

Anti-Immunoglobulin E (Omalizumab) Therapy in Seasonal Allergic Rhinitis

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Anti-immunoglobulin E (anti-IgE) (omalizumab), a humanized monoclonal anti-IgE antibody that binds to circulating IgE, has been studied in several large double-blind, randomized, placebo-controlled clinical trials to determine its pharmacokinetic characteristics, efficacy, and safety in ragweed- or birch pollen-induced seasonal allergic rhinitis (SAR). The consequences of readministering omalizumab after a lapse of time have also been studied. These studies have confirmed that serum-free IgE declines in a dose-related manner with such treatment and that omalizumab-induced declines in IgE correlate with symptom improvement. Whether omalizumab is administered intravenously or subcutaneously, its pharmacokinetics do not differ. A Phase II dose-ranging study demonstrated that the optimum efficacious dose of omalizumab for the treatment of seasonal allergic rhinitis is 300 mg administered subcutaneously. The dosing frequency, in terms of whether the antibody is administered every 3 or 4 wk, is based on the patient's baseline IgE level. With adequate dosing, nasal and ocular symptoms are significantly reduced, and quality of life is significantly improved. Omalizumab is safe and well tolerated and can be safely readministered in subsequent pollen seasons.

Keywords: allergic rhinitis; anti-IgE; ragweed; birch pollen; omalizumab

Seasonal allergic rhinitis (SAR) is the most common atopic disease in the United States (1), afflicting approximately 40% of children and 10% to 30% of adults (2). It is responsible for substantial impairment of quality of life, and it has serious consequences on productivity at the workplace as well as at school. Studies of children with allergic rhinitis have shown that they perform certain school tasks less effectively than do their non-atopic peers (3) and that the disorder has been estimated to be responsible for more than 820,000 missed school days (4). The economic burden imposed by allergic rhinitis in terms of both direct and indirect costs is extremely large (4, 5). Furthermore, allergic rhinitis is a well-known risk factor for asthma (6–8).

The relationship between allergic rhinitis and asthma is attributed to both a shared immunologic pathogenesis and the actual physical contiguity between the upper and lower airways (6–8). Many patients with allergic rhinitis who have no perceived asthma symptoms have bronchial hyperresponsiveness to natural stimuli such as exercise or to bronchial challenge with chemical stimuli (7, 9). In addition, the underlying pathophysiologic processes, immunoglobulin E (IgE)-dependent sensitivity and chronic allergic inflammation (10), are similar in the upper and lower airways (8). Studies have reinforced the link between allergic rhinitis and asthma, demonstrating that when the former condition is treated appropriately, the latter improves as well (11–14).

The pathophysiologic connection between allergic rhinitis and asthma has important implications for the development of novel treatment options for these diseases. In this context, the development of the monoclonal anti-IgE antibody (omalizumab), a novel drug that works in a broader, non-allergen-specific manner and is designed to block IgE-mediated disease early in the cascade of biologic events, has merited careful study. Phase II and III studies of treatment with omalizumab have demonstrated its efficacy and safety in treating allergic asthma and rhinitis as separate diseases (15, 16). Ongoing studies will elucidate whether treatment with omalizumab in patients with both asthma and allergic rhinitis will attenuate the allergic response and therefore demonstrate improved control of both diseases.

INITIAL CLINICAL INVESTIGATION OF OMALIZUMAB IN ALLERGIC RHINITIS

The first large clinical trial of omalizumab in allergic rhinitis was conducted in 1994, with the aim of evaluating the safety and efficacy of repeated doses of the drug in adults with a history of significant ragweed-induced disease (17). It also examined the pharmacodynamic relationship between omalizumab and blood IgE levels.

The trial was a seven-center, double-blind, placebo-controlled study that enrolled 240 patients, who were randomized into one of five groups. Altogether, 181 patients received an intravenous loading dose of omalizumab 1 mo before ragweed season, followed by one of three additional doses of omalizumab, given either subcutaneously or intravenously, in a ratio to body weight of 0.15 mg/kg (subcutaneous), 0.15 mg/kg (intravenous), or 0.5 mg/kg (intravenous). The other two groups were given placebo intravenously and placebo subcutaneously. The drug was administered every other week during the ragweed season for 12 wk, with an 8-wk follow-up period added thereafter (17).

The trial findings confirmed that ragweed-specific IgE levels correlated with symptom scores. Omalizumab-treated subjects experienced a rapid dose- and baseline IgE-dependent decrease in free IgE levels in their serum. The clearance of IgE bound to omalizumab is slower than the typical clearance of free IgE in serum. Therefore, there was a simultaneous increase in total IgE in the omalizumab-treated subjects. Importantly, it was also observed that omalizumab produced the same pharmacokinetic effects whether it was administered subcutaneously or intravenously. In addition, the study confirmed earlier data regarding the safety and tolerability of omalizumab (18). Adverse events were mild, and their frequencies did not differ between the active drug and the placebo groups (17).

Efficacy, however, was not demonstrated, since only 11 patients achieved IgE levels that were below detectable limits. Nevertheless, the finding that symptom scores correlated with IgE and that free IgE in serum declined in a dose-dependent manner suggested that omalizumab could ameliorate seasonal allergic rhinitis symptoms if given in adequate doses. In fact, our analysis of unbound and complexed IgE suggested that the efficacy of omalizumab would improve if its dosing were based on the patient's baseline IgE value (17).

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DOSE-RANGING TRIAL

Based on the results of this study, a second large multicenter study compared three subcutaneous doses of omalizumab: 50 mg, 150 mg, and 300 mg, with placebo (19). The dose-response relationships to symptoms, quality of life, and reduction in the use of rescue medication were studied in 536 patients with moderate to severe ragweed-induced allergic rhinitis of at least 2-yr duration.

In the double-blind trial, patients were randomized to placebo or one of the three doses of omalizumab approximately 2 wk before the onset of the ragweed pollen season. Hypothesizing that baseline IgE levels were important in the dosing strategy, the investigators established the frequency with which patients received their assigned treatment according to baseline IgE levels: those with serum IgE levels of 30 to 150 IU/ml received their assigned treatment at 0, 4, and 8 wk and those with IgE levels of 151 to 700 IU/ml received treatment at 0, 3, 6, and 9 wk. Patients were initially followed for 12 wk, recording nasal and ocular symptom severity scores (on scales of 0 to 3), the use of rescue medication, and changes in quality of life. An additional 12-wk observation period was included in the study design (19).

As anticipated, the mean daily nasal symptom severity scores (sneezing or itchy, runny, or stuffy nose), rated on a scale of 0 to 3 depending on the severity of symptoms (0 = no symptoms, 3 = severe symptoms) for patients receiving placebo, rose with the pollen count, but in patients receiving the 300-mg dose of omalizumab, there was no increase in these scores, not even during the peak ragweed season. The difference between the placebo and the 300-mg omalizumab groups was statistically significant throughout the pollen season as well as the peak season ($p = 0.001$, one-sided t test). Patients receiving the 150-mg dose of omalizumab had lower mean symptom scores with drug levels, but the difference from the scores in the placebo group was not statistically significant (19).

Regression analysis of the daily nasal symptom scores confirmed a linear dose-response relationship ($p < 0.001$). The mean daily ocular symptom severity scores were 0.41, 0.45, 0.49, and 0.67 for the 300-mg omalizumab, 150-mg omalizumab, 50-mg omalizumab, and placebo groups, respectively, for the entire season. The reduction in ocular symptoms for all three omalizumab groups as compared with the placebo group was significant ($p \leq 0.012$) (19).

The Rhinoconjunctivitis Quality-of-Life Questionnaire (RQLQ), a disease-specific measuring instrument with seven domains consisting of 28 items relating to activities, sleep, non-nose/eye-associated symptoms, practical problems, nasal and ocular symptoms, and emotional concerns was used to assess changes in quality of life. In the placebo group, increases in pollen count correlated with a deterioration of quality of life as manifested by higher RQLQ scores. At the highest dose of omalizumab, RQLQ scores during the peak pollen season were lower (20).

Patients who experienced unrelieved symptoms were permitted to use antihistamines as rescue medication. The proportion of days on which rescue medication was taken and the number of tablets ingested were reduced by approximately 50% in the 300-mg omalizumab group as compared with the placebo group. These parameters were also significantly reduced in the 150-mg omalizumab group, but not in the 50-mg omalizumab group (19).

The relationship between the dose of omalizumab and free IgE in serum was linear. At the 300-mg dose of omalizumab, the percentage of patients with serum IgE levels below the detectable level of 25 ng/ml was approximately 65%; at the 150-mg dose, only half as many patients reached such low serum IgE

levels. A similar relationship existed between IgE levels and nasal symptom severity scores. Patients with IgE levels from 50 ng/ml to 150 ng/ml had higher symptom scores than did patients with IgE levels below 50 ng/ml (21). Changes in the use of rescue medication in relation to IgE were noteworthy. Patients with the lowest IgE levels had a striking reduction in the use of rescue medication during the pollen season (21).

The overall incidence of adverse events across all three doses of omalizumab and placebo was similar. The adverse events thought to be drug-related and which occurred in more than 2% of patients were weight increase and headache, and this was also similar in the placebo group. Drug-related urticaria was reported in 0.5% of patients (two of 400), a number smaller than would be expected with traditional immunotherapy. There were no drug-related serious adverse events, and no anti-omalizumab antibodies were detected (19).

OMALIZUMAB IN BIRCH POLLEN ALLERGIC RHINITIS

A Scandinavian group subsequently studied the efficacy of omalizumab in treating seasonal allergic rhinitis caused by birch pollen (16). The double-blind, multicenter, placebo-controlled, parallel-group trial involved 251 patients who were randomized to receive omalizumab at 300 mg subcutaneously—the maximum effective dose determined by the previous study—or placebo in a two-to-one ratio. The study design was similar to that of the earlier trial, with dosing frequency dependent on the patients' baseline IgE levels: if levels were 150 IU/ml or lower, patients received omalizumab or placebo twice, at monthly intervals; if their baseline IgE levels were greater than 150 IU/ml, they were treated three times at 3-wk intervals. The study design was also similar to that of the earlier trial in that the first dose was intended to be given a week or two before the onset of the pollen season, but the season started early, and some patients received their initial medication at the beginning of the season or after it had begun (16).

The primary efficacy variable was the patients' average daily nasal symptom severity score. Secondary efficacy variables included the average number of rescue antihistamine tablets taken per day, the proportion of days on which any medication for seasonal allergic rhinoconjunctivitis was used, and responses to the RQLQ (16).

In all parameters of efficacy, omalizumab was superior to placebo. The average daily nasal severity score in the omalizumab group was 0.71 at baseline, varying little throughout the trial period (final value: 0.70), whereas it increased in the placebo group from 0.78 to 0.98, a significant difference from the baseline value ($p < 0.001$) (Figure 1). Treatment was also evaluated for efficacy in preventing eye symptoms, using the daily ocular symptom severity scale score. Treatment with omalizumab conferred significant improvement over placebo ($p = 0.031$). It should be noted that the late start of omalizumab treatment in relation to the start of the pollen season in some individuals may have blunted some of these already favorable results of omalizumab treatment (16).

The average number of tablets of rescue medication taken per day was significantly lower in the omalizumab group than in the placebo group (0.59 and 1.37 tablets per day, respectively; $p < 0.001$), and the proportion of days on which any rescue medication was taken was almost twice as high in the placebo group as in the omalizumab group (49% and 28%, respectively; $p < 0.001$).

Statistically significant differences in favor of omalizumab were observed in all of the RQLQ domains and in the total RQLQ score (Figure 2). Differences from placebo of more than 0.5 units are clinically meaningful (20). Twenty-one per-

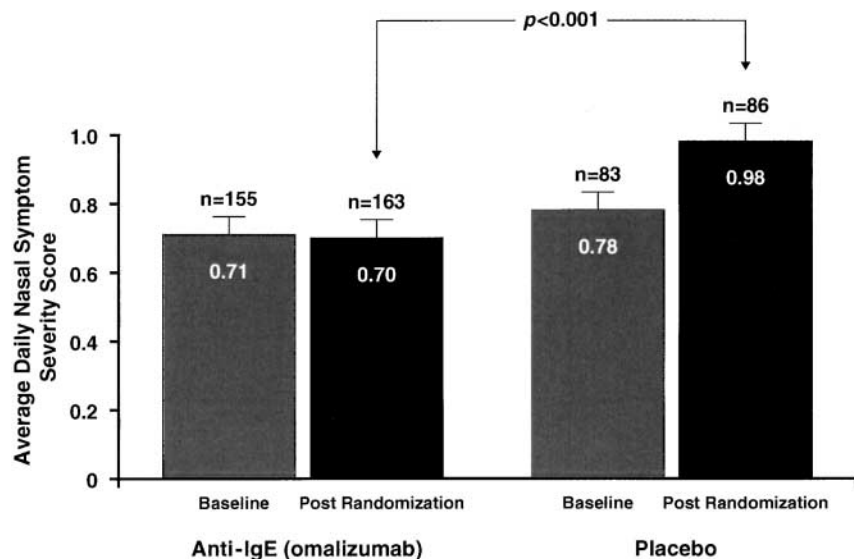


Figure 1. Average daily nasal symptom severity scores (with SEs) over the entire postrandomization period (all randomized subjects in an intent-to-treat analysis). Nasal symptom scores were rated on a scale of 0 to 3, depending on the severity of symptoms (0 = no symptoms, 3 = severe symptoms). Adapted by permission from Ädelroth E, Rak S, Haahtela T, Assand G, Rosenhall L, Zetterstrom O, Byrne A, Champain K, Thirlwell J, Cioppa GD, *et al*. Recombinant humanized mAb-E25, an anti-IgE mAb, in birch pollen-induced allergic rhinitis. *J Allergy Clin Immunol* 2000;106:253-259.

cent of patients in the omalizumab group considered their symptoms completely controlled, as compared with 2% of placebo-treated patients, and a further 59% receiving omalizumab reported improvement, as compared with 35% in the placebo group (16).

Omalizumab was also well tolerated, and no significant differences were found in either the overall incidence of adverse events or in the incidence of drug-related adverse events between the omalizumab and placebo groups. Injection-site reactions were similar in both groups, and three patients reported a total of four episodes of urticaria after administration of omalizumab, but these were mild and required no treatment. No drug-related serious adverse events were noted, and no anaphylactic reactions or serum sickness occurred. No anti-omalizumab antibodies were detected (16).

READMINISTERING OMALIZUMAB AFTER A LAPSE IN TREATMENT

One concern about omalizumab treatment that remained unresolved after these trials was whether omalizumab could be safely readministered after treatment had been discontinued for a prolonged period. This question was addressed in an extension of our dose-ranging study of omalizumab in patients with ragweed-induced seasonal allergic rhinitis.

Of the 374 patients treated with omalizumab in the original trial, 287 participated in the 12-wk open-label extension trial (22). The maximum effective dose of omalizumab from the dose-ranging study, 300 mg, was administered subcutaneously every 3 wk to subjects with baseline serum IgE levels above 150 IU/ml (37% of patients), or every 4 wk to those with baseline IgE levels of 150 IU/ml or lower (63% of patients). No placebo arm was involved, and no efficacy parameters were studied.

The incidence of adverse events was similar in both treatment groups (43% and 50%, respectively). The incidence of drug-related adverse events was also similar in both treatment groups (1.9% and 2.7%, respectively). The most frequent adverse events were headache and upper respiratory tract infection, and five patients withdrew prematurely because of adverse events, only two of which were considered drug-related, and both of which involved rashes. No adverse events were considered serious. Injection-site reactions were few and mild. No antibodies against omalizumab were detected (21).

CONCLUSION

The use of the humanized monoclonal anti-IgE antibody omalizumab, administered subcutaneously, appears to be clinically valuable in the treatment of seasonal allergic rhinitis. Nasal

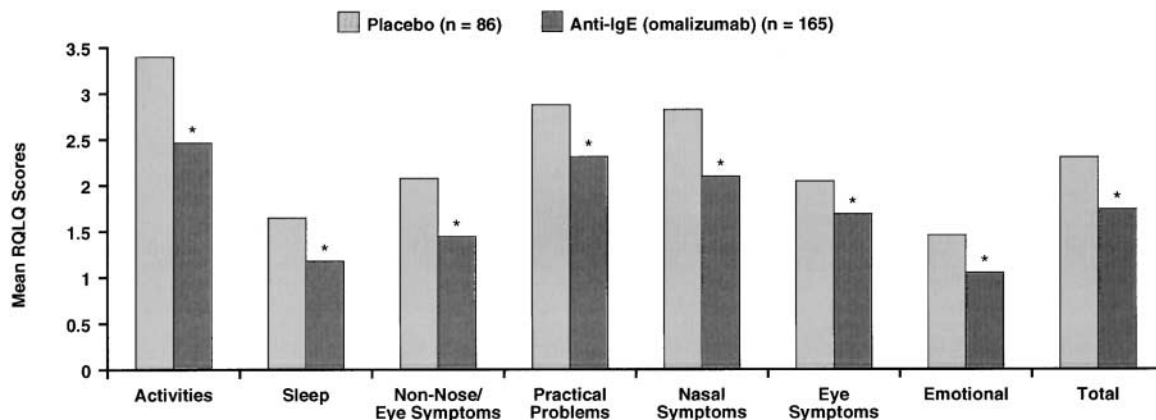


Figure 2. RQLQ scores at Week 3 or 4. Quality of life was assessed with the RQLQ (16). *p < 0.05.

and ocular symptoms are effectively controlled by this agent, and it substantially improves quality of life for patients with seasonal allergic rhinitis. Treatment with omalizumab is safe and well tolerated. Because omalizumab treatment is not allergen specific, it might be expected to help patients with seasonal allergic rhinitis caused by multiple allergens. Furthermore, because omalizumab also has proven efficacy in allergic asthma, patients with the comorbid conditions of allergic rhinitis and asthma might benefit from this novel therapeutic agent.

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