

Experiences with monoclonal antibody therapy for allergic asthma

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Identification of the central role IgE plays in the pathogenesis of allergic diseases made it a key target for therapy. The first selective anti-IgE therapy, a unique humanized monoclonal anti-IgE antibody (omalizumab), binds with high affinity to the FcεRI receptor binding site on IgE, thereby reducing the amount of free IgE available to bind to FcεRI receptors on mast cells, basophils, and other cells. In addition, administration of omalizumab indirectly reduces FcεRI receptor density on cells involved in allergic responses. In two bronchoprovocation trials involving patients with mild allergic asthma, omalizumab attenuated both early- and late-phase allergic responses. Omalizumab was subsequently evaluated as a treatment for asthma in large, multicenter, randomized, double-blind phase II and III trials involving patients with moderate to severe asthma who required corticosteroid therapy. When added to treatment with oral or inhaled corticosteroids, omalizumab reduced symptoms and exacerbations, improved lung function and quality of life, and reduced the need for rescue medications. These benefits persisted even in the "corticosteroid reduction" phase of these trials, when omalizumab treatment was shown to allow patients to reduce or discontinue their inhaled and/or oral corticosteroids. These effects of omalizumab in improving asthma control, as well as its excellent safety profile, may ultimately make this agent a useful addition to the physician's armamentarium of treatments for asthma. (*J Allergy Clin Immunol* 2001;108:S77-83.)

Key words: Asthma, IgE, anti-IgE, omalizumab, allergic disease, atopy

Allergic diseases affect the airways, skin, and eyes and are the result of abnormal immune responsiveness to ordinarily innocuous materials in the environment (ie, allergens). IgE has been thought to be important in mediating this allergic responsiveness ever since it was identified as the soluble factor responsible for passive transfer of cutaneous reactivity to antigen^{1,2} and since serum levels of IgE were shown to correlate closely with cutaneous reactivity to common allergens, as well as with bronchial hyperresponsiveness.³⁻⁵ Because its role in the pathogenesis of allergic disease seems to be central, IgE is an attractive target for therapy. The first specific, selective anti-IgE therapy developed for study of humans is a unique humanized monoclonal anti-IgE antibody called rhuMab-E25 (E25, or "omalizumab").

Abbreviations used

BDP: Beclomethasone dipropionate
FcεRI: High-affinity IgE receptor
MAE11: Murine anti-human IgE antibody
PC₁₅: Provocative dose of inhaled allergen needed to cause a 15% fall in FEV₁
PC_{20M}: Provocative concentration of methacholine needed to cause a 20% fall in FEV₁
QOL: Quality of life

The predisposition to developing allergic diseases, referred to as *atopy*, is genetically determined. The first step in the development of disease is sensitization to a particular allergen. Subsequent exposure to that allergen typically causes an immediate response characterized by vasodilation, edema, and, in the airways, bronchoconstriction. Left untreated, this immediate response resolves spontaneously but is often followed 4 to 6 hours later by a sustained inflammatory response characterized by the influx of eosinophils, mononuclear cells, and neutrophils. The immediate response has long been thought to depend on an allergen-specific IgE antibody, which binds tightly to high-affinity receptors on mast cells and basophils. Recent data suggest that the late response may depend on IgE antibody as well, perhaps through activation not just of mast cells and basophils but also of cells that express low-affinity receptors for IgE on their surface, such as antigen-presenting cells, including dendritic cells and macrophages, and other cell types.

The immediate response to contact with specific allergen is thought to depend on the activation of mast cells, and possibly other cells, through the binding of allergen to specific IgE anchored to receptors on the cell surface. This interaction of allergen and specific IgE on the cell surface triggers mast cells (and basophils) to degranulate, releasing histamine, tryptase, chymase, and other active mediators.

The mechanisms by which mast cells themselves might contribute to the late-phase response include the elaboration and release of chemokines, such as microbicidal cationic peptide 1, macrophage inflammatory protein 1β, macrophage inflammatory protein 1α, and RANTES, which attract inflammatory cells, and the release of cytokines, such as TNF-α, which induce the expression of cell adhesion molecules by endothelial cells, enabling the binding and migration of inflammatory cells from the vascular compartment into the airway mucosa. It is also possible that IgE plays a role in stimulating the production of other cytokines, such as IL-5, by other cells, such as T_H2 lymphocytes, through IgE's facilitation of antigen presentation.⁶ The observation that omalizumab treatment inhibits both the early- and late-

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phase response to inhalation of allergen indicates that IgE plays some role in both responses but does not pinpoint the cellular source of the mediators responsible.^{7,8}

DEVELOPMENT OF ANTI-IgE (OMALIZUMAB) MONOCLONAL ANTIBODY

Initially, monoclonal antibodies against IgE were developed in mice to produce a murine anti-human IgE antibody (MAE11). MAE11 attached to free IgE and prevented its association with the high-affinity IgE receptor (FcεRI), but these xenobiotic molecules had the potential to trigger a host reaction. Therefore, they were "humanized" by insertion of the mouse-derived complementarity-determining region into a human IgG1 consensus sequence. About 5% of this humanized version of the omalizumab consists of IgE-binding regions derived from MAE11; the balance, about 95% of the sequence, is made up of the human IgG1 framework (Fig 1). This humanized anti-IgE antibody (omalizumab) displays a high affinity for a specific epitope within the C3 domain of IgE, the site of binding to the FcεRI receptor.^{9,10}

Mechanism of action

Omalizumab offers a novel strategic approach to allergy treatment in that it binds with high affinity to the same site on IgE as does the FcεRI receptor (Fcε3 domain). Omalizumab thereby reduces the amount of free IgE (circulating or unbound) that is available to bind to the FcεRI receptors on mast cells, basophils, and other cells.^{11,12} When omalizumab binds to free IgE in the systemic circulation and tissues, it forms small complexes, usually trimers of two omalizumab molecules and one IgE. These complexes cannot interact with FcεRI receptors or FcεRII receptors on effector cells.^{13,14}

Effects on early- and late-phase allergic responses

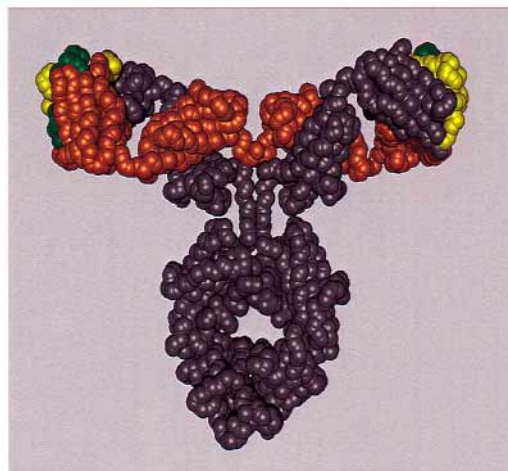
Results from two clinical studies provide evidence for the ability of omalizumab to inhibit both early- and late-phase allergic responses.^{15,16} Both bronchoprovocation trials were conducted in patients with mild asthma. In the first, a multicenter, randomized, double-blind, parallel-group study, the effect of omalizumab on the provocative dose of inhaled allergen needed to cause a 15% fall in FEV₁ (PC₁₅) during a bronchial allergen challenge was assessed in 11 patients.¹⁵ Omalizumab was administered intravenously at a dose of 2 mg/kg on day 0 and at a dose of 1 mg/kg on days 7, 14, 28, 42, 56, and 70. Overall, the 11 patients who received active treatment tolerated it well. Omalizumab treatment decreased serum free IgE levels by 89% and reduced the early allergic response, as indicated by a significant increase in median allergen PC₁₅ on days 27, 55, and 77 ($\Delta \log PC_{15}/0.3$; $P < .002$ vs placebo) (Fig 2). Thus, changes observed in this study of patients given regular intravenous omalizumab injections over a 10-week period reflect the antibody's role in inhibiting early allergic response.

Fahy et al¹⁶ studied the effects of omalizumab on the late-phase, as well as the early-phase, allergic response in a randomized, double-blind, parallel-group, placebo-controlled trial of 19 patients with asthma. Again, free serum IgE levels fell significantly after treatment with omalizumab but did not change in the placebo group. Further, omalizumab significantly attenuated the early-phase response to allergen as demonstrated by a significantly reduced mean maximal fall in FEV₁ during the first hour after allergen challenge ($P = .01$). A similar effect was observed for the late-phase response to allergen (2 to 7 hours after allergen challenge; $P = .047$) (Fig 3). The effect of omalizumab treatment on the early response was also reflected by an increase in the concentration of allergen required to cause an early or "immediate" 20% fall in FEV₁: 7 of 9 subjects in the omalizumab group required more allergen to induce this fall in FEV₁ at the second challenge, which was performed after 10 weeks of treatment. This was true of only two subjects in the placebo group. Similarly, there was additional evidence that omalizumab treatment altered the mechanisms of the late response, for the rise in sputum eosinophils and the fall in PC_{20M} usually caused by allergen challenge were significantly reduced in the treated group.

It should be noted that these studies evaluated the effects of omalizumab at 28 and 56 days, respectively. Although the lowering of free IgE was seen almost immediately, further studies would be required to determine how quickly the allergen responses are attenuated. Nonetheless, the studies demonstrate the ability of omalizumab to attenuate early- and late-phase allergic responses in patients with asthma.

High-affinity IgE receptor

IgE receptor density is believed to correlate with mast cell excitability; therefore, upregulation of the number of IgE receptors on the cells activated by specific allergens, such as mast cells and basophils, will enhance immediate hypersensitivity responses. As suggested previously, treatments that downregulate serum IgE concentrations may be expected to decrease or suppress allergic responses. In atopic subjects, treatment with omalizumab was found to decrease the number of FcεRI receptors on basophils (Fig 4), as well as the level of serum free IgE.¹⁷ This decrease in the density of IgE receptors on the surface of basophils was found to develop rapidly, with a half-life of 3 days. The study also showed a modest increase in the number of unoccupied receptors with omalizumab treatment, indicating not just a reduction in IgE concentration but also a reduction in the binding of the remaining free IgE to its receptors on the cell surface. Basophils from these patients showed a 90% reduction in their release of histamine after challenge with house dust mite allergen in vitro, providing evidence that IgE receptor density is correlated with in vitro allergic responses. Omalizumab thus appears to have two actions expected to reduce allergic responsiveness: it reduces plasma free IgE levels and also reduces FcεRI receptor density on the cells involved in allergic responses.



Heavy Chain Light Chain Mouse CDR Framework Changes

FIG 1. Omalizumab molecular structure. Omalizumab is a recombinant humanized monoclonal antibody containing 5% murine sequence and 95% human sequence. Because omalizumab contains 95% human sequence, the monoclonal antibody does not trigger an immune response.

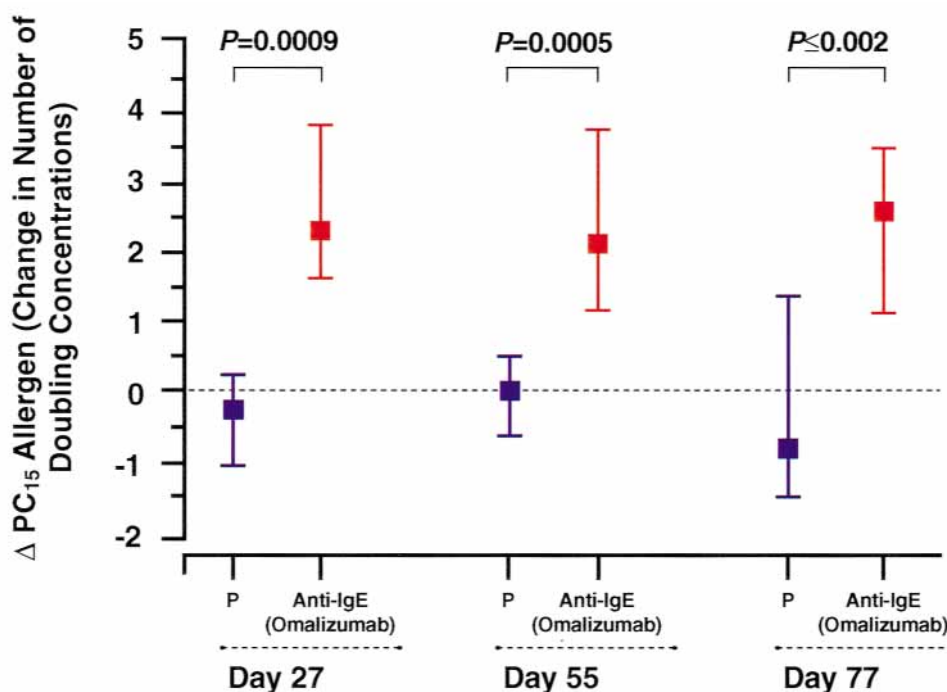


FIG 2. Omalizumab had significant inhibitory effects on allergen-induced bronchoconstriction, with an increase in PC_{15} of 2.3, 2.2, and 2.7 doubling concentrations of allergen (median and 25th-75th quartiles) on days 27, 55, and 77 (-0.3 , $+0.1$, and -0.8 with placebo, $P < .002$). (Adapted with permission from Boulet L-P, Chapman KR, Côté J, et al. Inhibitory effects of an anti-IgE antibody E25 on allergen-induced early asthmatic response. *Am J Respir Crit Care Med* 1997;155:1835-40. Official Journal of the American Thoracic Society © American Lung Association.)

PHASE II STUDY OF PATIENTS WITH MODERATE TO SEVERE ALLERGIC ASTHMA

Study design

In 1999, the Omalizumab Study Group reported the results of a multicenter, double-blind, placebo-controlled

study of 317 patients with moderate to severe perennial allergic asthma who required daily use of inhaled and/or oral corticosteroids. The subjects ranged in age from 11 to 50 years (mean age, 30 years). They were randomly assigned to receive omalizumab, at either a low dose ($2.5 \mu\text{g/kg/ng IgE/mL}$) or a high dose ($5.8 \mu\text{g/kg/ng IgE/mL}$),

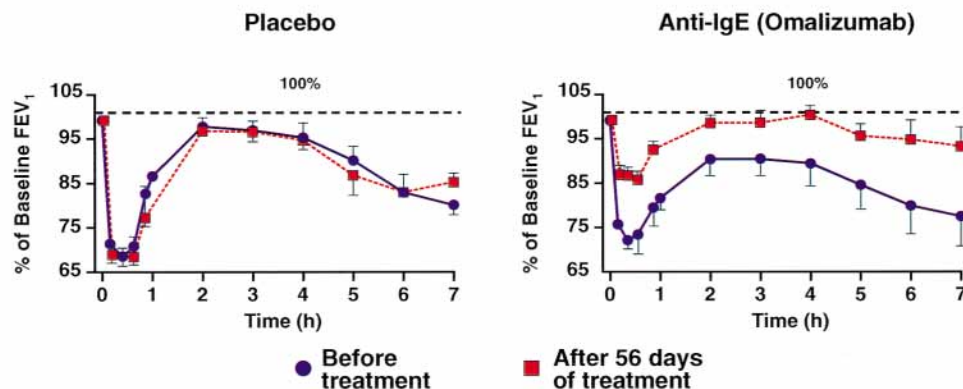


FIG 3. FEV₁ as a percent of baseline in the first hour after allergen challenge (early-phase response) and from 2 to 7 hours after allergen challenge (late-phase response) in the placebo-treated (**left panel**) and omalizumab-treated (**right panel**) groups at baseline (circles) and at the end of treatment (squares). (Adapted with permission from Fahy JV, Fleming HE, Wong HH, et al. The effect of an anti-IgE monoclonal antibody on the early- and late-phase responses to allergen inhalation in asthmatic subjects. *Am J Respir Crit Care Med* 1997;155:1828-34. Official Journal of the American Thoracic Society © American Lung Association.)

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FIG 4. Expression of endogenous FcεRI on basophils of subjects undergoing omalizumab treatment. Results for 12 treated patients and 2 control subjects are shown. Data were generated by using the acetate buffer "stripping" technique. The graph plots results of IgE measurements for cells fully sensitized and therefore essentially plots total receptor densities. (Adapted with permission from MacGlashan DW Jr, Bochner BS, Adelman DC, et al. *J Immunol* 1997;158:1438-45. Copyright 1997. The American Association of Immunologists.)

or placebo. The study drugs were administered intravenously at half a dose on days 0 and 4, at a full dose on day 7, and then once every 2 weeks thereafter for 20 weeks. For the first 12 of these weeks, the study drugs were used as adjuncts to the patients' current regimen of β -agonists and corticosteroids; during the remaining 8 weeks, the corticosteroid dose was tapered.¹⁸

Improvement in asthma symptom scores

Improvements in asthma symptom scores with omalizumab treatment were noted. The asthma symptom scores were found to improve by an average of 42% in the high-dose omalizumab group, 40% in the low-dose group, and 30% in the placebo group. At 12 weeks, a 50% improvement in asthma symptom score was reported in approximately half of the patients treated with omal-

izumab (low-dose and high-dose) compared with 24% of patients in the placebo group. The improvement in asthma symptom scores was shown to continue even when the steroid dose was reduced.¹⁸

Steroid-sparing effects

Treatment with omalizumab also resulted in a decreased need for both oral and inhaled corticosteroids.¹⁸ A 50% or greater reduction in dose of oral corticosteroids was reported in 78% of subjects in the high-dose group and 57% of those in the low-dose group versus 33% of subjects in the placebo group ($P = .04$) (Fig 5, A). More than one third of the subjects in the omalizumab groups were able to discontinue taking oral corticosteroids (Fig 5, B). A decreased requirement for inhaled corticosteroids was noted, with about half of the subjects

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FIG 5. Results of efforts to taper dose of corticosteroids. **A,** Percentage of subjects in each group who were able to reduce their daily corticosteroid dose by at least 50% at 20 weeks. **B,** Percentage of subjects in each group who were able to discontinue corticosteroid therapy. In the placebo, low-dose, and high-dose groups, 12, 14, and 9 subjects, respectively, were taking oral corticosteroids and 93, 92, and 97 subjects, respectively, were taking inhaled corticosteroids. Subjects who left the study had their last recorded dose carried forward. (Adapted with permission from Milgrom H, Fick RB Jr, Su JQ, et al. Treatment of allergic asthma with monoclonal anti-IgE antibody. *N Engl J Med* 1999;341:1966-73. Copyright © 1999 Massachusetts Medical Society. All rights reserved.)

requiring a > 50% lower dose of steroids with omalizumab treatment (Fig 5, A). Approximately one fifth of the subjects taking inhaled corticosteroids for control of asthma symptoms were able to completely discontinue steroid use after being treated with omalizumab (Fig 5, B).

Asthma exacerbations

Asthma exacerbations were significantly less frequent in the omalizumab groups than in the placebo group ($P < .03$). During the 20-week study period, 45% of patients receiving placebo reported an exacerbation, compared with only 28% of patients in the low-dose group ($P = .01$) and 30% of patients in the high-dose group ($P = .03$). The significance of this decline in exacerbations in patients treated with omalizumab is evident when analyzed in the context of concomitant corticosteroid use. Patients treated with omalizumab not only experienced significantly fewer exacerbations than those treated with placebo, but

they were also able to either discontinue or significantly reduce their concomitant corticosteroid treatment.

Other outcomes

β -Agonist use was also modestly reduced by omalizumab therapy. In the high-dose group, the mean number of puffs per day of albuterol dropped from 8.8 at baseline to 7.0 at 12 weeks ($P = .02$), whereas in the low-dose group, it dropped from 8.8 to 7.6 ($P = .24$). The corresponding values in patients in the placebo group were 8.2 and 7.4 puffs per day. In the omalizumab groups, the need for rescue albuterol remained decreased even during the 8-week corticosteroid-tapering phase.¹⁸

At 20 weeks, the improvements in peak expiratory flow were significant in the high-dose group ($P = .02$) and marginally significant in the low-dose group ($P = .046$).¹⁸ It should be noted that all subjects were receiving optimized treatment with oral and/or inhaled corti-

costeroids and were regularly evaluated and encouraged to comply with treatment. Hence, even subjects receiving placebo experienced some improvement, meaning that differences from active treatment were difficult to demonstrate.¹⁸

Treatment with omalizumab has also been shown to improve quality of life (QOL) scores in both adults and adolescents after 12 weeks.¹⁸ QOL was assessed by an asthma-specific QOL questionnaire. The overall score for adults on the asthma-specific QOL questionnaire had increased by a mean of 1.4 in the high-dose group ($P < .001$), 1.2 in the low-dose group ($P = .007$), and 0.8 in the placebo group. Results indicated that improvements in scores were similar over the 4 areas (activity limitations, asthma symptoms, emotional function, and environmental exposure) covered by the questionnaire and were maintained during the steroid withdrawal phase.¹⁸

These data indicated that omalizumab could be used to reduce asthma symptoms and prevent exacerbations in adults and adolescents with moderate to severe asthma, even while corticosteroid and β -agonist use is reduced. A reduced need for adjunctive medications may simplify therapy and avoid potentially serious side effects. Overall, the drug's safety and tolerability were excellent, and withdrawals from treatment were rare. These promising results prompted further evaluation of omalizumab treatment in larger, slightly modified trials.

PHASE III CLINICAL TRIALS OF OMALIZUMAB IN ADOLESCENTS AND ADULTS

A pivotal randomized, double-blind, placebo-controlled, multicenter, parallel-group study was conducted in patients 12 to 75 years of age. The study population was composed of adults and adolescents who were symptomatic despite receiving maintenance treatment with beclomethasone dipropionate (BDP) (420-1008 $\mu\text{g}/\text{d}$) and as-needed rescue albuterol (4 to 5 puffs/d). These symptomatic patients had had asthma for an average of 20 years and were receiving specialist care on a regular basis. Seventy-nine percent and 21 percent of subjects had diagnoses of moderate persistent and severe persistent asthma, respectively.¹⁹

During the run-in phase of the study before randomization, background controller therapy was standardized by either continuing or switching treatment to BDP in all patients. Approximately 4 weeks were allowed for this switch, and patients had to be symptomatic yet exacerbation-free when they entered the core study period. Patients were then randomly assigned to receive placebo, administered subcutaneously, or an appropriate dose of omalizumab in addition to the maintenance therapy established during the run-in phase. Subcutaneous administration of omalizumab, either 150 to 300 mg every 4 weeks or 225 to 375 mg every 2 weeks, was determined by body weight and baseline IgE levels. Patients continued this treatment regimen for the 4-month stable-steroid phase.

During the steroid reduction phase, patients continued the study treatment, but their BDP dose was reduced by 25% of baseline dose every 2 weeks. This was continued during the first 8 weeks until total elimination of inhaled steroid had been achieved or uncontrolled asthma had developed. Over the final 4 weeks, the lowest stable tolerated dose of BDP was continued. All patients were evaluated at the end of 12 weeks. Patients were again evaluated over a 5-month extension period, in which they continued to receive the same double-blind treatment as in the 7-month core study, primarily to assess long-term safety of omalizumab.

Phase III clinical trial results

Treatment with omalizumab was significantly superior to placebo in decreasing the number of asthma exacerbations experienced by patients in both the stable steroid and the steroid reduction phases of the trial. Compared with the placebo group, the mean number of exacerbations per patient in the omalizumab treatment group during the stable steroid and steroid reduction phases were 58% and 52% lower, respectively ($P < .001$ for both).¹⁹

The median dose of inhaled corticosteroids at the end of the 28-week treatment phase was 126 $\mu\text{g}/\text{d}$ in the omalizumab treatment group compared with 210 $\mu\text{g}/\text{d}$ in the placebo group. Omalizumab was significantly superior to placebo with respect to median actual BDP reduction ($P < .001$) and proportion of patients with 100% BDP reduction (43% omalizumab vs 19% placebo, $P < .001$).¹⁹

Patients also kept diary cards to record asthma symptoms on a scale of 0 to 9. Both placebo-treated and actively treated patients showed improvement in symptom scores, with significantly greater improvements in the patients receiving omalizumab.¹⁹

Treatment with omalizumab was found to be generally safe and well tolerated. Comparison of adverse events revealed little difference in incidence between the two treatment arms.¹⁹ Specifically, the patients receiving omalizumab showed no evidence for an increase in events that would indicate immune complex or allergic mediated disease.¹⁹

CONCLUSIONS

A novel asthma medication, anti-IgE monoclonal antibody, omalizumab, offers a new approach to controlling asthma. IgE antibody plays an important role in initiating and orchestrating the inflammatory responses to antigen exposure. Omalizumab forms complexes with serum free IgE and prevents it from binding to its receptors on mast cells and other inflammatory cells, thereby blocking the mechanisms responsible for the release of the cascade of mediators involved in the early-phase and late-phase asthmatic responses to allergen inhalation. Preclinical studies have demonstrated that omalizumab reduces serum IgE to levels typical for non-atopic patients. Ex vivo analyses of circulating basophils from treated patients showed

reduced histamine release after house dust mite challenge. In clinical phase II/III trials involving patients with moderate to severe asthma who required corticosteroid therapy, treatment with omalizumab allowed these patients to reduce or discontinue both inhaled and oral corticosteroids. This therapy also reduced symptoms and exacerbations, improved lung function and QOL, and reduced the need for rescue medications. The actions of omalizumab in diminishing both early- and late-phase allergic inflammatory responses and controlling asthma, as well as its excellent safety profile, may ultimately make this agent a useful addition to the therapeutic options for maintaining control of asthma.

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