The effects of omalizumab on asthma exacerbations in patients with concomitant asthma and rhinitis. A total of 405 patients with moderate-to-severe asthma on stable treatment who had concomitant persistent allergic rhinitis received omalizumab or placebo for 28 wk. (A) Patients treated with omalizumab experienced fewer asthma exacerbations than placebo-treated patients, and (B) had a lower exacerbation rate per treatment period. (Adapted from ref. 53.)

only 6.6% were suspected to be treatment-related in the omalizumab group (compared to 5.6% in the placebo group). Most adverse events were considered mild-to-moderate in severity. Serious adverse events were reported in 2.6% of the patients treated with omalizumab and in 2.8% of the patients given placebo. A total of 0.6 and 1.1% of omalizumab and placebo recipients, respectively, withdrew from treatment because of adverse events.

Berger et al. (55) examined the safety of omalizumab in more than 300 children in a 28-wk long, randomized, double-blind, placebo-controlled study. This was followed by a 24-wk open-label extension in which all patients received omalizumab. During the 52-wk period, upper respiratory tract infection and headache were the most frequently reported adverse events (47.1 and 42.7%, respectively) in those patients who underwent 52 wk of therapy with omalizumab. The incidence rates of these events were similar between the group treated with omalizumab and the group given placebo during the 28-wk, double-blind core trial. Eleven patients (4.9%) reported urticaria, and all cases resolved spontaneously or with antihistamines, with the exception of a single severe case in which the patient withdrew from the study.

The authors reported that the incidence of adverse events in the extension phase was similar to that of the omalizumab-treated patients in the 28-wk core trial, which, in turn, was similar to placebo. The authors concluded that omalizumab is safe and well-tolerated in children (55).

Malignancies have been reported in 20 of 4127 (0.5%) patients treated with omalizumab compared to 5 of 2236 (0.2%) of controls in clinical studies (54). Various malignancies were described, and most were solid tumors. Only one case of lymphoma was reported in the patients treated with omalizumab. An independent panel of oncologists found no association between omalizumab therapy and development of malignancy. The onset of most tumors preceded treatment with omalizumab, and 60% of tumors presented within less than 6 mo of treatment. Overall, the clinical data do not suggest a causal relationship between omalizumab and cancer. Nonetheless, postmarketing surveillance is ongoing.

Omalizumab Plus Immunotherapy

Omalizumab does not completely ameliorate symptoms of allergic respiratory symptoms, and upon discontinuation, serum IgE levels return to pretreatment levels (7,49,50,

56–60). There are no data concerning long-lasting immune tolerance resulting from anti-IgE therapy. To date, no studies have been performed to evaluate the use of omalizumab in addition to immunotherapy in treating asthma. In allergic rhinitis, a study evaluating the use of omalizumab prior to immunotherapy has just been completed (61,62). Both the efficacy and safety of immunotherapy were improved with the addition of omalizumab. Results from this study should improve the understanding of the role of IgE and potential benefits of anti-IgE therapy with immunotherapy.

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