Omalizumab pretreatment decreases acute reactions after rush immunotherapy for ragweed-induced seasonal allergic rhinitis

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Background: Rush immunotherapy (RIT) presents an attractive alternative to standard immunotherapy. However, RIT carries a much greater risk of acute allergic reactions, including anaphylaxis.

Objectives: We hypothesized that omalizumab, a humanized monoclonal anti-IgE antibody, would be effective in enhancing both safety and efficacy of RIT.

Methods: Adult patients with ragweed allergic rhinitis were enrolled in a 3-center, 4-arm, double-blind, parallel-group, placebo-controlled trial. Patients received either 9 weeks of omalizumab (0.016 mg/kg/IgE [IU/mL]/mo) or placebo, followed by 1-day rush (maximal dose 1.2-4.0 μg Amb a 1) or placebo immunotherapy, then 12 weeks of omalizumab or placebo plus immunotherapy.

Results: Of the 159 patients enrolled, 123 completed all treatments. Ragweed-specific IgG levels increased >11-fold in immunotherapy patients, and free IgE levels declined >10-fold in omalizumab patients. Patients receiving omalizumab plus immunotherapy had fewer adverse events than those receiving immunotherapy alone. Post hoc analysis of groups receiving immunotherapy demonstrated that addition of omalizumab resulted in a 5-fold decrease in risk of anaphylaxis caused by RIT (odds ratio, 0.17; $P = .026$). On an intent-to-treat basis, patients receiving both omalizumab and immunotherapy showed a significant improvement in severity scores during the ragweed season compared with those receiving immunotherapy alone (0.69 vs 0.86; $P = .044$).

Conclusion: Omalizumab pretreatment enhances the safety of RIT for ragweed allergic rhinitis. Furthermore, combined therapy with omalizumab and allergen immunotherapy may be an effective strategy to permit more rapid and higher doses of allergen immunotherapy to be given more safely and with greater efficacy to patients with allergic diseases. (J Allergy Clin Immunol 2006;117:134-40.)

Key words: *Allergy, immunotherapy, omalizumab, IgE, IgG, ragweed, rhinitis, clinical trial*

Allergen immunotherapy has been used for more than 90 years for the management of allergic disorders, including seasonal and perennial allergic rhinitis, allergic asthma, and *Hymenoptera* sensitivity.[1-5] It is the only antigen-specific immunomodulatory treatment routinely available to clinicians. Unlike other current treatments for allergic disorders, immunotherapy provides long-term benefits and modifies the natural history of allergic diseases, preventing the development of neosensitization and asthma in children.[5-7] Among its biological effects, conventional immunotherapy prevents a seasonal rise in allergen-specific IgE levels while increasing levels of allergen-specific IgG, particularly IgG_4. IgG_4 blocks allergen-induced IgE-dependent histamine release by basophils[8] and suppresses allergen-specific T-cell responses *in vitro* by inhibiting the binding of allergen-IgE complexes to antigen presenting cells.[9]

However, despite its clinical efficacy and tolerogenic effects, the use of allergen-specific immunotherapy has been limited by the potential for serious adverse reactions, including anaphylaxis,[10,11] and difficulty with patient

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Abbreviations used
NIAID: National Institute of Allergy and Infectious Diseases
OR: Odds ratio
RIT: Rush immunotherapy
RS: Ragweed-specific

compliance because of the extended treatment duration required.[12,13] Rush immunotherapy (RIT) offers an attractive alternative, providing better compliance because of its more immediate efficacy, as well as greater cost-effectiveness. However, rush protocols are associated with a significantly increased frequency of systemic reactions, from <5% to >65%.[14-17] Because of the accelerated dosing schedule, early increases in total and specific IgE concentrations have been observed after RIT[18] that could predispose individuals to allergic reactions during the subsequent build-up and early maintenance phase of immunotherapy.

Omalizumab (Xolair; Novartis Pharmaceuticals Corp, East Hanover NJ, Genentech Inc, South San Francisco, Calif, Tanox Inc, Houston, Tex) is a humanized monoclonal anti-IgE antibody with established efficacy for moderate-to-severe allergic asthma and intermittent (seasonal) and persistent (perennial) allergic rhinitis.[19] In addition to causing a rapid and pronounced decrease in serum IgE levels that is correlated with an improvement in symptom severity, omalizumab reduces free IgE and increases total IgE, and downregulates the expression of IgE receptors (FcεRI) on mast cells and basophils.[20]

We hypothesized that administration of omalizumab before and during allergen-specific immunotherapy would lead to a decrease in serum free IgE levels and reduced FcεR1 expression, resulting in increased safety and efficacy. To evaluate this possibility, a 3-center, double-blind, placebo-controlled trial in patients with ragweed-induced seasonal allergic rhinitis was conducted to examine whether omalizumab given 9 weeks before rush allergen immunotherapy, followed by 12 weeks of dual omalizumab and immunotherapy, is safer and more effective than immunotherapy alone.

METHODS

Patients

Patients between ages 18 and 50 years with a minimum 2-year history of ragweed allergic rhinitis and no recent immunotherapy were enrolled at 3 US centers where ragweed seasons were historically similar in timing and severity. The protocol was reviewed and approved by the National Institute of Allergy and Infectious Diseases (NIAID) Allergy and Asthma Data and Safety Monitoring Board and the Institutional Review Boards at each institution. All patients signed an informed consent. Patients were required to have a positive skin prick test result to short ragweed extract (ALK-Abelló, Round Rock, Tex) as defined by a wheal 3 mm greater in diameter than saline control, and a baseline serum IgE level of >10 and <700 IU/mL. Asthma and the concomitant use of medications that could affect study outcomes were exclusionary criteria (see this article's Table E1 in the Online Repository at www.jacionline.org for all inclusion and exclusion criteria).

Study design

This was a randomized, double-blind, placebo-controlled study. Patients were randomly assigned to 4 treatment groups (1:1:1:1) as shown in Fig 1.

Pretreatment with omalizumab (weeks −9 to 0), in which patients received either omalizumab or placebo, lasted 9 weeks to optimize the potential for protection against immunotherapy-induced acute allergic reactions.[20,21] One-day RIT (week 0, approximately the first week of July 2003) was completed at least 3 weeks before the start of the ragweed season. After RIT, patients had 12 weekly visits to receive immunotherapy and omalizumab injections (weeks 0-12). Patients had 3 additional follow-up visits (weeks 13, 19, and 31) after the end of the ragweed season (weeks 13-31).

Patients received 180 mg fexofenadine the night before and 1 hour before RIT[16,22] and were permitted 60 mg fexofenadine as rescue medication after experiencing moderate symptoms.

Omalizumab

Omalizumab (Xolair) or a matching placebo was administered subcutaneously to patients during the 9-week pretreatment phase and 12-week immunotherapy phase. Minimum omalizumab dose was 0.016 mg/kg/IgE (IU/mL)/mo every 2 or 4 weeks, depending on weight and baseline IgE levels.

Immunotherapy

On the day of RIT, patients received 6 injections of either placebo or aqueous short ragweed extract (ALK-Abelló; and Greer Laboratories, Lenoir, NC). Ragweed dosing started with a diluted extract containing 0.012 μg of Amb a 1 and, over a 3-hour period, reached a maximum of 100-fold greater dose, containing 1.2 mcg of Amb a 1.[16,22] As discussed in this article, some subjects received 2 additional injections of ragweed extract, with doses of Amb a 1 reaching a maximum of 4 mcg over a period of 5 hours. Weekly during the immunotherapy period, patients received increasing doses of short ragweed extract (2, 4, 6, and 8 μg Amb a 1), followed by 8 weekly maintenance injections of 12 μg Amb a 1, for a total of 12 weeks. Placebo immunotherapy contained increasing concentrations of histamine to maintain the blinding (0.002-0.032 mg/mL in lieu of the RIT and as much as 0.3 mL of a 1.25-mg/mL solution during the build-up and maintenance immunotherapy injections).

Ragweed season

The beginning and end of the ragweed season were defined by 2 consecutive days of airborne ragweed pollen counts $\geq$10 or $\leq$10 grains/mm^3 over a period of 24 hours, for 2 consecutive measurements, respectively.[23]

Study outcomes

The primary efficacy endpoint was the comparison of the average daily allergy severity scores (measured on a scale of 0-3) between patients receiving omalizumab plus immunotherapy versus those receiving immunotherapy alone. The score was calculated as the average of individual scores for nasal congestion; sneezing; itchy nose, throat and palate; itchy, watery eyes; and rhinorrhea during the ragweed season. A major secondary endpoint was a comparison of the incidence of adverse events among the study groups, to examine the effects of omalizumab on the safety of immunotherapy.

Immunologic assays

Serum free IgE, ragweed-specific (RS) IgG, and RS-IgE levels were measured in serum samples collected from 113 patients (with

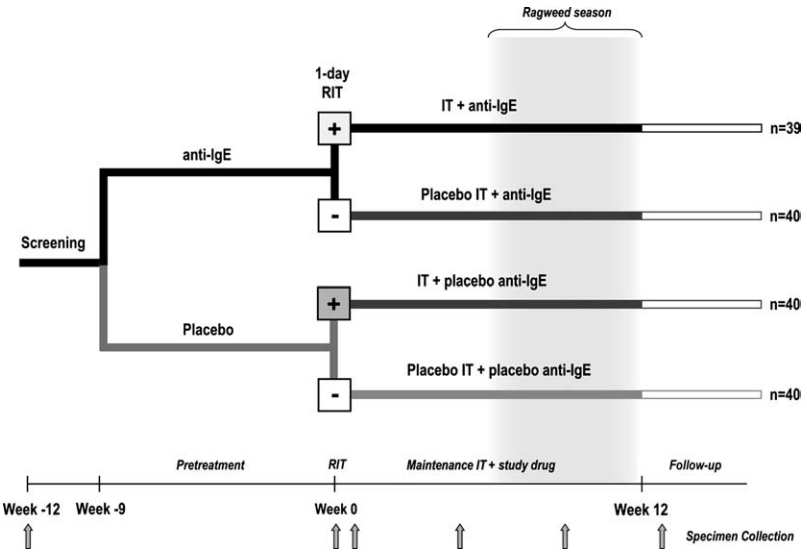

FIG 1. Study design indicating dosing regimens and specimen collection timeline for immunologic assays. Additional specimens were collected at 19 and 31 weeks. An approximation of the ragweed season based on pollen counts in relation to treatment visits is noted by the *shaded area. IT,* Weekly immunotherapy.

equivalent distribution across treatment groups) before omalizumab pretreatment, on the day of RIT and at intervals before, during, and after the ragweed season (Fig 1).

Ragweed-specific IgG levels were measured by using a double antibody-sandwich ELISA (purified goat antihuman IgG capture Ab-unlabeled [UNLB], IgG ELISA Standard; Jackson ImmunoResearch Laboratories Inc, West Grove, Penn, R&D Systems, Minneapolis, Minn). RS-IgE was measured by using the Pharmacia CAP system (Pharmacia, Uppsala, Sweden).

Serum free IgE levels were measured by Novartis Pharmaceuticals (Basel, Switzerland) using a solid-phase ELISA with a fluorometric technique and human serum as standard.[23]

Statistical analysis

Patient symptom severity scores were recorded twice daily (AM and PM) for approximately 12 weeks overlapping the ragweed season and were computed by averaging individual symptom scores. Daily severity scores (average of all individual symptom scores over AM and PM) were averaged over the time between the first immunotherapy visit and the beginning of ragweed season to obtain run-in period scores, and averaged over days in ragweed season to obtain average allergy severity scores. The primary endpoint compared average daily allergy severity scores of the omalizumab plus ragweed immunotherapy treatment group versus the placebo plus ragweed immunotherapy treatment group. As prespecified in the protocol, analysis was on an intent-to-treat basis, using ANOVA models including terms for treatment, site, and run-in period scores, with 1-sided .05 significance level. Per protocol and secondary analyses were performed at 2-sided .05 significance level, with Bonferroni adjustment for multiple comparisons.

Two-way comparisons of the frequency of adverse events between study groups were performed by using the Fisher exact test. Odds ratios (ORs), 95% CIs, and 2-sided *P* values were calculated. All data were analyzed by using SAS version 8.02 (SAS Institute Inc, Cary, NC).

RESULTS

Patient demographics

A total of 159 patients were randomized equally into the 4 treatment arms between April 7 and May 13, 2003, and this group constituted the safety sample (Table I). Baseline characteristics were similar among the 4 treatment arms, with no significant differences in age, sex, race, weight, height, body mass index, IgE level, or percentage of patients who had previously received allergy immunotherapy. The mean IgE level (IU/mL) was 106 (range, 10-650).

Treatment disposition

One hundred fifty-nine patients received at least 1 dose of omalizumab or placebo, and 150 received all preimmunotherapy injections. One hundred forty-nine patients received at least 1 dose of RIT or placebo, and 143 patients received all 6 injections through hour 3 on the day of RIT: 92.3% in the omalizumab plus immunotherapy group and 85% in the placebo plus immunotherapy group. One hundred thirty-three patients received at least 1 dose of weekly immunotherapy or placebo. Overall, 123 patients received all weekly doses of immunotherapy or placebo and made up the per protocol group: 30 of 39 (76.9%) in the omalizumab plus immunotherapy group and 26 of 40 (65%) in the placebo plus immunotherapy group (see this article's Fig E1 in the Online Repository at www.jacionline.org).

Of the 36 patients who discontinued study therapy, 10 did so before RIT, 19 during RIT, and 7 during the weekly immunotherapy phase. Among the 26 patients who discontinued study therapy during either RIT or weekly immunotherapy, 21 patients did so because of an associated adverse event. Eleven of these were in the immunotherapy alone group (27.5% of the group), whereas only 5 (12.8%) were in the omalizumab plus immunotherapy group (see this article's Fig E1 in the Online Repository at www.jacionline.org).

Adverse events during immunotherapy

Before July 1, 2003, 10 out of 17 patients (5 of 7, 2 of 3, 3 of 3, and 0 of 4 in the omalizumab +immunotherapy,

TABLE I. Baseline characteristics for all 4 groups of patients enrolled in the study

Characteristic	OM + IT (N = 39)	OM only (N = 40)	IT only (N = 40)	Placebo (N = 40)	Total (N = 159)
Age, y, mean (SD)	35.3 (9.56)	32.5 (10.67)	31.7 (8.72)	33.8 (9.66)	33.3 (9.68)
Age categories, y, N (%)					
18-29	14 (35.9)	22 (55.0)	20 (50.0)	14 (35.0)	70 (44.0)
30-39	10 (25.6)	4 (10.0)	11 (27.5)	13 (32.5)	38 (23.9)
40-50	15 (38.5)	14 (35.0)	9 (22.5)	13 (32.5)	51 (32.1)
Sex, N (%)					
Male	22 (56.4)	12 (30.0)	20 (50.0)	18 (45.0)	72 (45.3)
Female	17 (43.6)	28 (70.0)	20 (50.0)	22 (55.0)	87 (54.7)
Weight, kg, mean (SD)	82.29 (16.55)	76.25 (17.02)	79.32 (14.45)	79.73 (16.63)	79.38 (16.18)
Height, cm, mean (SD)	170.72 (8.85)	169.61 (10.05)	172.25 (9.17)	169.00 (9.15)	170.38 (9.31)
Body mass index, kg/m^2, mean (SD)	28.16 (5.12)	26.61 (6.08)	26.72 (4.39)	27.92 (5.32)	27.35 (5.26)
Total IgE, IU/mL, mean (SD)	106.7 (108.88)	91.2 (118.85)	108.0 (107.34)	118.3 (130.67)	106.1 (116.21)
Ragweed skin test, mm, mean (SD)					
Wheal response	9.5 (3.60)	8.7 (3.27)	9.0 (4.15)	8.3 (3.73)	8.8 (3.69)
Erythema response	32.8 (15.57)	34.5 (15.22)	35.7 (17.59)	32.4 (14.94)	33.9 (15.77)
Previously received IT (%)	12.8	25.0	17.5	22.5	19.5

IT, Immunotherapy; *OM,* omalizumab.

TABLE II. Systemic and other adverse reactions reported on the day of RIT for all patients (0-7 hours postinjection)*

	OM + IT (n = 36)	OM (n = 37)	IT (n = 39)	PL (n = 37)	Total (n = 149)
Wheezing	0	0	3	0	3
Flushing†	5	1	16	3	25
Urticaria†	3	2	11	0	16
Angioedema	1	0	3	1	5
Mean drop of BP $\geq$ 15 mm	4	4	3	3	14
Lightheadedness	2	2	7	2	13
Itching†	5	5	12	1	23
Abdominal pain	0	0	3	0	3
Nausea	0	0	2	0	2
Any reaction†	12 (33.3%)	11 (29.7%)	22 (56.4%)	7 (18.9%)	52 (34.9%)
Anaphylaxis†	2 (5.6%)	1 (2.7%)	10 (25.6%)	1 (2.7%)	14 (3.3%)

IT, Immunotherapy; *OM,* omalizumab; *PL,* placebo; *BP,* blood pressure.
*Rates of anaphylaxis, defined as reactions involving 2 or more organ systems concurrently and/or severe enough to require epinephrine, were assessed via post hoc blind analysis.
†Significant differences among the 4 treatment arms; $P \leq .05$.

omalizumab alone, immunotherapy alone, and placebo groups, respectively) who received RIT had adverse events consistent with allergic reactions. The NIAID Allergy and Asthma Data and Safety Monitoring Board was notified, and the protocol was subsequently modified so that after July 1, 2003, the last 2 doses of RIT (2.0 and 4.0 mcg Amb a 1) were given during the weekly build-up/maintenance phase of immunotherapy.

The number, scope, and severity of adverse events associated with RIT were highest in those patients receiving immunotherapy only (Table II). Only small differences in the percentage of patients with adverse events were noted between treatment arms receiving omalizumab plus immunotherapy, omalizumab alone, and placebo/placebo. In contrast, the patients receiving immunotherapy only had a much greater rate of allergic-like reactions during RIT, and the percentage of these patients having allergic-like reactions during the RIT was allergen dose-dependent, as shown in Fig 2. More patients in the immunotherapy-only group (20.5%) versus the group receiving omalizumab plus immunotherapy (13.9%) received epinephrine for allergic-like reactions on the RIT day. The percentages of patients with serious adverse events during RIT were 2.6, 0, 15.0, and 5.0 for the omalizumab plus immunotherapy, omalizumab-only, immunotherapy-only, and placebo-only groups, respectively. Allergic-like reaction rates in the omalizumab alone and placebo groups were 0% and 2.7%, respectively.

Overall rates of allergic reactions during RIT (including those treated before or after July 1, 2003) were 33.3%, omalizumab plus immunotherapy; 29.7%, omalizumab plus placebo; 56.4%, placebo plus immunotherapy; and 18.9%, placebo/placebo. Pairwise comparisons of adverse events in each group illustrate that immunotherapy alone was associated with a greater than 5-fold significant increase in risk of adverse events compared with placebo (OR, 5.41; $P = .001$). This significant increase is lost with the addition of omalizumab to RIT, which carried only an

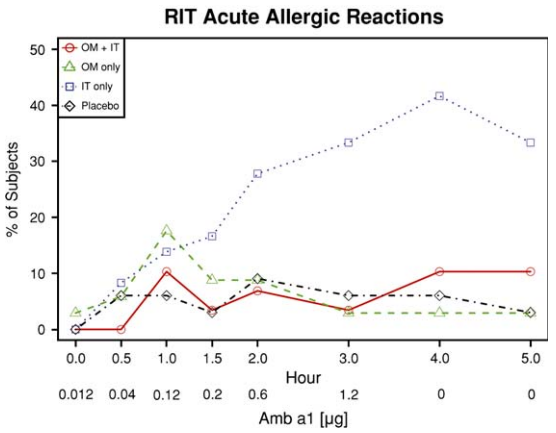

FIG 2. RIT time-dependent and dose-dependent allergic reactions among patients dosed after July 1, 2003. The data represent percentages of patients with acute allergic reactions based on the time after RIT was initiated in hours and the corresponding dose of Amb a 1 in the RIT (in patients receiving omalizumab plus immunotherapy and placebo plus immunotherapy). *IT,* Immunotherapy; *OM,* omalizumab.

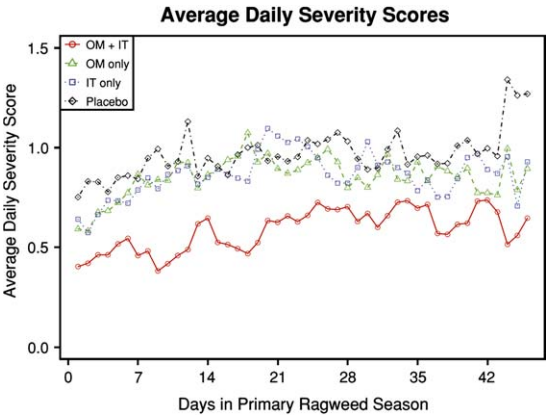

FIG 3. Average allergy severity scores over the ragweed pollen season for per protocol patients. Area under the curve analysis indicated a statistically significant improvement in severity scores for patients treated with omalizumab and immunotherapy versus immunotherapy alone ($P = .02$). The length of the ragweed season differed by site: Creighton University had a length of 46 days; University of Wisconsin, Madison; 39 days; and University of Iowa, 43 days. *IT,* Immunotherapy; *OM,* omalizumab.

approximately 2-fold risk of adverse events compared with placebo (OR, 2.12; $P = .19$). After RIT, comparison of groups receiving build-up or maintenance immunotherapy with or without omalizumab revealed a trend toward a decreased risk of adverse events with the addition of omalizumab (OR, 0.39), although statistical significance was not reached ($P = .064$), possibly because of the low frequency of events. No significant differences in the incidence of immediate postinjection adverse events were observed between groups during the build-up and maintenance phase.

Results of a post hoc blind analysis of patients judged to have anaphylactic reactions (defined as reactions involving 2 or more organ systems concurrently and/or severe enough to require epinephrine; judged by independent observers) during RIT also indicated a protective effect of omalizumab (Table II). In pairwise analysis, immunotherapy alone was shown to increase significantly the risk of anaphylaxis compared with placebo (OR, 12.08; $P = .007$), whereas the addition of omalizumab reduced this increased risk to levels that were no longer significant (OR, 2.10; $P = .615$). A comparison of groups receiving immunotherapy (omalizumab + immunotherapy vs immunotherapy only) demonstrated that the addition of omalizumab resulted in a significant, 5-fold decrease in risk of anaphylaxis caused by RIT (OR, 0.17; $P = .026$). Using the same definition of anaphylaxis, 0% of patients in the omalizumab plus immunotherapy arm versus 9.7% in the placebo plus immunotherapy arm had anaphylaxis during the weekly build-up/maintenance phase of immunotherapy, but this difference did not reach statistical significance ($P = .238$), perhaps reflecting the low number of anaphylactic events during immunotherapy.

Efficacy analysis

Daily allergy severity scores during the ragweed season were consistently lower in the omalizumab plus immunotherapy group versus immunotherapy alone (Fig 3). On an intent-to-treat basis, the benefit of omalizumab addition to immunotherapy was significant but modest: average severity scores were 0.69 in patients treated with omalizumab plus immunotherapy versus 0.86 in those treated with placebo plus immunotherapy ($P = .044$). Analysis of per protocol patients also indicated a significant difference in the primary endpoint between patients treated with omalizumab plus immunotherapy versus those treated with placebo plus immunotherapy, 0.61 and 0.85, respectively ($P = .012$). Similar trends favoring omalizumab plus immunotherapy versus either omalizumab alone or placebo alone were noted for symptom scores (Fig 3). Patients treated with omalizumab plus immunotherapy had the lowest symptom scores for all of the individual treatments as well.

Immunologic studies

Preragweed season, on the day of RIT, minimal differences in RS-IgE or RS-IgG were observed among treatment groups. One to 4 weeks into the ragweed season, the group receiving immunotherapy only showed a greater than 10-fold increase in RS-IgG levels (Fig 4). Omalizumab pretreatment before immunotherapy resulted in a similar increase in RS-IgG as observed in the immunotherapy-only group. No significant changes in RS-IgG levels were noted in the omalizumab-only or placebo groups.

After onset of the ragweed season, total RS-IgE levels in the groups receiving omalizumab increased approximately 10-fold from baseline levels (Fig 4) that peaked between study weeks 5 and 9. Patients receiving immunotherapy only exhibited a more muted increase in RS-IgE. This reflects the slower clearance of the allergen-IgE complexes when bound by the anti-IgE antibody.[24]

As expected, groups receiving omalizumab showed a greater than 10-fold average reduction in serum free IgE

levels after 9-week pretreatment with omalizumab (data not shown) that remained consistent through the duration of the study. Free IgE was unchanged from baseline levels throughout the study in the immunotherapy-only and placebo groups.

DISCUSSION

This study has demonstrated the potential utility of omalizumab pretreatment in allergen-specific immunotherapy of ragweed-induced allergy rhinitis. It is unique in showing that omalizumab pretreatment can provide substantial protection against acute allergic reactions, including anaphylaxis, during a RIT protocol.

Pretreatment of patients with omalizumab for 9 weeks reduced the rate of anaphylactic events during RIT by almost 80%. All systemic reactions were decreased in the omalizumab plus immunotherapy group versus the immunotherapy-alone group, except for declines in mean blood pressure of 15 mm or greater. These events were likely related to patients lying in bed for a prolonged time and in most cases were not thought by the investigator to be clinically significant or caused by the immunotherapy. The systemic and anaphylactic events noted in placebo immunotherapy patients may have been caused, in part, by the increasing doses of histamine and reflect proper blinding of both investigators and patients. This protective effect was more robust during the RIT phase of the study; however, the low frequency of events observed during the weekly build-up/maintenance phase of immunotherapy renders such comparisons problematic.

A previous study in children showed that concomitant treatment with omalizumab and allergen-specific (tree or grass) immunotherapy was more effective than immunotherapy alone.[25,26] In the current study, the addition of omalizumab pretreatment to immunotherapy resulted in significant improvement in severity scores during the ragweed season. Interpretation of the efficacy data is confounded by the generally low symptom scores observed in the placebo group and the lack of impressive treatment effects of either omalizumab or immunotherapy alone, as would be expected. Thus, the improvement in symptom scores noted with the combination of omalizumab plus immunotherapy might indicate a synergistic effect. It is likely that the subjective nature of diary cards, the variability in pollen seasons, and site-specific differences contributed to the observed treatment effects noted for all 4 arms. Immunologic parameters provide evidence of the biological activity of both the omalizumab and immunotherapy protocol used. The drastic reduction in free IgE levels observed after omalizumab pretreatment indicates that the drug was exerting the intended biological effect. In addition, the increase in RS-IgG levels observed in both groups of patients receiving immunotherapy in this study is consistent with general observations of successful allergen-specific immunotherapy protocols.[4] In immunotherapy, the elevated levels of IgG are believed to disrupt the formation of allergen-IgE complexes that bind to

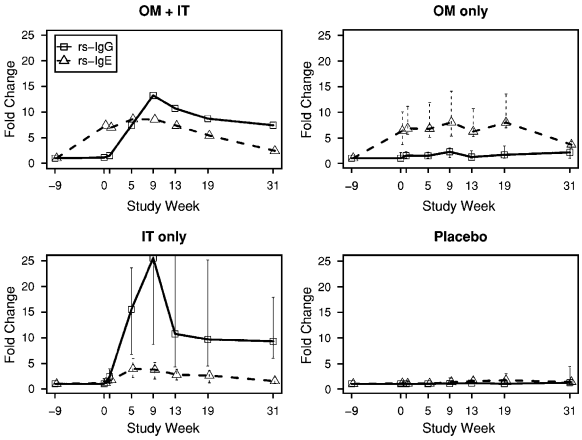

FIG 4. Changes in median RS-IgG *(squares, solid lines)* and RS-IgE *(triangles, dotted lines)* relative to pretreatment levels (weeks −12 to −9) over the course of the study. Rush immunotherapy administered on the first day of week 0 with 12 subsequent weeks of maintenance immunotherapy was followed by increases in RS-IgG and RS-IgE levels. *IT,* Immunotherapy; *OM,* omalizumab.

antigen-presenting cells, thus increasing the threshold of allergen exposure for T-cell activation.[9,27] In fact, in the current study, RS-IgE increased after treatment in the immunotherapy-only group, 1 to 4 weeks after RIT. Patients receiving neither immunotherapy nor omalizumab maintained low levels of RS-IgE throughout the study. Thus, the protocols applied in this study exhibited biological effects consistent with previously observed features and presumed mechanisms of immunotherapy.

The protective effect of omalizumab on allergen immunotherapy-induced allergic reactions has important clinical implications. Many patients in whom allergen immunotherapy might be clinically beneficial cannot tolerate it or are considered to be at increased risk for adverse events, and therefore, treatment may be withheld. Patients with venom hypersensitivity, for example, often cannot tolerate this potentially life-saving therapy. Patients with more severe or brittle asthma are at higher risks for acute fatal allergic reactions caused by immunotherapy[10,11] and are unsuitable candidates for immunotherapy. Moreover, attempts at developing immunotherapy for food allergies have often failed because of acute allergic reactions.[28]

In RIT, a common strategy to decrease the risk of adverse events is premedication with mediator antagonists and/or corticosteroids. Pretreatment with fexofenadine, a histamine H1-receptor antagonist, for example, has been shown to reduce the incidence of systemic reactions caused by RIT.[28,29] Still, reactions have been observed in as many as 40% of patients receiving RIT with mixed allergen extracts, despite pretreatment with H1 or H2 antagonists and/or prednisone.[22,30] In the current study, patients in the immunotherapy-only group still showed a substantial number of acute allergic reactions during RIT despite receiving 180 mg fexofenadine the night before and 1 hour before RIT. Omalizumab pretreatment appeared several-fold more effective than fexofenadine

in preventing these reactions and may provide a more effective means of reducing the risk of systemic reactions and bringing increased safety to rush immunotherapy protocols.

An improved safety profile for immunotherapy may have additional benefits. Many patients have difficulty achieving appropriately recommended allergen doses because of adverse events. Given that several studies have shown the importance of allergen dose in the success of immunotherapy,[31-35] it follows that a reduced incidence of serious adverse events using omalizumab pretreatment would allow a greater proportion of patients to reach target allergen doses. Furthermore, one could envision that omalizumab pretreatment might permit the administration of higher doses of allergen, which could result in further improvements in efficacy.

In summary, omalizumab pretreatment appears to offer substantial protection from serious allergic reactions after RIT. With further investigation, omalizumab pretreatment appropriately dosed and timed could ultimately lead to the safer and more effective use of allergen-specific immunotherapy for a variety of patients and disorders.

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REFERENCES

1. Casale TB. Status of immunotherapy: current and future. J Allergy Clin Immunol 2004;113:1036-9.
2. Norman PS. Immunotherapy: past and present. J Allergy Clin Immunol 1998;102:1-10.
3. Norman PS. Immunotherapy: 1999-2004. J Allergy Clin Immunol 2004; 113:1013-23.
4. Till SJ, Francis JN, Nouri-Aria K, Durham SR. Mechanisms of immunotherapy. J Allergy Clin Immunol 2004;113:1025-34.
5. Durham SR, Walker SM, Varga EM, Jacobson MR, O'Brien F, Noble W, et al. Long-term clinical efficacy of grass-pollen immunotherapy. N Engl J Med 1999;341:468-75.
6. Des RA, Paradis L, Menardo JL, Bouges S, Daures JP, Bousquet J. Immunotherapy with a standardized Dermatophagoides pteronyssinus extract, VI: specific immunotherapy prevents the onset of new sensitizations in children. J Allergy Clin Immunol 1997;99:450-3.
7. Moller C, Dreborg S, Ferdousi HA, Halken S, Host A, Jacobsen L, et al. Pollen immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis (the PAT-study). J Allergy Clin Immunol 2002;109:251-6.
8. Garcia BE, Sanz ML, Gato JJ, Fernandez J, Oehling A. IgG4 blocking effect on the release of antigen-specific histamine. J Investig Allergol Clin Immunol 1993;3:26-33.
9. Wachholz PA, Soni NK, Till SJ, Durham SR. Inhibition of allergen-IgE binding to B cells by IgG antibodies after grass pollen immunotherapy. J Allergy Clin Immunol 2003;112:915-22.
10. Allergen immunotherapy: a practice parameter. American Academy of Allergy, Asthma and Immunology. American College of Allergy, Asthma and Immunology. Ann Allergy Asthma Immunol 2003;90:1-40.
11. Bernstein DI, Wanner M, Borish L, Liss GM. Twelve-year survey of fatal reactions to allergen injections and skin testing: 1990-2001. J Allergy Clin Immunol 2004;113:1129-36.
12. Lower T, Henry J, Mandik L, Janosky J, Friday GA Jr. Compliance with allergen immunotherapy. Ann Allergy 1993;70:480-2.
13. Tinkelman D, Smith F, Cole WQ III, Silk HJ. Compliance with an allergen immunotherapy regime. Ann Allergy Asthma Immunol 1995;74:241-6.
14. Lockey RF, Nicoara-Kasti GL, Theodoropoulos DS, Bukantz SC. Systemic reactions and fatalities associated with allergen immunotherapy. Ann Allergy Asthma Immunol 2001;87:47-55.
15. Malling HJ. Minimising the risks of allergen-specific injection immunotherapy. Drug Saf 2000;23:323-32.
16. Portnoy J, King K, Kanarek H, Horner S. Incidence of systemic reactions during rush immunotherapy. Ann Allergy 1992;68:493-8.
17. Sturm G, Kranke B, Rudolph C, Aberer W. Rush Hymenoptera venom immunotherapy: a safe and practical protocol for high-risk patients. J Allergy Clin Immunol 2002;110:928-33.
18. Moverare R, Vesterinen E, Metso T, Sorva R, Elfman L, Haahtela T. Pollen-specific rush immunotherapy: clinical efficacy and effects on antibody concentrations. Ann Allergy Asthma Immunol 2001;86:337-42.
19. Casale TB. Omalizumab: an effective anti-IgE treatment for allergic asthma and rhinitis. Drugs Today (Barc) 2004;40:367-76.
20. Holgate ST, Djukanovic R, Casale T, Bousquet J. Anti-immunoglobulin E treatment with omalizumab in allergic diseases: an update on anti-inflammatory activity and clinical efficacy. Clin Exp Allergy 2005;35: 408-16.
21. Beck LA, Marcotte GV, MacGlashan D, Togias A, Saini S. Omalizumab-induced reductions in mast cell Fcepsilon RI expression and function. J Allergy Clin Immunol 2004;114:527-30.
22. Portnoy J, Bagstad K, Kanarek H, Pacheco F, Hall B, Barnes C. Premedication reduces the incidence of systemic reactions during inhalant rush immunotherapy with mixtures of allergenic extracts. Ann Allergy 1994;73:409-18.
23. Casale TB, Condemi J, LaForce C, Nayak A, Rowe M, Watrous M, et al. Effect of omalizumab on symptoms of seasonal allergic rhinitis: a randomized controlled trial. JAMA 2001;286:2956-67.
24. Casale TB. Anti-immunoglobulin E (omalizumab) therapy in seasonal allergic rhinitis. Am J Respir Crit Care Med 2001;164:S18-21.
25. Kuehr J, Brauburger J, Zielen S, Schauer U, Kamin W, Von BA, et al. Efficacy of combination treatment with anti-IgE plus specific immunotherapy in polysensitized children and adolescents with seasonal allergic rhinitis. J Allergy Clin Immunol 2002;109:274-80.
26. Rolinck-Werninghaus C, Hamelmann E, Keil T, Kulig M, Koetz K, Gerstner B, et al. The co-seasonal application of anti-IgE after preseasonal specific immunotherapy decreases ocular and nasal symptom scores and rescue medication use in grass pollen allergic children. Allergy 2004;59:973-9.
27. Nouri-Aria KT, Wachholz PA, Francis JN, Jacobson MR, Walker SM, Wilcock LK, et al. Grass pollen immunotherapy induces mucosal and peripheral IL-10 responses and blocking IgG activity. J Immunol 2004; 172:3252-9.
28. Eigenmann PA. Future therapeutic options in food allergy. Allergy 2003; 58:1217-23.
29. Reimers A, Hari Y, Muller U. Reduction of side-effects from ultrarush immunotherapy with honeybee venom by pretreatment with fexofenadine: a double-blind, placebo-controlled trial. Allergy 2000;55:484-8.
30. Matuska J, Bajer M, Hrstkova M. Rush immunotherapy with the standardized grass-pollen extract in children with mild allergic asthma: a comparison of two premedication regimens. Scr Med (Brno) 2005;74:367-78.
31. Creticos PS, Marsh DG, Proud D, Kagey-Sobotka A, Adkinson NF Jr, Friedhoff L, et al. Responses to ragweed-pollen nasal challenge before and after immunotherapy. J Allergy Clin Immunol 1989;84:197-205.
32. Franklin W, Lowell FC. Comparison of two dosages of ragweed extract in the treatment of pollenosis. JAMA 1967;201:915-7.
33. Furin MJ, Norman PS, Creticos PS, Proud D, Kagey-Sobotka A, Lichtenstein LM, et al. Immunotherapy decreases antigen-induced eosinophil cell migration into the nasal cavity. J Allergy Clin Immunol 1991;88:27-32.
34. Haugaard L, Dahl R, Jacobsen L. A controlled dose-response study of immunotherapy with standardized, partially purified extract of house dust mite: clinical efficacy and side effects. J Allergy Clin Immunol 1993;91:709-22.
35. Majchel AM, Proud D, Freidhoff L, Creticos PS, Norman PS, Naclerio RM. The nasal response to histamine challenge: effect of the pollen season and immunotherapy. J Allergy Clin Immunol 1992;90:85-91.