

REVIEW ARTICLE

Omalizumab in the Treatment of Allergic Respiratory Disease

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Originally described in 1967 (1), the importance of immunoglobulin E (IgE) in atopic disorders has since been established by the work of numerous investigators. An elevation of total serum IgE is found in many atopic patients. In predisposed individuals, allergen-specific IgE is produced. IgE is then bound by the high-affinity IgE receptor, FcεRI, and subsequently expressed on the surface of a number of cell types, including mast cells, basophils, dendritic cells, and, to a lesser extent, other cell types. Allergen binds to the Fab portion of the IgE molecule. Cross-linking of two adjacent IgE molecules on the surface of allergic effector cells initiates an intracellular signaling pathway that ultimately results in the release of pre-formed and rapidly synthesized mediators. This series of cellular events is central to the pathogenesis of atopic disorders.

Allergists and immunologists have long strived to develop a specific therapy to prevent the degranulation of these allergic effector cells. Although rather weak inhibitors of mediator release, the cromones have long been available to treat allergic disorders, but are not particularly effective. Chronic therapy of allergic diseases has largely been limited to blocking the effects of specific mediators (leukotriene modifiers and anti-histamines) or the use of corticosteroids to reduce the consequences of mediator release.

Omalizumab is a humanized, monoclonal antibody that recognizes and binds to the Fc portion of the IgE molecule. Approximately 5% of omalizumab is composed of murine sequences; it is these sequences that contain the binding regions of the molecule. The murine sequences were engrafted onto a human IgG1k framework (2, 3). Omalizumab binds to the CH3 domain of the IgE molecule, which is conserved among all IgE molecules (4). This is the same site to which FcεRI binds. The binding of omalizumab to IgE results in the formation of soluble immune complexes that are subsequently cleared by the reticuloendothelial system. In essence, binding of omalizumab to IgE blocks binding of FcεRI and the subsequent expression of IgE on the surface of allergic effector cells. Because omalizumab binds to the same site as FcεRI, it cannot cross-link cell surface-expressed IgE. In other words, omalizumab can bind only to soluble IgE and

therefore cannot precipitate degranulation of effector cells (5).

IgE AND IgE RECEPTORS

IgE is present in the serum in far lesser amounts than IgG, IgM, or IgA. The half-life of IgE in the serum is only 2 days. As mentioned above, IgE exerts its effects principally through its interaction with the high-affinity IgE receptor, FcεRI. Furthermore, IgE appears to upregulate the expression of FcεRI on basophils. This effect likely occurs through the direct interaction of IgE with FcεRIα (6). Another IgE receptor, FcεRII, (CD23) whose role is less certain, binds with much lower affinity to IgE. FcεRII appears to have opposing effects dependent on whether the molecule is expressed on the cell surface or exists free in the serum. Soluble FcεRII appears to upregulate the production of IgE through interaction with CD21 in the B cell co-receptor. In contrast, ligation of cell surface-expressed FcεRII appears to inhibit IgE production (7).

Administration of omalizumab results in a rapid and substantial decrease in free serum IgE (8). By virtue of this dramatic reduction in serum free IgE levels, omalizumab appears to decrease the expression of FcεRI on several cell types (8–11). In 15 dust mite-sensitive patients, MacGlashan et al. showed a 99% reduction in serum free IgE levels within 2 hours of omalizumab administration. Furthermore, within 3 months of therapy with omalizumab, the expression of FcεRI on the surface of basophils was reduced by 97% (8). Casale et al. examined the kinetics of reduction in free serum IgE and basophil FcεRI expression in 24 ragweed-sensitive allergic rhinitis patients. Within 3 days, the investigators showed a 96% reduction in mean serum IgE levels in the omalizumab group ($p < 0.001$). Expression of FcεRI on basophils was reduced by 73% ($p < 0.001$) within 7 days of treatment in the omalizumab group (9).

Antigen presentation by dendritic cells is facilitated by the surface expression of FcεRI (12). Two subtypes of dendritic cells, DC1 and DC2, appear to be instrumental in the phenotypic development of Th1 and Th2 cells respectively. (13). Foster et al. showed that the expression of FcεRI on dendritic cells is greater in asthmatics than nonatopic controls and correlates with serum IgE levels (14). Prussin et al. investigated the effect of omalizumab on dendritic cell FcεRI expression. A total of 24 patients with ragweed-sensitive seasonal allergic rhinitis (16 treatment, 8 placebo) were given a study drug on days 0 and 28. Both DC1 and DC2 cells showed

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a significant decrease in FcεRI expression by day 7, which persisted through day 42. The decrease in FcεRI expression also correlated with a decrease in serum free IgE as well as basophil FcεRI expression (10). These results suggest that omalizumab may have a significant effect on the sensitization phase of the allergic response by regulation of FcεRI expression on dendritic cells.

Unlike the rapid decrease in FcεRI expression induced in basophils and dendritic cells, omalizumab's effect on cutaneous mast cell FcεRI expression appears to occur more gradually. A recent small study evaluated the effect of omalizumab on FcεRI expression on intradermal skin test titration and skin biopsy. Omalizumab had no effect on FcεRI on day 7, however, by day 70, there was a 90% reduction in FcεRI expression in biopsy specimens. Furthermore, there was no change in the number of tryptase positive cells in the biopsy specimens. The authors interpreted this as a decrease in the expression of FcεRI by cutaneous mast cells (11).

MARKERS OF AIRWAY INFLAMMATION

Nitric oxide (NO) has been identified as an important non-invasive marker of airway inflammation in asthmatics. After exclusion of nasal NO, the majority of NO in the breath originates in the lower airway. NO is produced from L-arginine by constitutive isoforms of nitric oxide synthase (NOS) on a continuous basis. These NOS isoforms include neuronal NOS (NOS type I) and endothelial NOS (NOS type III). Another isoform known as inducible NOS (NOS type II) is highly expressed in the airways of asthmatic patients, and, unlike constitutive NOS, appears to be steroid-responsive (15).

Silkoff et al. examined the effects of omalizumab on fractional exhaled nitric oxide (FENO) in 29 children with moderate-to-severe allergic asthma. Subjects were randomized to omalizumab or placebo and subsequently received follow-up during three consecutive study periods: (1) a 16-week stable dosing period of inhaled beclomethasone; (2) a 12-week steroid reduction phase; and (3) a 24-week open-label extension phase during which subjects in the placebo group were switched to active treatment. During the steroid reduction phase, the variability in FENO was greater in the placebo group at most visits. Furthermore, there was a significant reduction in the FENO in the omalizumab group compared with placebo during the steroid reduction phase ($p = 0.031$). The omalizumab group showed a significant reduction in FENO from baseline to the end of the 52-week study period (41.9 ± 29.0 to 18.0 ± 21.8 ppb [$p = 0.032$]) despite a substantial reduction in the dose of inhaled corticosteroids (16).

Djukanović et al. examined the effects of omalizumab on inflammatory cells in sputum and bronchial biopsies, thus providing further evidence of the anti-inflammatory effects of omalizumab. Forty-five patients with mild to moderate persistent asthma with sputum eosinophilia more than 2% were treated with omalizumab ($n = 22$) or placebo ($n = 23$) for 16 weeks. Subjects underwent sputum induction and bronchoscopy with bronchial biopsy before and after treatment. Treatment with omalizumab resulted in a significant decrease in the mean percentage of sputum eosinophils from 6.6 to 1.7% ($p < 0.001$). This reduction in sputum eosinophils was significantly greater than placebo ($p = 0.05$). In the omalizumab group, eosinophil counts were also significantly de-

creased in the epithelial and submucosal compartments. Furthermore, the treatment group showed a significant reduction in FcεRI-expressing cells in the airway (17).

ASTHMA

A number of studies have established the efficacy of omalizumab in the treatment of asthma. The U.S. Food and Drug Administration has approved the use of omalizumab in the treatment of moderate to severe persistent allergic asthma in patients 12 years of age or older.

Two early investigations evaluated the ability of omalizumab to suppress allergen bronchoprovocation challenges; the results of these studies suggested omalizumab inhibits both the early and late phase asthmatic response (18, 19).

A phase II study examined asthma symptom scores in 317 moderate to severe allergic asthmatics on inhaled and/or oral corticosteroids (20). Two intravenous treatment protocols were used, low dose and high dose (2.5 and $5.8 \mu\text{g}$ per kg body weight per nanogram of IgE per mL, respectively). Subjects maintained the same dose of corticosteroids throughout the first 12 weeks of the study. The dose of corticosteroids was subsequently tapered during the following 8 weeks. Symptom scores improved in both the low- and high-dose groups at 12 weeks ($p = 0.005$ and $p = 0.008$, respectively). Subjects in the omalizumab treatment groups had fewer asthma exacerbations and were able to reduce or discontinue corticosteroids to a greater extent than subjects treated with placebo.

Three phase III trials sharing a similar design were later conducted on a total of 1,405 patients with moderate to severe allergic asthma (Figure 1) (21–23). Two trials were conducted in subjects 12 years of age and older treated with inhaled corticosteroids (21, 23). Another trial was conducted in children 6 to 12 years of age receiving inhaled corticosteroids (22). Omalizumab was administered subcutaneously every 2 to 4 weeks in doses ranging from 150 to 375 mg. Dosing provided at least 0.016 mg/kg omalizumab per IU/mL IgE every 4 weeks (Figure 2). During the initial 16 weeks, omalizumab was added on to inhaled corticosteroids at a stable dose. Subjects then underwent a steroid-reduction phase lasting 12 weeks. Doses of corticosteroids were reduced by up to 25% every 2 weeks to the lowest level required for optimal disease control. The primary endpoint in all three studies was a reduction in asthma exacerbations. A number of secondary endpoints were also evaluated including daily and nocturnal asthma symptoms, reduced use of inhaled corticosteroids, quality of life, use of rescue medications, and lung function measurements.

A reduction in asthma exacerbations when compared with placebo was shown in all three studies. Furthermore, omalizumab demonstrated a corticosteroid-sparing effect in all three studies. A significant number of omalizumab-treated patients were able to decrease or, in many cases, discontinue inhaled corticosteroids. There was a twofold greater number of subjects in the omalizumab group who successfully discontinued corticosteroids compared with placebo-treated subjects. In addition, fewer asthma symptoms, less rescue medication usage, and improved quality-of-life scores were noted in the omalizumab-treated patients.

The data from these three studies were later pooled to determine the effect of omalizumab on serious asthma

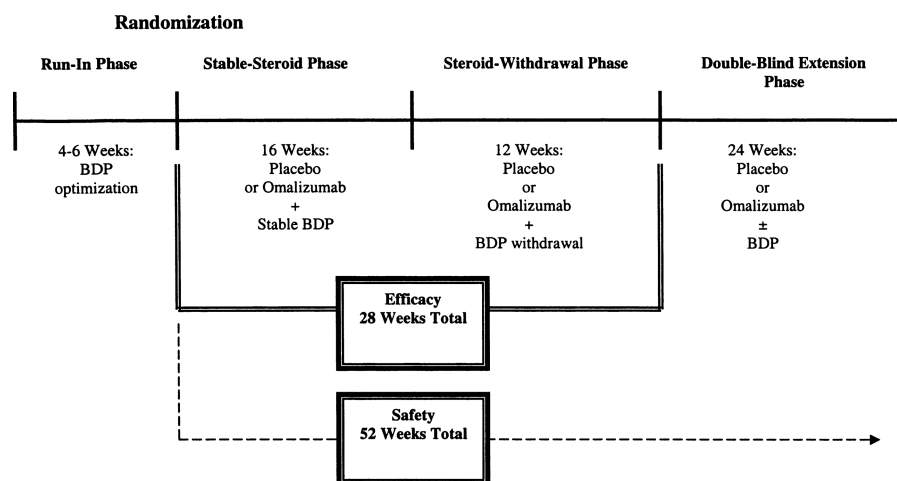


FIGURE 1.—Study design of three large, multicenter phase III studies of omalizumab versus placebo in the treatment of allergic asthma. The dose of inhaled corticosteroid was optimized during a 4 to 6-week run-in phase. Following the run-in phase, patients were randomized to receive omalizumab or placebo plus the stable dose of inhaled beclomethasone (BDP) for the next 16 weeks. This was followed by a 12-week steroid-withdrawal phase. A 24-week extension phase was added on. Drug efficacy was evaluated over 28 weeks, and safety was assessed over 52 weeks. Adapted from references 21–23.

exacerbations (24). Significantly fewer unscheduled outpatient visits and emergency-room visits were observed in the omalizumab-treated patients compared with placebo (rate ratios 0.60 and 0.47, respectively, $p \leq 0.05$). Hospitalizations were also significantly reduced from 3.42 events per 100 patient-years on placebo to 0.26 on omalizumab treatment (rate ratio of 0.08, $p < 0.01$).

To examine baseline characteristics predictive of a response to omalizumab, Bousquet et al. pooled the data from 1,070 adolescents and adults from two of these phase III trials (25). Patients with features suggestive of greater disease severity appeared to obtain the greatest benefit from the addition of omalizumab to their therapeutic regimen. These included patients with a history of emergency treat-

ment of asthma in the last year, patients on $\geq 800 \mu\text{g}$ inhaled beclomethasone per day, and patients with a forced expiratory volume in 1 second (FEV_1) $\leq 65\%$ of predicted. The greatest benefits were noted in patients who had two or more of these characteristics.

Holgate and colleagues examined 246 patients with severe allergic asthma who required high-dose fluticasone ($\geq 1,000 \mu\text{g/day}$) with or without oral corticosteroids. At 32 weeks, the investigators showed a significant reduction in the dose of inhaled corticosteroids in the omalizumab group when compared with placebo (mean 57.2% vs. 43.3%, $p = 0.003$). Improved symptoms, less rescue medication usage, and improved quality of life were also observed in the omalizumab group when compared with placebo (26).

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				

FIGURE 2.—Omalizumab dosing table. Omalizumab doses (milligrams) administered by subcutaneous injection every 4 weeks for adults and adolescents (12 years of age and older) with asthma. Dosing is based on weight (kg) and pretreatment total IgE level (IU/mL). Adopted from the package insert (42, 43).

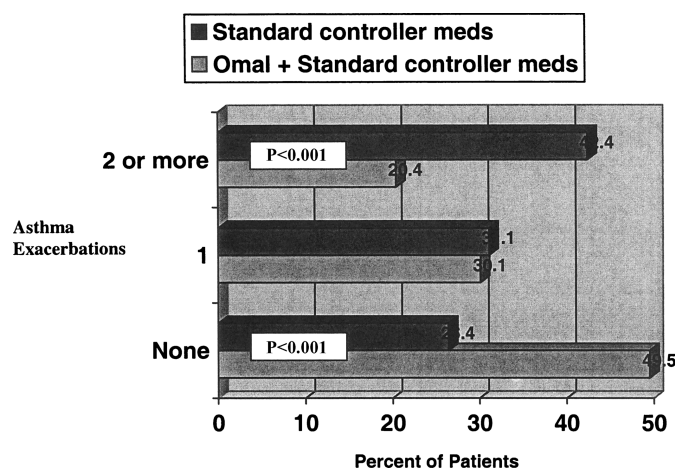


FIGURE 3.—Percent of patients experiencing clinically significant asthma exacerbations. 312 symptomatic patients with moderate to severe allergic asthma treated with omalizumab or placebo were studied. Exacerbation is defined as a course of systemic corticosteroids with an associated asthma worsening adverse event. Adapted from Ayres et al. (28).

However, no significant reduction in exacerbations was observed.

In practice, omalizumab is typically added to the therapeutic regimen in patients who remain poorly controlled despite maximal medical therapy. It is these severe asthmatics that are at greatest risk of serious disease complications and mortality (27). The addition of omalizumab to maximal conventional asthma therapy was evaluated in a 52-week trial of 312 symptomatic patients with moderate to severe allergic asthma (28). Despite treatment with high doses of inhaled corticosteroids plus long-acting β_2 -agonists, antileukotrienes, or oral steroids, these patients remained symptomatic. Compared with placebo, the omalizumab group showed a greater reduction of asthma exacerbations (60%), unscheduled physician visits, and days missed from work or school (Figure 3). Two recent investigations have evaluated the efficacy of add-on therapy with omalizumab in patients with severe persistent asthma (29, 30). Bousquet et al. examined the effect of add-on therapy with omalizumab on asthma exacerbations in severe asthmatics (29). The data from five double-blind trials and two open-label studies were pooled for this analysis. A total of 4,308 patients were included (2,511 treated with omalizumab). Omalizumab decreased the rate of asthma exacerbations by 38% and also decreased the rate of emergency visits by 47%. In a 28-week randomized trial of 419 patients, Humbert et al. evaluated the efficacy of omalizumab as add-on therapy in patients who were symptomatic despite therapy with high-dose inhaled corticosteroids and long-acting β_2 -agonists (30). A significant reduction in the rate of severe asthma exacerbations and emergency visits was observed in the omalizumab group. Taken together, these studies suggest that omalizumab is effective as an add-on therapy in severe asthmatics who are poorly controlled despite maximal medical therapy.

The cost of omalizumab is substantially higher than other asthma medications. However, despite its high cost, it may still be cost-effective when its use is limited to those pa-

tients with more severe disease. This includes patients with frequent exacerbations, those requiring emergency care, and those patients requiring hospitalization. It is this relatively small group of patients who account for the bulk of health-care expenditures associated with asthma care (27).

ALLERGIC RHINITIS

A total of 20 to 40 million Americans suffer from allergic rhinitis annually. This includes 10 to 30% of adults and up to 40% of children (31). Although not a life-threatening condition, allergic rhinitis has a substantial impact on the quality of life of millions of Americans.

Patients suffer from symptoms ranging from mild to debilitating (32). A significant loss of work and school days occurs annually as a result of allergic rhinitis. Perhaps the most concerning aspect of allergic rhinitis is its frequent co-existence with asthma. Most allergic asthmatics also suffer from allergic rhinitis. Unfortunately, poor control of rhinitis may exert a detrimental effect on asthma (33). Several studies have demonstrated improved asthma control when concomitant allergic rhinitis is properly treated (33–36).

The effect of omalizumab on birch-pollen sensitive seasonal allergic rhinitis was examined in 251 adolescents and adults. Subjects received 300 mg omalizumab or placebo two or three times during the birch pollen season dependent on their baseline total serum IgE values. The omalizumab-treated group showed significant improvements over placebo in average daily symptom scores, usage of rescue antihistamines, and quality of life measures (37).

Another large study evaluated 536 patients with ragweed-sensitive allergic rhinitis. Patients were randomized to receive one of three omalizumab doses (50 mg, 150 mg, or 300 mg) or placebo. Omalizumab or placebo was administered just before the onset of the ragweed season and every 3 to 4 weeks throughout the pollen season. Subjects treated with 300 mg omalizumab demonstrated significantly lower nasal symptoms scores and quality-of-life scores (RQLQ) when compared with placebo. In addition, a significant correlation was observed between reduction in serum IgE and improvements in nasal symptoms and rescue antihistamine use (38).

Omalizumab has also been shown to be effective in the treatment of perennial allergic rhinitis. A total of 289 patients with moderate-to-severe disease were evaluated in a 16-week trial. Patients were randomized to omalizumab (0.016 mg/kg/IgE [IU/mL]) or placebo every 4 weeks. Both mean daily nasal severity scores and rescue antihistamine use were significantly lower in the omalizumab group when compared with placebo ($p < 0.001$ and $p \leq 0.005$, respectively) (39).

The effect of omalizumab on early nasal response to allergen challenge was investigated in a randomized, double-blind, placebo-controlled trial of 23 patients with allergic rhinitis. At 2- or 4-week intervals, subjects were given omalizumab ($n = 12$) or placebo ($n = 11$). After 16 weeks of treatment, omalizumab-treated patients showed significantly inhibited allergen-induced nasal symptoms compared to placebo-treated patients. A significant decrease in basal TNF- α and albumin in the nasal lavage fluid (a marker of vascular permeability) was also shown in the

omalizumab-treated patients (40). Lin et al. showed that nasal allergen challenge responses were significantly inhibited by 2 weeks after omalizumab treatment (9).

As mentioned previously, allergic rhinitis and asthma frequently coexist, and poor control of rhinitis may negatively influence the course of asthma. The SOLAR study evaluated 405 patients with moderate-to-severe asthma on stable therapy who also had persistent allergic rhinitis. Patients received omalizumab or placebo for 28 weeks. Fewer asthma exacerbations were observed in the omalizumab-treated patients than placebo (20.6% vs. 30.1%). Furthermore, more patients in the omalizumab group demonstrated a clinically significant improvement in both asthma and rhinitis quality of life indices (57.7% vs. 40.6%). The results of this study suggest that omalizumab is effective in the treatment of upper and lower airway symptoms in the same patients (41).

SAFETY

Omalizumab has proven to be a well-tolerated medication with few adverse reactions. The most common adverse event is a local reaction at the injection site that may include burning, pruritis, hives, pain, redness, induration, swelling, warmth, and bruising. In asthmatics receiving omalizumab or placebo, a local cutaneous reaction was observed in 45% and 43% of subjects, respectively. Severe local cutaneous reactions occurred in 12% of omalizumab-treated subjects and 9% of placebo-treated subjects (42, 43).

A meta-analysis of 3,041 patients from eight phase II and III trials evaluated the safety profile of omalizumab (44). The number and type of adverse events were very similar when omalizumab-treated patients were compared to placebo-treated patients. The most frequent adverse events in patients treated with omalizumab versus placebo were viral infection (23 vs. 28%), headaches (23 vs. 24.5%), upper respiratory infections (20 vs. 22%), sinusitis (11.5 vs. 16%), and pharyngitis (12% in both groups). Only 6.6% of the total adverse events were felt to be treatment-related in the omalizumab group versus 5.6% in the placebo group. Six tenths of a percent of omalizumab-treated patients and 1.1% of placebo-treated patients withdrew as a result of adverse events.

Berger et al. examined the safety of omalizumab in more than 300 children in a randomized, double-blind, placebo-controlled study (45). Subjects were treated for 28 weeks followed by a 24-week open label extension. In patients who underwent 52 weeks of treatment with omalizumab, upper respiratory infections and headaches were the most commonly encountered adverse events (47.1% and 42.7%, respectively). During the double-blind 28-week treatment period, the incidence rate of events was similar between omalizumab and placebo. Urticaria was reported in 11 patients (4.9%). With the exception of one severe case of urticaria that necessitated withdrawal from the study, all patients with urticaria had either spontaneous remission or resolution with antihistamine treatment. Adverse event incidence during the open label extension was similar to the omalizumab-treated group during the 28-week double-blind phase. The results of this study suggested that omalizumab is well tolerated in children and has a good safety profile.

Malignancy has been reported in 20 of 4,127 (0.5%) of patients treated with omalizumab and 5 of 2236 (0.2%) of patients treated with placebo (44). Various types of malignancies were reported, most of which were solid tumors. A single case of lymphoma was reported in the omalizumab-treated patients. An independent panel of oncologists failed to find a causal association between omalizumab and cancer. Most tumors were preexisting, and 60% of all tumors presented within the first 6 months of therapy. Thus far, there does not appear to be a causal relationship between omalizumab and cancer. Nonetheless, postapproval surveillance is appropriate.

OMALIZUMAB PLUS IMMUNOTHERAPY

The rationale for using the combination of anti-IgE and allergen immunotherapy comes from pre-existing data about the biologic and immunologic effects of both therapies. Allergen immunotherapy has been used for more than 90 years for the management of allergic disorders and is the only antigen-specific immunomodulatory treatment routinely available to clinicians. The immunomodulatory effects of immunotherapy are due to a number of proposed mechanisms, including blunting of seasonal increases in IgE levels, increasing allergen-specific IgG levels, shifting the balance of T-lymphocyte subsets away from a Th2 phenotype and toward a Th1 phenotype, and production of allergen-specific IL-10 (46–51). However, immunotherapy is associated with the risk of allergic reactions to the extract injections.

Omalizumab does not completely ameliorate symptoms of allergic respiratory symptoms, and upon discontinuation, serum IgE levels return to pre-treatment levels (2, 37, 38, 52–56). There are no data concerning long-lasting immune tolerance as a result of anti-IgE therapy. Nonetheless, omalizumab-induced decreases in serum IgE and the expression of FcεRI on key immune effector cells, including basophils and dendritic cells (8–10), could lead to important immunologic changes that could enhance the immune tolerance to allergens delivered by immunotherapy. The rationale for combining omalizumab plus allergen immunotherapy includes the prospects of improved clinical benefits and safety. A study evaluating the use of omalizumab before immunotherapy has just been completed (57). The primary objective of this study was to determine whether omalizumab, given 9 weeks before rush immunotherapy, followed by 12 weeks of dual omalizumab and immunotherapy, is more effective than rush immunotherapy followed by immunotherapy alone. The secondary objective considers both the efficacy and safety of dual omalizumab and immunotherapy compared with omalizumab alone or placebo. Clinical tolerance and the immunological mechanisms involved were also assessed. Initial results showed that omalizumab improved both the efficacy and safety of immunotherapy. Results from this study should improve the understanding of the role of IgE and potential benefits of anti-IgE therapy with immunotherapy.

CONCLUSION

Despite intensive research, the number of available treatment options for allergic disorders has remained limited for many years. Rather than therapy directed at underlying

disease processes, past pharmacologic options have largely been limited to the global effects of corticosteroids or targeting specific mediators. Although immune-modifying agents, such as methotrexate, have been used sparingly in severe asthmatics, the side effects and limited efficacy have precluded their widespread use. Omalizumab represents the first new therapeutic option for severe asthmatics in decades. Furthermore, the data suggest omalizumab has significant anti-inflammatory properties. Finally, omalizumab appears to be a safe, well-tolerated medication. In years to come, the role of omalizumab in the treatment of asthma and the central role of IgE in the pathogenesis of allergic disorders will continue to evolve.

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