

Effect of pretreatment with omalizumab on the tolerability of specific immunotherapy in allergic asthma

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Background: Although specific immunotherapy is a valuable treatment option for patients with allergic asthma, the potential for systemic allergic reactions has limited its use, especially for patients with symptomatic disease.

Objective: To evaluate omalizumab's effect on the tolerability of specific immunotherapy in patients with symptomatic persistent asthma not adequately controlled with inhaled corticosteroids.

Methods: This multicenter, double-blind, parallel-group study randomized patients to treatment with omalizumab or placebo, after which they received specific immunotherapy to at least 1 of 3 perennial aeroallergens (cat, dog, and house dust mite) according to a 4-week, 18-injection cluster regimen, followed by 7 weeks of maintenance therapy. The primary efficacy variable, a systemic allergic reaction after immunotherapy, was analyzed by using the Cochrane-Mantel-Haenszel test.

Results: A total of 248 randomized patients (126 omalizumab, 122 placebo) received at least 1 dose of immunotherapy and were evaluated for efficacy. Patients receiving omalizumab experienced significantly fewer systemic allergic reactions to immunotherapy than those receiving placebo (17/126 [13.5%] vs 32/122 [26.2%]; $P = .017$; 95% CI, 2.91% to 22.56%) and had fewer respiratory-related (grade 3) systemic allergic reactions (6 vs 24, respectively). Grade 4 reactions were reported in 2 patients in each group. More omalizumab patients were able to reach the target maintenance immunotherapy dose (110 [87.3%] vs 88 [72.1%], respectively; $P = .004$).

Conclusion: Use of omalizumab in patients whose asthma was symptomatic despite use of inhaled corticosteroids was associated with fewer systemic allergic reactions to specific immunotherapy and enabled more patients to achieve the target

immunotherapy maintenance dose. (*J Allergy Clin Immunol* 2010;125:383-9.)

Key words: Omalizumab, allergic asthma, immunotherapy, systemic allergic reactions, cluster immunotherapy, cat, dog, house dust mites

Allergen-specific immunotherapy (SIT) can be an effective adjunct in the treatment of both allergic rhinitis and allergic asthma.¹⁻³ The advantage of this distinct modality, which produces immunomodulation and is often used in conjunction with pharmacotherapy, is that it may provide beneficial effects that persist for years after treatment is discontinued. However, the frequency and duration of therapy and the potential for systemic allergic reactions (SARs) have limited its use, especially in patients with symptomatic persistent asthma, who are at greater risk for severe reactions.⁴

Omalizumab is an anti-IgE recombinant humanized mAb that decreases the concentration of IgE antibody and has also been shown to reduce FcεR1 expression on basophils and dendritic cells.^{5,6} The addition of omalizumab to the treatment of persistent allergic asthma inadequately controlled with inhaled corticosteroids has been demonstrated to improve asthma control by reducing the number of asthma exacerbations and improving daytime and nocturnal symptoms.^{7,8}

In a study of patients with ragweed-sensitive allergic rhinitis, the effects of pretreatment with omalizumab on the efficacy and safety of SIT was investigated. The efficacy of combined therapy was better than that of either therapy alone or placebo. The rate of subcutaneous allergic reactions during rush immunotherapy was 56.4% (SIT alone) and 33.3% (SIT + omalizumab).⁹ A *post hoc* analysis of study patients with anaphylactic reactions (defined as reactions involving 2 or more organ systems concurrently and/or severe enough to require epinephrine) revealed a rate of 25.6% for SIT alone versus 5.6% for SIT + omalizumab.⁹ However, patients with allergic asthma were excluded from this study. In a separate study, omalizumab reduced the symptom load (defined as the sum of daily symptom severity scores plus rescue medication use), regardless of the nature of the allergen, when combined with specific immunotherapy in polysensitized children and adolescents with seasonal allergic rhinitis.¹⁰

To evaluate the effect of omalizumab on SARs to subcutaneous SIT in those at higher risk of such reactions, the current study was designed to investigate the use of omalizumab as a pretreatment for patients with at least moderate persistent allergic asthma who were candidates for allergen immunotherapy and would otherwise qualify for treatment with omalizumab.

A cluster dosing protocol was chosen to initiate subcutaneous SIT in the current study.¹¹ Cluster regimens have been used to treat patients with seasonal allergic rhinitis and asthma.¹² They facilitate more rapid achievement of therapeutically effective doses of SIT compared with conventional schedules and have been reported to have less risk of systemic reactions than rush protocols.¹³

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Abbreviations used

AE: Adverse event
 CMH: Cochran-Mantel-Haenszel
 HDM: House dust mite
 ICS: Inhaled corticosteroid
 PEFr: Peak expiratory flow rate
 SAR: Systemic allergic reaction
 SIT: Specific immunotherapy

METHODS**Patients**

Patients ($n = 275$) age 18 to 55 years with at least moderate persistent allergic asthma (consistent with Global Initiative for Asthma guidelines)¹⁴ inadequately controlled with inhaled corticosteroids (ICSs) were enrolled. To detect patients with unstable asthma, a daily asthma diary including symptom scores, peak expiratory flow rate (PEFR), rescue β -agonist use, and health care use was completed. To limit the risk of immunotherapy at baseline, patients were required to have a minimum FEV₁ of at least 75% predicted. A daily asthma diary was completed during the screening period and also included symptom scores, PEFr, rescue β -agonist use, and health care use. Patients with unstable asthma on the basis of a mean total symptom score >3 (on a 9-point scale), mean nocturnal symptom score >0.5 , or mean PEFr variability $>20\%$ were excluded, as were those with a history of an asthma exacerbation requiring either treatment with systemic corticosteroids within the preceding 3 months or hospitalization within 6 months. A history of allergic sensitivity as evidenced by a positive skin prick test defined by a wheal ≥ 5 mm greater than that of the saline control to at least 1 of 3 perennial aeroallergens (house dust mite [HDM], dog, or cat) at screening or within the preceding year was required. The study was planned and performed according to the principles of Good Clinical Practice, the declaration of Helsinki, and national laws and regulations about clinical studies. Before its implementation, the study received written approval from the Institutional Review Board, the Independent Ethics Committee, and/or the Research Ethics Board. Written informed consent was obtained from each patient.

Study design

This was a 26-week, randomized, double-blind, parallel-group, placebo-controlled study that consisted of 4 periods: screening (2 weeks), treatment with omalizumab or placebo (16 weeks), cluster SIT (4 weeks, including 3 weeks overlap with omalizumab/placebo), and maintenance SIT (7 weeks). A schematic of the study design is shown in Fig 1.

Omalizumab

Study patients were randomized 1:1 to receive 16 weeks of subcutaneous omalizumab or matching placebo. The randomization was stratified according to single-allergen or multiple-allergen sensitivity. The dose of omalizumab was determined according to the dosing algorithm contained in the Xolair product insert (Novartis Pharmaceuticals Corp, East Hanover, NJ; Genentech USA, Inc, South San Francisco, Calif), ensuring that a minimum dose of 0.016 mg/kg/IgE (IU/mL) per month was delivered every 2 or 4 weeks, depending on baseline weight and serum IgE. Both omalizumab and matching placebo were supplied by Novartis as lyophilized powder in a single-use, 5-mL vial for subcutaneous administration on reconstitution. Because reconstituted placebo vials did not exactly match those containing omalizumab, a study technician not involved with any patient study assessments was responsible for preparing and administering all injections.

Specific immunotherapy

After 13 weeks of omalizumab/placebo treatment, individually customized extracts of perennial aeroallergens for SIT (cat and HDM [*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*] extracts from Greer

Laboratories, Lenoir, NC; dog extract from Hollister-Stier, Spokane, Wash) based on the patient's skin prick test results were administered according to a 4-week, 18-injection cluster regimen followed by 7 weeks of weekly maintenance therapy. The targeted maintenance dose of extract contained 15 μ g Fel d 1 or Can f 1, and 5 μ g Der f 1 and 3.5 μ g Der p 1. Pretreatment with oral antihistamines was permitted at the discretion of the investigator. Before each SIT injection, PEFr and vital signs (pulse, respiratory rate, and blood pressure) were measured. Vital signs and PEFr were assessed 30 minutes after each injection and 60 minutes after the last SIT dose of the day.

Study outcomes

The primary efficacy variable was a SAR within 1 hour after injection of SIT. SARs were graded on a 4-point scale adapted from Müller¹⁵:

- Grade 1: skin (generalized urticaria, itching, or erythema)
- Grade 2: gastrointestinal (stomach pain, nausea, or vomiting)
- Grade 3: respiratory (clinically significant nasal symptoms and/or dyspnea, wheezing, persistent cough, chest tightness, stridor, or hoarseness) or angioedema of the lips or tongue
- Grade 4: cardiovascular (cyanosis, hypotension, collapse, arrhythmias, or angina pectoris)

Secondary efficacy variables included the severity of the first SAR to SIT, achievement of the target maintenance SIT dose, number of visits required to complete the cluster SIT regimen, and number of doses of rescue medications for managing SIT reactions. If a SAR occurred during period 3, the patient could be discontinued or remain in the study at the discretion of the investigator. However, at the next visit, the dose of immunotherapy was reduced to the last tolerated dose. If systemic symptoms recurred, the patient was discontinued. Patients who experienced a grade 4 (cardiovascular) SAR were discontinued from the study immediately. Participants who experienced any grade of a SAR during maintenance immunotherapy were also discontinued.

Statistical methods

The safety population consisted of all randomized patients who received at least 1 dose of study medication (ie, omalizumab or placebo). The efficacy population consisted of all randomized patients who completed period 2 and received at least 1 dose of immunotherapy.

The primary efficacy variable, a SAR to SIT, which occurred within 1 hour after the allergen injection, was analyzed for the efficacy population. The primary analysis time point was the end of period 4 (maintenance immunotherapy). Time to first SAR was summarized by Kaplan-Meier curves, and the 2 treatment groups were compared using the log-rank test.¹⁶ Time to first SAR for patients who discontinued from the study early (not related to a SAR to SIT) or patients who did not have a SAR by the end of the maintenance immunotherapy period was considered censored. At each specified time point, the difference in the proportion of patients with a SAR between the treatment groups was examined by using the large sample test of equality of survival probabilities.¹⁷

In addition, SAR (yes/no) was analyzed by using the Cochran-Mantel-Haenszel (CMH) test, adjusting for dosing regimen (every 4 weeks or every 2 weeks), perennial allergen sensitivity (single or multiple), and cat sensitivity (yes/no).¹⁸ A 95% CI for the difference in SAR rates between treatments was calculated by using the normal approximation to the binomial distribution. If after initiating immunotherapy, a patient discontinued the study prematurely and the reason on the case report form was "unsatisfactory therapeutic effect," the patient was considered as having had a SAR for the analysis.

Severity of the first systemic reaction and the number of visits required to complete the cluster SIT dosing regimen were each analyzed by using the van Elteren test, adjusting for dosing regimen (every 4 weeks or every 2 weeks), perennial allergen sensitivity (single or multiple), and cat sensitivity (yes/no).¹⁸ The analysis of achievement of target maintenance immunotherapy dose was similar to that of the primary efficacy variable, using the log-rank test and CMH test. The number of doses of rescue medication for each treatment group was summarized.

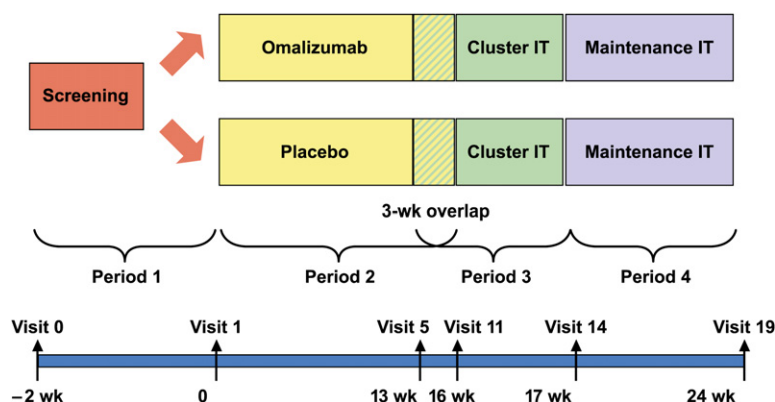


FIG 1. Study design.

TABLE I. Patient baseline demographics (safety population)

Patient Demographic	Placebo n = 136	Omalizumab n = 139	All patients n = 275
Age (y), mean $\pm$ SD	38.2 $\pm$ 10.02	38.2 $\pm$ 9.89	38.2 $\pm$ 9.93
Sex, n (%)			
Male	37 (27.2)	51 (36.7)	88 (32.0)
Female	99 (72.8)	88 (63.3)	187 (68.0)
Race, n (%)			
White	112 (82.4)	118 (84.9)	230 (83.6)
Black	11 (8.1)	17 (12.2)	28 (10.2)
Asian	0 (0.0)	1 (0.7)	1 (0.4)
Other	13 (9.6)	3 (2.2)	16 (5.8)
Height (cm), mean $\pm$ SD	167.3 $\pm$ 9.40	169.7 $\pm$ 10.50	168.5 $\pm$ 10.03
Weight (kg), mean $\pm$ SD	82.80 $\pm$ 19.077	84.72 $\pm$ 19.579	83.77 $\pm$ 19.321

For the sample size calculation, it was assumed that the proportion of patients with a SAR at the end of period 4 would be 0.24 and 0.06 in the placebo and omalizumab groups, respectively. Using an allocation ratio of 1:1, a 2-sided log-rank test, a significance level of .05, a statistical power of 0.95, and an assumed overall dropout rate of 0.20, approximately 274 randomized patients were required.¹⁹

All statistical tests were conducted against a 2-sided alternative hypothesis using a significance level of .05. All statistical analyses were performed by using SAS software, version 9.1 (SAS Statistics, Cary, NC).

RESULTS

A total of 275 patients were randomized to treatment, 136 to placebo and 139 to omalizumab. Demographic information is summarized for the overall safety population and by treatment group in Table I. More women than men were enrolled. The 2 treatment groups were similar in age and weight (Table I) as well as in mean baseline total IgE, symptom scores, FEV₁, and other characteristics (Table II). Most patients had a positive skin test result to 2 or more perennial aeroallergens and were sensitive to cat dander. Therefore, most patients received more than 1 allergen in their SIT mixture (20% received a single allergen, 34% received any 2, and 46% received all 3 allergens).

More patients in the omalizumab group (105 patients; 75.5%) than in the placebo group (83 patients; 61.0%) completed the study. The most common reason for early withdrawal from the study in the placebo group was occurrence of a SAR (21 patients).

Efficacy analysis

Overall, 49 of the 248 patients (19.8%) in the efficacy population experienced a SAR within 1 hour of an injection with SIT: 32 (26.2%) in the placebo group and 17 (13.5%) in the omalizumab group. The difference between treatment groups was significant ($P = .006$, using log-rank test). A significant difference in the proportion of patients with a SAR was also observed between the treatment groups when adjustments for dosing regimen (every 4 weeks or every 2 weeks), single or multiple perennial allergen sensitivity, and sensitivity to cat allergens (yes/no) were included using the CMH test ($P = .017$). The estimated treatment difference in the proportion of patients who experienced a SAR was 0.127, with a 95% CI of 0.029 to 0.226 (using the normal approximation to the binomial distribution). The proportion of patients who had their first SAR was estimated over time by using the Kaplan-Meier method (Fig 2). Cluster immunotherapy was initiated at day 85. By day 98, 13 patients in the placebo group and 3 patients in the omalizumab treatment group had experienced a SAR. This difference was significant ($P = .007$) and remained significant for the duration of the study. Most patients' first SARs occurred during the cluster immunotherapy period, while SIT doses were being escalated (43/49 SARs, 31 placebo, 12 omalizumab).

Most patients experiencing a SAR had respiratory-related (grade 3) symptoms (30/49 patients; 61.2%; Table III). Twenty-four of those 30 patients were in the placebo group and 6 in the omalizumab treatment group. While the difference in the number

TABLE II. Patient baseline characteristics (safety population)

Patient Characteristic	Placebo n = 136	Omalizumab n = 139	All patients n = 275
Perennial allergen sensitivity, n (%)			
Single	26 (19.1)	29 (20.9)	55 (20.0)
Multiple	110 (80.9)	110 (79.1)	220 (80.0)
Cat	114 (83.8)	113 (81.3)	227 (82.5)
Dog	92 (67.7)	92 (66.2)	184 (66.9)
HDM	103 (75.7)	108 (77.7)	211 (76.7)
Total IgE at screening (IU/mL)			
Mean $\pm$ SD	185.70 $\pm$ 138.331	167.76 $\pm$ 137.628	176.63 $\pm$ 138.018
Median	144.55	119.20	128.60
(Minimum, maximum)	(30.6, 681.0)	(26.9, 657.9)	(26.9, 681.0)
Average total asthma symptom score*			
Mean $\pm$ SD	1.17 $\pm$ 0.88	1.15 $\pm$ 0.92	1.16 $\pm$ 0.90
Median	1.0	1.1	1.0
(Minimum, maximum)	(0, 4)	(0, 4)	(0, 4)
Average number of rescue puffs of β -agonist*			
Mean $\pm$ SD	1.08 $\pm$ 1.24	0.89 $\pm$ 0.98	0.98 $\pm$ 1.12
Median	0.6	0.5	0.5
(Minimum, maximum)	(0, 5)	(0, 6)	(0, 6)
Baseline FEV ₁ (L)			
Mean $\pm$ SD	2.836 $\pm$ 0.6177	2.934 $\pm$ 0.6872	2.885 $\pm$ 0.6544
Median	2.725	2.780	2.770
(Minimum, maximum)	(1.60, 4.85)	(1.58, 4.83)	(1.58, 4.85)
FEV ₁ % predicted			
n	131	134	265
Mean $\pm$ SD	88.1 $\pm$ 11.64	86.1 $\pm$ 11.18	87.1 $\pm$ 11.43
Median	88.0	84.5	86.0
(Minimum, maximum)	(50, 120)	(61, 129)	(50, 129)
FVC (L)			
n	134	134	268
Mean $\pm$ SD	3.799 $\pm$ 0.7925	4.009 $\pm$ 1.0098	3.904 $\pm$ 0.9121
Median	3.670	3.730	3.690
(Minimum, maximum)	(2.17, 6.56)	(2.28, 6.45)	(2.17, 6.56)
FEF _{25%-75%} (L/s)			
n	134	134	268
Mean $\pm$ SD	2.523 $\pm$ 0.9070	2.487 $\pm$ 0.8433	2.505 $\pm$ 0.8743
Median	2.455	2.320	2.430
(Minimum, maximum)	(0.69, 5.88)	(1.09, 5.80)	(0.69, 5.88)
Dosing regimen, n (%)			
2-wk	70 (51.5)	67 (48.2)	137 (49.8)
4-wk	66 (48.5)	72 (51.8)	138 (50.2)

FEF_{25%-75%}, Forced expiratory flow 25% to 75%; FVC, forced vital capacity.

*Data are for the efficacy population and are daily averages over the 14-day screening period.

of grade 3 SARs was clinically meaningful, the difference in the severity of the first SAR between treatment groups trended to, but did not reach, statistical significance ($P = .192$; $n = 49$; van Elteren test). Grade 4 SARs were reported in 4 patients (2 placebo, 2 omalizumab). One patient (placebo) experienced hypotension (76/38 mm Hg), whereas the other 3 reported various signs/symptoms that included lightheadedness, dizziness, and peripheral cyanosis. Symptoms consistent with a possible SAR occurred after the predefined observation period of 1 hour in 5 patients (4 placebo [one grade 1 and three grade 3] and 1 omalizumab [grade 3]).

More patients achieved target maintenance SIT dose in the omalizumab treatment group (110 patients; 87.3%) than in the placebo group (88 patients; 72.1%). After adjusting for dosing regimen (every 4 weeks or every 2 weeks), perennial allergen sensitivity (single or multiple), and sensitivity to cats (yes or no), there were significant differences, in favor of omalizumab, in the number of visits required to complete the cluster SIT regimen (ie, to achieve the target maintenance SIT dose; $P = .004$; van Elteren test).

Treatment with omalizumab decreased the proportion of patients receiving at least 1 rescue medication during SIT (10.3% for omalizumab vs 24.6% for placebo). Of the 126 total doses of rescue medication, 89 were administered to patients in the placebo group. Thirty-one doses of epinephrine were administered: 9 doses to patients in the omalizumab group and 22 doses to those in the placebo group (Table IV).

Exploratory analyses

A *post hoc* subgroup analysis was conducted to determine whether antihistamine pretreatment to SIT affected the rate of SARs. Overall, antihistamines were used in 87 (35%) patients in the efficacy population. SARs occurred in 12.0% (6/50) of patients in the omalizumab group pretreated with antihistamines versus 24.3% (9/37) of patients in the placebo group. In patients not given antihistamines, SARs occurred in 14.5% (11/76) of omalizumab patients versus 27.1% (23/85) of placebo patients.

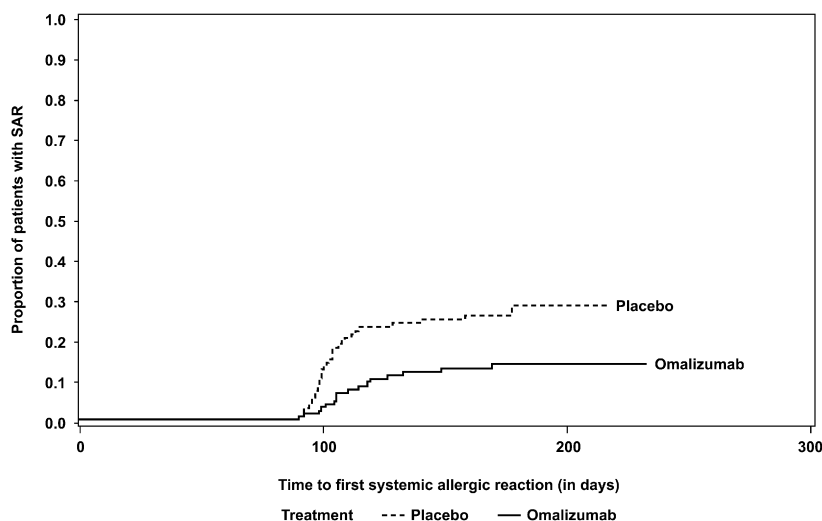


FIG 2. Time (in days) to first SAR using the Kaplan-Meier method (efficacy population).

TABLE III. Analysis of the severity of the first SAR among patients with this event (efficacy population)

Severity of first SAR*	Placebo n = 32	Omalizumab n = 17
Grade 1 (skin symptoms)	6	7
Grade 2 (gastrointestinal symptoms)	0	2
Grade 3 (respiratory symptoms)	24	6
Grade 4 (cardiovascular symptoms)	2	2

* $P = .192$ for placebo vs omalizumab. The P value was calculated from the van Elteren test, adjusting for dosing regimen (every 4 weeks or every 2 weeks), perennial allergen sensitivity (single or multiple), and cat sensitivity (yes/no).

In the week before beginning cluster SIT, those patients pretreated with omalizumab had lower average total asthma symptom scores (mean, 0.46 vs 0.69, respectively) and lower average daily puffs of rescue β -agonist (mean, 0.45 vs 0.72, respectively) compared with patients who received placebo. The influence of markers of asthma control (total asthma symptom score, rescue puffs of β -agonists) was investigated *post hoc* to determine their effect on the incidence of grade 3 (respiratory) SARs. Among patients with an average total asthma score >0 in the week preceding the initiation of immunotherapy ($n = 128$), grade 3 respiratory SARs occurred in 2 of 57 (3.5%) omalizumab patients compared with 17 of 71 (23.9%) placebo patients. For those who had no symptoms in the week preceding SIT ($n = 116$), rates of grade 3 respiratory SARs were 5 of 68 or 7.4% (omalizumab) and 6 of 48 or 12.5% (placebo). Among patients with >0 average daily puffs of rescue β -agonist use in the week preceding SIT ($n = 120$), grade 3 respiratory SARs occurred in 1 of 58 (1.7%) omalizumab patients compared with 14 of 62 (22.6%) placebo patients. For those who did not use any puffs of rescue β -agonist in the week preceding cluster SIT ($n = 123$), 6 of 67 (9.0%) (omalizumab), and 9 of 56 (6.1%) (placebo) experienced grade 3 SARs.

The effect of omalizumab on local reactions during SIT was examined. The proportion of patients experiencing a local reaction was similar in the omalizumab and placebo groups (67/126 [53.2%] vs 60/122 [49.2%]; $P = .525$; 95% CI, -16.4%, 8.4%, respectively).

TABLE IV. Number of doses of rescue medications used for SARs to SIT (efficacy population)

No. doses of rescue medications for SARs*	Placebo n	Omalizumab n
No. of doses for all rescue medications	89	37
No. of doses of epinephrine	22	9
No. of doses of oral steroids	13	7
No. of doses of antihistamines	27	15
No. of doses of β -agonists	25	3

*One entry on the case report form page, "concomitant medications/significant nondrug therapies associated with immunotherapy," in response to the question, "Was this medication given in response to a systemic allergic reaction?" was considered equivalent to 1 dose of rescue medication for SIT reactions.

Safety

Omalizumab was well tolerated during the study. The most commonly reported adverse events (AEs) across treatment groups were injection site reaction (48 patients; 17.5%), injection site pruritus (43 patients; 15.6%), and injection site erythema (42 patients; 15.3%). The frequency of these events was generally similar between the treatment groups. Some AEs occurred more often in the placebo group, including worsening of asthma (8.8% vs 0.7% omalizumab) and sinusitis (9.6% vs 5.0% omalizumab). Serious AEs occurred in 7 patients (4 omalizumab, 3 placebo); none of the events were considered related to study drug. Serious AEs among the omalizumab patients included sexual abuse, staphylococcus cellulitis, rectal carcinoma (detected on day 69), and an induced abortion. Serious AEs among patients receiving placebo were a benign spinal cord neoplasm (detected on day 61), food-induced anaphylaxis, and a delayed SAR (occurred >1 hour after SIT dose). The frequency of having an AE that led to discontinuation was higher in the placebo group (9.6%) than in the omalizumab group (5.0%).

DISCUSSION

Individuals with allergic asthma who continue to experience symptoms despite use of ICSs may benefit from alternative

treatment options such as the addition of immunomodulators like omalizumab or SIT. In this study, pretreatment with omalizumab improved asthma symptoms and reduced rescue use of β -agonists while significantly reducing the proportion of patients who experienced a SAR to SIT; however, 17 (13.5%) patients in the omalizumab group experienced a SAR. In addition, omalizumab enabled more patients to achieve the target maintenance dose of immunotherapy. These results are especially relevant to physicians caring for patients with allergic asthma whose symptoms are inadequately controlled. Such patients may benefit from SIT, but guidelines advise against initiating immunotherapy because of an increased risk for SARs, especially grade 3 respiratory SARs.

The study findings are consistent with those of a previous study that investigated the use of omalizumab as pretreatment for ragweed rush SIT in patients with allergic rhinitis.⁹ However, the pattern of SARs in the current study was different; the predominant reaction was respiratory. This may be attributed to the nature of the study population, which consisted of patients having allergic asthma (patients with asthma were excluded in the study by Casale et al).⁹ Importantly, in the current study, omalizumab was associated with a clinically meaningful reduction in the number of patients who experienced a grade 3 respiratory SAR compared with placebo. Grade 4 cardiovascular SARs were rare in both treatment groups (occurring in 2 patients within each group). Most of the patients' SARs occurred during the cluster immunotherapy period. The maintenance SIT period was too short to allow observation of the incidence of SARs without the influence of treatment because of the 26-day half life of omalizumab.

Although 13 weeks of pretreatment with omalizumab markedly reduced the incidence of SARs, it was not totally protective. The highest incidence of SARs occurred during the early phases of SIT, while doses were being escalated (peak incidence of the first SAR occurred after the ninth dose of SIT; data not shown). The incomplete inhibition of SARs may reflect incomplete depletion of circulating free-IgE or the existence of allergen-specific IgE already bound to mast cells. Whether these responses were mediated by IgE, and to what degree depletion of IgE and/or reduction of Fc ϵ RI were achieved by the prescribed regimen at the time SIT was initiated, can only be speculated, because this was not directly assessed. In addition, there are individual variations in the sensitivity to antigen-provoked mediator release, and reactions may have been diminished but not abolished in some patients. Patient-dependent factors, including responsiveness to omalizumab, are not established or apparent from our study.

Patients were carefully selected for cluster SIT, and most reached the prescribed maintenance dose of SIT. Use of omalizumab further increased the percentage of patients who reached the targeted dose of SIT. The influence of asthma control on SAR rate was investigated. As might be expected, those patients receiving placebo who had persistent symptoms or used rescue β -agonist the week before initiation of SIT experienced a greater rate of SARs (particularly grade 3 respiratory-related SARs) than did those who were asymptomatic at the initiation of SIT.

Pretreatment with antihistamines had little effect on the rate of SARs. Several studies have shown that pretreatment with corticosteroids and/or antihistamines reduces the rate of reactions to rush SIT by more than 50%.¹³ In 1 study that investigated use of antihistamines as pretreatment to cluster SIT, reactions decreased from 79% to 33%.²⁰ Contrary to this previous experience, in this

study the rate of SARs in patients who did or did not receive pretreatment with antihistamines in both the omalizumab and placebo groups was similar. Although interesting, these observations are based on a *post hoc* analysis. Omalizumab may have provided broader protection against histamine-induced events by preventing more general release of mast cell vasoactive mediators, thus obviating any potential effect of antihistamines. The placebo group would have been the one to test this hypothesis best and may have been underpowered for this outcome. Finally, antihistamine use was not specifically required by the protocol, but was at the discretion of the investigator. This may have introduced a practice bias regarding which patients received antihistamine pretreatment.

Omalizumab was well tolerated in the study. The rates of AEs and serious AEs were similar to those observed in previous omalizumab clinical trials including use of omalizumab by patients with allergic rhinitis undergoing SIT.^{9,10,21,22} No serious AEs were attributed to the study drug. In conclusion, omalizumab pretreatment of patients with persistent symptomatic allergic asthma despite treatment with ICSs facilitated the use of SIT by decreasing the likelihood of SARs and enabling more patients to achieve a target immunotherapy maintenance dose.

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Clinical implications: Omalizumab pretreatment of patients with persistent symptomatic allergic asthma despite treatment with inhaled corticosteroids facilitates the use of specific immunotherapy by decreasing the likelihood of SARs.

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