

Re-Treatment with Omalizumab at One Year Interval for Japanese Cedar Pollen-Induced Seasonal Allergic Rhinitis Is Effective and Well Tolerated

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Key Words

Omalizumab · Seasonal allergic rhinitis · Anti-IgE antibody

Abstract

Background: Seasonal allergic rhinitis (SAR) induced by Japanese cedar pollens is a serious problem in Japan. Omalizumab, a humanized monoclonal anti-IgE antibody, improves symptoms associated with SAR, but a study comprehensively investigating the clinical efficacy, safety and pharmacological effects of omalizumab re-treatment has not yet been conducted. **Methods:** The open-label, 12-week study was carried out in 34 patients who had been treated with omalizumab in the core study conducted in the previous Japanese cedar pollen season. The study plan including study period, efficacy and safety endpoints, as well as dose regimen, was designed to be the same as in the core study. Omalizumab was administered subcutaneously every 2 or 4 weeks based on the serum IgE level and body weight of each patient. **Results:** Time course changes in daily nasal symptom medication scores as well as in daily ocular symptom medication scores throughout the pollen period were comparable with those in the omalizumab group in the core study. Serum free IgE levels decreased to below the target level in all patients and were equal to those in the omalizumab group in the core study. The adverse reaction profiles

were similar to those in the core study. In addition, the overall incidence of drug-related adverse events and injection site reactions in the re-treatment study did not increase compared with those in the omalizumab group in the core study. There were no serious adverse events, and no anti-omalizumab antibodies were detected. **Conclusion:** Omalizumab was effective and safe when consecutively readministered in the second Japanese cedar pollen season.

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Introduction

Seasonal allergic rhinitis (SAR), especially Japanese cedar pollen-induced SAR, is a considerable medical problem in Japan, afflicting approximately 20% of the Japanese people [1]. Symptoms can range from mild to seriously debilitating and can influence the quality of life by causing fatigue, headache, cognitive impairment and other systemic symptoms. Such symptoms can result in the loss of work productivity and in missed school days [2].

Omalizumab is a recombinant humanized monoclonal anti-IgE antibody currently approved in the US and Europe for treating inadequately controlled allergic asthma which selectively binds to the Cε3 domain of IgE that interacts with IgE receptors on effector cells [3]. This an-

Table 1. Dosing tables for omalizumab administered every 4 (A) or every 2 weeks (B)

Baseline IgE IU/ml	Body weight, kg				
	≥30–60	>60–70	>70–80	>80–90	>90–150
A ≥30–100	150	150	150	150	300
>100–200	300	300	300	300	
>200–300	300				
B ≥30–100					
>100–200					225
>200–300		225	225	225	300
>300–400	225	225	300	300	
>400–500	300	300	375	375	
>500–600	300	375			
>600–700	375				

Omalizumab doses are given in mg/dose.

tibody blocks the binding of IgE to high-affinity receptors, thereby preventing the IgE-mediated cellular responses [4].

We have previously demonstrated the noticeable clinical effects of this novel antibody on Japanese cedar pollen-induced moderate to severe SAR against placebo [5] and suplatast tosilate [6]. Because Japanese cedar pollen-induced SAR develops between February and April every year, we further tried to investigate the clinical efficacy, safety and pharmacological effects of re-treatment with omalizumab.

This open-label re-treatment study was an extension of the placebo-controlled core study which had been conducted in the previous year [5] and was undertaken during the following Japanese cedar pollen season in patients who had received omalizumab in the placebo-controlled core study. This is the first study to comprehensively investigate the clinical efficacy, safety and pharmacological effects of omalizumab re-treatment, and we have compared the results obtained from this re-treatment study with those from the core study.

Materials and Methods

Participants

Patients who met the following criteria were considered eligible for enrollment: (1) having received omalizumab in the core study conducted in the previous Japanese cedar pollen season; (2) serum total IgE levels of 30–700 IU/ml and body weights of 30–150 kg at baseline.

Patients who had a history or clinical status of the following were excluded from the study: (1) specific immunotherapy to Japanese cedar pollens in the previous 2 years; (2) severe anaphylactoid or anaphylactic reactions; (3) active or recent development (within 3 months prior to the study onset) of any other type(s) of rhinitis; (4) positive reaction to omalizumab in the skin test at screening; (5) pregnant/nursing women, and (6) serious medical conditions (e.g., cancer, hepatic failure and renal failure).

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 open-label study was conducted in 2 regions of Japan (Tokyo and Osaka) between October 2002 and April 2003 and consisted of a 4-week screening period, a 12-week treatment period and a 12-week follow-up period after final dosing. The study design including study period, efficacy and safety endpoints, as well as dose regimen, was the same as in the core study.

Daily pollen counts were measured in Tokyo and Osaka. The first day of the pollen period was defined as the first of 2 consecutive days when ≥ 1 grain/cm² was counted; the last day of the pollen period was the first of 3 consecutive days when no grain was counted.

Doses and Administration

Omalizumab (150 or 300 mg every 4 weeks, or 225, 300 or 375 mg every 2 weeks) was administered to patients subcutaneously based on their serum total IgE level and body weight at baseline (table 1), which ensured a minimum dose of 0.016 mg/kg/IgE (IU/ml) every 4 weeks [7]. The initial dose was administered at least 1 month prior to the expected starting date of the pollen 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). Agents, which were prohibited for use as concomitant drugs, were leukotriene antagonists, corticosteroids, antihistamines (except for rescue medications), anticholinergic agents, nasal vasoconstrictors (except for rescue medications), tricyclic antidepressants, and monoamine oxidase inhibitors. Specific immunotherapy was prohibited.

Evaluation of Efficacy

Patients enrolled were requested to fill in the patient diary in order to describe their 7 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; 3 = severe) and to document their rescue medication use, if any. Regarding each rescue medication, its usage was scored as 1 point regardless of dose and frequency.

The daily nasal symptom medication score (0–15 points) consisted of the sum of the daily nasal symptom severity score (0–12 points) and the daily nasal rescue medication score (0–3 points). The daily ocular symptom medication score (0–10 points) also consisted of the sum of the daily ocular symptom severity score (0–9 points) and the daily ocular rescue medication score (0–1 point).

Serum Total and Free IgE Levels

Blood samples were collected for the measurement of total and free IgE at baseline and at 2, 4, 8 and 12 weeks of the treatment period. Total and free IgE were measured by ELISA, as previously described [8].

Evaluation of Safety

Adverse events were examined throughout the treatment period. Clinical laboratory tests were conducted at baseline and at 2, 4, 8 and 12 weeks of the treatment period. Anti-omalizumab antibodies (IgG subtype) were measured by using solid-phase ELISA at baseline, as well as 12 weeks after the final dosing [9].

Statistical Analysis

In efficacy and serum free IgE analyses, patients who completed both the re-treatment and core studies without protocol violations were included. In safety and serum total IgE analyses, data from the patients in the core study who also enrolled in the re-treatment study were used to compare the re-treatment study data. Comparisons of serum total IgE were made using Wilcoxon's signed rank sum test. A 2-tailed p value <0.05 was considered statistically significant.

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

Results

Of the 48 patients treated with omalizumab in the core study, 34 patients entered this study. None of the patients showed a positive reaction to omalizumab in the skin test at screening. Only 1 patient discontinued the study due to adverse events, but none of the patients discontinued the study because of unsatisfactory therapeutic effect. Patient characteristics are shown in table 2. Thirty-one patients completed both the re-treatment and core study without protocol violations.

The pollen period started at the beginning of February and continued to the end of April, which was the same as in the previous year (fig. 1). The total amount of Japanese cedar pollens during the season in Tokyo and Osaka was as follows: re-treatment study, 3,542 grains/cm² for Tokyo and 1,855 grains/cm² for Osaka; core study, 5,648 grains/cm² for Tokyo and 913 grains/cm² for Osaka.

All patients received the first administration at least 3 weeks prior to the starting date of the pollen period.

Daily Nasal and Ocular Symptom Medication Score

Time course changes in daily nasal and ocular symptom medication scores are shown in figure 1a, b. Daily nasal symptom medication scores as well as daily ocular symptom medication scores throughout the pollen period were comparable with those in the omalizumab group in the core study and were markedly lower than those in

Table 2. Patient characteristics in the omalizumab group (n = 34)

Gender	
Male/female	20/14
Age, years	
Mean $\pm$ SD	32.4 $\pm$ 11.9
Range	21 – 64
History of SAR induced by Japanese cedar pollens, years	
Mean $\pm$ SD	12.5 $\pm$ 6.2
Range	5 – 36
Specific IgE levels against Japanese cedar pollens (CAP-RAST) ¹	
Class 2 (0.70–3.49 UA/ml)	7
Class 3 (3.50–17.49 UA/ml)	18
Class 4 (17.50–49.99 UA/ml)	9
Serum total IgE levels at baseline, IU/ml	
Mean $\pm$ SD	127.8 $\pm$ 110.9
Range	29.4 – 447.8

¹ Specific IgE levels against Japanese cedar pollens at baseline were categorized into 7 groups (classes 0–6), and a class ≥ 2 group was assessed to be positive against the allergen.

the placebo group in the core study. Similar results were obtained with respect to mean daily nasal symptom medication scores as well as to mean daily ocular symptom medication scores during the pollen period (table 3). The use of the rescue medications was infrequent and was comparable with that in the omalizumab group in the core study (data not shown).

Baseline Serum Total IgE Levels

Baseline serum total IgE levels were comparable with those in the omalizumab group in the core study (median 88.6 IU/ml, range 29.4–447.8, for the re-treatment study, and median 82.5 IU/ml, range 36.2–441.0, for the core study; $p = 0.09$; fig. 2).

Serum Free IgE Levels

Serum free IgE levels decreased markedly, compared with the baseline levels, to below the target (50 ng/ml) at 2, 4, 8 and 12 weeks of the treatment period in all patients (range 4.2–36.7 ng/ml; fig. 3). Serum free IgE levels at 4 and 12 weeks were equal to those in the omalizumab group in the core study.

Safety

Re-treatment with omalizumab was generally well tolerated. The overall incidence of drug-related adverse events in the re-treatment study was lower than that in both the omalizumab group (table 4) and the placebo

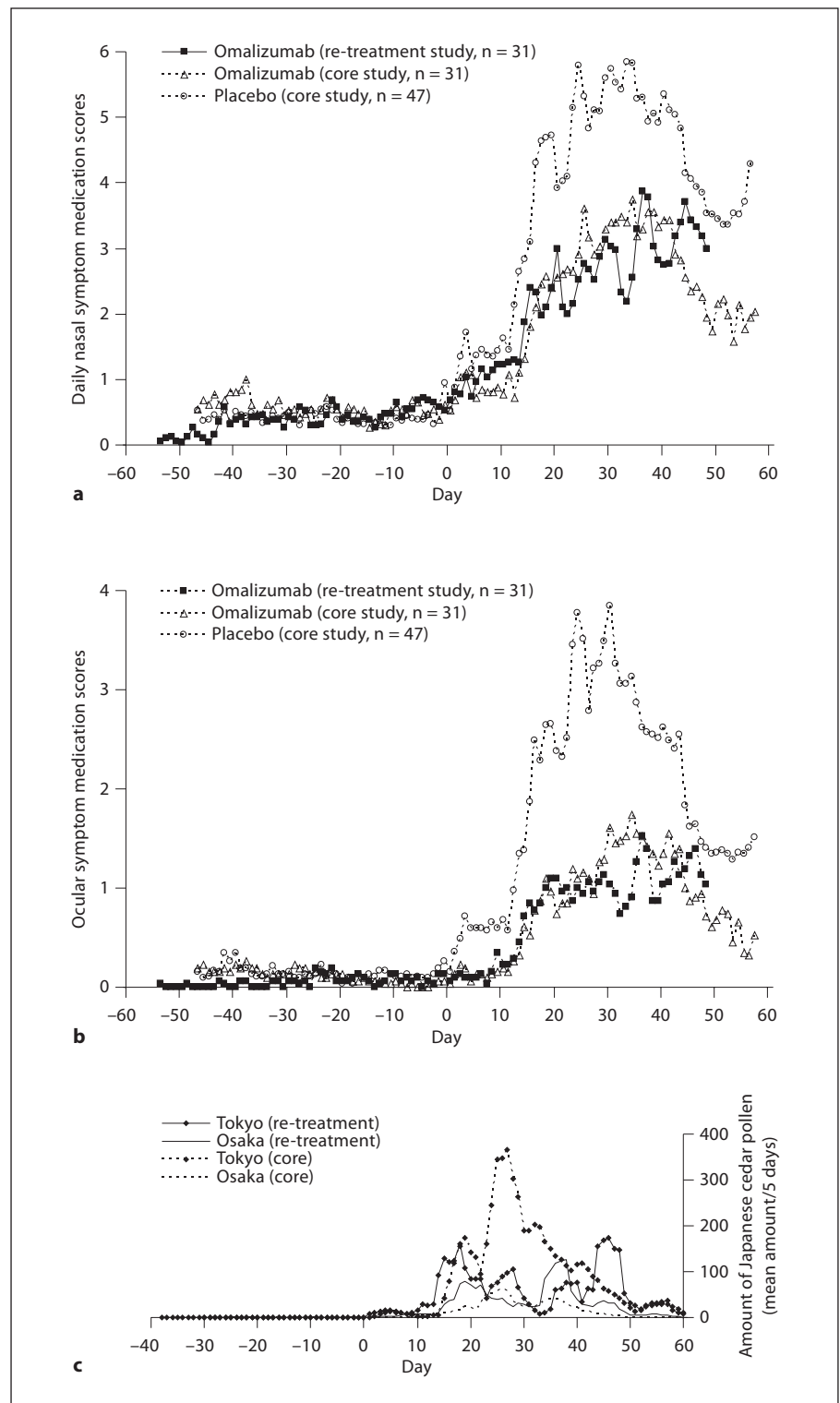
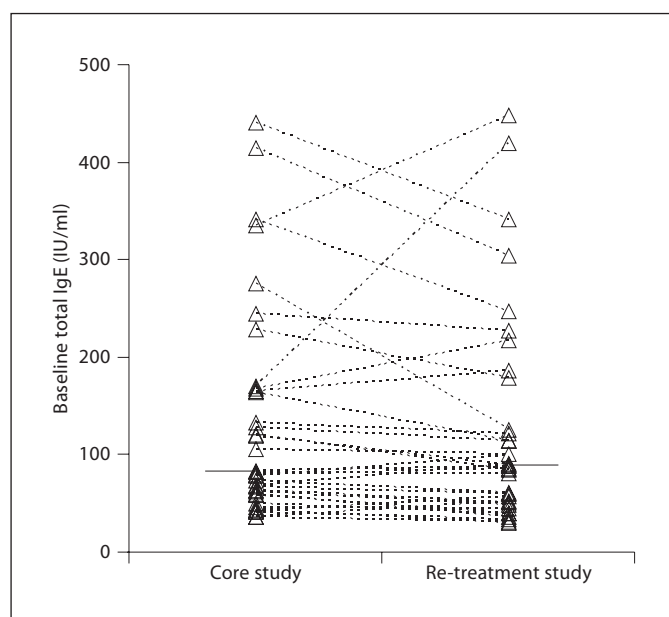


Fig. 1. Time course changes in daily nasal symptom medication score (a), daily ocular symptom medication score (b), and amount of Japanese cedar pollen (c). Day 0 represents the start day of the pollen period in Tokyo and Osaka.

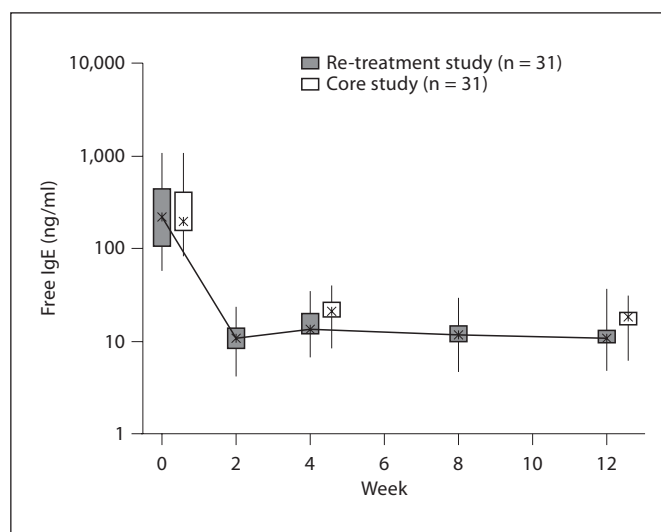
Table 3. Mean daily nasal and ocular symptom medication scores (mean $\pm$ SE)

	Re-treatment study	Core study	
	omalizumab (n = 31)	omalizumab (n = 31)	placebo (n = 47)
Mean daily nasal symptom medication scores	2.345 $\pm$ 0.2736	2.206 $\pm$ 0.2723	3.753 $\pm$ 0.2484
Mean daily ocular symptom medication scores	0.820 $\pm$ 0.1459	0.795 $\pm$ 0.1562	1.904 $\pm$ 0.1642

**Fig. 2.** Comparison of serum total IgE level of each patient (n = 34) at baseline between the re-treatment study and the core study (omalizumab group). Each symbol shows an individual value; horizontal bars are median values.

group (20.0%, 10/50) in the core study. The most frequently reported drug-related adverse events in both studies were injection site reactions, but the incidence rate in the re-treatment study was lower than that in the omalizumab group and higher than that in the placebo group (8.0%, 4/50) in the core study.

One patient discontinued treatment because of severe adverse events (injection site pain and injection site discomfort) which developed 23 days after the first dose of omalizumab and disappeared without additional treatment. The investigator considered their relations with the drug not denied because the causes were unclear. All adverse events except those two were of mild degree in the re-treatment study.

**Fig. 3.** Time course changes in serum free IgE levels (n = 31) in the re-treatment study (grey boxes) and in the core study (omalizumab group, white boxes). The boxes include the interval between the 25th and 75th percentiles. The extremes represent the minimum and maximum values. The median is shown as an asterisk. Day 0 represents the first day of therapy with omalizumab.

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 is the first study comprehensively investigating the clinical efficacy, safety and pharmacological effects of omalizumab re-treatment. Because Japanese cedar pollen-induced SAR develops between February and April every year, the results in this study seem valuable for the clinical use of omalizumab.

Daily nasal as well as ocular symptom medication scores throughout the pollen period were comparable with those in the omalizumab group and were markedly lower than those in the placebo group in the core study. As the amount of Japanese cedar pollen scattering varies with place and year, those in the re-treatment and core studies were within the usual range in each area. Though there are limitations in the direct comparison between the efficacy results of the 2 studies, the results that daily nasal as well as ocular symptom medication scores in the re-treatment study were comparable with those in the omalizumab group in the core study suggest that there is no evidence of a loss of efficacy with re-treatment in the clinical use of omalizumab.

Re-treatment with omalizumab was generally well tolerated. The overall incidence of drug-related adverse events in the re-treatment study did not increase compared with the core study. In addition, the incidence rate of injection site reactions in the re-treatment study, which were most frequently reported adverse events, did not increase either compared with that in the omalizumab group in the core study. Only 1 patient discontinued treatment because of severe adverse events (injection site pain and injection site discomfort) whose causalities with the drug were not denied, but they disappeared without additional treatment. All adverse events except those two were of mild degree. No anti-omalizumab antibodies and no significant immune complex-mediated disorders were detected. Furthermore, no cases of anaphylaxis were reported. Therefore, the safety profile of omalizumab in the re-treatment of SAR seems favorable and does not represent an increased risk of adverse events, which corresponds to the preliminary data reported by Nayak et al. [10].

In terms of acquired resistance to molecular targeting drugs, development of antibodies to the drug would be one of the possible mechanisms [11], but other mechanisms such as overexpression of the target molecule [12], decreased sensitivity of the drug induced by mutations in the target molecule [13, 14] and increased metabolism/excretion of the drug [15] could also cause resistance to the drug. Since omalizumab acts as a neutralizing antibody by binding to IgE at the same site as high-affinity receptor, to compare serum free IgE levels in the re-treatment study with those in the core study was thought to be important. Consistent with the efficacy results, serum free IgE levels in the re-treatment study decreased markedly to <50 ng/ml at 2, 4, 8 and 12 weeks of the treatment period in all patients and were equal to those in the omalizumab group in the core study.

Table 4. Drug-related adverse events

	Omalizumab (n = 34)	
	re-treatment study	previous study
Total number of patients with drug-related adverse event	5 (14.7)	15 (44.1)
General disorders and administration site conditions	5 (14.7)	11 (32.4)
Injection site		
Reactions	5 (14.7)	10 (29.4)
Erythema	3 (8.8)	5 (14.7)
Hemorrhage	1 (2.9)	0
Induration	0	1 (2.9)
Edema	0	2 (5.9)
Pain	2 (5.9)	2 (5.9)
Pruritus	0	2 (5.9)
Swelling	2 (5.9)	6 (17.6)
Discomfort	1 (2.9)	0
Feeling hot	0	1 (2.9)
Investigations	0	4 (11.8)
Blood bilirubin increased	0	1 (2.9)
Neutrophil count decreased	0	1 (2.9)
White blood cell count		
Decreased	0	1 (2.9)
Increased	0	2 (5.9)
Musculoskeletal and connective tissue disorders	1 (2.9)	0
Muscle stiffness	1 (2.9)	0

Figures in parentheses are percentages.

Though there are a lot of reports showing that treatment with omalizumab reduces serum free IgE levels [16] and downregulates the expression of high-affinity receptor for IgE on basophils [17] and mast cells [18], its effect on IgE synthesis is unclear. It was demonstrated that treatment with omalizumab in asthma patients induced significant inhibition of stimulated IgE release from peripheral blood mononuclear cells and reduction in the number of circulating B cells [19]. In contrast, Corren et al. [20] reported that omalizumab treatment for 6 months in rhinitis patients did not have an effect on IgE-secreting B cells and ϵ mRNA in nasal lavage fluid. The results of this study show that serum total IgE levels at baseline in the re-treatment study were comparable with those in the core study imply that a 12-week treatment with omalizumab does not modulate IgE synthesis.

As already mentioned, Nayak et al. [10] have previously reported the tolerability and pharmacological effects (but not the clinical efficacy) of re-treatment with oma-

lizumab, but there are some differences in the study design. According to the report of Nayak et al. [10], the dose regimen in the re-treatment study (300 mg every 3 or 4 weeks) was different from that in the core study (50, 150 or 300 mg every 3 or 4 weeks), and both dose regimens could not ensure a minimum effective dose of 0.016 mg/kg/IgE (IU/ml) every 4 weeks. In this study, the study plan was designed to be the same as in the core study, including study period, efficacy and safety endpoints, as well as dose regimen, which was approved for allergic asthma in the US and ensures the minimum effective dose [7]. From the aspect of safety evaluation, the amount of exposure to omalizumab per patient in the study of Nayak et al. [10] was thought to be relatively low compared with this study due to the difference in dose regimen. Though the num-

ber of patients in this study was smaller than that in the study of Nayak et al. [10], we investigated the total effects of re-treatment with omalizumab more precisely, under a condition closer to clinical practice.

In conclusion, re-treatment with omalizumab was effective and well tolerated in patients with moderate to severe Japanese cedar pollen-induced SAR. Therefore, omalizumab represents a new promising treatment for patients with SAR induced by Japanese cedar pollens.

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