Omalizumab and the Treatment of Allergic Rhinitis

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Anti-IgE therapy affects mechanisms in the allergic response that are IgE-dependent or IgE-mediated and common to both allergic asthma and allergic rhinitis. Clinical trials of omalizumab in the treatment of patients with allergic rhinitis or comorbid allergic rhinitis and moderate to severe allergic asthma have recorded significant reductions in symptom severity scores of both conditions. This novel therapy has increased the knowledge base concerning IgE-mediated allergic responses, and, in keeping with its actions established in the treatment of asthma, appears to be useful in the treatment of moderate to severe allergic rhinitis, as well.

Introduction

Four out of every five individuals with allergic asthma also have allergic rhinitis [1]. One in five patients with allergic rhinitis also has allergic asthma [1]. Although allergic rhinitis is an important disease in its own right, it has an important impact on asthma and could be treated concomitantly with asthma by agents that affect the allergic response. Thus, an approach to allergic disease that affects the basic mechanisms of allergy might benefit either asthma or rhinitis, or both diseases simultaneously.

IgE-mediated Pathogenesis in Allergic Rhinitis

The allergen-specific IgE response

Basophils and mast cells in the nasal passages initiate immediate hypersensitivity responses via activation of cell-surface, high-affinity receptors (FcEpsilonRI) that bind allergen-specific IgE, as synthesized in susceptible patients [2,3]. In allergic rhinitis, when the offending allergens are inhaled into the nose of previously sensitized individuals, they bind to the IgE on mast cell surfaces [4]. This aggregation of receptor-bound IgE molecules triggers cell degranulation. Degranulation releases preformed mediators (histamine, tryptase, proteoglycans, chemotactic factors), newly formed mediators (arachidonic acid metabolites, cyclooxygenase products, platelet-activating factor, adenosine, bradykinin), and cytokines (interleukin [IL]-4, IL-5, IL-6, IL-13, tumor necrosis factor [TNF]-α), the aggregation of which prompt symptoms specific to allergic rhinitis (sneezing, pruritic rhinorrhea, nasal congestion, watery eyes) as well as airway responses common to both allergic rhinitis and asthma (mucus production, eosinophil recruitment, lymphocyte activation) [2,3,5–8].

Clinical correlation in allergic rhinitis

The immediate clinical allergic response includes copious nasal mucus production, plasma exudate from increased vascular permeability, nasal-tissue edema, congestion and pressure from resulting vasodilation, and sneezing and itching caused by stimulated sensory nerves [4]. During the next 4 hours to 8 hours (the late-phase response) following exposure, the complex interaction of mediators and cell responses leads to cell recruitment of eosinophils, neutrophils, lymphocytes, and macrophages to the nasal mucosa, perpetuating the inflammation [4].

Rationale for Anti-IgE Therapy in Allergic Rhinitis

Mechanisms of action in anti-IgE therapy

Monoclonal anti-IgE antibody therapy for allergic airway disease was initially developed for and tested in the treatment of allergic asthma and is, in essence, a disease-modifying anti-inflammatory treatment. It changes or interrupts the disease process associated with IgE-mediated allergic disease at the point of IgE mediation. Omalizumab is a nonimmunogenic, nonanaphylactogenic monoclonal anti-IgE antibody that binds with and reduces levels of serum-free IgE [9]. By binding with serum-free IgE, anti-IgE therapy reduces the amount of free circulating IgE available to bind with high-affinity receptors on mast cells, and, thereby, reduces the amount of degranulation and subsequent mediator release [9]. This, in turn, reduces the severity of IgE-mediated symptoms in the allergic response [10••].

Allergic rhinitis as primary diagnosis

Although not fatal, allergic rhinitis has a very high morbidity, affects quality of life, and is associated with significant symptoms. It contributes to several other complicating conditions including sinusitis, nasal polyps, otitis media, eustachian-tube dysfunction, snoring, obstructive sleep apnea, and asthma [4].

Allergic rhinitis as comorbid disease with allergic asthma

Conceptually, allergic rhinitis and allergic asthma are two aspects of the same disease. The term "unified airway disease" is one name used to describe the connection that exists between these two aspects of hyperreactive airway disease. Many recent studies have shown the comorbidity of and relationship between the two conditions.

In a well-documented Brown University study, Greisner *et al.* [1] conducted a 23-year follow-up study of 738 college students with asthma or allergic rhinitis as the primary diagnosis. Among those with asthma as the primary diagnosis, allergic rhinitis occurred in 85.7%. Among individuals with allergic rhinitis as the primary diagnosis, asthma occurred in 21.3%.

Seasonal allergic rhinitis (SAR) patients exhibit a high susceptibility for incident asthma. Beeh *et al.* [11] investigators found that a single nasal allergen challenge in SAR patients increased markers of allergic inflammation in the lower respiratory tract, possibly via pronounced activation of inflammatory cells through circulating immediate-type reaction cytokines, such as IL-5.

Histologic characteristics, such as eosinophilic inflammation, epithelial shedding, and basement membrane thickening, normally associated with asthma, are also found in sinonasal mucosal specimens from patients with chronic rhinosinusitis [12].

Allergic rhinitis and allergic asthma share a contiguous mucosa, replete with the same or similar cellular and mediator responses. Stimulation of the nasal mucosa might result in changes in bronchial hyperresponsiveness. Nasal and sinus receptor stimulation might affect trigeminal afferent nerves, thereby stimulating parasympathetic fibers via the vagus nerve [13], which can result in changes in bronchomotor tone.

Cell mechanisms and mediator responses similar to those in the airway mucosa of allergic asthma patients exist in the nasal mucosa of patients with allergic rhinitis. Pharmacologic interventions for allergic airway disease include rescue and modifier medications, the latter comprising cromolyn sodium, corticosteroids, and allergen-specific immunotherapy. Allergen immunotherapy can be used alone or in conjunction with other pharmacologic interventions for long-term symptom relief, but the spectrum of the effect of allergen immunotherapy is antigen-specific. What might prove to be a useful additional therapy is such that is broad, acts at basic allergic mechanism levels, and is antigen-nonspecific [14••].

Omalizumab

Omalizumab is antigen-nonspecific anti-IgE therapy. It binds specifically to the CHepsilon3 domain of IgE, inhibiting the binding of IgE to the high-affinity IgE receptor (FCepsilonRI) on the surface of mast cells and basophils. Omalizumab does not bind to IgG or IgA, nor to IgE bound to the IgE receptor on mast cells or basophils. Less free IgE results in less surface-bound IgE. Reduction in surface-bound IgE on FCepsilonRI-bearing cells limits the release of mediators of the allergic response. Treatment with omalizumab also reduces the number of FCepsilonRI receptors on basophils in atopic patients [15]. Omalizumab does not bind to basophil- or mast cell–bound IgE, so the possibility of cross-linking IgE molecules on these cells, producing acute anaphylaxis, is eliminated [10••].

In addition, omalizumab does not bind to or induce histamine release from basophils. The immune complexes formed between IgE and omalizumab in the circulation in vivo are relatively small (molecular weight < 1 million) and do not activate the complement system or cause organ damage [16].

Omalizumab efficacy depends on dose, the patient's weight, and baseline IgE levels. Studies of omalizumab therapy in patients with IgE-mediated diseases of the airways have shown that clinical benefit is derived when serum-free IgE levels are reduced to less than 50 ng/mL (20.8 IU/mL) or less (target 25 ng/mL [10.4 IU/mL]).

Pivotal studies with omalizumab have documented its efficacy in the treatment of severe allergic asthma and in relationship to patients' needs for corticosteroids and rescue medications [17••,18]. Importantly, investigators found that anti-IgE therapy (omalizumab) significantly reduced the severity of asthma symptoms and the number (frequency) of exacerbations. Combined results of the two double-phase (steroid-stable and reduced steroid use) pivotal studies of omalizumab in asthma therapy showed the following (summary):

- Significant reduction in number of exacerbations per patient during both study phases (Busse: P = 0.006 and 0.003; Soler: $P < 0.001$ and < 0.001) [17••,18]
- Reduction in asthma-symptom severity scores in both phases
- 2:1 omalizumab patients (vs placebo) discontinued use of inhaled steroids in 28 days
- 2:1 placebo patients (vs omalizumab)⇒no change from baseline steroid use in 28 days
- Significant improvement in asthma-related quality of life scores, with the greatest reduction (> 1.5 U change) observed as the use of inhaled corticosteroids were being reduced (Busse: $P < 0.001$; Soler: P = 0.002) [17••,18]

Omalizumab is a recombinant, humanized, chimeric, anti-IgE monoclonal antibody. It is approved and indicated for the treatment of adults and adolescents with the following:

- Moderate-to-severe, persistent asthma
- Positive skin test or in vitro reactivity to a perennial aeroallergen
- Serum IgE between 30 and 700 IU/mL

- Symptoms inadequately controlled with inhaled corticosteroids [15]

The activity of omalizumab might be useful in treating allergic rhinitis as well. Several groups of researchers have explored such use of omalizumab, and their findings are discussed in the next section.

Literature Overview: Anti-IgE Research (Airway)

The initial clinical trials in the use of anti-IgE therapy for allergic airway disease were centered on treating moderate to severe allergic asthma. Although there were data on allergic rhinitis patients within the study populations, the data were secondary in most of the asthma studies and, in some cases, not evaluated until several years later [14••,19•]. Since then, several studies designed to test omalizumab efficacy in patients with allergic rhinitis have been reported.

Efficacy and safety clinical studies in patients with allergic rhinitis

Table 1 shows a brief summary of selected studies of anti-IgE therapy (omalizumab) in patients with allergic rhinitis [14••,19•,20,21,22••,23,24] and includes the studies discussed in the following.

In 1997, a report of the first full-scale study using omalizumab specifically in the treatment of patients with moderate to severe allergic rhinitis was published. Casale *et al.* [14••] hypothesized that rhuMAb-E25 (omalizumab) would decrease total serum IgE and reduce allergic rhinitis symptoms. A total of 240 subjects (ragweed-induced allergic rhinitis) were divided into five groups in an 84-day treatment period that was followed by a 42-day observation period. One hundred eighty-one subjects received an initial intravenous loading dose (day 0, 1 month before ragweed season), followed by administration of rhuMAb-E25 (in mg/kg body weight) of 0.15 mg/kg subcutaneously, 0.15 mg/kg intravenously, or 0.5 mg/kg intravenously on days 7, 14, 28, 42, 56, 70, and 84. A subcutaneous injection placebo group and an intravenous infusion placebo group were included. Casale *et al.* [14••] found that adverse events were mild, and that the rate of adverse events was no different between the three active groups and the two placebo groups. RhuMAb-E25 decreased serum-free IgE levels in a dose and baseline IgE–dependent fashion, and the decrease in ragweed-specific IgE levels correlated with reduced symptom severity scores. These data suggested that for omalizumab to be effective, the IgE levels had to be reduced to less than 50 IU/mL. Figure 1, showing a weekly total symptom score by baseline ragweed-specific total IgE, correlates data indicating that patients with lower baseline ragweed-specific IgE levels recorded lower symptom scores.

The case for overall efficacy could not be proven because the number of patients whose IgE levels were suppressed to appropriate levels was too small (11) to demonstrate significant differences and clinical efficacy. However, repeated dosing over more than 1 month proved safe [14••].

Data and analysis from this study regarding rhinitis-specific quality of life scores were published in 2001, when investigators reported that the ragweed-induced allergic rhinitis patients tested showed greater improvement in quality of life when given doses of 300 mg, versus scores for those receiving lower doses or placebo. Also, quality of life scores for the 300 mg-dose patients remained improved, even during peak allergy season exposure [19•].

In 2000, Adelroth *et al.* [21] reported results of their placebo-controlled study of birch-pollen–induced seasonal allergic rhinitis patients (n = 250, total) treated with omalizumab. They randomly assigned 251 adult subjects, who had a history of SAR and a positive skin-test response to birch pollen, to receive 300 mg of rhuMAb-E25 or placebo, to be given 2 or 3 times during the season, depending on baseline IgE levels. As judged by daily nasal symptom severity scores and subjects' use of rescue antihistamine tablets per day, the proportion of days with any SAR medication use, and all domains of rhinitis-specific quality of life scores, there were significant between-treatment differences in favor of rhuMAb-E25. Clinical effectiveness correlated with markedly lower serum-free IgE levels in rhuMAb-E25–treated subjects (Table 2), and no anti-rhuMAb-E25 antibodies were detected [21].

Busse *et al.* [20] reported data analysis for a subset of perennial allergic rhinitis (PAR) subjects from a larger, multicenter trial. The subset of patients (n = 289, total; age range: 12 to 75) had symptomatic PAR that was unresponsive to nasal steroids or immunotherapy. In the 16-week trial, those who received doses of at least 0.016 mg/kg/IgE [IU/mL] of omalizumab, subcutaneously (n = 144) at least every 4 weeks reported significantly reduced nasal symptom severity ($P < 0.001$) versus placebo.

In assessing the long-term benefits of using omalizumab in the treatment of patients with allergic airway disease, one only has to revisit the data from the asthma trials, where controlled study periods lasted a total of 52 weeks. There were no significant increases in adverse effects in the period after the 28-week core trials, and symptom severity scores continued to be reduced.

Clinical Realities of Using Anti-IgE Therapy for Allergic Rhinitis

Comorbid asthma

A factor in the real-world use of anti-IgE therapy for patients with allergic rhinitis is that many of these patients have comorbid allergic asthma. At a recent meeting of the American College of Chest Physicians (2003), Boulet *et al.* [23] reported for the SOLAR study group on their work to determine the effects of anti-IgE therapy (omalizumab) on PAR symptoms in patients with comorbid allergic asthma and perennial allergic rhinitis. This was the first study

Table 1. Selected studies of anti-IgE therapy in patients with allergic rhinitis

Study	Investigative agent	Subject diagnosis and (*n* = ITT)	Results
Casale *et al.* [14••]	Omalizumab	SAR (ragweed); baseline IgE levels 30–700 IU/mL; 3 test groups (dose-ranges) and placebo control	Decreased serum-free IgE levels in test groups; nasal symptom severity score significantly reduced at 300-mg dose vs placebo ($P = 0.002$); adverse event frequency not significantly different between dose groups or placebo.
Adelroth *et al.* [21]	(rhu)mAb-E25 (omalizumab)	SAR (birch pollen) (*n* = 164; placebo = 86)	Reduced serum-free IgE levels; severity of nasal symptoms significantly reduced ($P < 0.001$) with omalizumab vs placebo; no significant difference in adverse event frequency between groups.
Busse *et al.* [20]	Omalizumab	(Subset) PAR unresponsive to nasal steroids or immunotherapy (*n* = 144; placebo = 145)	16-week trial; severity of nasal symptoms significantly reduced ($P < 0.001$) with omalizumab vs placebo.
Casale *et al.* [19•]	Omalizumab	SAR (ragweed); data from 1997 group study (see above).	Rhinitis-specific quality of life scores consistently better with 300 mg omalizumab than lower dosages or placebo; scores did not worsen during peak season exposure.
Kuehr *et al.* [22••]	Omalizumab in combination with SIT vs immunotherapy alone	SAR (birch pollen, grass pollen) (*n* = 221, total)	24-week study; 4 treatment groups; groups with unrelated specific immunotherapy per season considered control groups; combination therapy significantly reduced symptom load ($P < 0.001$) vs SIT alone.
Boulet *et al.* [23]	Omalizumab (as add-on to existing therapy)	Comorbid moderate to severe asthma and moderate to severe PAR (*n* = 405, total)	Double blind, 28-week, placebo-controlled study; significant and similar reductions from baseline in nasal and asthmatic symptom scores with omalizumab ($P < 0.001$) vs placebo; significant improvement in both asthma- and allergic rhinitis–related quality of life scores with omalizumab ($P < 0.001$) vs placebo; no serious side effects; treatment provides parallel improvement.
Nayak *et al.* [24]	Omalizumab (as retreatment)	SAR (ragweed) IgE levels < or = 150 IU/mL (*n* = 182); IgE levels > 150 IU/mL (*n* = 105) at screening	Open-label, 12-week study, second ragweed season; overall incidence and pattern of adverse events similar to previous studies; no anti-omalizumab antibodies were detected and no serious adverse events; free IgE levels decreased to levels associated with symptom reduction in core study; treatment well-tolerated and no significant immunologic reactions.

ITT—intention-to-treat; PAR—perennial allergic rhinitis; SAR—seasonal allergic rhinitis; SIT—specific immunotherapy.

designed to compare omalizumab effects on both asthma and allergic rhinitis in the same patients. With consideration to yet another aspect of "real world" treatment conditions, 405 patients with moderate-to-severe allergic asthma and concomitant moderate to severe PAR were randomized to receive omalizumab or placebo, in addition to their current therapies, for a period of 28 weeks. Dosing was designed to lower serum free IgE levels to below 25 ng/mL. Concurrent therapies included inhaled budesonide, long-acting beta-agonists, and nasal steroids. Omalizumab demonstrated significant and similar reductions from baseline in both nasal and asthmatic symptom scores ($P < 0.001$) versus placebo. Also, omalizumab significantly improved asthma- and rhinitis-related quality of life scores, compared with placebo ($P < 0.001$), and researchers concluded that omalizumab provides parallel improvements in comorbid asthma and PAR [23].

Repeat dosing

Repeat dosing (every 2 weeks to 4 weeks) of anti-IgE therapy is the US Food and Drug Administration–approved schedule for allergic asthma patients, and will likely be employed as the treatment schedule in patients with allergic rhinitis. A concern is whether atopic patients will develop antibodies to the murine portions of omalizumab (<5% of the molecule is murine, the remainder is humanized), although test results for this adverse effect have, so far, been unremarkable. Nayak *et al.* [24] conducted a 12-

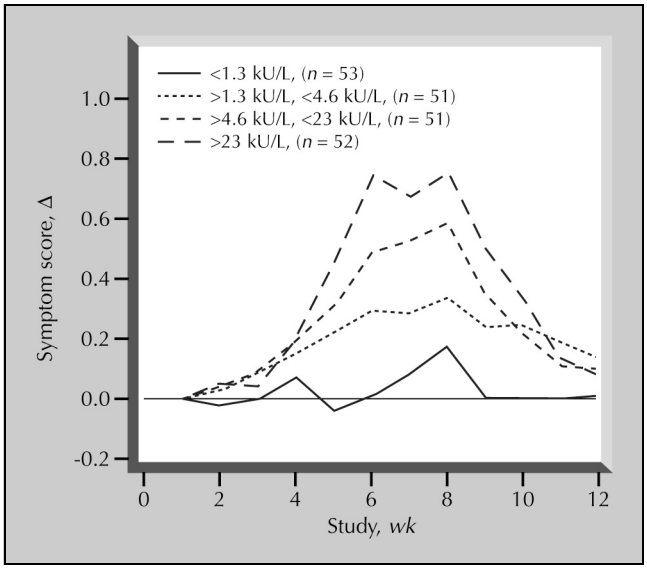

Figure 1. Weekly total symptom score by baseline ragweed-specific total IgE. Symptom scores correlated significantly with baseline ragweed-specific IgE levels ($P = 0.33$; $P = 0.0001$). Key: *Lines* reflect baseline levels of ragweed-specific total IgE. Subjects with the lowest baseline levels of ragweed-specific total IgE (<1.3 kU/L) had little or no change in symptoms during the ragweed season, whereas patients with progressively higher baseline levels of ragweed-specific total IgE experienced progressively greater increase in symptoms during the ragweed season. During peak season (the 2-week period with highest daily pollen counts), average symptom scores were 1.0 for patients receiving placebo and 0.8 to 0.9 for treated patients. (*Adapted from* Casale *et al.* [14••].)

week, open label study ($n = 287$) assessing the safety and tolerability of omalizumab retreatment (a second ragweed season) in patients who received omalizumab in earlier studies (Table 3).

In this study extension, the use of rescue medications was lower than the original core study numbers (29.3% vs 55.2%, respectively) in patients receiving omalizumab (300 mg). In comparing data between studies, the reduction in serum free IgE levels in the extension study was equivalent to that achieved in the initial study, regardless of whether patients were dosed once every 4 weeks or once every 3 weeks. The general incidence and severity of adverse events (study-related) were similar between the studies, and serum-free IgE levels in the follow-up study were reduced to levels associated with symptom reduction. Treatment was well tolerated, and there were no signs of significant immunologic reactions to omalizumab [24]. Therefore, exposure to omalizumab over a several-year period did not cause the formation of antibodies to anti-IgE.

Combination therapy

Another clinical reality of treatment with anti-IgE therapy for allergic rhinitis is that it will be an add-on therapy and can be combined with allergen-specific immunotherapy. Regarding this issue and to provide data from patients on concomitant therapy for allergic rhinitis, Kuehr *et al.* [22••] studied a total of 221 patients (ages 6 to 17) with SAR (birch pollen, grass pollen) who were on concomitant allergen-specific immunotherapy (SIT). The study was conducted through both a birch pollen season and a grass pollen season. Each subject was started on SIT-birch or SIT-grass, and either omalizumab or placebo was started before and maintained during the anticipated pollen seasons (a total of 24 weeks).

Patients were randomized to one of four treatment arms. For at least 14 weeks before the start of the birch pollen season, two of the groups (A and B) received SIT-birch given subcutaneously; the other 2 groups (C and D) received SIT-grass pollen. The mean cumulative dose of SIT-birch allergen extracts administered before the birch season was 394,300 U subcutaneously (SQ); the mean cumulative dose of SIT-grass allergen extracts administered before the grass season was 478,000 U SQ. After 12 weeks of SIT titration, placebo (A and C) or omalizumab (B and D) was added for 24 weeks.

Overall, combination therapy (SIT and omalizumab) reduced symptom load over the two-pollen seasons by 48% ($P < 0.001$) versus SIT alone. In either season, two of the four groups were receiving unrelated SIT and were considered "placebo" controls for analysis purposes. Per season, those receiving combination therapy with omalizumab in addition to SIT (whether related or not) saw reductions in symptom loads ranging from 32% to 71%, versus placebo controls (Fig. 2) [22••].

Researchers determined that omalizumab provided additional clinical benefit in both pollen seasons, whether there was coverage by related SIT or not, and concluded that combination therapy might prove useful for the treatment of allergic rhinitis in patients with multiple sensitivities [22••]. As a logical extension of these observations, it is possible that omalizumab might make initial doses of SIT safer, allowing wider application of rush immunotherapy.

Discussion

Studies of standard therapy for allergic rhinitis in patients with comorbid asthma have shown that improvement in the status of allergic rhinitis leads to improvement in asthma status. Accordingly, considering the mechanisms of action and pharmacodynamics of omalizumab, and the mechanisms involved in allergic rhinitis, whether comorbid with allergic asthma or not, the possibility that omalizumab will reduce symptoms of concomitant allergic rhinitis is likely. Additionally, patients with severe allergic rhinitis who are receiving SIT, but whose response is inadequate, might benefit from the addition of omalizumab. It is logical to anticipate that with omalizumab reducing circulating free IgE and SIT reducing allergen specific IgE, the agents might act additively or synergistically. Therefore, once omalizumab is available for use in treating allergic rhinitis, it is likely that it will be combined with SIT.

Table 2. Relationship between clinical efficacy variables and free IgE concentration groups (all treated subjects)

Efficacy variable (entire postrandomization period)	Free IgE concentration group	Patients, *n*	Mean	LSM difference (SE) relative to group 4	*P* value relative to group 4
Average daily nasal	1: 25 ng/mL	113	0.68	-0.37 (0.08)	<.001
symptom severity	2: >25–50 ng/mL	48	0.77	-0.25 (0.10)	0.01
score	3: >50–150 ng/mL	33	0.86	-0.20 (0.11)	0.056
	4: >150 ng/mL	54	1.03		
Average daily number	1: 25 ng/mL	113	0.46	-1.07 (0.18)	<.001
of tablets of rescue	2: >25–50 ng/mL	49	0.58	-0.84 (0.21)	<.001
antihistamine	3: >50–150 ng/mL	33	0.87	-0.64 (0.24)	0.008
	4: >150 ng/mL	54	1.49		
Proportion of days with	1: 25 ng/mL	113	0.22	-0.27 (0.05)	<.001
SAR medication use	2: >25–50 ng/mL	49	0.27	-0.22 (0.06)	<.001
	3: >50–150 ng/mL	33	0.37	-0.13 (0.06)	0.041
	4: >150 ng/mL	54	0.49		

LSM—least-squares mean; SAR—seasonal allergic rhinitis.
Adapted from Adelroth *et al.* [21].

Table 3. Severity of all adverse events in the retreatment trial compared with selected groups from core study

	Retreatment trial			Core trial*	
	Omalizumab 300 mg every 4 wks	Omalizumab 300 mg every 4 wks	All	Omalizumab 300 mg every 3 and 4 wks	Placebo
Patients, *n*	182	105	287	129	136
Severity of adverse events					
Mild	36 (19.8)	19 (18.1)	55 (19.2)	22 (17.1)	25 (18.4)
Moderate	46 (25.3)	22 (21.0)	68 (23.7)	34 (26.4)	45 (33.1)
Severe	9 (4.9)	4 (3.8)	13 (4.5)	5 (3.9)	8 (5.9)

*Data on file, Novartis (Basel, Switzerland).
Adapted from Nayak *et al.* [24].

Likelihood of monotherapy versus combination therapy

In the placebo-controlled studies cited earlier, omalizumab monotherapy has demonstrated effectiveness when used at appropriate doses and clinical effects correlated with serum-free IgE level reductions. However, patients in the trials to date were permitted rescue medications, and some did use them, suggesting that doses of anti-IgE therapy employed as monotherapy did not by themselves completely reduce the symptoms of SAR or PAR. Researchers commented that not enough subjects had serum-free IgE levels lowered to appropriate amounts to determine significance, and, therefore, efficacy as monotherapy could not be determined.

The greater likelihood is that omalizumab, once approved for use in patients with allergic rhinitis, will find its greatest use in combination therapy for those who do not respond successfully to standard therapies. The combination might be with existing oral or inhaled therapies, as seen in the studies using rescue oral antihistamines or inhaled glucocorticoids. However, in cases of moderate-to-severe allergic rhinitis symptoms refractory to oral or inhaled therapy, or in patients with comorbid allergic asthma of similar severity, the combination might be with SIT, as demonstrated in the Kuehr *et al.* study [22••]. SIT has been shown to be effective in many reported studies over many decades but in the few studies assessing SIT when given in combination with omalizumab, the patients' conditions were significantly improved by omalizumab.

As additional rationale for omalizumab combination therapy with SIT, consider that patients with allergic rhinitis often have multiple allergies, some of which might never be identified exactly. Without SIT, the unidentified allergens continue to prompt the IgE allergic response, further complicating the patient's condition. Omalizumab is a broad-based, allergen-nonspecific therapy, reducing serum-free IgE levels and preventing IgE binding to high-

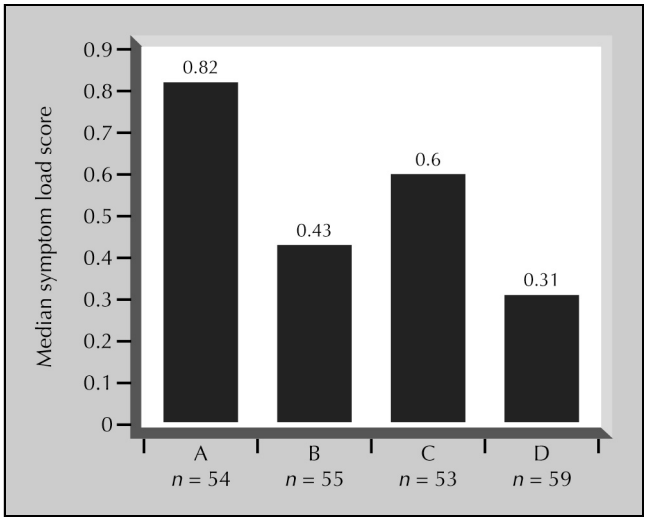

Figure 2. Effect of omalizumab on SIT treatment of birch- or grass-pollen–sensitive patients. Key: Values = median "symptom load" score (sum of the mean daily symptom severity score plus the mean daily rescue medication score). Symptom severity score: A 4-point severity scale (0 = none; 3 = severe); itchy, runny, or stuffy nose or sneezing; itchy, watery, or red eyes; recorded daily. Rescue medication score: A 4-point scale (0 = no rhinitis medication; 1 = topical nasal, ocular, or lung treatment apart from corticosteroids; 2 = systemic antihistamines; 3 = systemic or topical corticosteroids for nose or lung), recorded daily. If more than one rescue medication per day, only the maximal-score medication recorded. SIT—allergen-specific immunotherapy. *A*—SIT birch + placebo; *B*—SIT birch + omalizumab ($P < 0.001$); *C*—SIT grass + placebo; *D*—SIT grass + omalizumab ($P < 0.001$). (*Adapted from* Kuehr *et al*. [22••].)

affinity receptors, regardless of the inducing allergens. It not only has the capacity to be effective against the IgE produced in response to unidentified allergens, as complementary therapy, but might facilitate safer immunotherapy by lowering the risk of anaphylaxis.

Patient compliance issues

Patients with moderate-to-severe allergic rhinitis symptoms, especially those with multiple sensitivities who are on immunotherapy, are already used to the idea that they need injections on a frequent basis. For this reason, and because omalizumab has a mild adverse event profile, patients whose conditions warrant the addition of injectable anti-IgE therapy with omalizumab should not find compliance an issue.

Conclusions

Principal to the immediate allergic response are IgE-mediated mast cell and basophil degranulation and the subsequent production and release of mediators that promote inflammation and edema, giving rise to the primary symptoms of allergic rhinitis and asthma. Anti-IgE therapy in the form of the recombinant humanized murine monoclonal antibody omalizumab, which is currently approved for use in the treatment of moderate-to-severe allergic asthma, holds promise in the treatment of allergic rhinitis, as well. Placebo-controlled monotherapy studies have shown significant decreases in serum-free IgE that correlate to the reductions in allergic rhinitis symptom severity in these patients. However, additional, well-designed, comparative trials of omalizumab in conjunction with oral antihistamine and nasally inhaled glucocorticoid therapy, or with allergen-specific immunotherapy, represent the next steps necessary in determining the usefulness of omalizumab in treating allergic rhinitis patients under real-world conditions. Initial efforts in those respects have been promising, but more studies are required. Meanwhile, because preliminary trials of omalizumab in patients with comorbid allergic asthma and allergic rhinitis have shown significant parallel improvement in both conditions, the potential that providers will prescribe omalizumab for use in treating both diseases is likely.

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- •• Of major importance

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