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ORIGINAL ARTICLE

Omalizumab is Effective and Safe in the Treatment of Japanese Cedar Pollen-induced Seasonal Allergic Rhinitis

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ABSTRACT

Background: Seasonal allergic rhinitis (SAR) induced by Japanese cedar pollen is a substantial problem in Japan. Omalizumab, a novel humanized monoclonal anti-immunoglobulin E (IgE) antibody, has already been proven to reduce symptoms associated with SAR. We investigated the safety and efficacy of omalizumab in the treatment of patients with Japanese cedar pollen-induced SAR compared to placebo.

Methods: A randomized, placebo-controlled, double-blind study was conducted in 100 Japanese patients with a history of moderate-to-severe SAR induced by Japanese cedar pollens. Omalizumab (150, 225, 300, or 375 mg) or placebo was administered subcutaneously every 2 or 4 weeks based on serum total IgE and body weight at baseline. The primary efficacy variable was the mean of daily nasal symptom medication scores (sum of the daily nasal symptom severity score and daily nasal rescue medication score) during the treatment period. Secondary efficacy variables included the daily ocular symptom medication score and related variables.

Results: Primary and all secondary efficacy variable scores were significantly lower in the omalizumab group than in the placebo group ($P < .01$). Serum free IgE levels markedly decreased in the omalizumab group and were associated with clinical efficacy. The overall incidence of injection site reactions was higher in the omalizumab group than in the placebo group; however, the adverse reaction profile was similar between the two groups when excluding injection site reactions. No anti-omalizumab antibodies were detected.

Conclusions: Omalizumab was effective and safe in the treatment of SAR induced by Japanese cedar pollen.

KEY WORDS

anti-IgE antibody, IgE, omalizumab, pollinosis, seasonal allergic rhinitis (SAR)

INTRODUCTION

Allergic rhinitis, especially Japanese cedar pollen-induced seasonal allergic rhinitis (SAR), is a highly prevalent disease in Japan.[1-3] Twelve percent of the total land in Japan is covered by Japanese cedar. Approximately 20 million people in Japan, who account for about 17% of the population, experience this form of SAR.[3] During the pollen season (February to April), the majority of these patients undergo treatment, *i.e.*, pharmacotherapy with antihistamines and corticosteroids, specific immunotherapy, folk medicine, and protective measures, such as masks, glasses, caps, and coats, to reduce pollen inhalation or their adhesion to the body.[1] The total direct cost of medical treatments for Japanese cedar pollen-induced SAR is estimated to be at least 120 billion yen ($1 billion dollars) annually.[4] Furthermore, daily activities and quality of life are reduced during the pollen season due to rhinoconjunctival symptoms or pharmacological side-effects.[5] Thus, SAR induced by Japanese cedar pollen is a substantial social problem in Ja-

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Omalizumab, a recombinant humanized monoclonal anti-IgE antibody, which binds to the serum free IgE molecule and forms small biologically inert complexes, blocks the interaction between IgE and effector cells which trigger the allergic response irrespective of allergen type.[6,7] Circulating free IgE can be reduced up to 99% with omalizumab,[8] thus suppressing the activation of effector cells (e.g., mast cells). Furthermore, an omalizumab-induced reduction in serum-free IgE levels eventually down-regulates FcεRI expression on basophils[8] and mast cells.[9] Down-regulation of the receptor reduces the availability of receptor sites for cross-linking of IgE. Based on this mechanism of action, omalizumab is expected to be effective for type I allergic diseases mediated by allergen-specific IgE antibodies.[10,11] Indeed, omalizumab has already been shown to be effective for birch- and ragweed-induced SAR, perennial allergic rhinitis (PAR), and allergic asthma,[12-19] and is now approved for the treatment of allergic asthma in the United States and Europe.

To investigate the safety and efficacy of omalizumab and to examine the appropriateness of its dose in Japanese patients with SAR, we conducted a randomized, placebo-controlled, double-blind study in Japanese patients with moderate-to-severe Japanese cedar pollen-induced SAR. This was the first clinical trial to treat Japanese SAR patients with omalizumab. On the basis of previous oversea studies, the dose and regimen which we employed in the present study were expected to reduce serumfree IgE levels to below 50 ng/mL, a level which is considered important to gain optimal efficacy.[20]

METHODS

STUDY SUBJECTS

Patients who met the following criteria were considered eligible for enrollment: age (20 to 64 years); a history of SAR induced by Japanese cedar pollen in at least 2 consecutive years; presentation of at least 4 of 8 moderate-to-severe symptoms (sneezing, itchy nose, runny nose, stuffy nose, itchy eyes, watery eyes, red eyes, and itchy throat), which persisted for one or more weeks during the last Japanese cedar pollen season; presence of IgE specific to Japanese cedar pollens (CAP-RAST: $\geq$2+) at baseline; serum total IgE levels of 30 to 700 IU/mL and body weights of 30 to 150 kg at baseline; and no symptoms of allergic rhinitis at 1 month prior to the onset of the screening period.

Patients who had a history of the following were excluded from the study: specific immunotherapy to Japanese cedar pollen in the previous 2 years; severe anaphylactoid or anaphylactic reactions; active or recent development (within 3 months) of any other type of rhinitis; positive reaction to omalizumab at screening; pregnant/nursing women; and serious medical conditions.

The present study was conducted in compliance with the current good clinical practice, and the protocol was approved by each institutional ethical committee. Prior to the onset of the study, written informed consent was obtained from all the patients who were enrolled.

STUDY DESIGN

This randomized, placebo-controlled, double-blind study was conducted in two regions of Japan (Tokyo and Osaka) between October 2001 and April 2002 and consisted of a 4-week screening period, a 12-week treatment period, and a 12-week follow-up period after final dosing. Following screening, eligible patients were assigned to receive omalizumab or placebo at a 1 : 1 ratio.

The start day of the Japanese cedar pollen scattering period was defined as the first of 2 consecutive days when $\geq$1 grain/cm^2 were counted; the final day of the pollen season was the first of 3 consecutive days when no grain was counted. The peak Japanese cedar pollen scattering period was defined as the span between the first and last days when $\geq$ 30 grains/cm^2 were counted.

DOSES AND ADMINISTRATION

Omalizumab (150, 225, 300, or 375 mg) or placebo was administered to patients subcutaneously every 2 or 4 weeks based on their serum total IgE level and body weight at baseline. The initial dose was administered at least at 1 month prior to the expected starting date of the Japanese cedar pollen scattering period. Omalizumab or placebo was administered to patients 3 or 6 times in total during the 12-week treatment period.

The following drugs were permitted as rescue medications: for nasal use [clemastine fumarate (tablet), sodium cromoglycate (nose drop), naphazoline nitrate (nose drop)] and for ocular use [sodium cromoglycate (eye drop)]. Concomitant use of agents were prohibited except for rescue medications. Specific immunotherapy was prohibited.

EVALUATION OF EFFICACY

Patients enrolled were requested to fill in the patient diary in order to describe their seven rhinoconjunctival symptoms (sneezing, itchy nose, runny nose, stuffy nose, itchy eyes, watery eyes, and red eyes) according to the 4-point scale (0: none, 1: mild, 2: moderate, and 3: severe) and to document rescue medication use, if any. Regarding each rescue medication, its usage was scored 1 point regardless of dose and frequency.

The primary efficacy variable was the mean of daily nasal symptom medication scores (DNSMS) during the treatment period. DNSMS (0−15 points) consisted of the sum of the daily nasal symptom severity

score (DNSS) (0–12 points) and the daily nasal rescue medication score (0–3 points).

Secondary efficacy variables included the daily ocular symptom medication score (DOSMS) (0–10 points) [sum of the daily ocular symptom severity score (DOSS) (0–9 points) and daily ocular rescue medication score (0–1 point)]; DNSS; the daily nasal rescue medication score; DOSS; the daily ocular rescue medication score; the consumption per day of rescue medications; and the proportion of days in which any rescue medication was taken.

ESTIMATION OF SERUM FREE IgE LEVELS

To investigate the relationship between serum IgE level and efficacy of omalizumab, serum free IgE levels were measured before dosing and at 4 and 12 weeks of the treatment period.[12]

EVALUATION OF SAFETY

Adverse events were examined throughout the treatment period. Laboratory tests and check-up of vital signs were conducted during the screening period and at 4 and 12 weeks of the treatment period.

During the screening period and at 12 weeks after final dosing, anti-omalizumab antibodies (IgG isotype) were measured using two solid-phase ELISA methods: one assay was to detect anti-omalizumab Fab responses; and another was to detect anti-omalizumab Fc responses.[12]

STATISTICAL ANALYSIS

One hundred patients, assigned to the omalizumab group and the placebo group at a 1 : 1 ratio, were required to detect a 0.30-point difference in the mean DNSMS between treatment groups. This calculation assumed 90% power at a significance level of 0.05, 2-sided, and at a standard deviation of 0.50 for the difference.

Regarding efficacy, the following hypothesis tests were used to examine study group comparability with respect to demographic and baseline characteristics: Fisher's exact test for gender; and Wilcoxon rank sum test for age, history of Japanese cedar pollen-induced SAR, IgE specific to Japanese cedar pollens, and serum total IgE at baseline.

The full analysis set was used to analyze the primary variable (*i.e.*, the mean DNSMS during the treatment period) and to analyze the mean DNSMS during the Japanese cedar pollen scattering period and the peak Japanese cedar pollen scattering period. These comparisons were based on the null hypothesis that there is no difference between the study groups. The mean DNSMS was analyzed using an ANCOVA model which included study group, location, and administration interval (2- or 4-week interval). The least-squares mean (LSM) for each group and the difference in LSM between the study groups were determined. The mean DOSMS, each of symptom severity scores, and each of rescue medication scores were also analyzed similarly to the analysis of the mean DNSMS.

The safety and tolerability of the study drugs are summarized by appropriate descriptive methods.

RESULTS

PATIENT CHARACTERISTICS

Ninety-eight of 100 randomized subjects received either of the study drugs: 48 received omalizumab (50 randomized) and 50 received placebo. The remaining two subjects in the omalizumab group withdrew during the screening period due to personal reasons. No significant difference was found between the omalizumab group and the placebo group with respect to patient characteristics (Table 1).

The Japanese cedar pollen scattering period started at the beginning of February and finished at the end of April (Fig. 1). All subjects received the first administration at least at 1 month prior to the starting date of the Japanese cedar pollen scattering period.

Five subjects (three receiving omalizumab and two receiving placebo) discontinued the study prematurely; among them, three (two receiving omalizumab and one receiving placebo) ceased the study due to adverse events.

EFFICACY

Daily Nasal Symptom Medication Score (DNSMS)

Changes in DNSMS over time are shown in Figure 1. DNSMS throughout the Japanese cedar pollen scattering period were consistently lower in the omalizumab group than in the placebo group.

The omalizumab group showed significantly lower mean DNSMS compared to the placebo group during the treatment period [LSM ± (SE), 1.391 ± 0.1769 for the omalizumab group and 2.499±0.1740 for the placebo group; $P < .001$; Figure 2A]. Statistical analyses revealed similar results with respect to the relevant scores during the Japanese cedar pollen scattering period (1.915 ± 0.2267 and 3.528 ± 0.2258, respectively; $P < .001$; Figure 2A) and the peak Japanese cedar pollen scattering period (2.586 ± 0.2907 and 4.511 ± 0.2886, respectively; $P<.001$; Figure 2A). During the Japanese cedar pollen scattering period, subjects with lower mean DNSMS were distributed predominantly in the omalizumab group than in the placebo group, with greater numbers of subjects with scores of 0–1 and >2–4 in the former and latter groups, respectively. About half of subjects in the omalizumab group had a mean DNSMS of≤2 (mild or less severe symptoms) in contrast to 15% in the placebo group. More than 10% of subjects in the placebo group had scores of >6 (severe symptoms) compared to none in the omalizumab group (Fig. 2B).

As shown in Figure 1, the amount of Japanese cedar pollen in Tokyo was larger than that of Osaka

Table 1 Patient characteristics

	Omalizumab (n = 48)	Placebo (n = 50)
Gender		
Male	25	28
Age (years)		
Mean ± SD	32.2 ± 12.1	31.5 ± 12.3
Range	20 – 62	20 – 64
History of SAR induced by Japanese cedar pollens (years)		
Mean± SD	11.3 ± 6.2	9.6 ± 5.4
Range	4 – 35	3 – 26
Specific IgE levels against Japanese cedar pollens (CAP-RAST)*		
Class 2 (0.70 – 3.49 UA/mL)	3	0
Class 3 (3.50 – 17.49 UA/mL)	15	12
Class 4 (17.50 – 49.99 UA/mL)	19	25
Class 5 (50.00 – 99.99 UA/mL)	8	9
Class 6 (≥ 100 UA/mL)	3	4
Serum total IgE levels at baseline (IU/mL)		
Mean ± SD	193.7 ± 166.6	188.7 ± 145.8
Range	32.0 ± 590.0	34.0 ± 570.0

*: Specific IgE levels against Japanese cedar pollens at baseline were categorized into 7 groups (Classes 0 to 6), and a ≥2 class group was assessed to be positive against the allergen.

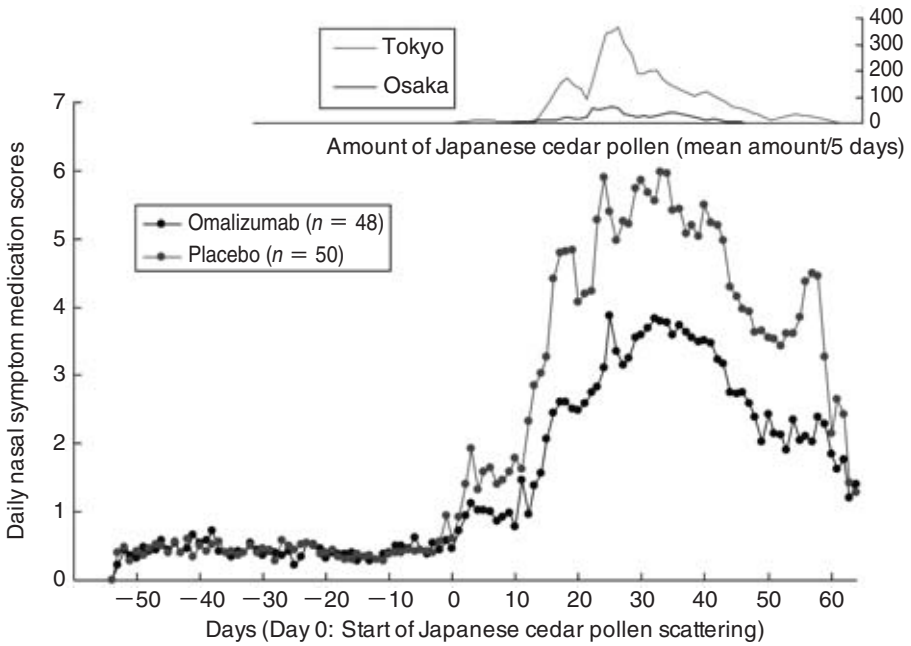

Fig. 1 Time-course changes in daily nasal symptom medication score (FAS) and in amount of Japanese cedar pollen. Day 0 represents the start day of the Japanese cedar pollen scattering period in Tokyo and Osaka.

(5648 grains/cm^2 for Tokyo and 913 grains/cm^2 for Osaka). Although in the placebo group as well as in the omalizumab group, the subgroup of Tokyo showed higher mean DNSMS compared to that of Osaka, the mean DNSMS were consistently lower in the omalizumab group than in the placebo group in Tokyo and Osaka, respectively [Mean ± (SE), 3.020 ± 0.2576 and 4.697 ± 0.3390 for Tokyo, 1.141 ± 0.2423 and 2.705 ± 0.2682 for Osaka, the Japanese cedar pollen scattering period]. Statistically, there was no interaction between the treatment group and the region (P = .8429).

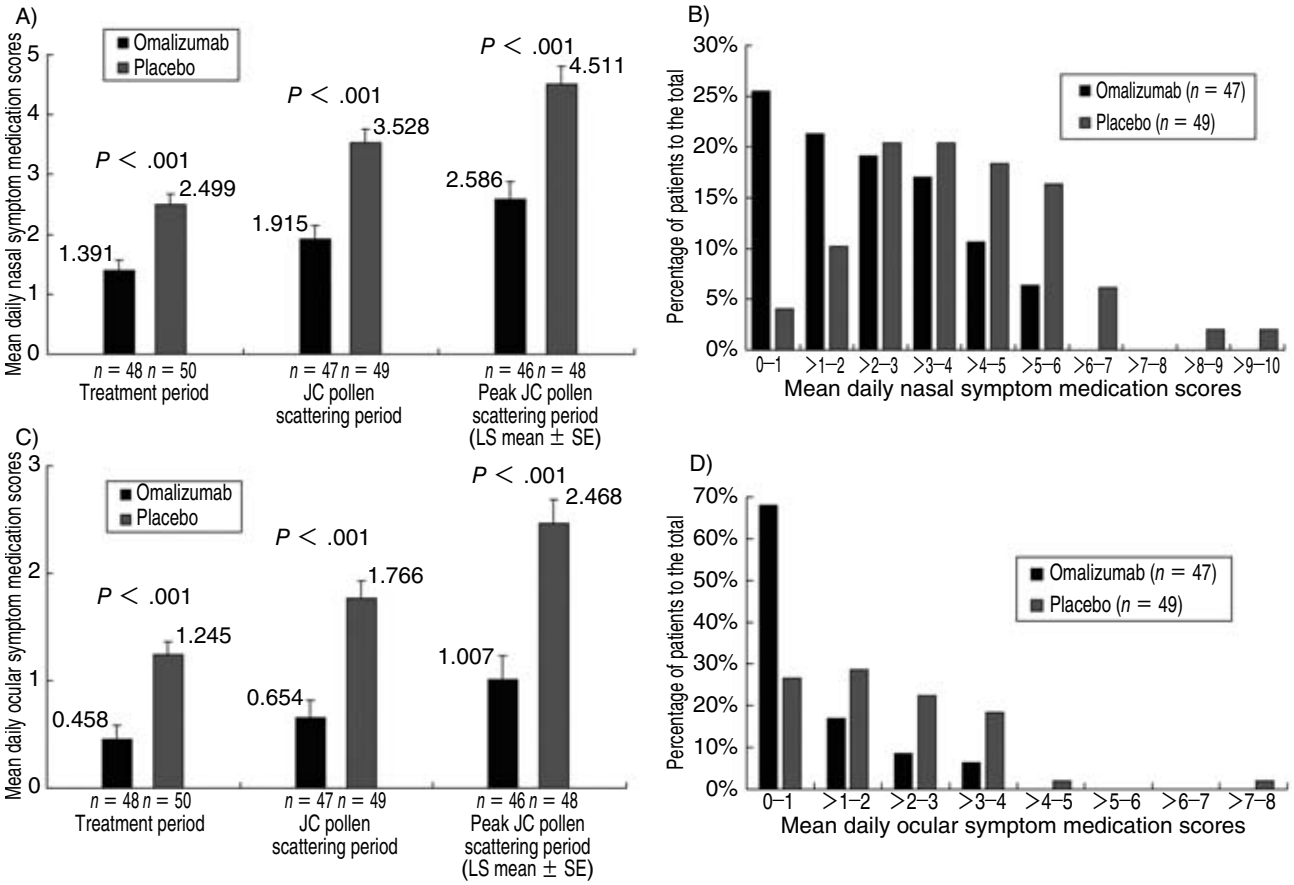

Fig. 2 **A**) Mean daily nasal symptom medication scores (DNSMS) and **C**) mean daily ocular symptom medication scores (DOSMS) during the treatment period, the Japanese cedar (JC) pollen scattering period, and the peak JC pollen scattering period. Percentages of the total of patients with **B**) mean DNSMS and **D**) mean DOSMS during the JC pollen scattering period.

Daily Nasal Rescue Medication Score

The mean daily nasal rescue medication scores were significantly lower in the omalizumab group than in the placebo group during the three evaluation periods (e.g., 0.055 ± 0.0503 and 0.260 ± 0.0499, respectively; $P = .002$, the peak Japanese cedar pollen scattering period).

Daily ocular symptom medication score (DOSMS)

The omalizumab group had significantly lower mean DOSMS compared to the placebo group during the treatment period (0.458 ± 0.1248 and 1.245 ± 0.1227, respectively; $P < .001$; Fig. 2C). Statistical analyses revealed similar results with respect to the relevant scores during the Japanese cedar pollen scattering period (0.654 ± 0.1675 and 1.766 ± 0.1688, respectively; $P < .001$) and the peak Japanese cedar pollen scattering period (1.007 ± 0.2244 and 2.468 ± 0.2228, respectively; $P<.001$). During the Japanese cedar pollen scattering period, approximately 70% (32/47) of subjects in the omalizumab group had ocular symptom medication scores of≤1 (Fig. 2D).

Daily Ocular Rescue Medication Score

The mean ocular rescue medication scores were significantly lower in the omalizumab group than in the placebo group during the three evaluation periods (e.g., 0.031 ± 0.0360 and 0.191 ± 0.0357, respectively; $P< .001$, the peak Japanese cedar pollen scattering period).

Daily nasal and ocular symptom severity scores (DNSS & DOSS)

The omalizumab group had significantly lower mean DNSS compared to the placebo group during the three evaluation periods (e.g., 1.880 ± 0.2183 and 3.349 ± 0.2175, respectively; $P < .001$, the Japanese cedar pollen scattering period). Each of the mean DNSS and DOSS during the three evaluation periods (sneezing, runny nose, stuffy nose, itchy nose, itchy eyes, watery eyes, and red eyes) was significantly lower in the omalizumab group (P values ranging from < .001 to .003; Fig. 3).

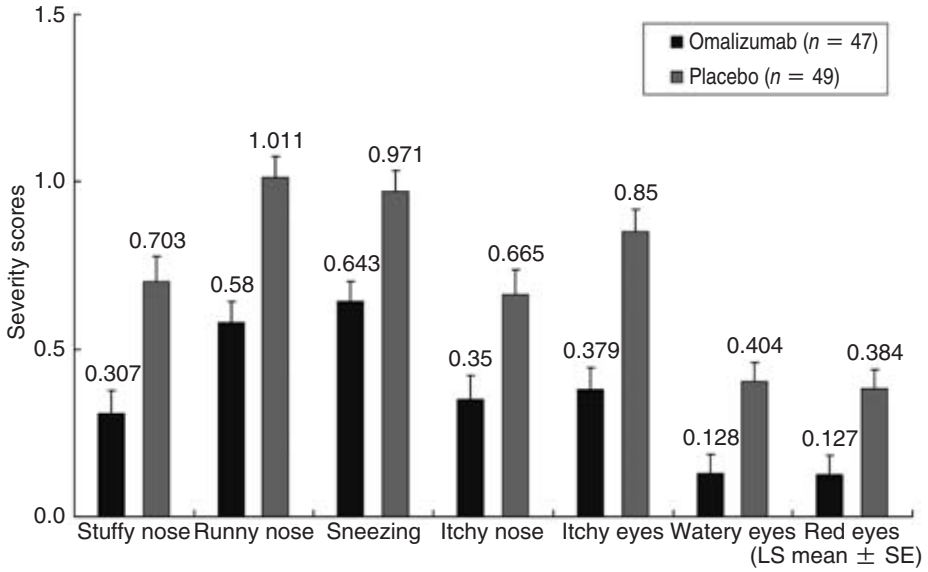

Fig. 3 Effects of omalizumab on each of the mean daily nasal and ocular symptom severity scores (FAS) during the Japanese cedar pollen scattering period ($P < .001$ for all variables). Statistically significant differences were noted during the treatment period and peak Japanese cedar pollen scattering periods.

Use of Rescue Medications

The mean consumption per day of each of the three rescue medications [clemastine fumarate (tablet), sodium cromoglycate (nose drop, eye drop)] was significantly lower in the omalizumab group than in the placebo group during the three evaluation periods (P values ranging from .002 to .017), and naphazoline nitrate (nose drop) tended to show a significant difference in consumption. The proportions of days in which any rescue medication was taken were almost 5-fold higher in the placebo group than in the omalizumab group (e.g., 25.4% and 5.6%, respectively; $P < .001$, the peak Japanese cedar pollen scattering period).

SERUM FREE IgE LEVELS

Serum free (total) IgE levels in the omalizumab group and the placebo group at baseline were at similar levels (Table 1). After administrations, serum free IgE levels in the omalizumab group decreased markedly, compared to the baseline levels to below 50 ng/mL at 4 and 12 weeks of the treatment period in all subjects (range from 6.1 ng/mL to 39.6 ng/mL). In the placebo group, serum free IgE levels were comparable to the baseline levels throughout the treatment period (range from 39.7 ng/mL to 1314 ng/mL).

SAFETY

Treatment with omalizumab was generally well tolerated. Due to the higher overall incidence of injection site reactions in the omalizumab group, the overall incidences of drug-related adverse events were significantly higher in the omalizumab group than in the placebo group; nevertheless, the adverse reaction profile was similar between the study groups when excluding injection site reactions (Table 2). One serious adverse event (colitis ulcerative) was reported in one subject in the omalizumab group, who was subsequently withdrawn from this study. However, the investigator considered its causality with the drug unlikely. Another subject in the omalizumab group and one subject in the placebo group discontinued treatment because of non-serious adverse events which were not drug-related. There were no anaphylactic reactions, and neither evidence of immune complex disease, nor clinically important abnormalities in vital signs and laboratory tests were found. No anti-omalizumab antibodies were detected.

DISCUSSION

This randomized, placebo-controlled, double-blind study revealed that omalizumab was generally well tolerated and was effective in preventing and controlling rhinoconjunctival symptoms associated with Japanese cedar pollen-induced SAR and in reducing rescue medication use for rhinoconjunctival symptoms.

Although the amount of Japanese cedar pollen in Tokyo was larger than that of Osaka, the mean DNSMS were consistently lower in the omalizumab group than in the placebo group in Tokyo and Osaka, respectively. Statistically, there was no interaction between the treatment group and the region. Taken to-

Table 2 Drug-related adverse events

		Omalizumab ($n = 48$)	Placebo ($n = 50$)
Total number of patients with ADR*		19 (39.6)	10 (20.0)
Gastrointestinal disorders		1 (2.1)	1 (2.0)
Colitis ulcerative		1 (2.1)	0
Diarrhea		0	1 (2.0)
General disorders and administration site conditions		13 (27.1)	5 (10.0)
Injection site*	Erythema	7 (14.6)	2 (4.0)
	Induration	1 (2.1)	1 (2.0)
	Edema	8 (16.7)	1 (2.0)
	Pain	2 (4.2)	1 (2.0)
	Pruritus	2 (4.2)	0
Feeling hot		1 (2.1)	0
Fatigue		0	1 (2.0)
Pain		1 (2.1)	0
Fever		0	1 (2.0)
Nervous system disorders		0	2 (4.0)
Headache		0	2 (4.0)
Skin and subcutaneous tissue disorders		1 (2.1)	2 (4.0)
Dry skin		1 (2.1)	0
Rash		0	1 (2.0)
Face edema (lip swelling)		0	1 (2.0)
Investigations		4 (8.3) #1	4 (8.0) #2

*: $P < .05$; ↑ : increased; ↓ : decreased

#1: Bilirubin ↑ (1), neutrophil ↓ (1), WBC ↓ (1), WBC ↑ (2)

#2: GPT ↑ (1), eosinophil ↑ (2), lymphocyte ↓ (1), WBC ↑ (1)

gether, regardless of the amount of Japanese cedar pollens, omalizumab would be more effective against SAR.

Our results indicate that subjects treated with omalizumab not only had significantly less severe nasal and ocular symptoms, but also required significantly less rescue medication compared to subjects receiving placebo. In addition, we conducted a double-blind controlled studyusing a competing antiallergy drug in the next Japanese cedar pollen scattering period, *i.e.*, from February to April 2003. The results showed that omalizumab had significantly lower nasal symptoms and consumption of rescue medications than the competitor (data not shown). Our results suggest that monotherapy with omalizumab at a 2- or 4-week interval can control both nasal and ocular symptoms, thus simplifying SAR therapy.

The omalizumab regimen in the present study was considered appropriate also for Japanese patients with SAR because the regimen successfully decreased serum free IgE levels to below 50 ng/mL, providing proper clinical efficacy, in contrast to the results obtained in foreign studies.

In the omalizumab group, all adverse events except for one (colitis ulcerative) were mild or moderate in severity. The most frequently observed drug-related adverse event in the omalizumab group and the placebo group were injection site reactions, with a significantly higher overall incidence in the former; however, the adverse reaction profile was similar between the two groups when excluding the incidences of injection site reactions. No clinically important abnormal values in laboratory tests or vital signs were reported; no anti-omalizumab antibodies were detected. Furthermore, no cases of anaphylaxis were reported. Therefore, the safety profile of omalizumab in the treatment of SAR seems favorable.

To determine whether omalizumab could consistently provide safety and efficacy in the subsequent season, we conducted an open-label study in the next Japanese cedar pollen scattering period, *i.e.*, from February to April 2003, in order to administer omalizumab to the same subjects who had received the drug in the present study. Consequently, the open-label study revealed no serious adverse events at all and was comparable to the present study with respect to both efficacy and safety (data not shown).

The site of action of omalizumab is localized in free IgE in the circulation, probably local tissues. Omalizumab forms small biologically inert immunocomplexes with free IgE and blocks the interaction between IgE and FcεR which is expressed on the surface of target cells. Additionally, decreases in free IgE levels in microenvironments around mast cells and dendritic cells have been proven to induce the down-regulation of FcεRI expression on the cell surface;[9,21]

the relevant down-regulation is noteworthy because it provides a clinical benefit of possibly reducing the reactivity of mast cells. B lymphocyte apoptosis, the inhibition of IgE production by B lymphocytes,[22,23] and the inhibition of Th2 cytokine production[24] may also be induced by omalizumab treatment. A significant decrease in serum free-IgE levels induced by omalizumab only resembles the transient knockout of IgE because it recovers in a few months after the completion of administration.[12] Considered comprehensively, omalizumab may be potentially beneficial for SAR patients in the clinical settings because it strategically targets sites upstream from the allergic reaction cascade.

Other studies have shown the efficacy of omalizumab for SAR induced by ragweed or birch pollens.[12-14] Recently, its efficacy in perennial allergic rhinitis (PAR)[15] has also been reported. Thus, omalizumab has also clinically been proven to be effective for allergic rhinitis regardless of allergen type and clinical entity. Furthermore, omalizumab induces a non-anaphylactogenic condition, and its combination with specific immunotherapy effectively suppresses enhanced immune responsiveness of patients to a particular allergen and also enhances the efficacy of specific immunotherapy.[25]

In conclusion, omalizumab was well tolerated and effective in preventing and controlling symptoms and in reducing rescue medication use in patients with moderate-to-severe Japanese cedar pollen-induced SAR. Therefore, omalizumab represents a new promising therapeutic modality for patients with SAR induced by Japanese cedar pollens.

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