

Tolerability of Retreatment with Omalizumab, a Recombinant Humanized Monoclonal Anti-IgE Antibody, during a Second Ragweed Pollen Season in Patients with Seasonal Allergic Rhinitis

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ABSTRACT

Two randomized, placebo-controlled, double-blind studies have shown clinical benefit with omalizumab (Xolair), a recombinant humanized monoclonal anti-immunoglobulin E (IgE) antibody, at a dose of 300 mg every 3 or 4 weeks in patients with seasonal allergic rhinitis. The present open-label, 12-week

study was designed to assess the safety and tolerability of retreatment with omalizumab in 287 patients previously treated with this agent in one of the latter studies. Omalizumab, 300 mg, was administered subcutaneously every 4 weeks (three injections) to patients with IgE levels ≤ 150 IU/mL ($n = 182$) and every 3 weeks (four injections) to patients with IgE levels > 150 IU/mL ($n = 105$) at screening before retreatment. Reported adverse events were monitored and blood samples were analyzed for laboratory safety (hematology and serum chemistry) and IgE levels. Urinalysis also was completed as part of the laboratory safety evaluation. The overall incidence and pattern of adverse events were similar to those reported in the primary study. There were no severe or serious adverse events related to omalizumab treatment and no anti-omalizumab antibodies were detected in any patient. Two patients withdrew from treatment because of adverse events (skin rash and nausea; facial erythema and edema) related to study treatment. Free IgE levels decreased to the levels associated with symptom reduction in the core study. In summary, retreatment during a second pollen season with omalizumab, 300 mg every 3 or 4 weeks, was well tolerated and was not associated with any significant immunologic reactions. (Allergy and Asthma Proc 24:323–329, 2003)

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Allergic rhinitis is a common allergic condition, with a self-reported prevalence of up to 41%,¹⁻³ which appears to be on the increase.^{3,4} Although often trivialized, allergic rhinitis has an enormous economic impact; in the United States, the total economic burden is estimated at \$6 billion/year.⁵ In addition, the indirect cost of allergic rhinitis is not insignificant, with many patients suffering a diminished quality of life as a direct result of their symptoms.⁶

Because allergic rhinitis is thought to be mediated by immunoglobulin E (IgE)-triggered degranulation of mast cells and basophils with release of a variety of inflammatory mediators, cytokines, and chemokines, there is a clear rationale for anti-IgE therapy in allergic rhinitis and in other similar inflammatory conditions. Omalizumab (Xolair, Genentech, USA/Tanor, Inc., USA/Novartis Pharma AG, Switzerland) is a recently developed, recombinant humanized monoclonal anti-IgE antibody; it binds to the high (FcεRI)- and low (FcεRII)-affinity binding site on the Fc3 domain of IgE⁷ and currently is undergoing evaluation for the treatment of IgE-mediated diseases.⁸⁻¹¹ By forming complexes with serum-free IgE, omalizumab prevents IgE from binding to mast cells and basophils, thereby halting the sequence of inflammatory processes initiated by IgE. Omalizumab has been shown to produce a dose-dependent reduction in serum-free IgE levels in humans,^{12,13} and its efficacy in seasonal allergic rhinitis (SAR) has been established in two double-blind, placebo-controlled trials in patients with allergy to ragweed pollen¹³ and birch pollen.¹⁴ The incidence of adverse events in these studies was low and similar for the omalizumab and placebo groups and no anti-omalizumab antibodies were detected in any patients. In addition, omalizumab has shown to benefit patients with allergic asthma, where it has an excellent safety profile and offers an innovative solution for disease control, allowing corticosteroid consumption to be significantly reduced.^{8,9}

The results of a randomized, double-blind, dose-finding study in 536 patients with moderate-to-severe SAR due to ragweed pollen recently have been published.¹³ Treatment consisted of 50, 150, or 300 mg of omalizumab or placebo every 3 or 4 weeks according to baseline serum IgE levels. Results showed the higher dose of omalizumab (300 mg) offered consistently and significantly superior efficacy and improvement in quality of life relative to placebo. This open-label retreatment study was an extension of the double-blind trial and was undertaken to evaluate the safety and tolerability of omalizumab retreatment during a second ragweed allergic rhinitis season in those patients who had received this study drug during the core trial. This new safety data were compared with results obtained during the original study and with other safety data to evaluate any new findings. Efficacy measurements were not undertaken during this retreatment study.

METHODS

All patients (12-75 years) who had been treated with omalizumab and had successfully completed the core study were eligible for inclusion in the retreatment trial.

The study was designed as open-label and was conducted during the ragweed pollen season between July 1998 and October 1998 at 24 centers in the United States, in accordance with the revised amendments to the Declaration of Helsinki and local institutional review board approval. Patients were screened for 1-2 weeks before entry and then received subcutaneous (s.c.) omalizumab, 300 mg, every 3 or 4 weeks over a 12-week treatment period, beginning ~2 weeks before the onset of the ragweed pollen season in their region. All patients provided written informed consent before inclusion.

Oral rescue medication with 4 mg of chlorpheniramine or 60 mg of fexofenadine HCl was allowed on an as-needed basis to control symptoms of severe SAR during the time between each visit. Use of oral or topical decongestants for temporary relief of severe nasal congestion and/or eyedrops for temporary relief of severe ocular itching also was permitted after consultation with the study investigator. The use of intranasal corticosteroids was not allowed during the study period. Patients could continue to use regular chronic medication such as oral contraceptives, hormonal replacement therapy, or inhaled corticosteroids for asthma treatment during the study.

Adverse events were classified according to a modified version of the World Health Organization Adverse Reaction Terminology dictionary. Investigators rated events as mild, moderate, or severe and related or not related to treatment. Laboratory safety tests (routine hematology, serum chemistry, urinalysis, and pretreatment IgE) were performed at baseline and at the end of treatment.

Background and demographic variables and all study parameters were summarized for each subgroup (*i.e.*, dosing every 4 weeks/IgE <150 IU/mL and dosing every 3 weeks/IgE >150 IU/mL). All patients who received at least one dose of study medication were included in the safety analysis. Adverse events were summarized by body system, relationship to study medication, and severity. No formal statistical between-group comparisons were performed.

RESULTS

Demographics

Of the 374 patients treated with omalizumab who completed the core study, 287 patients (76.7%) were enrolled in the retreatment study; of these, 95 patients had originally received 300 mg of omalizumab, 97 patients received 150 mg of omalizumab, and 95 patients received 50 mg of omalizumab. At screening before retreatment, 182 patients had serum IgE levels ≤150 IU/mL and received 300 mg of omalizumab s.c. every 4 weeks, and the remaining 105 patients had baseline serum IgE levels >150 IU/mL and were treated every 3 weeks. The two groups were well

TABLE I

Baseline Demographic and Medical History for a Retreatment Study and Core Study

Characteristic	Omalizumab 300 mg Every 4 Weeks (n = 182)	Omalizumab 300 mg Every 3 Weeks (n = 105)	All (n = 287)	Core Study All ¹³ (n = 536)
Sex (%)				
Male	84 (46)	52 (50)	136 (47)	240 (45)
Female	98 (54)	53 (51)	151 (53)	289 (55)
Age, mean (SD), years	36.8 (10.90)	34.5 (13.11)	36.0 (11.79)	35.4 (12.5)
Screening IgE level, mean (SD), IU/mL	76.8 (34.5)	293.8 (185.8)	156.2 (155.8)	173.6 (145.3)
Asthma history	23 (12.6)	10 (9.5)	33 (11.5)	137 (26)
History of seasonal asthma exacerbations	23 (12.6)	10 (9.5)	33 (11.5)	86 (16)

Values are numbers (percentage) unless otherwise indicated.

TABLE II

Adverse Events, Reported in >3% of Patients in Retreatment and Core Studies by Treatment Group

Adverse Event	Retreatment Trial		Core Trial ¹³		
	Omalizumab 300 mg Every 4 Weeks (n = 182)	Omalizumab 300 mg Every 3 Weeks (n = 105)	Omalizumab 300 mg Every 3 or 4 Weeks (n = 129)	Omalizumab 50 mg Every 3 or 4 Weeks (n = 137)	Placebo (n = 136)
Headache	19 (10.4%)	13 (12.4%)	15 (11.6%)	21 (15.3%)	22 (16.2%)
URTI	14 (7.7%)	12 (11.4%)	8 (6.2%)	13 (9.5%)	11 (8.1%)
Viral infection	10 (5.5%)	6 (5.7%)	7 (5.4%)	9 (6.6%)	9 (6.6%)
Sinusitis	7 (3.8%)	3 (2.9%)	3 (2.3%)	5 (3.6%)	12 (8.8%)

matched with respect to demographic characteristics (Table I).

The majority of patients received all scheduled doses of study medication in both IgE subgroups (97% in the IgE ≤ 150 IU/mL group, 99% in the IgE > 150 IU/mL group). Six patients (2.1%) discontinued the study prematurely, five patients discontinued because of adverse events (four patients from the IgE ≤ 150 IU/mL group; one patient from the IgE > 150 IU/mL group) and 1 patient discontinued because of a protocol violation (IgE ≤ 150 IU/mL group). A well-defined ragweed pollen season was experienced at all study locations. Exposure to pollen season and severe pollen season (defined as pollen counts >10 and 100 grains/m³, respectively) was similar for both groups.

Use of rescue medication in this extension study was low. In the original core study, 55.2% of patients in the group treated with 300 mg of omalizumab (69/125) used rescue medication compared with 76.6% of the placebo-treated patients (102/133). In the extension study, 29.3% (84/287) of all patients who re-enrolled in the trial needed rescue medication.

Adverse Events

In total, 47.4% of patients in the retreatment trial experienced an adverse event. Of these, headache, upper respiratory tract infection (URTI), and viral infection were the most commonly reported. Headache, URTI, and viral infection were also the most common adverse events seen in the core study although, interestingly, these adverse events were reported less frequently in the 300-mg group than in the other omalizumab dosage groups.¹³ Headache, sinusitis, URTI, and viral infection were the most frequently reported adverse events in the placebo group in the core trial. Table II outlines these frequent adverse events and compares them with those reported in the core study in the highest-dosage group, the lowest-dosage group, and the placebo group.

The incidence of adverse events that were considered related to the study drug was small and comparable across both treatment groups (Table III). Overall, the most frequently reported adverse events that were considered to be drug related occurred in the body as a whole in 1% of patients and fatigue was the most frequent of these body system adverse events (0.7% of patients). In the core study,

TABLE III

Number (%) of Patients with Adverse Events Considered to be Study Drug Related in the Retreatment Trial Compared with Selected Groups from the Core Study

	Retreatment Trial			Core Trial*	
	Omalizumab 300 mg Every 4 Weeks	Omalizumab 300 mg Every 3 Weeks	All	Omalizumab 300 mg Every 3 and 4 Weeks	Placebo
Total patients	182	105	287	129	136
Total patients with AEs (%)	5 (2.7)	2 (1.9)	7 (2.4)	8 (6.2)	9 (6.6)
Body as a whole	1 (0.5)	2 (1.9)	3 (1)	3 (2.3)	3 (2.2)
Digestive system	1 (0.5)	1 (1)	2 (0.7)	0	0
Musculoskeletal system	1 (0.5)	0	1 (0.3)	2 (1.6)	0
Nervous system	2 (1.1)	0	2 (0.7)	1 (0.8)	5 (3.7)
Respiratory system	1 (0.5)	0	1 (0.3)	2 (1.6)	0
Skin and appendages	1 (0.5)	1 (1)	2 (0.7)	1 (0.8)	0
Special senses	1 (0.5)	1 (1)	2 (0.7)	0	0

AEs = adverse events. * Data on file, Novartis.

TABLE IV

Severity of all Adverse Events in the Retreatment Trial Compared with Selected Groups from the Core Study

	Retreatment Trial			Core Trial*	
	Omalizumab 300 mg Every 4 Weeks	Omalizumab 300 mg Every 3 Weeks	All	Omalizumab 300 mg Every 3 and 4 Weeks	Placebo
Total patients	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.

the most frequently reported adverse events considered to be study drug related in all groups, including the placebo group, were weight gain ($\leq 3.0\%$) and headache ($\leq 2.2\%$).¹³ Data from individual treatment groups in the core study show little difference in the profile of these adverse events and suggest a similar overall profile to that seen in the retreatment trial (Table III).

Urticaria was reported in one patient (IgE >150 IU/mL group) in the retreatment trial. This 18-year old, white woman developed mild urticaria, involving the back, abdomen, and arms, 1 week after the first dose of omalizumab. The urticaria resolved spontaneously in 2 hours without treatment and did not recur with the subsequent doses. The investigator considered that this was not related to the study drug so no additional laboratory tests were performed. Urticaria, considered to be drug related, was reported in two patients in the core trial; both were receiving active treatment with omalizumab.¹³ Both cases of urticaria resolved within 2 hours after antihistamine treatment. One of these patients discontinued and the other patient completed the

trial using prophylactic antihistamines before subsequent omalizumab doses.

The majority of adverse events experienced were considered as mild or moderate in nature and the two treatment subgroups were comparable with respect to distribution of severity of the adverse events. None of the adverse events that were considered to be drug related were rated as severe. Again, the severity of adverse events reported in the core study showed a similar pattern¹³ (Table IV).

Of the five adverse events that resulted in withdrawal from the extension study, two were suspected to be related to omalizumab. One patient (IgE > 150 IU/mL group) developed swollen red eyes; facial erythema; and edema of the face, hands, and forearms 2 days after the second dose of omalizumab. The patient was treated with antihistamine and recovered completely in 2 days. Approximately 10 weeks later, after written consent was obtained, the patient underwent skin-prick testing with positive control (histamine phosphate, 2.75 mg/mL), negative control (buffered saline, 50% glycerinated), and omalizumab. The patient

showed a cutaneous reaction only to histamine. When re-challenged with subcutaneous omalizumab, no reaction was seen after 150 mg of omalizumab. However, after a 300-mg dose, the patient experienced facial flushing and redness of the right eye. This patient did not have any proteinuria or other laboratory abnormalities. Another patient in the $\text{IgE} \leq 150$ IU/mL group experienced nausea and a generalized fine erythematous papular rash 48 hours after the first dose of omalizumab and was discontinued from the study. Neither of these patients was reported to have had a skin rash or hypersensitivity-type reaction in the primary study and there were no associated laboratory abnormalities. No anti-omalizumab antibodies were detected in any patients at the 12-week posttrial follow-up.

Three patients in the $\text{IgE} \leq 150$ IU/mL group experienced adverse events requiring withdrawal that were not considered to be related to omalizumab. One patient developed malaise, myalgia, and low-grade fever that were subsequently diagnosed as acute infectious mononucleosis. A second patient developed muscle tenderness after the first dose of omalizumab, and a third patient developed generalized muscle spasms involving the left side of the body and blepharospasm 7 days after the first dose of omalizumab. No differential diagnosis was suggested for these patients.

No reports of serum sickness-like syndrome or immune complex-related hypersensitivity-type adverse reactions were observed during either the core study¹³ or the retreatment trial. Furthermore, no clusters of adverse events associated with serum sickness-like syndrome or immune complex-related hypersensitivity were identified. Local injection site reactions (*e.g.*, burning, itching, warmth, bruising, redness, or hive formation) assessed prospectively were mild and relatively common, with one of five injections being associated with some form of injection site reaction in both of the groups. These results were similar to those of the original study, in which the mean symptom score for injection site reaction was the same in each treatment group.¹³

Laboratory Tests and Vital Signs

There were no clinically significant changes from baseline in laboratory values for any tests (hematology, serum chemistry, or urinalysis), and no anti-omalizumab antibodies were detected in any patients. No urinary abnormalities consistent with deposition of immune complexes in the kidney were observed. Posttreatment elevation (≥ 3 times upper limit of normal) in serum aspartate aminotransferase/alanine aminotransferase in three patients was attributed to acute infectious mononucleosis, alcohol intake, and use of muscle enhancers, respectively. Similarly, in the core study, there were no clinically significant changes in laboratory values in any group and no anti-omalizumab antibodies were detected in any patient.¹³

There were no clinically significant changes in diastolic or systolic blood pressure, pulse rate, respiratory rate, or temperature after study drug administration over the course of the study.

IgE Levels

Treatment with omalizumab resulted in a dose-dependent decrease in serum-free IgE levels in the core study,¹³ where analysis showed a significant association between free IgE levels and daily nasal symptom severity and rescue antihistamine use; patients with the lowest IgE levels had the lowest symptom scores and least rescue use. The core trial was a dose-ranging study (patients receiving 50, 150, or 300 mg with dosing interval dependent on baseline IgE) and thus intrasubject comparisons were made between the core and the extension of those patients in the core trial who received the identical dosing regimen of omalizumab in the extension. Free IgE levels for those patients with no change to their dosing regimen from the core trial to the extension were put into one of four bins: (1) <10.33 IU/mL, (2) between 10.33 and 20.66 IU/mL, (3) between 20.66 and 61.98 IU/mL, and (4) >61.98 IU/mL. Analysis of serum-free IgE levels among evaluable patients who received identical dosing regimens during the core and retreatment studies showed no loss in IgE suppression. In the 56 patients who received a dose of 300 mg every 4 weeks, *e.g.*, 43 (76.8%) patients achieved levels <10.33 IU/mL at week 12 in both studies, 2 (3.6%) patients achieved levels between 10.33 and 20.66 IU/mL in both studies, 1 (1.8%) patient achieved a level between 20.66 and 61.98 IU/mL in both studies, and the 10 (17.9%) remaining patients were in a lower bin for free IgE in the extension. In the 30 patients who received a dose of 300 mg every 3 weeks, 10 (33.3%) patients achieved levels <10.33 IU/mL at week 12 in both studies, 7 (23.3%) patients had levels between 10.33 and 20.66 IU/mL in both studies, 1 (3.33%) patient had a level between 20.66 and 61.98 IU/mL in both studies, 10 (33.3%) patients were in a lower bin in the extension, and 2 (6.7%) patients were in a higher bin in the extension.

Serum levels of total IgE (includes both free IgE and IgE bound up in the IgE-omalizumab complex) increased in the retreatment trial during treatment as it had in the core trial. Within-patient ratios of total IgE in the extension to that in the core trial were computed for those patients on the same dosing regimen in the core and extension. For the 60 patients who received 300 mg every 4 weeks, the 90% confidence interval on the ratio of mean total IgE (extension divided by core) was [0.78, 0.95] and for the patients treated with 300 mg every 3 weeks, the 90% confidence interval was [0.75, 85].

DISCUSSION

The results from this trial suggest that retreatment with omalizumab during a second ragweed pollen season is well tolerated and associated with an acceptable safety profile. In addition, the results confirm the safety profile of omalizumab that has already been established in larger, double-blind, placebo-controlled studies in patients with allergic asthma and SAR in which no significant difference

in the frequency of adverse events was found between treatment and placebo groups.^{8,9,13,14} In the original core study, Casale *et al.* found the frequency of adverse events to be similar in all active treatment groups and in the placebo group (47.3%, 300 mg of omalizumab; 53.7%, 150 mg of omalizumab; 51.8%, 50 mg of omalizumab; and 57.4%, placebo).¹³ In another similar study in SAR, Ådelroth *et al.* found the adverse event profile to be similar between omalizumab-treated patients and placebo recipients, with 36% of omalizumab recipients reporting adverse events compared with 37% of placebo recipients.¹⁴ Results from studies in allergic asthma also have suggested that there is no significant difference in the incidence of adverse events between omalizumab-treated patients and placebo recipients.^{8,9}

The majority of adverse events in this retreatment study were mild to moderate in severity. Overall, the adverse events that did occur generally were complaints that would be expected in a population of individuals with SAR. Headache, URTI, and viral infection were the most frequently reported adverse events. These same adverse events also were the most frequently reported in the original study in all treatment groups, including the placebo group.¹³ More importantly, the incidence and pattern of adverse events suspected to be drug related in the retreatment study were similar to previous placebo-controlled trials.

In this retreatment study, the proportion of patients who experienced adverse events that were considered related to omalizumab was very low (2.4%) and none were rated as severe. The most frequently reported adverse reaction considered to be drug related was fatigue, which occurred in 0.7% of patients. In the core study, the most frequently reported, drug-related adverse events were weight gain and headache in all groups.¹³ In a study in allergic asthma, fatigue and paresthesia were the most common drug-related adverse events occurring in 1.1% of patients receiving omalizumab.⁸

In all clinical trials to date, in which two-thirds of patients have been exposed to anti-IgE therapy for at least 24 weeks (data on file, Novartis), anti-omalizumab antibodies have not been detected and there has been no suggestion of the development of significant immune complex disorders in any treated patient. These observations are important and suggest that treatment with this anti-IgE antibody can maintain efficacy and is unlikely to result in unwanted effects on the immune system. These findings are also consistent with data from animal studies, which found that omalizumab-IgE complexes were small and did not fix complement.¹⁵ The results of testing for anti-omalizumab antibodies in a retreatment trial are of even greater importance, because they will suggest what happens during rechallenge. In this study no anti-omalizumab antibodies were detected in any patient, and no significant immune complex-mediated disorders were observed. Therefore, these observations suggest that retreatment with omalizumab is not associated with an increased risk of adverse events.

Although this study was not designed to assess efficacy, the results do suggest that retreatment with omalizumab achieves the same rationale for efficacy as in previous studies designed to investigate efficacy and safety. Mean baseline serum IgE levels were comparable in both the core and the retreatment studies and free IgE levels dropped dramatically after omalizumab treatment in both studies. Results reported by Casale *et al.*¹³ suggested that suppression of serum-free IgE levels below 17 IU/mL correlates with clinical efficacy. In the majority of patients in the retreatment study, the free IgE levels in both treatment groups were <20.66 IU/mL and >75% of patients receiving 300 mg of omalizumab every 4 weeks achieved serum-free IgE levels of <10.33 IU/mL at week 12 of treatment. Notably, analysis of serum-free IgE levels among evaluable patients who received identical dosing regimens during the core and retreatment studies showed no evidence of loss of efficacy (in terms of IgE suppression) with retreatment.

The increase in serum total IgE (free IgE and IgE bound to omalizumab) that was observed in this study also was seen during the core trial, and is thought to be related to the formation of IgE-omalizumab complexes. These results were not unexpected because omalizumab complexes have been shown to have a much longer serum half-life than free IgE.^{12,16–19} Because of its IgG₁ antibody framework, such complexes are thought to be cleared by the body mainly through Fcγ receptors of the hepatic sinusoidal endothelial cells of the reticuloendothelial system.

In conclusion, this 12-week study in patients with SAR shows that retreatment with omalizumab appears safe and well tolerated with a similar profile of adverse events to that seen in randomized, placebo-controlled studies. Although there was no suggestion of any new adverse events and no significant immunologic reactions, isolated reports of allergy-type reactions possibly associated with this therapy suggest the need for cautious observation during treatment with omalizumab.

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