

Anti-IgE therapy

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First characterized by Ishizaka in 1967 [1], IgE is the immunoglobulin responsible for the initiation of type I hypersensitivity reactions, such as those in the primary allergic diseases of asthma, allergic rhinitis, and food allergy [2]. Allergic disorders, including asthma, allergic rhinoconjunctivitis, and food allergy, represent a significant health and socioeconomic burden. Asthma alone accounts for more than 2 million emergency room visits and 500,000 hospitalizations a year [3]. In 1998, the estimated costs for caring for patients with allergic rhinitis and asthma topped \$12.6 billion dollars, with \$7.3 billion in direct costs and \$5.3 billion in indirect costs resulting from decreased productivity at work, home, and school [4]. Food allergy is estimated to affect more than 4 million people in the United States, and a minimum of 150 deaths are attributed to food-associated anaphylaxis each year [5]. An increased prevalence of allergic diseases worldwide has heralded renewed interest in research in the prevention and treatment of asthma and allergic rhinitis [6]. Although therapeutic modalities such as antihistamines, inhaled steroids, and antileukotrienes demonstrate some effectiveness in ameliorating allergy symptoms, a significant number of patients with allergy still experience daily discomfort. Therapies that more effectively block the effects of IgE hold promise for preventing symptoms caused by allergic reactions.

In genetically predisposed individuals, the inhalation of allergens (such as animal dander, grass, or weed pollens) stimulates a unique immunologic response, ending in the production of allergen-specific IgE by B cells and plasma cells. Once released, free IgE enters the bloodstream, where it binds to mast

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cells and basophils by means of high-affinity cell surface receptors (FcεRI). Basophil and mast cell degranulation occurs when specific allergen molecules of the appropriate size and configuration form cross-links between the Fab portions of two adjacent IgE molecules on the cell surface [7]. Such degranulation results in the release of mediators (histamine, prostaglandins, leukotrienes) and cytokines (interleukin 4 [IL-4], IL-5, IL-13) that bring about the pathophysiologic consequences and symptoms of allergic diseases, such as asthma, rhinitis, and food allergy (Fig. 1).

Epidemiologic studies have confirmed the importance of IgE in allergic respiratory disorders [8,9]. The prevalence of asthma has been correlated with increased levels of serum IgE, and serum IgE levels have been linked to persistent wheezing in children. These levels also have been shown to predict human airway reactivity in vitro [10]. Epidemiologic and basic research studies have confirmed a clear relationship between IgE and the pathogenesis and development of symptoms associated with allergic respiratory diseases.

Because of the central role that IgE has in allergic respiratory diseases, therapy to inhibit IgE-mediated responses through the use of anti-IgE antibodies is a logical step. Anti-IgE therapy differs from all other forms of allergy treatment and holds promise for preventing the first reactions in the allergic cascade, preventing mast cell degranulation, and preventing the subsequent influx of inflammatory

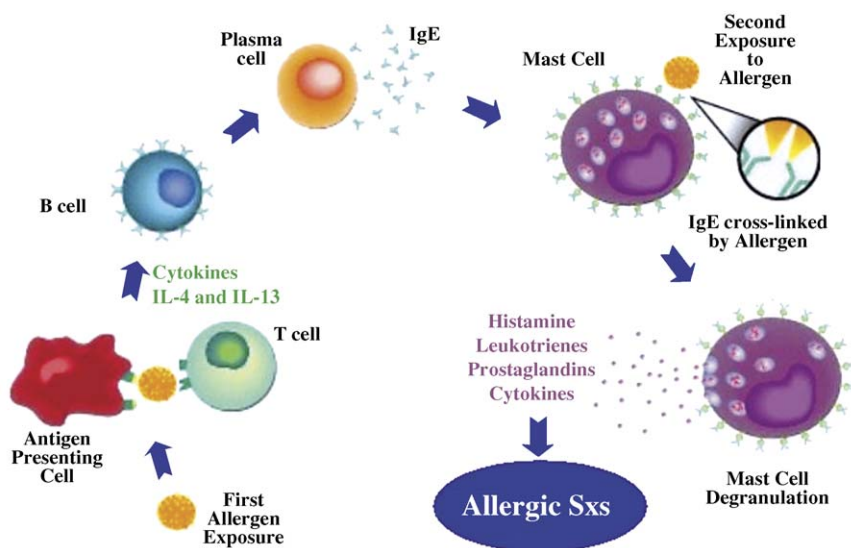


Fig. 1. The allergic cascade. In atopic individuals, the inhalation of allergens stimulates T cells to produce IL-4 and IL-13. These cytokines stimulate B cells to produce allergen-specific IgE. The IgE molecules are secreted into the circulation where they bind to high-affinity receptors on the surface of mast cells and basophils. On subsequent allergen exposure, cross-linking of IgE by allergen results in the release of the histamine, prostaglandins, leukotrienes, and cytokines that are responsible for the symptoms (Sxs) of allergy. (From Genentech, Inc. Clear breathing. Available at: <http://www.clearbreathing.com>; with permission. Accessed February 12, 2004.)

cells and mediators. This article focuses on the biology of IgE and strategies aimed to counteract its effects through use of humanized monoclonal antibodies directed against IgE.

IgE synthesis

The synthesis of IgE is dependent on T cells. IgE synthesis occurs after a complex process of allergen uptake and processing and the subsequent presentation of allergen in the context of major histocompatibility complex class II molecules to T cells. [7] T cells cause B cells to switch immunoglobulin synthesis from IgM or IgG to IgE by means of two critical signals. The first signal is delivered by IL-4 or IL-13, which bind to receptors on B cells (their receptors use the same signal transduction pathway [STAT 6]). The second signal is delivered when CD40 on B cells binds to its ligand on T cells, the CD40 ligand. [7] These two signals bring about B-cell DNA rearrangement and splicing, preferentially favoring the production of IgE.

Regulation of IgE receptor levels and pharmacokinetics of IgE

IgE can modulate the level of expression of its own high-affinity receptors (FcεRI) [11]. Higher IgE levels are associated with increased numbers of IgE receptors expressed on mast cells and basophils. IgE affects positive feedback mechanisms that enhance the density of FcεRI receptors and the releasability of mast cells. IgE-mediated up-regulation of FcεRI substantially enhances the ability of mast cells or basophils sensitized with IgE to degranulate in response to allergen. Down-regulation of IgE levels and IgE receptor levels on mast cells and basophils decrease the potential of these cells to degranulate [11].

IgE has a short serum half-life (less than 2 days) and is present in much lower concentrations in the circulation than IgG, IgM, and IgA [12]. IgE is biologically active despite low concentrations in the circulation. IgE antibodies bind to the high-affinity receptors on mast cells and basophils, so that these cells may be primed to respond to allergens, even when circulating IgE concentrations are low. IgE that is bound to tissue mast cells has a half-life of 2 weeks.

Decreasing levels of total serum IgE in atopic patients should result in decreased amounts of antigen-specific IgE that is available to bind to and sensitize basophils and tissue mast cells. This reduction of available IgE levels should lead to a decrease in IgE-mediated symptoms and improvement in control of allergic diseases. In asthma and allergic rhinitis studies, the reduction in serum-free IgE levels caused by an anti-IgE monoclonal antibody was correlated with improvement in symptom scores and rescue medication use [13].

Omalizumab (Xolair) is the only anti-IgE modulator approved by the Federal Drug Administration for clinical use. Federally approved in June 2003, omalizumab (Xolair) is indicated for use only in adults and adolescents (age, ≥12)

with moderate-to-severe persistent asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen and whose symptoms inadequately are controlled with inhaled corticosteroids [14]. Clinical studies of omalizumab have demonstrated its effectiveness in the treatment of allergic rhinitis and are underway for the treatment of food allergy.

Development and characteristics of omalizumab

Omalizumab is a recombinant humanized monoclonal anti-IgE antibody that binds to IgE on the same Fc site as FcεRI and contains 5% murine sequences (needed for the IgE-binding portion) and 95% human residues (Fig. 2) [15,16]. The antibody was humanized by grafting the mouse amino acid residues responsible for binding to IgE onto a human IgG1 framework. Removing murine residues that could trigger an immune response results in the nonanaphylactogenic properties of omalizumab when used in humans [17]. Omalizumab displays a high affinity for a specific epitope within the C3 domain of IgE, the site of binding of the FcεRI receptor [18]. Omalizumab binds to free IgE in the circulation regardless of specificity, but does not bind to receptor-bound IgE. This latter characteristic is important, because it means that omalizumab does not trigger degranulation by cross-linking IgE located on FcεRI receptors of mast cells or basophils.

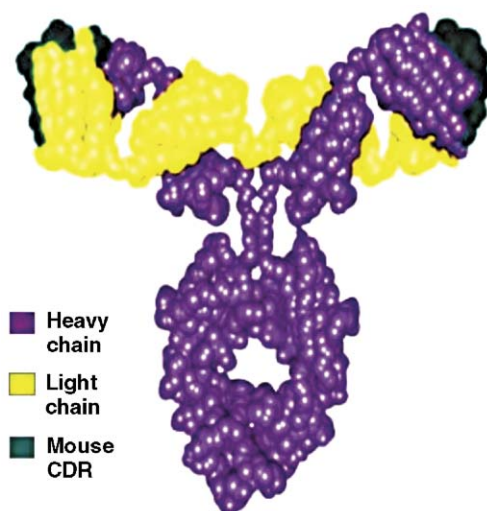


Fig. 2. Structure of omalizumab. Omalizumab is a recombinant humanized monoclonal anti-IgE antibody that contains 5% murine sequences and 95% human residues. CDR, complementarity determining region (*Adapted from* Boushey H. Experiences with monoclonal antibody therapy for allergic asthma. *J Allergy Clin Immunol* 2001;108(2 Suppl):S79; with permission.)

The primary mechanism of action of omalizumab is the binding of free IgE in the circulation [19]. When omalizumab binds to free IgE, it forms small, biologically inert complexes, usually trimers consisting of two omalizumab molecules and one IgE molecule [19]. These complexes cannot activate complement and typically are cleared by the reticular endothelial system in shorter time frames than is human IgG (Fig. 3) [14].

Omalizumab is demonstrated to have a secondary mechanism of action through the reduction of FcεRI and possibly the low-affinity IgE receptor CD23. In human studies, omalizumab resulted in a dramatic reduction in the number of FcεRI receptors on basophils, from about 220,000 receptors per cell to about 8300 receptors per cell [11]. The functional consequence of the FcεRI down-regulation was a 90% decrease in histamine release from basophils in response to ex vivo challenge with dust mite [11]. Omalizumab was demonstrated to cause rapid reduction in expression of basophil and dendritic cell FcεRI and measurable inhibition of nasal allergic responses to in vivo challenge with ragweed [20,21].

Several proof-of-concept studies tested the therapeutic potential of omalizumab in asthma. Omalizumab inhibited early- and late-phase asthmatic responses caused by allergens and prevented the development of airway hyperresponsiveness and sputum eosinophilia [22]. It also inhibited allergen-induced skin test responses [23]. Individualized dosing by way of intravenous bolus administration was used for the pivotal proof-of-concept phase II study in allergic asthma [24].

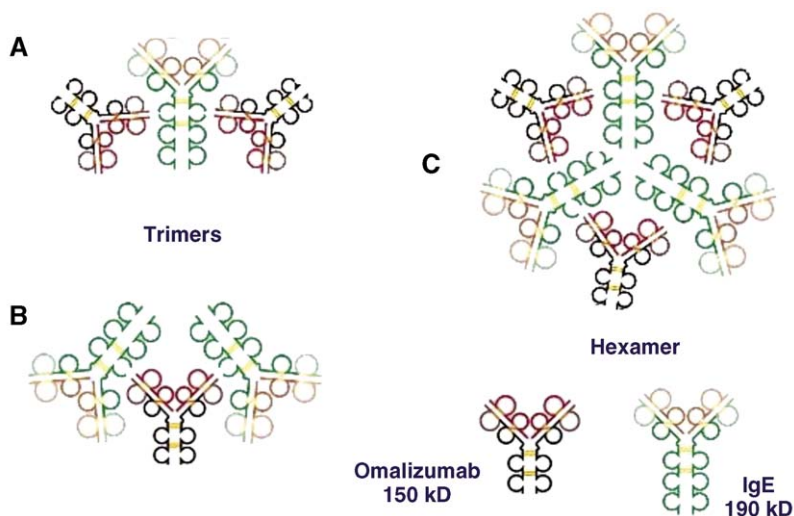


Fig. 3. Omalizumab-IgE complexes. Omalizumab binds IgE at the same site as FcεRI, the high-affinity IgE receptor. (A) When omalizumab binds to free IgE, it forms small, biologically inert complexes, usually trimers, consisting of two omalizumab molecules and one IgE molecule. Trimers of one IgE molecule and two omalizumab molecules (B) and hexamers (C) also may form. These complexes do not activate complement and are cleared by the reticular endothelial system.

Body Weight (kg)	30-60	> 60-70	> 70-90	> 90-150	Frequency of Dosing
Baseline IgE (IU/ml)	Mg/dose				
≥ 30 - 100	150	150	150	300	Q 4 week
> 100 - 200	300	300	300	225	Q 2 week
> 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. 4. Dosing table for subcutaneous administration of omalizumab. Dosing is based on weight (kg) and pretreatment total IgE level (IU/mL). For full dosing information and questions, readers are referred to the Xolair website (<http://www.xolair.com>) under prescribing information. (From Genentech, Inc. Xolair. Available at: <http://xolair.com>; with permission. Accessed January 3, 2004.)

A dosing table based on baseline IgE level and body weight has been developed to assist in the administration of subcutaneous omalizumab (Fig. 4) [25].

Phase III pivotal studies

Clinical protocols designed to study the efficacy of omalizumab in asthma have shown that the drug can be an effective and safe therapy for this disorder. Three large, multicenter phase III pivotal trials assessed the efficacy and safety of omalizumab versus placebo in the treatment of moderate-to-severe allergic asthma. The demographics of the subjects are shown in Table 1.

The efficacy and safety of omalizumab versus placebo were examined in symptomatic adults and adolescents (studies 008 and 009) who were treated with inhaled corticosteroids and in asymptomatic children (study 010) who were treated with inhaled corticosteroids [26–28]. The study design was fundamentally the same for the three studies (Fig. 5). During a 4- to 6-week run-in phase, the dose of inhaled beclomethasone was optimized. Patients subsequently were treated with omalizumab or placebo plus the stable dose of beclomethasone for 16 weeks. Omalizumab dosing was tailored to baseline bodyweight and serum free IgE levels. Patients received an approximate dose of omalizumab of 0.016 mg/kg body weight/IgE (IU/mL) monthly by subcutaneous injections. This step was followed by a 12-week phase of steroid withdrawal in conjunction with continued omalizumab treatment. During this period, an attempt was made to

Table 1
Demographics of subjects in phase III pivotal omalizumab trials in asthma

Characteristic	Adults and adolescents (Protocol 008)		Adults and adolescents (Protocol 009)		Children (Protocol 010)	
	Omalizumab	Placebo	Omalizumab	Placebo	Omalizumab	Placebo
Number treated	268	257	274	272	225	109
Mean age (y)	39	39	40	39	9	10
Mean duration of asthma (y)	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

Abbreviation: BDP, beclomethasone d propionate.

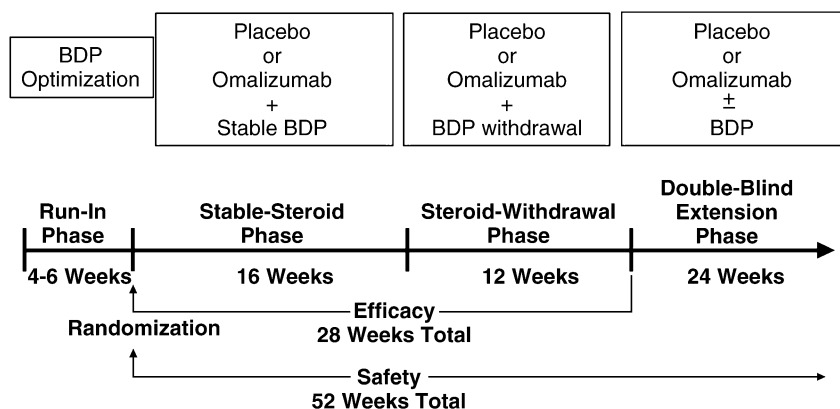


Fig. 5. Study design of phase III pivotal omalizumab trials in asthma. These three large multicenter trials assessed the efficacy and safety of omalizumab versus placebo in the treatment of moderate-to-severe allergic asthma. The study design included a 4- to 6-week run-in phase during which the dose of inhaled steroid was optimized. Patients then were randomized to receive placebo or omalizumab plus the stable dose of inhaled steroid (beclomethasone dipropionate [BDP]) for the next 16 weeks. This step was followed by a 12-week steroid-withdrawal phase. A 24-week extension phase was added. The study design allowed evaluation of drug efficacy over 28 weeks, and safety was assessed over a period of 52 weeks.

reduce the dose of inhaled beclomethasone by 25% every 2 weeks. A double-blind extension phase of 20 weeks was included (an open-label phase was used in the pediatric study). The primary outcome measure was the number of asthma exacerbations per patient. 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.

In all three studies, omalizumab decreased the number of asthma exacerbations per patient during the steroid-stable dosing period (Fig. 6). The reduction in exacerbation rate was significant in the two studies of adults and adolescents but did not meet statistical significance in the pediatric study. This finding likely occurred because the children were asymptomatic and had milder disease at enrollment. During the steroid-withdrawal phase, omalizumab, compared with placebo, resulted in significant reductions in the number of exacerbations per patient (approximately 50%) in all three studies. The time to first exacerbation also was reduced significantly (Fig. 7) [29]. Omalizumab demonstrated a corticosteroid-sparing effect in all three studies. Approximately twice as many omalizumab recipients completely withdrew from use of inhaled corticosteroids as compared with placebo recipients.

Omalizumab also demonstrated improvement in typical asthma parameters during the steroid-stable and steroid-reduction phases. In all three studies, omalizumab recipients had improvements in nocturnal symptom scores, daytime symptom scores, and the number of β -agonist puffs per day, compared with placebo recipients. There was also a small but statistically significant improve-

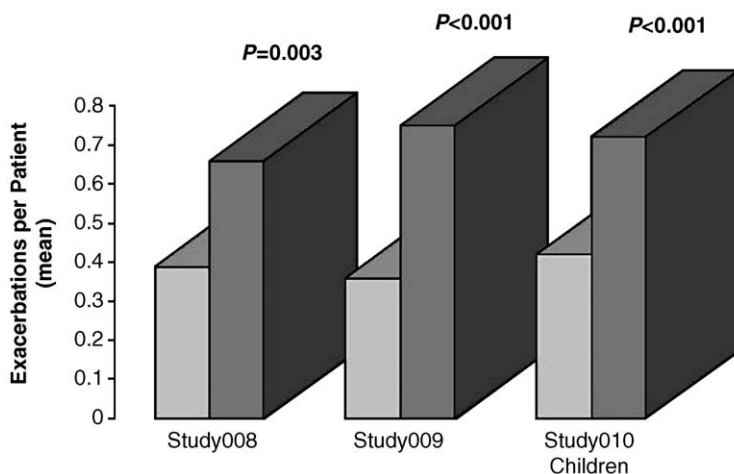


Fig. 6. Effects of omalizumab (light gray bars) and placebo (dark gray bars) on asthma exacerbations during the steroid-withdrawal phase. Omalizumab decreased the number of asthma exacerbations per patient in all three clinical trials. (Data from Refs. [26–28].)

ment in forced expiratory volume in 1 second (FEV_1) percentage predicted of approximately 3% to 5%, compared with placebo. Unscheduled outpatient visits, emergency room treatments, and hospitalizations, which account for a significant burden of costs attributed to asthma, were reduced significantly in the omalizumab group versus the placebo group [30].

The ability of omalizumab to improve quality of life, compared with placebo, was measured using the standard questionnaire developed by Juniper et al [31,32].

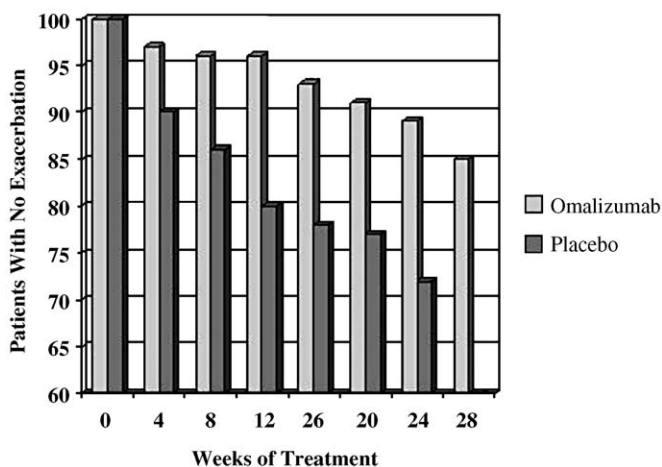


Fig. 7. Omalizumab (light gray bars) and placebo (dark gray bars) prevention of asthma exacerbations. Omalizumab significantly increased the time to first exacerbation, compared with placebo ($P = 0.0001$).

At the end of the corticosteroid-reduction phase, statistically significant improvements were observed in all domains (including overall score and scores on emotions, activities, symptoms, and environmental exposure) in the studies of adults and adolescents [33]. In the active-treatment groups, mean changes from baseline were approximately 1.0 versus 0.7 for the placebo group ($P < 0.01$). Approximately 64% of omalizumab recipients achieved improvements in the quality-of-life scores of at least 0.5 compared with placebo recipients; this measure is believed to be clinically significant. A total of 33% of omalizumab recipients achieved a large improvement in this score (≥ 1.5 points). In the pediatric study, statistically significant improvements were observed in scores for activities, symptoms, and overall domains but not for the emotional domain. Approximately 50% more omalizumab recipients achieved at least a 0.5-point improvement in the overall quality-of-life-domain score, compared with the placebo group [34].

Results from the extension phase of these trials demonstrated that the beneficial effects of omalizumab are sustained over treatment of up to 52 weeks' duration [35–37]. In studies 008 and 009, 68% and 76% of patients in the omalizumab groups, respectively, had no exacerbations during the extension phase, and overall about one third of patients (compared with approximately 10% in the placebo group) completed 1 year of treatment without using corticosteroids ($P < 0.05$ for both variables) [35,36]. Similar findings were observed in the pediatric study: 91% of the subjects who had completely withdrawn from corticosteroids during the course of the study were still steroid free at the end of the extension [37].

These three pivotal studies showed that in adults, adolescents, and children with moderate-to-severe allergic asthma, omalizumab prevented asthma exacerbations and allowed reduced use of or withdrawal of inhaled corticosteroids to a greater degree than did placebo. Concomitant with this reduction in inhaled corticosteroids, patients treated with omalizumab had greater improvements in symptoms, quality of life, and rescue use of β -agonists.

Omalizumab and severe asthma

Patients with severe asthma are characterized by poorly controlled symptoms despite treatment with high doses of inhaled or oral corticosteroids. These patients experience a greater number of asthma exacerbations, which contribute to a large proportion of the morbidity, mortality, and costs associated with asthma. The availability of effective and well-tolerated therapeutic options in these patients is limited, so the efficacy of omalizumab in this population could have considerable clinical and socioeconomic implications [38].

Study 011 was a double-blind, randomized, placebo-controlled phase III study that included 246 patients with severe asthma. Selected patients were symptomatic despite receiving high fluticasone dosages of 1000 to 2000 $\mu\text{g/d}$ (FEV_1 64% of predicted; mean fluticasone dosage, 1369 $\mu\text{g/d}$). A subset of subjects

($n = 95$) also received oral corticosteroids in addition to fluticasone, but results for these subjects are not yet available [39].

The design of this study was similar to that of other phase III studies. Patients initially underwent a run-in period during which the dosage of fluticasone was optimized. Omalizumab ($n = 126$) or placebo ($n = 120$) then was added to the regimen for 32 weeks. For the first 16 weeks of combined treatment, patients maintained a stable dosage of fluticasone (steroid-stable phase), followed by a 16-week steroid-reduction phase during which the dosage of fluticasone was reduced gradually [39].

Compared with placebo recipients, subjects receiving omalizumab (≥ 0.016 mg/kg/IgE [IU/ml] every 4 weeks) showed a significantly greater reduction in corticosteroid use, which was the primary endpoint of the study. Overall, 60.3% of omalizumab recipients and 45.8% of placebo recipients reduced their fluticasone use to less than 500 $\mu\text{g/d}$ ($P < 0.01$). A greater than 50% reduction in baseline fluticasone use was observed in 74% of patients receiving omalizumab versus 51% of patients receiving placebo. A 100% reduction in fluticasone use was observed in 21% versus 15%, respectively, by the end of the trial [39].

The frequency of asthma exacerbations was reduced significantly in subjects receiving omalizumab. During the steroid-reduction phase, the exacerbation rates per subject were 0.19 and 0.34 for omalizumab and placebo recipients, respectively ($P = 0.003$). The frequency of exacerbations was related to the severity of disease at baseline; subjects with more severe disease had a greater difference than did subjects with better-controlled symptoms [40].

Subjects receiving omalizumab also showed pronounced improvements in quality of life. A total of 57.5% of these subjects achieved a clinically meaningful improvement of at least 0.5 in asthma-specific quality-of-life scores, compared with only 38.6% of placebo recipients ($P < 0.05$). The mean change from baseline for the overall score was 0.61 in omalizumab recipients and 0.24 in placebo recipients ($P < 0.01$). Significant differences, compared with placebo, were observed for all domains, including activities, emotions, symptoms, and environmental exposure [41].

The efficacy of omalizumab in patients with severe asthma was evaluated in a meta-analysis of a subgroup of 254 patients from studies 008, 009, and 011 (total number of patients in all three studies, 1412) who were considered to be at high risk for asthma exacerbations [38]. This group included patients who had been intubated for an asthma-related event at any time before screening and patients who had visited an emergency room, experienced overnight hospitalization, or undergone treatment in an ICU during the previous year for asthma-related events. The primary outcome measure was the annualized rate of significant asthma exacerbation episodes, based on data from the 16-week steroid-stable phase and from the whole study (study duration, ≤ 1 year).

The subgroup analysis during the steroid-stable phase showed that high-risk patients who were treated with inhaled corticosteroids alone were expected to have significantly more exacerbations per year (1.56 per patient-year) than patients who were treated with omalizumab. The addition of omalizumab to

inhaled corticosteroid treatment more than halved this expected rate to 0.69 exacerbations ($P < 0.007$). Based on these results, it was estimated that for every 100 patients who were treated with omalizumab, 87 exacerbations were prevented. This estimate is much larger than the estimate for overall population (44 exacerbations prevented per 100 people). Similar findings were observed for the whole study period. Patients receiving omalizumab also showed significantly greater improvements from baseline in asthma symptom scores, quality of life, and peak expiratory flow rate.

The public health impact of omalizumab also was assessed. Omalizumab prevented the development of exacerbations in approximately 17 (steroid-stable phase) and 22 (whole study period) additional patients for every 100 patients treated. This estimate translated to a need to treat 5.7 and 4.6 patients with omalizumab to maintain one patient free of serious exacerbations during exposures of approximately 16 weeks or 1 year, respectively. These results are of economic significance considering that the cost of treating acute asthma attacks is greater than the cost of providing preventive drug treatment [41].

Omalizumab and allergic rhinitis

Four seasonal allergic rhinitis studies have examined the therapeutic effectiveness and safety of omalizumab. In 1994, Casale et al [13] conducted a double-blind placebo controlled study involving 240 patients, who received intravenous or subcutaneous omalizumab (maximum dose, 0.5 mg/kg IV). Omalizumab induced a rapid dose-dependent reduction in serum free IgE levels that was related to the baseline IgE levels. Consistent suppression of serum free IgE to the lowest levels of detection required an initial ratio of omalizumab-to-total IgE of approximately 10, or 15:1. This finding implied that omalizumab dosing must be calculated based on individual baseline IgE levels and not just body weight. Only 11 patients at the highest dose experienced a suppression of IgE to undetectable levels. Most patients did not have a significant reduction in symptoms [13].

Based on these findings a 12-week, multicenter, randomized, double-blind, dose-ranging, placebo-controlled study was performed in the United States [42]. A total of 536 patients were randomized to receive 50, 150, or 300 mg of omalizumab or placebo starting just before ragweed season and continuing every 3 to 4 weeks throughout the pollen season. Dosing was stratified based on IgE levels. Omalizumab produced dose-related reductions in serum free IgE levels and improvements in symptoms, rescue antihistamine use, and quality of life. The 300-mg group showed significant improvements in severity and duration of nasal and ocular symptoms and a reduction in the median proportion of minimal symptom days, compared with placebo (41 days versus 18 days; $P = 0.001$). A significant association was observed between IgE reduction and lower nasal symptoms and rescue antihistamine use.

As an extension to the study, patients who had received omalizumab were retreated during the subsequent ragweed season. A subcutaneous, 300-mg dose of omalizumab was administered every 3 or 4 weeks for 12 weeks. There were no severe or serious adverse events related to omalizumab use, and no human antihuman antibodies were detected. Retreatment with omalizumab during the second pollen season was well tolerated and not associated with significant immunologic problems [43].

Based on the results of the ragweed studies, 300-mg omalizumab was studied for the treatment of birch pollen-induced seasonal allergic rhinitis in Scandinavia [44]. Two hundred and fifty patients randomly were assigned to receive omalizumab or placebo. The frequency of drug or placebo administration was based on baseline total IgE levels. Omalizumab improved quality of life and significantly lowered average daily nasal and ocular symptoms, number of rescue antihistamines used per day, and proportion of days with any seasonal allergic rhinitis medication use. After discontinuation of omalizumab, IgE levels returned to normal over the subsequent 2 to 3 months [44].

The effects of adding omalizumab to specific immunotherapy (SIT) were evaluated in 221 children and adolescents with birch pollen- or grass pollen-induced seasonal allergic rhinitis. Combination treatment with SIT and omalizumab (approximately 0.016 mg/kg/IgE [IU/mL] every 4 weeks) significantly reduced the use of rescue medication and significantly improved allergy symptoms, compared with SIT alone [45]. This improvement was independent of the type of allergen. In a subgroup of patients in the same study, omalizumab reduced leukotriene release of peripheral blood leukocytes; this effect was also independent of the type of SIT allergen used [46].

Omalizumab has proved to be efficacious in patients with perennial allergic rhinitis. In a trial including 289 patients with moderate-to-severe perennial allergic rhinitis, 16 weeks of treatment with subcutaneous omalizumab (approximately 0.016 mg/kg/IgE [IU/mL] every 4 weeks) significantly reduced rescue medication use and severity of nasal and ocular symptoms and significantly improved rhinoconjunctivitis-specific quality of life, compared with placebo [47].

Omalizumab in concomitant asthma and allergic rhinitis

A multicenter, double-blind, randomized, placebo-controlled clinical trial examined the efficacy of omalizumab in 405 patients with comorbid moderate-to-severe allergic asthma and perennial allergic rhinitis [48]. The patients were randomized to receive supplemental baseline therapy with placebo or omalizumab (at least 0.016 mg/kg/IgE [IU/mL] administered every 4 weeks) for 28 weeks. At the end of the study, omalizumab-treated patients showed significant reductions in baseline symptom scores for rhinitis and asthma, compared with placebo-treated patients. The drug also was associated with better control of

rhinitis symptoms, greater reduction in the asthma exacerbation rate, and greater improvement in the quality of life, compared with placebo.

Omalizumab and safety

Omalizumab was well tolerated in clinical trials. In a meta-analysis of eight phase IIB or III studies involving 3041 patients with allergic asthma or rhinitis who were treated with omalizumab ($n = 1763$) or placebo ($n = 1278$) for 24 to 52 weeks, the frequency and type of adverse events were comparable between the two treatment groups [49].

The most frequent adverse events in omalizumab and placebo recipients were viral infection (23% versus 28%), headache (23% versus 24.5%), upper respiratory infections (20% versus 22%), sinusitis (11.5% versus 16%), and pharyngitis (12% for both), but overall only a few events (6.6% versus 5.6%) were suspected to be drug related.

Most adverse events were classified as mild to moderate in severity. Serious adverse events were observed in only 2.6% and 2.8% of omalizumab and placebo recipients, respectively, and only 0.6% and 1.1% of patients, respectively, withdrew from treatment because of adverse events. Of the serious events, none were considered drug related.

There were no reports of serum sickness or serum sickness-like syndrome during omalizumab therapy, and there was no excess risk for bleeding-related disorders. Malignant neoplasms were observed in 20 of 4127 (0.5%) omalizumab-treated patients compared with 5 of 2236 (0.2%) controls in clinical studies of asthma and other allergic disorders. These malignancies represented a variety of different types, and only 1 of 20 cases in the omalizumab-treated group was a non-Hodgkins lymphoma. An independent review panel did not believe that omalizumab treatment was associated with the development of malignant neoplasms, and the differences in the rates of malignant neoplasms were not significant between the omalizumab and placebo groups.

Omalizumab was not associated with an increased risk for immunologic reactions [50]. Allergic symptoms, including fever, rash, urticaria, and influenza-like symptoms, rarely were reported and were observed at similar frequencies in omalizumab and placebo recipients (1%–8%). There were no omalizumab-related anaphylactic episodes; however, the manufacturer's prescribing information describes the occurrence of anaphylaxis in three patients (<0.1%) who were without any other identifiable allergic triggers [14].

Injection-site reactions of any severity (bruising, redness, warmth, burning, stinging, itching, hive formation, pain, indurations, mass, inflammation) were observed in about 45% and 43% of asthmatics receiving omalizumab or placebo, respectively, and severe reactions occurred in 12% and 9%, respectively. These events typically occurred less than 1 hour after dosing and lasted less than 8 days, generally decreasing in frequency by the time of subsequent dosing visits [14].

Anti-IgE therapy and food allergy

TNX 901 is a humanized IgG1 monoclonal antibody that is capable of binding IgE. Demonstrated to have high affinity for the C3 domain of IgE, this drug also can bind free serum IgE, preventing mast cell and basophil binding through FcεRI and subsequent degranulation.

The safety and efficacy of TNX 901 in increasing tolerance to peanut antigen was demonstrated by Leung et al [51] in a double-blind, randomized, placebo-controlled, dose-ranging trial. Subjects were recruited based on a history of peanut allergy that was confirmed by positive skin prick test to peanut and a double-blind oral food challenge. Only patients aged 12 to 60 years were included in the study, and no patients had a history of previous exposure to monoclonal antibodies. The threshold for peanut reactivity was established before randomization at the time of oral food challenge. Patients were randomized to receive monthly subcutaneous injections of placebo or 150, 300, or 450 mg of TNX-901 for 4 months. The patients underwent a final food challenge with peanut flour within 2 to 4 weeks after the last injection of study drug. The primary measure of efficacy was the change from baseline in the amount of ingested peanut flour that the patient could tolerate before the onset of an allergic reaction.

Study results indicate that TNX 901 was effective in promoting a sustained reduction (greater than 8 weeks) in serum free IgE levels at all three doses. The drug also increased the mean threshold of peanut sensitivity in a dose-dependent manner. Although the results only reached statistical significance for the 450-mg group, TNX 901 increased the threshold sensitivity to peanut from 250 mg (one peanut) to 2900 mg (eight peanuts), an amount believed to provide protection against accidental peanut ingestion.

Summary

The anti-IgE drug omalizumab is a novel agent that has been proved to be useful in the therapy of allergic respiratory disorders. It reduces levels of serum IgE and FcεRI receptors as its primary mechanisms of action. It has been shown to improve asthma in adults, adolescents, and children, allowing reduction in steroid doses. It also improves symptoms, rates of urgent care visits, rescue medication use, and quality of life. In these studies, omalizumab seemed to be safe and well tolerated. It has been approved for the therapy of adults and adolescents with moderate-to-severe allergic asthma who have persistent symptoms despite therapy, intolerable side effects from therapy, or poor compliance. Patients with asthma who have concomitant IgE-mediated disorders, such as allergic rhinitis and food allergy, are likely to benefit from this drug, but further studies are necessary before such recommendations can be made.

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