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Omalizumab is more effective than suplastast tosilate in the treatment of Japanese cedar pollen-induced seasonal allergic rhinitis

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Summary

Background Seasonal allergic rhinitis (SAR) induced by Japanese cedar pollens is a major problem in Japan. Omalizumab, a humanized monoclonal anti-IgE antibody, improves symptoms associated with SAR, but a comparative study with an anti-allergy drug has not yet been conducted.

Objective To compare the efficacy and safety of omalizumab with suplastast tosilate, a selective T-helper type 2 (Th2) cytokine inhibitor, in patients with Japanese cedar pollen-induced SAR. **Methods** A randomized, double-blind, double-dummy study was conducted in 308 Japanese patients with a history of moderate-to-severe SAR who showed a CAP-RAST value ($\geq 2+$) specifically to Japanese cedar pollens. Patients were treated for 12 weeks with omalizumab plus placebo of suplastast tosilate or suplastast tosilate plus placebo of omalizumab.

Results The mean daily nasal symptom medication scores (sum of the daily nasal symptom severity score and daily nasal rescue medication score) were significantly lower in the omalizumab group than in the suplastast tosilate group during three evaluation periods ($P < 0.001$). The omalizumab group also had significantly lower mean daily nasal severity scores, each of the mean daily nasal and ocular symptom severity scores (sneezing, runny nose, stuffy nose, itchy nose, itchy eyes, watery eyes, and red eyes). Omalizumab reduced rescue medication requirements, and the proportion of days with any rescue medication use in the omalizumab group was significantly lower. Serum-free IgE levels markedly decreased in the omalizumab group and it was associated with clinical efficacy. The adverse reaction profiles were similar between the two groups. The overall incidence of injection site reactions was higher in the omalizumab group than in the suplastast tosilate group, but all these events were of mild degree. No anti-omalizumab antibodies were detected.

Conclusion Omalizumab showed significantly greater improvements than suplastast tosilate in the treatment of SAR induced by Japanese cedar pollens.

Keywords anti-IgE antibody, omalizumab, seasonal allergic rhinitis, suplastast tosilate

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Introduction

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

Omalizumab is a recombinant humanized monoclonal anti-IgE antibody currently approved in the United States and Europe for treating allergic asthma that specifically binds to the Cε3 domain of IgE that interacts with IgE receptors on effector cells [3]. This antibody blocks the binding of IgE to high-affinity receptors (FcεRI), thereby preventing the IgE-mediated cellular responses, such as allergen-induced histamine release from basophils and mast cells [4, 5]. It also inhibits allergen-induced T-helper type 2 (Th2) cytokine production, IL-4, IL-5 [6], IL-13 [7],

leucotriene release [8], human IgE synthesis [4, 9], and reduces eosinophil counts in patients with allergic rhinitis (AR) or bronchial asthma [10–12]. Because it does not bind to effector cell-bound IgE, omalizumab is non-anaphylactogenic, which is crucial in its clinical application.

We had demonstrated previously the prominent clinical effects of this novel antibody on Japanese cedar pollen-induced SAR against placebo [13]. Therefore, we have further tried to investigate the clinical benefits of omalizumab by comparing with a current clinical medication. Although omalizumab has new and unique modes of action, we have chosen suplatast tosilate as a controller for comparison of the clinical efficacy. Suplatast tosilate is a new dimethylsulphonium agent that has been shown to be effective for allergic disease, such as bronchial asthma [14], AR [15], and atopic dermatitis [16]. It is classified into a selective Th2 cytokine inhibitor and is included in the list of drugs that can be used in the treatment of AR on clinical guidelines in Japan [17]. This anti-allergic agent has some modes of action similar to omalizumab; it suppresses the production of IL-4 and IL-5 from human and mouse Th2 clones [18], IgE synthesis [14, 19, 20], and eosinophil infiltration in patients with AR or bronchial asthma [15, 21, 22]. The other clinical medications for AR such as anti-histamine [23], topical corticosteroids [24], cromones [25], and anti-leukotriene [26] do not have such modes of action especially on IgE production.

Therefore, we compare the clinical effects of omalizumab with suplatast tosilate in patients with moderate to severe Japanese cedar pollen-induced SAR in a randomized, double-blind manner.

Materials and methods

Participants

Patients who met the following criteria were considered to be eligible for enrollment: (1) age (20–64 years); (2) a history of SAR induced by Japanese cedar pollens in at least 2 consecutive years; (3) presentation of at least four out of eight moderate-to-severe symptoms (sneezing, itchy nose, runny nose, stuffy nose, itchy eyes, watery eyes, red eyes, and itchy throat), with two or more nasal symptoms among these four or more symptoms that persisted for 1 or more weeks during the last Japanese cedar pollen season; (4) the presence of IgE specific to Japanese cedar pollens (CAP-RAST: $\geq 2+$) at baseline; (5) serum total IgE levels of 30–700 IU/mL and body weights of 30–150 kg at baseline; and (6) no symptoms of AR at 1 month before the onset of the screening period.

Patients who had a history or clinical status of the following were excluded from the study: (1) specific immunotherapy (SIT) to Japanese cedar pollens in the previous 2 years; (2) severe anaphylactoid or anaphylactic

reactions; (3) active or recent development (within 3 months before the study onset) of any other type(s) of rhinitis; (4) a 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. Before the onset of the study, written informed consent was obtained from all the patients who were enrolled.

Study design

This randomized, double-blind, double-dummy, parallel-group study was conducted in two 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 the final dosing. Following screening, eligible patients were assigned to the omalizumab group or the suplatast tosilate group at a 1 : 1 ratio.

Daily pollen counts were measured in Tokyo and Osaka. The start day of the pollen period was defined as the first of 2 consecutive days when ≥ 1 grain/cm² were counted; the end day of the pollen period was the first of 3 consecutive days when no grain was counted. The severe pollen period was defined as the span between the first and last days when ≥ 30 grains/cm² were counted.

Doses and administration

Patients received either omalizumab plus placebo or suplatast tosilate (omalizumab group) or suplatast tosilate plus placebo of omalizumab (suplatast tosilate group).

Omalizumab (150, 225, 300, or 375 mg) or the matching placebo was administered to patients subcutaneously every 2 or 4 weeks based on their serum total IgE level and body weight at baseline, which ensured a minimum dose of 0.016 mg/kg/IgE (IU/mL) every 4 weeks. Suplatast tosilate (100 mg) or the matching placebo was administered orally three times a day. The initial dose was administered at least 1 month before the expected starting date of the pollen period.

The following drugs were allowed 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 that were prohibited from use as concomitant drugs were leucotriene antagonists, corticosteroids, antihistamines (except for rescue medications), anticholinergic agents, nasal vasoconstrictors (except for rescue medications), tricyclic antidepressants, and monoamine oxidase inhibitors. SIT was prohibited.

Evaluation of efficacy

The patients who were 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 their 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 the daily nasal symptom medication scores. 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).

Secondary efficacy variables included the daily ocular symptom medication score (0–10 points) [sum of the daily ocular symptom severity score (0–9 points) and the daily ocular rescue medication score (0–1 point)]; the daily nasal symptom severity score; each of the mean daily nasal and ocular symptom severity scores (sneezing, runny nose, stuffy nose, itchy nose, itchy eyes, watery eyes, and red eyes); the daily nasal rescue medication score; the daily ocular rescue medication score; the consumption per day of rescue medications; and the proportion of days on which any rescue medication was taken.

The primary and secondary variables were evaluated over three evaluation periods (the treatment period, the pollen period, and the severe pollen period).

Estimation of serum-free immunoglobulin E levels

Blood samples were collected for measurement of free IgE at baseline and at 4 and 12 weeks of the treatment period. Free IgE was measured using a solid-phase ELISA [27].

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 using solid-phase ELISA at baseline and 12 weeks post-final dosing [28].

Statistical analysis

Three hundred patients were planned to be assigned to the omalizumab group or to the suplatast tosilate group at a 1:1 ratio. The sample size was calculated under the assumption of 80% power, significance level of 0.05 (two-sided), and at a standard deviation of 1.50 for the difference. The non-inferiority margin was set to 0.5.

The mean daily nasal symptom medication scores were evaluated as the primary efficacy variables to demonstrate the non-inferiority of omalizumab compared with supla-

tast tosilate in the per protocol set (PPS). Statistical analysis for the non-inferiority was confirmed using a confidence interval for the difference. Once the non-inferiority was confirmed, the superiority of omalizumab was tested in the full-analysis set (FAS). The primary efficacy variable was evaluated using a mixed-effect model under the null hypothesis of no difference between the study groups and a two-sided significant level of 0.05. The mixed-effect model included covariates of the study group as a fixed effect, and location and administration interval (2- or 4-week interval) as random effects. The least-squares mean (LSM) for each study group and the difference in LSM between the study groups were estimated.

The mean daily ocular symptom medication scores, each of symptom severity scores, were also analysed similar to the analysis of the mean daily nasal symptom medication scores. The consumption per day of rescue medications and the proportion of days on which any rescue medication was taken were analysed using the Wilcoxon test.

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

Results

Three hundred and seven of 308 randomized patients received either of the study drugs: 154 received omalizumab (155 randomized) and 153 received suplatast tosilate. The remaining patients in the omalizumab group withdrew during the screening period due to use of prohibited concomitant medicine. The patient characteristics were comparable between the study groups (Table 1).

Table 1. Patient characteristics

	Omalizumab (n = 154)	Suplatast tosilate (n = 153)
Gender		
Male	69	75
Age (years)		
Mean $\pm$ SD	35.3 $\pm$ 13.0	34.9 $\pm$ 12.0
Range	20–64	20–62
History of SAR induced by Japanese cedar pollens (years)		
Mean $\pm$ SD	12.0 $\pm$ 6.6	12.2 $\pm$ 6.4
Range	2–38	3–34
Specific IgE levels against Japanese cedar pollens (CAP-RAST)*		
Class 2 (0.70–3.49 UA/mL)	11	18
Class 3 (3.50–17.49 UA/mL)	70	71
Class 4 (17.50–49.99 UA/mL)	60	56
Class 5 (50.00–99.99 UA/mL)	13	8
Serum total IgE levels at baseline (IU/mL)		
Mean $\pm$ SD	169.2 $\pm$ 139.8	159.9 $\pm$ 133.5
Range	31.0 $\pm$ 610.0	30.0 $\pm$ 560.0

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

SAR, Seasonal allergic rhinitis.

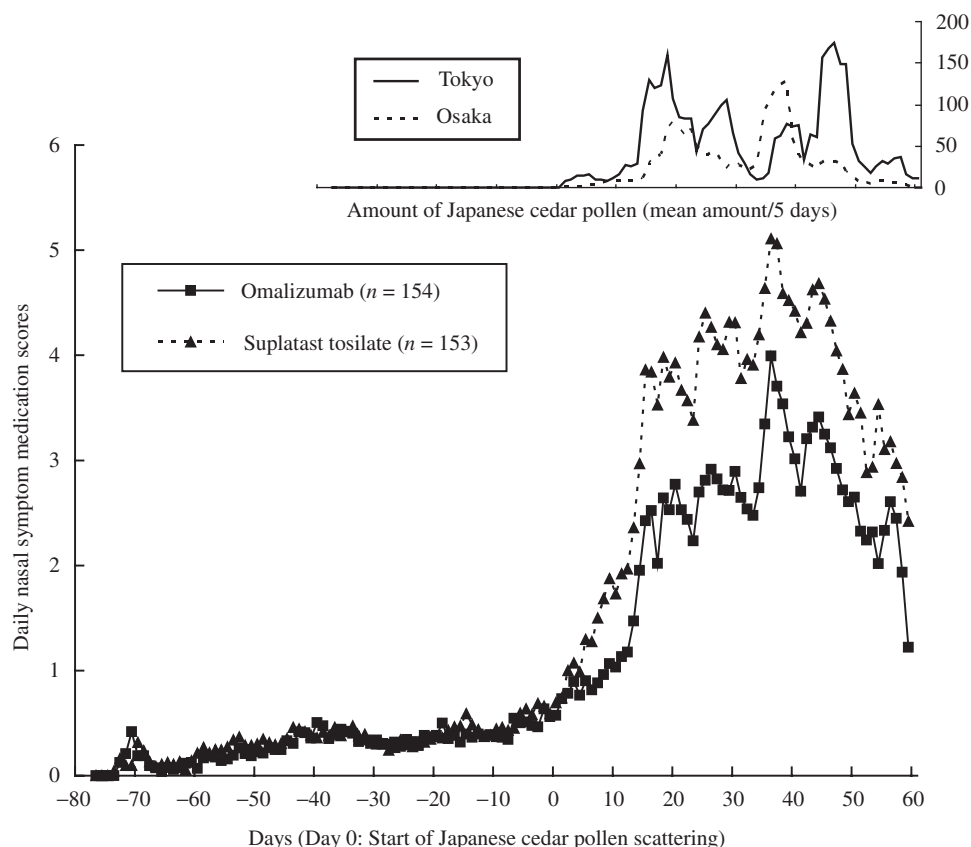


Fig. 1. Time-course changes in daily nasal symptom medication score [full analysis set (FAS)] and in the amount of Japanese cedar pollen. Day 0 represents the start day of the pollen period in Tokyo and Osaka.

Six patients (one receiving omalizumab and five receiving suplatast tosilate) discontinued the study prematurely; among them, four patients in the suplatast tosilate group ceased the study due to protocol deviations. One suplatast tosilate-treated patient discontinued because of adverse events, and one omalizumab-treated patient withdrew consent. None of the patients discontinued the study because of an unsatisfactory therapeutic effect.

The pollen period started at the beginning of February and continued till the end of April (Fig. 1). All patients received the first administration at least 3 weeks before the starting date of the pollen period.

Daily nasal symptom medication score

Time-course changes in daily nasal symptom medication scores are shown in Fig. 1. The daily nasal symptom medication scores throughout the pollen period were consistently lower in the omalizumab group than in the suplatast tosilate group.

The omalizumab group showed significantly lower mean daily nasal symptom medication scores compared with the suplatast tosilate group in the PPS during the three evaluation periods (e.g. LSM $\pm$ SE, 1.517 ± 0.348 for

the omalizumab group and 2.215 ± 0.347 for the suplatast tosilate group; $P < 0.001$, the treatment period). Statistical analyses revealed similar results with respect to the relevant scores in the FAS during the three evaluation periods (Fig. 2a). During the pollen period, patients with lower mean nasal symptom medication scores were distributed predominantly in the omalizumab group than in the suplatast tosilate group, with greater numbers of patients with scores of 0–1 and > 2 –3 in the former and latter groups, respectively. Over half of the patients in the omalizumab group had mean daily nasal symptom medication scores of ≤ 2 (mild or less severe symptoms) in contrast to 27% in the suplatast tosilate group. More than 10% of the patients in the suplatast tosilate group had scores of > 6 (severe symptoms) compared with 4.6% in the omalizumab group (Fig. 2b).

As shown in Fig. 1, although the amount of Japanese cedar pollens in Tokyo was approximately twice as much as that of Osaka (3542 grains/cm^2 for Tokyo and 1855 grains/cm^2 for Osaka), the mean daily nasal symptom medication scores were consistently lower in the omalizumab group than in the suplatast tosilate group in Tokyo and Osaka, respectively (mean $\pm$ SE, 1.931 ± 0.140 and 2.398 ± 0.163 for Tokyo, 1.313 ± 0.138 and 2.164 ± 0.152 for Osaka, the treatment period).

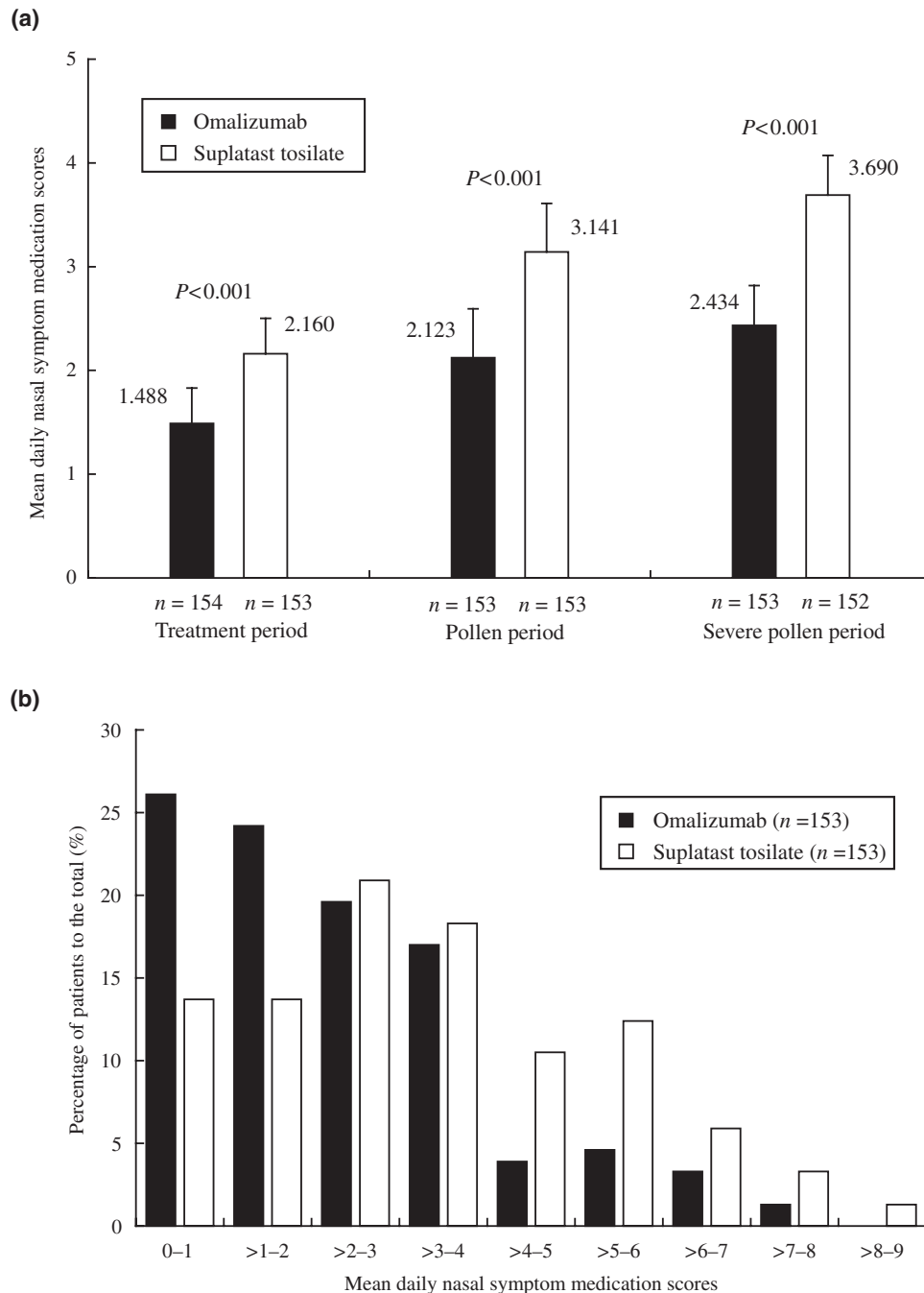


Fig. 2. (a) Mean daily nasal symptom medication scores [full analysis set (FAS)] during the treatment period, the pollen period, and the severe pollen period. (b) Percentages to the total of patients with the mean daily nasal symptom medication scores FAS during the pollen period.

Daily ocular symptom medication score

The omalizumab group had significantly lower mean daily ocular symptom medication scores compared with the suplatast tosilate group during the treatment period (0.734 ± 0.110 and 0.991 ± 0.110 , respectively; $P = 0.008$; Fig. 3). Statistical analyses revealed similar results with respect to the relevant scores during the pollen and the severe pollen period.

Daily nasal and ocular symptom severity scores

The omalizumab group had significantly lower mean daily nasal symptom severity scores compared with the suplatast tosilate group during the three evaluation periods (e.g. 1.458 ± 0.333 and 2.103 ± 0.333 , respectively; $P < 0.001$, the treatment period). Each of the mean daily nasal and ocular symptom severity scores 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 <0.001 to 0.025 ; Fig. 4).

Use of rescue medications

The mean daily nasal rescue medication scores were significantly lower in the omalizumab group than in the suplatast tosilate group during the pollen period (0.048 ± 0.016 and 0.090 ± 0.016 , respectively; $P = 0.039$), and the mean ocular rescue medication scores tended to show a significant difference.

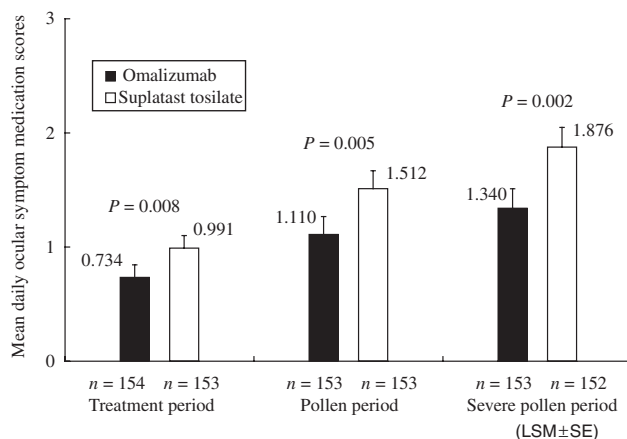


Fig. 3. Mean daily ocular symptom medication scores [full analysis set (FAS)] during the treatment period, the pollen period, and the severe pollen period. LSM, Least-square mean.

The mean consumption per day of each of two rescue medications [clemastine fumarate (tablet), sodium cromoglycate (eye drop)] was significantly lower in the omalizumab group than in the suplatast tosilate group during the pollen period ($P = 0.009$ and 0.001 , respectively), and sodium cromoglycate (nose drop) tended to show a significant difference in consumptions. Naphazoline nitrate (nose drop) was hardly used.

The proportions of days in which any rescue medication was taken were higher in the suplatast tosilate group than in the omalizumab group (e.g. 13.5% and 7.9%, respectively; $P < 0.001$, the pollen period).

Serum-free immunoglobulin E levels

In the omalizumab group, serum-free IgE levels decreased markedly, compared with the baseline levels, to below 50 ng/mL at 12 weeks of the treatment period in all patients (range from 6.39 to 46.83 ng/mL). In contrast, there were only two patients whose concentration of serum-free IgE was under 50 ng/mL at 12 weeks of the treatment period in the suplatast tosilate group.

Safety

Treatment with omalizumab was generally well tolerated. The adverse reaction profiles were similar between the study groups (Table 2). Although the overall incidences of injection site reactions were higher in the omalizumab

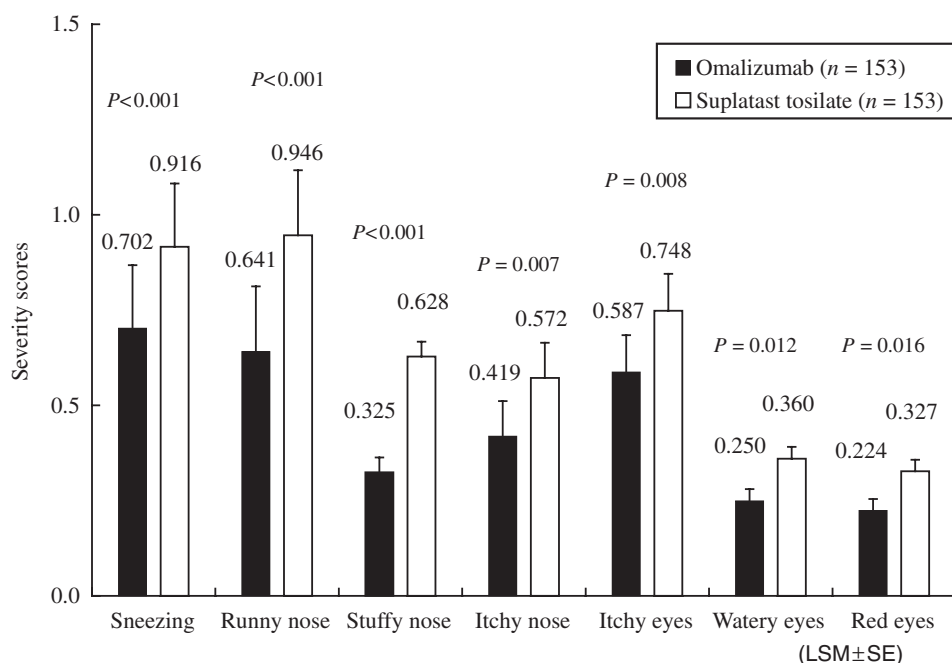


Fig. 4. Effects of omalizumab on each of the mean daily nasal and ocular symptom severity scores [full analysis set (FAS)] during the pollen period. Statistically significant differences were also noted during the treatment and severe pollen periods. LSM, Least-square mean.

Table 2. Drug-related adverse events ($\geq 1\%$ in either group)

	Omalizumab (<i>n</i> = 154), <i>n</i> (%)	Suplatast tosilate (<i>n</i> = 153), <i>n</i> (%)
Total number of patients with drug-related adverse event	45 (29.2)	40 (26.1)
Gastrointestinal disorders	3 (1.9)	7 (4.6)
General disorders and administration site conditions	34 (22.1)	16 (10.5)
Injection site reactions*	32 (20.8)	15 (9.8)
Erythema	12 (7.8)	6 (3.9)
Haemorrhage	13 (8.4)	7 (4.6)
Induration	2 (1.3)	1 (0.7)
Pain	6 (3.9)	4 (2.6)
Pruritus	8 (5.2)	0
Swelling	13 (8.4)	2 (1.3)
Malaise	2 (1.3)	0
Nervous system disorders	2 (1.3)	4 (2.6)
Headache	1 (0.6)	2 (1.3)
Somnolence	1 (0.6)	2 (1.3)
Skin and subcutaneous tissue disorders	3 (1.9)	1 (0.7)
Investigations	9 (5.8) [†]	13 (8.5) [‡]

*Injection site reactions in the suplatast tosilate group were caused by administration of placebo of omalizumab.

[†]ALT $\uparrow$ 2 (1.3), ALP $\uparrow$ 2 (1.3), glucose urine present 2 (1.3), red blood cells urine positive 2 (1.3).

[‡]ALT $\uparrow$ 3 (2.0), AST $\uparrow$ 3 (2.0), γ -GTP $\uparrow$ 3 (2.0), white blood cell $\uparrow$ 2 (1.3), eosinophil $\uparrow$ 2 (1.3), neutrophil $\uparrow$ 2 (1.3); $\uparrow$, increased; $\downarrow$, decreased.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GTP, guanosine triphosphate.

group than in the suplatast tosilate group, all these events were of a mild degree and disappeared without any additional treatment.

One patient in the suplatast tosilate group discontinued treatment because of severe adverse events (otitis media serous and nasopharyngitis) that were not drug related, while none discontinued treatment in the omalizumab group. During the follow-up period, one serious adverse event (ureteric calculus) was reported in one patient in the omalizumab group. However, the investigator considered its causality with the drug to be unrelated. There were no anaphylactic reactions, and no evidence of immune complex disease or clinically important abnormalities in vital signs and laboratory tests were found. No anti-omalizumab antibodies were detected.

Discussion

This is the first study directly comparing the effect of omalizumab on SAR patients with an anti-allergy drug, not placebo. This study revealed that omalizumab was more effective than suplatast tosilate in preventing and controlling rhinoconjunctival symptoms associated with Japanese cedar pollen-induced SAR and in reducing

rescue medication use for rhinoconjunctival symptoms. In addition, 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.

Suplatast tosilate is a selective Th2 cytokine inhibitor *in vitro* [18] and is shown to decrease symptoms of AR and bronchial asthma. It decreased symptom scores for puffy nose, rhinorrhoea, and sneezing in patients with perennial nasal allergies [15]. Furthermore, it inhibited the infiltration of CD4⁺ T cell and eosinophil infiltration, and also decreased the levels of Th2 cytokines (IL-4, IL-5, and IL-13) in human nasal mucosa obtained by nasal brushing [15]. Treatment with suplatast tosilate in steroid-dependent asthma improved lung function and symptoms, and allowed a decrease in the amount of inhaled corticosteroids [14].

In this study, the amount of Japanese cedar pollens in Tokyo was larger than that of Osaka; however, the mean daily nasal symptom medication scores were consistently lower in the omalizumab group than in the suplatast tosilate group in Tokyo and Osaka, respectively. Regardless of the amount of Japanese cedar pollens, omalizumab would be effective against SAR.

The adverse reaction profiles were similar between the study groups. In the omalizumab group, all adverse events, except for one (ureteric calculus), which was not drug related, were mild to moderate in severity. The most frequently reported drug-related adverse events in the omalizumab group were injection site reactions, with a higher incidence than in the suplatast tosilate group; however, all these events were of a mild degree and disappeared without an additional treatment. 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 appears to be favourable.

In the omalizumab group, serum-free IgE levels decreased markedly to below 50 ng/mL at 12 weeks of the treatment period in all patients and it was associated with clinical effectiveness. In contrast, there were only two patients whose concentration of serum-free IgE was under 50 ng/mL in the suplatast tosilate group.

Omalizumab has been reported not only to inhibit basophils and mast cells responses but to also have a profound effect on the numbers of inflammatory cells [29], such as eosinophils, T lymphocytes, B lymphocytes, and dendritic cells (DCs) [30].

Suplatast tosilate also has widespread anti-inflammatory effects. This drug selectively inhibits the Th2 cytokine production from T cells and this causes suppression of eosinophilic inflammation and IgE production and also inhibits the differentiation and function of monocyte-derived DCs [31]. In addition, inhibition of thymus- and

activation-regulated chemokine production from human Th2 cells [32], chemical mediator release from mast cells [19], and inhibition of murine mast cell differentiation [33] by suplatast tosilate have been demonstrated.

Although these two drugs have similar effects on inflammatory cells, the direct acting point of each drug is different, IgE for omalizumab and Th2 cytokine for suplatast tosilate, and suppression of free IgE was much stronger in the omalizumab group than the suplatast tosilate group. The result of this study that omalizumab was more effective than suplatast tosilate in the treatment of SAR suggests that IgE is likely more potent than Th2 cytokines whose generation is blocked by IPD as a therapeutic target of SAR.

For moderate to severe SAR, antihistamine drugs or nasal steroids are usually used, but in some cases, it is not sufficient and patient's QOL is impaired. The patients sometimes have to take oral steroids for several weeks. As shown in this study, when we used omalizumab, almost no rescue medication was needed. Although omalizumab is expensive, from the viewpoint of patients' QOL or adherence, there is an advantage to using omalizumab for moderate to severe SAR.

Other studies have shown the efficacy of omalizumab for both SAR and perennial allergic rhinitis (PAR) [34, 35]. Combination therapy with omalizumab and SIT not only reduced acute allergic reactions compared with SIT alone [36] but also enhanced the efficacy of SIT [36, 37]. Furthermore, as The World Health Organization-sponsored AR and its Impact on Asthma workshop report recommended that strategies that combine the treatment of upper and lower airways be used where possible [38], omalizumab has been shown to be effective against patients with moderate-to-severe asthma and concomitant moderate-to-severe PAR [39].

In conclusion, omalizumab was superior over suplatast tosilate in preventing and controlling symptoms and in reducing rescue medication use and was 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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