Ⅳ. 研究成果の刊行物・印刷

Inhibition of the Antigen Provoked Nasal Reaction by Second-generation Antihistamines in Patients with Japanese Cedar Pollinosis

Kimihiro Okubo and Minoru Gotoh

Allergology International
Vol 55, No 3:261-269 September 2006

Allergology International. 2006;55:261-269

ORIGINAL ARTICLE

Inhibition of the Antigen Provoked Nasal Reaction by Second-generation Antihistamines in Patients with Japanese Cedar Pollinosis

Kimihiro Okubo[1] and Minoru Gotoh[2]

ABSTRACT

Background: Epinastine hydrochloride and fexofenadine hydrochloride, the second-generation antihistamines, are largely used in the indication of allergic rhinitis in Japan. The purpose of this study was to compare the protective efficacy of epinastine hydrochloride or fexofenadine hydrochloride using a nasal provocation test with Japanese cedar pollen allergen.

Methods: A single-dose, placebo-controlled, single-blind crossover clinical study was conducted in patients with Japanese cedar pollinosis. The pollen exposure was done by the antigen provocation by disc method and involved repeated provocation five times per day.

Results: Among the active agents studied—epinastine hydrochloride and fexofenadine hydrochloride—epinastine hydrochloride significantly decreased the number of sneezing attacks and the quantity of nasal discharge for 3 hours after drug administration compared with placebo, a finding supported by the quantity of nasal discharge in the nasal findings. In this study, fexofenadine hydrochloride showed no significant difference compared with placebo.

Conclusions: This study demonstrates better protection with epinastine hydrochloride than with fexofenadine hydrochloride or placebo in a nasal provocation test with Japanese cedar pollen allergen.

KEY WORDS

allergic rhinitis, epinastine hydrochloride, fexofenadine hydrochloride, nasal provocation, rhinoscopy

INTRODUCTION

Pollinosis is seasonal allergic rhinitis due to pollen antigens, and its prevalence is high enough to be called a national disease in Japan. Among the many pollen antigens, Japanese cedar pollinosis is the most common.[1] Government policies after World War II led to the planting of Japanese cedar trees, and the area planted with Japanese cedar trees began to increase in the late 1960's. In the early 1970's, the number of patients increased rapidly, and currently 10–20% of the Japanese population suffers from Japanese cedar pollinosis, as has been reported in several studies.[2]

In the treatment of pollinosis, second-generation antihistamines are used as initial therapy to inhibit the hypersensitivity reaction caused by repeated antigen exposure.[3] The Practical Guideline for Management of Allergic Rhinitis states that these agents are the first-line agents of choice for the treatment after onset of symptoms such as sneezing and rhinorrhea, and thus are an essential component of pollinosis therapy.[4] Presently, several second-generation antihistamines are marketed with the allergic rhinitis indication. To provide objective information concerning drug selection, various studies to evaluate efficacy are being conducted in the form of clinical studies in the field,[5] studies in environmental exposure units,[6] anti-

[1]Departments of Otorhinolaryngology and Head/Neck Surgery, Nippon Medical School, Tokyo and [2]Department of Otorhinolaryngology, Nippon Medical School Chiba Hokusoh Hospital, Chiba, Japan.
Correspondence: Kimihiro Okubo, M.D., Ph.D., Department of Otorhinolaryngology, Nippon Medical School, 1-1-5 Sendagi, Bunkyo-ku, Tokyo 113-8603, Japan.
Email: ent-kimi@nms.ac.jp
Received 28 September 2005. Accepted for publication 24 January 2006.

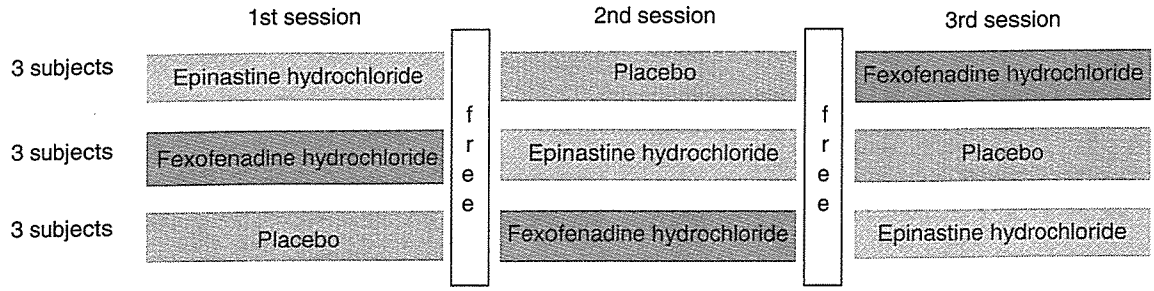

Fig. 1 Study design

Table 1 Nasal finding score

	Score			
Nasal Findings	3	2	1	0
Inferior nasal turbinate mucosal swelling	Middle turbinate not seen	Intermediate between (3) and (1)	To centre of middle turbinate	None
Nasal discharge	Filled	Intermediate between (3) and (1)	Small amount adhered to the skin	None

gen provocation tests,[7] and QOL surveys.[8] The antigen nasal provocation test is a test in which the antigen is applied directly to the nasal mucosa to elicit nasal symptoms from such a stimulation.[9] Since this is a quantitative clinical study, where a fixed amount of antigen is applied, it is possible to reproducibly elicit the allergy reactions and allows the evaluation of drugs for their treatment effect of nasal symptoms.

In this study, we examined patients with Japanese cedar pollinosis using Japanese cedar antigen discs to conduct the nasal provocation test and evaluated two second-generation antihistamines, epinastine hydrochloride tablets and fexofenadine hydrochloride tablets, for efficacy compared with placebo in a crossover clinical study.

METHODS

SUBJECTS

This study was conducted between August 14 and October 2, 2004. The subjects were male and female volunteers with Japanese cedar pollinosis who were 20 years old or older. The inclusion criteria required that the subjects have a CAP-RAST score for Japanese cedar of 2 or greater, show a positive nasal provocation reaction to the Japanese cedar antigen disc (more than two symptoms by the nasal provocation test from among nasal itching, sneezing, rhinorrhea and nasal congestion), and provide written consent to participate in this study.[10]

The following subjects were excluded.

* Subjects with a history of hypersensitivity to the components of the study drugs

* Subjects who were unable to stop smoking on the days of the clinical study

* Subjects who had used steroids within one month of the start day of the clinical study

* Subjects who within one week of the start day of the clinical study used drugs that may affect the results of the clinical study (antihistamines, antiallergic drugs, vasoconstrictors)

* Subjects undergoing desensitization therapy

* Subjects with nasal diseases that affect the assessment of the nasal provocation reaction, such as acute/chronic rhinitis, nasal polyps, hypertrophic rhinitis, deviated septum or sinusitis

* Subjects who were reactive to multiple antigens including pollens other than Japanese cedar (ragweed, mugwort), and had worsening of nasal symptoms when the nasal provocation test was conducted during the season of dispersion of the pollen

STUDY DRUGS, STUDY DESIGN

Study drugs were epinastine hydrochloride 20 mg tablets (epinastine), fexofenadine hydrochloride 60 mg tablets (fexofenadine), and placebo indistinguishable from epinastine (provided by Nippon Boehringer Ingelheim Co., Ltd., Hyogo, Japan with fees paid).

The clinical study consisted of four visits. Visit 1 consisted of screening tests, and visits 2, 3 and 4 involved nasal provocation tests using Japanese cedar antigen discs.

In the study design, the three study drugs were administered to subjects as a single dose on the days of the three nasal provocation tests in an open 3-way crossover method in the order assigned by the randomization (Fig. 1). A study drug administrator who was neither the physician nor the clinical study collaborator conducted the randomization, and the study

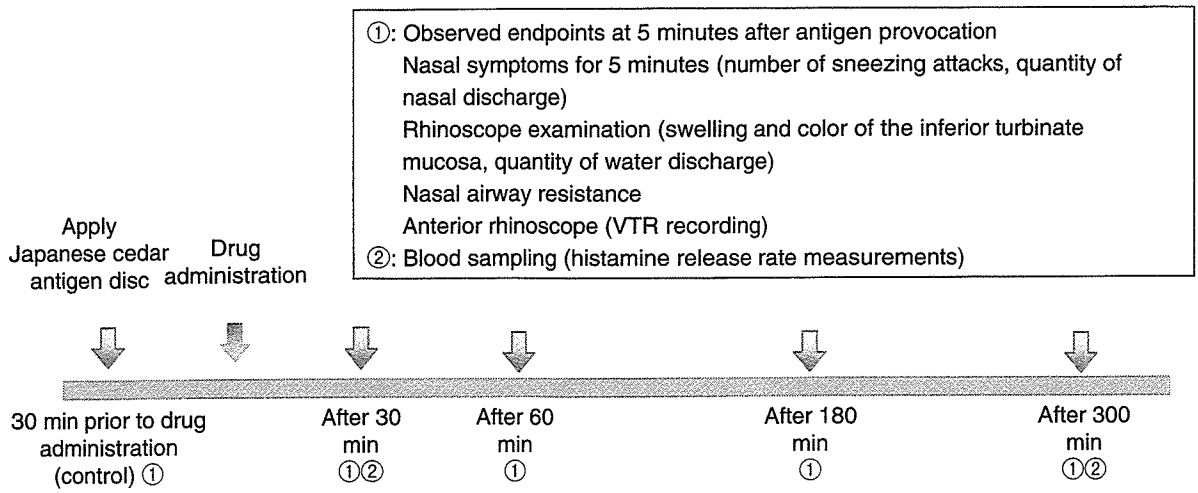

Fig. 2 Observed endpoints

Table 2 Characteristics of subjects

Sex	male	5
	female	4
Age (years)	mean ± S.E.	23.56 ± 0.57
Age at onset (years)	mean ± S.E.	16.67 ± 1.16
Disease type	sneezing, rhinorrhea	8
	nasal airway closure	1
CAP-RAST (score)	house dust	2.22 ± 0.82
	mites	2.33 ± 0.89
	Japanese cedar	3.22 ± 0.31
	mugwort	0.44 ± 0.38
	ragweed	0.56 ± 0.43
Co-existing illesses	no	1
	yes	8
	chronic allergic rhinitis	5
	seasonal allergic conjunctivitis	2
	allergic conjunctivitis	2
Allergy prior history	no	9
	yes	0
Prior therapy (desensitization, surgery)	no	9
	yes	0

drug administrator performed the drug administration in a way that could not be identified by the physician nor the clinical study collaborator.

OBSERVED ENDPOINTS

Efficacy

During the 5 minutes after provocation, the nasal symptoms were observed, including the number of sneezing attacks and quantity of nasal discharge (weight of tissues used).

At 5 minutes after provocation, a rhinoscope examination was conducted to examine and rate the swelling and color of the mucosa of the inferior nasal turbinates and nasal discharge. The rating was conducted according to the nasal finding classification of The Practical Guideline for Management of Allergic Rhinitis.[4] The extent of the inferior nasal turbinate mucosal swelling and nasal discharge were scored (3 points, 2 points, 1 point, none; Table 1), and the changes in the nasal finding score over time were determined for each drug.[10]

In addition, nasal airway resistance measurements,

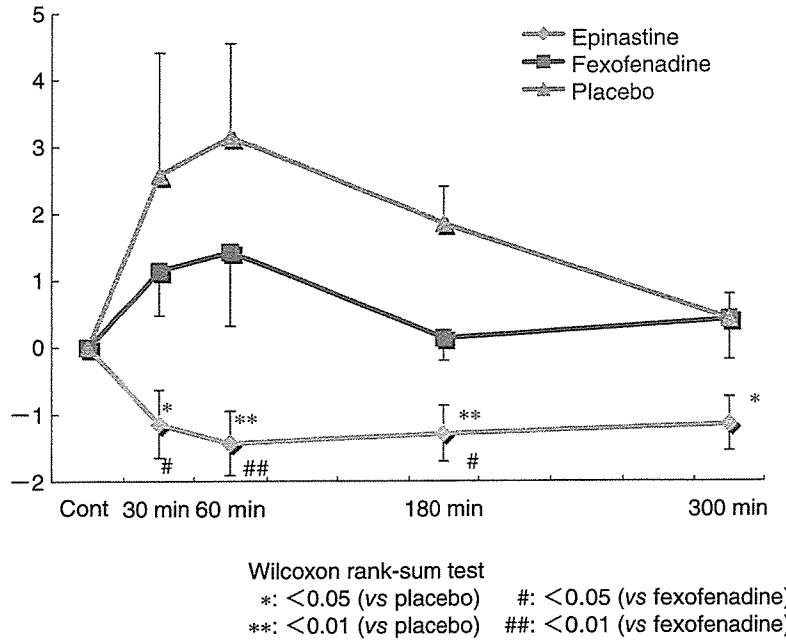

Fig. 3 Change in the number of sneezing attacks

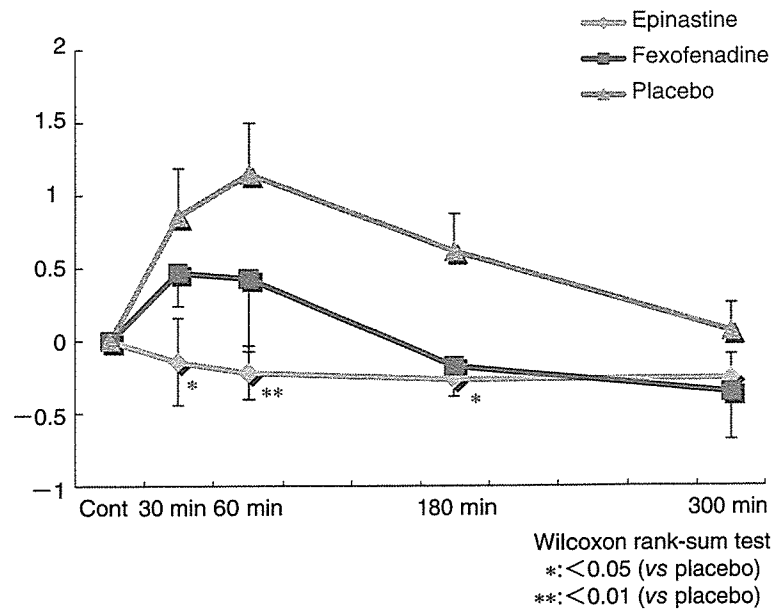

Fig. 4 Change in the quantity of nasal discharge (weight of tissues used)

VTR recording by anterior rhinoscopy for a one-minute period immediately after provocation and for a one-minute period beginning at 5 minutes after provocation, and histamine release rate (HRT Shionogi, Osaka, Japan) after first nasal provocation (30 minutes before drug administration) and at the end of the last nasal provocation (300 minutes after drug administration) were also observed.

Safety

At each visit, the physician conducted an examination at 30 minutes prior to drug administration before the nasal provocation and at 300 minutes after drug administration after the completion of the nasal provocation.

Patient-reported Evaluation

After completion of all clinical studies, subjects were

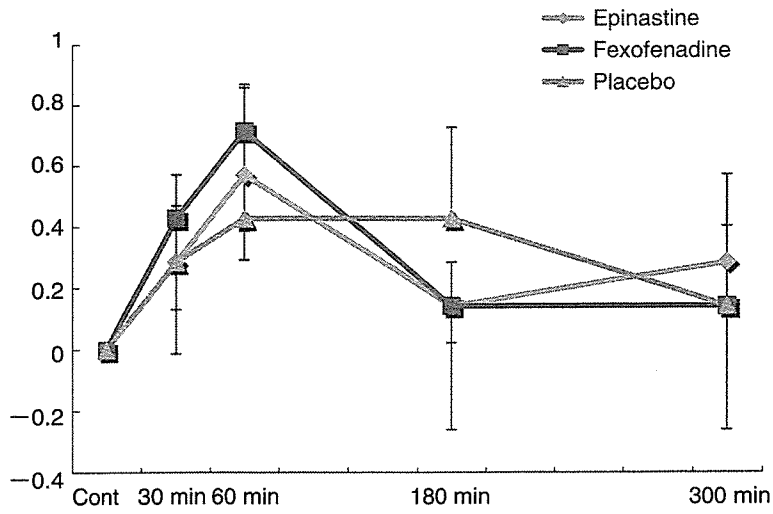

Fig. 5 Change in the inferior nasal turbinate mucosal swelling (nasal finding score)

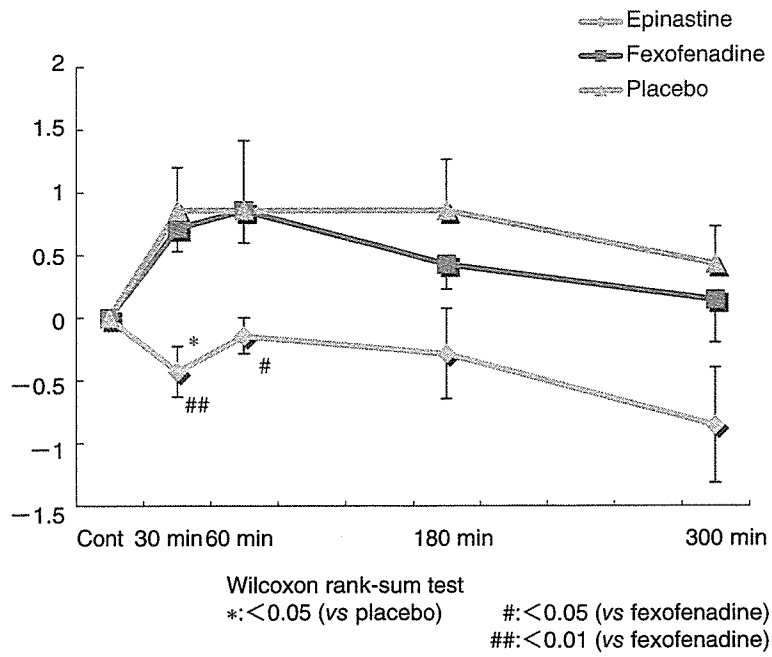

Fig. 6 Change in the nasal discharge (nasal finding score)

surveyed using questionnaires for their impressions on the efficacy of the study drugs to determine patients' opinions.

STUDY METHODS

The nasal provocation was done using Japanese cedar antigen discs containing 50 ng of Cry j1 (kindly provided by National Hospital Organization Sagamihara National Hospital, Kanagawa, Japan), and were applied to the anterior portion of both inferior nasal turbinates for 5 minutes. The procedures for each observation day are indicated below.

Day of Screening Tests (Visit 1)

Subjects were given an explanation regarding their participation in this clinical study and provided written consent.

The subjects underwent a physical examination, laboratory tests (hematology, blood chemistry, urinalysis) and the nasal provocation test. The subject's background, past medical history and co-existing illnesses, and concomitant drugs were surveyed to con-

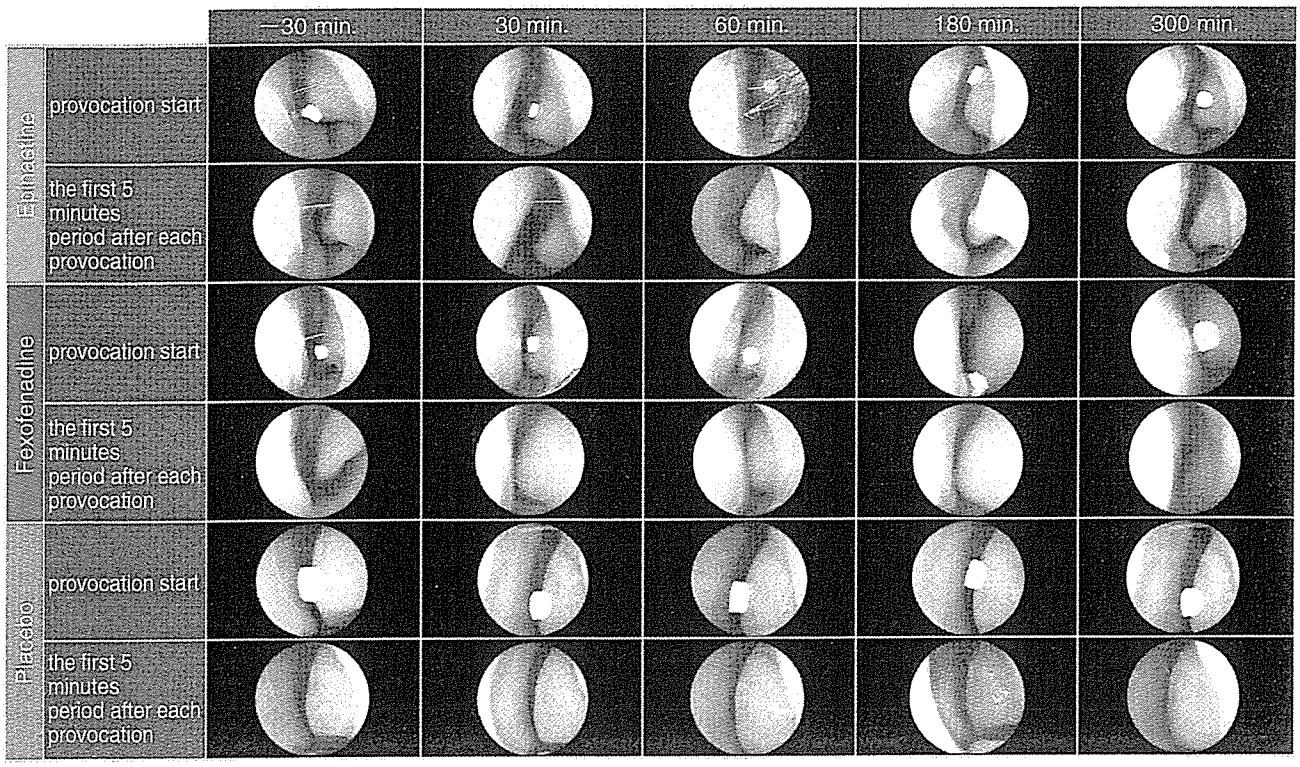

Fig. 7 The appearance of nasal mucosa by rhinoscope

firm inclusion criteria and exclusion criteria.

Days of Nasal Provocation Tests (Visits 2, 3, 4; Fig. 2)

The study drugs were administered at the three visits, and at each visit, a study drug was given as a single dose. There was a drug-free period of 14 days between visits.

The first nasal provocation was conducted at 30 minutes prior to any study drug administration, after which the study drug was administered. Then, subsequent nasal provocation was conducted at 30 minutes, 60 minutes, 180 minutes, and 300 minutes after drug administration (a total of five times). At each time point, the respective observations were conducted.

Statistical Analysis

The results were evaluated as the rate of change in the value after antigen provocation prior to drug administration compared with those after drug administration, and the value was expressed as a mean ± standard error. Comparison between study drugs was performed using the Wilcoxon rank-sum test.

This clinical study was conducted at the Tokyo Clinical Research Organization for Medicine Clinic (ToCROM). Prior to conducting the study, the study was reviewed by the Independent Ethics Committee of the Osaka Pharmacology Research Clinic and was approved by the clinic director.

RESULTS

There were nine subjects (5 men, 4 women), mean age 23.56 ± 0.57 years. The details of subjects' demographics are in Table 2. None of the subjects experienced safety problems during the study. One subject did not return for visits 3 and 4, while one subject did not return for visit 3. Thus, 7 subjects received all study drugs.

EFFICACY

Nasal Symptoms

Changes in the number of sneezing attacks and changes in the quantity of nasal discharge (weight of tissues used) are shown in Figures 3, 4. The number of sneezing attacks was maintained below baseline for up to 300 minutes after administration of epinastine. On the other hand, with fexofenadine and with placebo, the number of sneezing attacks increased during the 60 minutes after study drug administration, followed by a decrease. However, the number of attacks did not drop below baseline. Epinastine showed a significant difference against placebo from 30 minutes to 300 minutes after drug administration and against fexofenadine from 30 minutes to 180 minutes after drug administration.

The changes in the quantity of nasal discharge showed a trend that was similar to that of the number of sneezing attacks. Epinastine showed values below

Table 3 Subject impressions

	effective		neither effective nor ineffective		ineffective
Epinastine	3	42.86%	2	28.57%	2
Fexofenadine	2	28.57%	4	57.14%	1
Placebo	0	0.00%	3	42.86%	4

baseline continuously to 300 minutes after administration. The changes in the quantity of nasal discharge increased for 30 minutes after administration of fexofenadine and for 60 minutes after the administration of placebo, followed by a decrease. Epinastine showed significant differences in the changes in the quantity of nasal discharge compared with placebo from 30 minutes to 180 minutes after administration.

Nasal Findings

Figures 5, 6 show the changes over time in the swelling of the inferior nasal turbinate mucosa and nasal discharge expressed as the nasal finding score. The nasal finding score for swelling increased for 60 minutes after drug administration for all three study drugs. There were no significant differences among the study drugs.

The nasal finding score for the nasal discharge increased for 60 minutes after the administration of fexofenadine and placebo and was higher than baseline to 300 minutes after administration, while at no time point did epinastine show values above baseline. Epinastine showed significant differences compared with placebo at 30 minutes after administration and with fexofenadine at 30 minutes and 60 minutes after administration.

Nasal Airway Resistance

There were no significant differences among the study drugs.

VTR Recording By Anterior Rhinoscopy

Figure 7 shows examples of intranasal images at each measurement time point before and after nasal provocation.

The swelling of the inferior nasal turbinate mucosa was inhibited from 30 minutes after administration of epinastine and from 180 minutes after administration of fexofenadine.

Histamine Release Rates

The mean±standard error at 30 minutes before and 300 minutes after administration were 53.24 ± 15.67% and 50.16 ± 9.24% for epinastine, 43.00 ± 11.01% and 40.17 ± 10.25% for fexofenadine, and 49.56 ± 14.24% and 35.44 ± 11.06% for placebo, respectively, showing decreases with all three study drugs. There were no significant differences among the study drugs.

SAFETY

None of the subjects experienced any adverse events.

PATIENT-REPORTED EVALUATION

Table 3 shows the subjects' impressions concerning the study drugs after the completion of the clinical study. 3 of 7 subjects given epinastine (42.86%), 2 of 7 subjects given fexofenadine (28.57%) and 0 of 7 subjects given placebo reported that the "study drug was effective."

DISCUSSION

The nasal provocation test exposes a fixed amount of the antigen directly to the nasal mucosa and determines the changes in the extent of nasal allergy symptoms. Thus, it is a simple method for objectively evaluating the efficacy and duration of effect of antiallergic agents.[7,9,11] Usui *et al.* have studied the efficacy of Ketotifen oral agent and nasal agent by the nasal provocation test using house dust antigens.[12] Konno and Yoshida *et al.* have also repeated antigen nasal provocation using the Japanese cedar antigen and have reported that even during non-dispersion seasons, nasal symptoms seen in the field can be reproduced.[13,14] When there is no pollen dispersion, the specific IgE in the nasal mucosa is decreased, but when antigen in an amount sufficient to elicit the development of allergic symptoms is applied, then the disease becomes apparent. In recent years, many studies have also been conducted to observe nasal allergy symptoms and conduct drug efficacy evaluation in pollen (antigen) exposure chambers,[6] but from the standpoint of being able to expose all subjects to a fixed amount of antigen, the antigen provocation test is superior for evaluation of nasal symptoms. On the other hand, in terms of being able to reproduce symptoms of pollinosis during a pollen-dispersion season, exposure tests in pollen exposure chambers are superior to the antigen provocation test. This is because exposure chambers are closer to the exposure to pollen in the field and can elicit symptoms that do not arise in antigen provocation tests, such as symptoms in the eye and throat. However, studies like the present clinical study involving a small number of subjects, particularly studies that include detailed assessments such as rhinoscope examination, require exposure to a fixed amount of antigen. Thus, we adopted the antigen provocation test. In addition, repeated provocation reaction was used to reproduce repeated antigen exposure similar to the repeated ex-

posure in the field occurring during a pollen-dispersion season. In a simple one-time antigen exposure, the pollen is in a non-dispersion state and the allergy reaction that occurs is the pure immediate phase reaction followed by the late phase reaction.[7] However, in the actual clinical setting, since there is repeated exposure to large quantities of dispersed pollen, it may be important to determine the efficacy of drugs under conditions with immediate phase and late phase occurring simultaneously.

It was thought that repeated antigen provocation reactions can lead to better reproduction of the actual pollinosis symptoms, and that increasing the number of exposures may lead to an increase in reactivity. However, the reaction including nasal mucosal swelling after placebo administration increased to a certain point after antigen provocation but showed a trend towards a decrease beyond one hour, and by 5 hours the reactivity was at the level prior to drug administration with the first provocation. This may be because the current clinical study was started in a pollen-free state. Specific IgE in the nasal mucosa begins to increase at the time of the year when the pollen dispersion is starting,[15] and it has been shown in clinical studies in Japanese cedar pollinosis in Japan that at that time of the year, the hypersensitivity increases gradually.[13,14] For this reason, in this clinical study, the hypersensitivity becomes apparent for a short period of time, and thereafter, possibly because of the low level of specific IgE, the decreased reactivity of mast cells results in decreased production and release of histamine and decreased nasal discharge after four or five antigen provocation reactions.

The study drugs used here, epinastine hydrochloride and fexofenadine hydrochloride, are popular second-generation antihistamines in Japan. Fexofenadine hydrochloride in the pollen-dispersion season showed clinical efficacy starting around day 2 of administration, and improved QOL early in treatment.[8] There are no similar data for epinastine hydrochloride, but a rapid response has been reported in a clinical study involving the skin.[16] In this study, a comparison of these two agents and placebo was conducted under conditions close to pollen exposure in the field using repeated antigen provocations. The results indicated that epinastine hydrochloride showed the features characteristic of second-generation antihistamines, in which the number of sneezing attacks and quantity of nasal discharge decreased after antigen provocation at 30 minutes after administration. The single dose administration inhibited these symptoms for at least 3 hours, while the number of sneezing attacks was inhibited for 5 hours. Fexofenadine hydrochloride also showed a trend towards inhibition of these symptoms, but the effect was not significantly different from placebo. There are actual efficacy data for fexofenadine hydrochloride with respect to QOL in pollinosis,[8] and it is expected that the differences would become significant with a larger sample size, but no significant difference was observed in this study, possibly because the dose in this clinical study of once a day differs from the usual dosage used in clinical practice. The anti-histamine effect was not caused by only a single dose, but also by one-day dosage. If we add the second tablets of fexofenadine hydrochloride, the result of 300 minutes would be changed. Further work in the future is needed to determine whether significant differences can be seen using identical experimental methods in a larger number of subjects. On the other hand, it was evident that epinastine hydrochloride showed significant differences, and thus its rapid efficacy and usefulness need to be confirmed.

The observation that neither of the drugs showed significant differences compared with placebo with respect to efficacy measures such as the inferior nasal turbinate mucosal swelling score and nasal airway resistance may be explained by the fact that this study involved a single dose administration. The histamine release assay results may also be explained by this observation.

Based on the results of this clinical study, the efficacy of epinastine hydrochloride in the early phase of pollinosis treatment was demonstrated by the observation that a single dose administration led to the suppression of the nasal mucosal reaction elicited by repeated provocation. One may consider these data to be one line of evidence for pollinosis treatment in the early phase of pollen dispersion or when there is rapid increase in the quantity of pollen dispersed.

REFERENCES

1. Committee of Practical guideline for management of Allergic rhinitis. [II. Epidemiology.] *Practical guideline for management of Allergic rhinitis*, 4th edn. Tokyo: Life Science, 2002;7-12 (in Japanese).
2. Okuda M. Epidemiology of Japanese cedar pollinosis throughout Japan. *Ann. Allergy Asthma Immunol.* 2003;**91**: 288-296.
3. Shirasaka K, Yoshida H, Ikeda T *et al.* Effect of fexofenadine hydrochloride on repeated nasal provocation in patients with Japanese cedar pollinosis — Double-blind, placebo-controlled study—. *Allergol. Immunol.* 2005;**12**: 1722-1727.
4. Committee of Practical guideline for management of Allergic rhinitis. [V. Treatment.] *Practical guideline for management of Allergic rhinitis*, 4th edn. Tokyo: Life Science, 2002;29-44 (in Japanese).
5. Asaka H, Baba K, Konno W, Gama N, Shirasaka K. [Clinical efficacy of epinastine under placebo-controlled outdoors clinical study on cedar pollinosis.] *Oto-Rhino-Laryngology* 2003;**46**:101-107 (in Japanese).
6. Day JH, Briscoe MP, Welsh A *et al.* Onset of action, efficacy, and safety of a single dose of fexofenadine hydrochloride for ragweed allergy using an environmental exposure unit. *Ann. Allergy Asthma Immunol.* 1997;**79**:533-540.
7. Okubo K, Okuda M. Time-course changes in nasal airway resistance after house dust antigen challenge: With spe-

cial reference to late phase response. *Allergol. Int.* 1998; **47**:225-232.
8. Okubo K, Gotoh M, Shimada K, Ritsu M, Kobayashi M, Okuda M. Effect of fexofenadine on the quality of life of Japanese cedar pollinosis patients. *Allergol. Int.* 2004;**53**: 245-254.
9. Okuda M. Nasal provocation test. In: Settipane G (ed). *Rhinitis.* Oceanside Publications, Providence 1991;325-334.
10. Committee of Practical guideline for management of Allergic rhinitis. [IV. Examination and Diagnosis.] *Practical guideline for management of Allergic rhinitis*, 4th edn. Tokyo: Life Science, 2002;17-24 (in Japanese).
11. Gotoh M, Okubo K, Okuda M. Repeated antigen challenge in patients with perennial allergic rhinitis to house dust mites. *Allergol. Int.* 2003;**52**:207-212.
12. Usui N, Iwata A, Uchiyama M, Tsukasa M. [Assessment of inhibition by Ketotifen (HC20-511) in the nasal provocation test by house dust antigen.] *Oto-Rhino-Laryngology* 1984;**27**:107-114 (in Japanese).
13. Konno A. [Nasal hypersensitivity: its pathological and clinical features.] *Task report at the 97th meeting of the Otolaryngology Society of Japan.* Chiba: Sasaki publisher, 1996 (in Japanese).
14. Yoshida H, Shimizu H, Fukami S. [Relation between symptom and counts of scattering Japanese cedar pollen—Examination of clinical observation and repeated provocation—.] *Jpn. J. Allergol.* 1996;**45**:49-61 (in Japanese).
15. Otsuka H, Dolovich J, Befus AD *et al.* Basophilic cell progenitors, nasal methachromatic cells, and peripheral blood basophils in ragweed-allergic patients. *J. Allergy Clin. Immunol.* 1986;**78**:365-371.
16. Grant JA, Danielson L, Rihoux JP, De Vos C. A double-blind, single-dose, crossover comparison of cetirizine, ebastine, epinastine, fexofenadine, terfenadine, and loratadine versus placebo; suppression of histamine-induced wheal and flare response for 24 h in healthy male subjects. *Allergy* 1999;**54**:700-707.

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

Kimihiro Okubo, Satoshi Ogino, Toshikazu Nagakura and Takeru Ishikawa

Allergology International
Vol 55, No 4:379-386 December 2006

Allergology International. 2006;55:379-386

ORIGINAL ARTICLE

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

Kimihiro Okubo[1], Satoshi Ogino[2], Toshikazu Nagakura[3] and Takeru Ishikawa[4]

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-

[1]The Department of Otorhinolaryngology, Nippon Medical School, [3]The Allergy and Internal Medicine, Yoga Clinic, Tokyo, [2]The Department of Health and Hygiene, Osaka University School of Medicine, Osaka and [4]Professor Emeritus, Kumamoto University School of Medicine, Kumamoto, Japan.
Correspondence: Kimihiro Okubo, MD, PhD, Department of Otorhinolaryngology, Nippon Medical School, 1-1-5 Sendagi, Bunkyo-ku, Tokyo 113-8602, Japan.
Email: ent-kimi@nms.ac.jp
Received 9 December 2005. Accepted for publication 17 April 2006.

pan.

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.

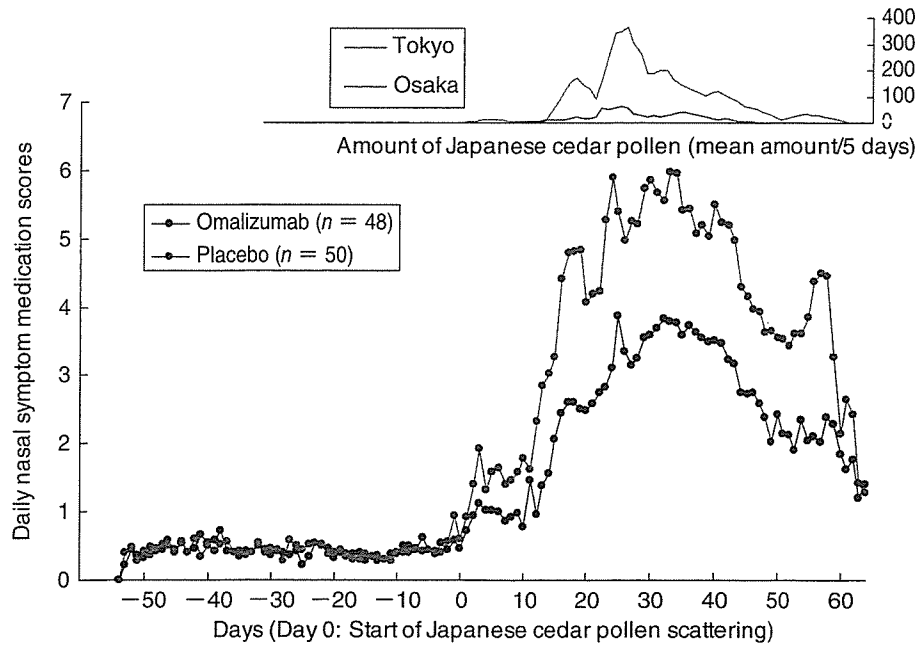

Fig. 1 Time-course changes in daily nasal symptom medication score (FAS) and in amount of Japanese cedar pollen. Day 0 represents the start day of the Japanese cedar pollen scattering period in Tokyo and Osaka.

(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).

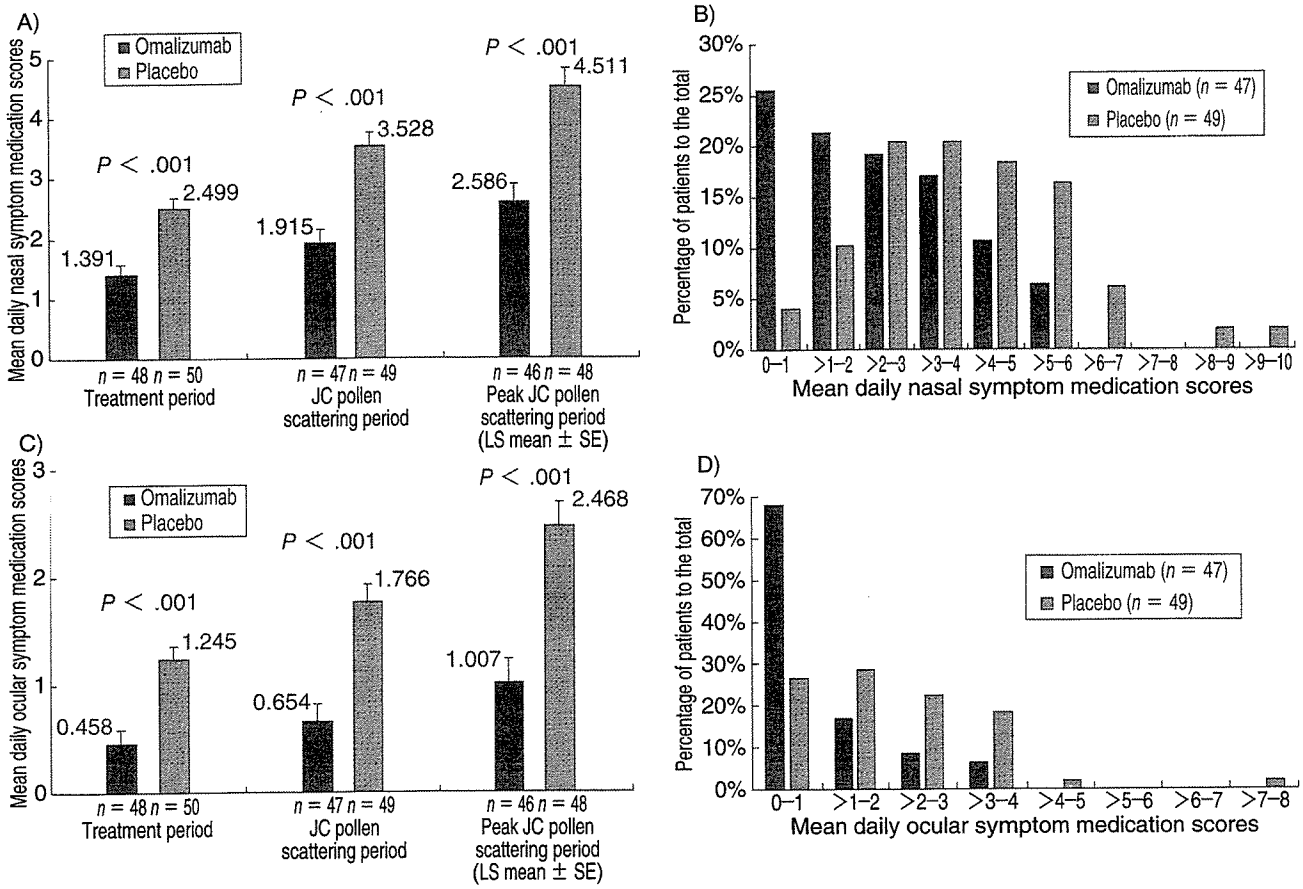

Fig. 2 **A**) Mean daily nasal symptom medication scores (DNSMS) and **C**) mean daily ocular symptom medication scores (DOSMS) during the treatment period, the Japanese cedar (JC) pollen scattering period, and the peak JC pollen scattering period. Percentages of the total of patients with **B**) mean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

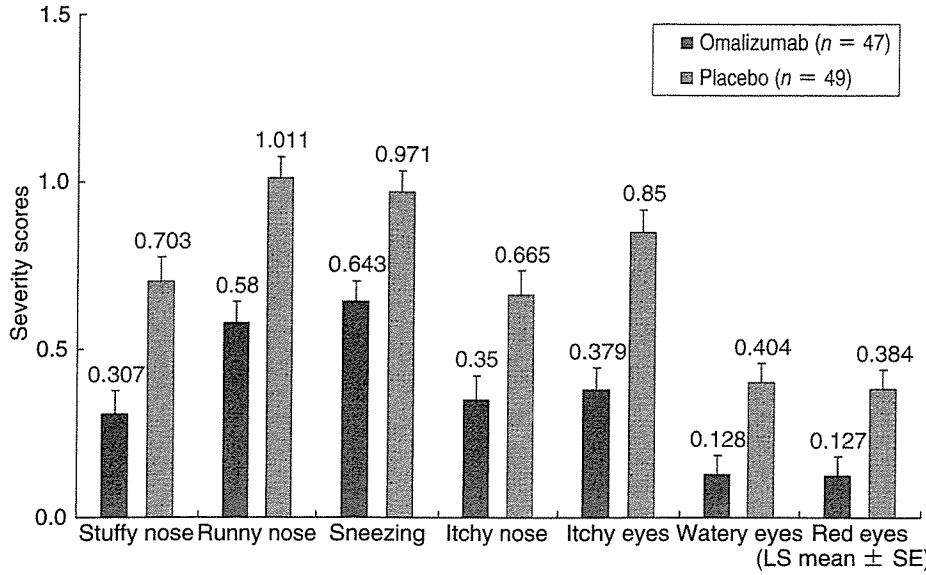

Fig. 3 Effects of omalizumab on each of the mean daily nasal and ocular symptom severity scores (FAS) during the Japanese cedar pollen scattering period ($P < .001$ for all variables). Statistically significant differences were noted during the treatment period and peak Japanese cedar pollen scattering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

REFERENCES

1. Establishment committee of the clinical guideline for allergic rhinitis(2002). [Clinical guideline for allergic rhinitis in Japan.]. *Perennial and seasonal allergic rhinitis,* 4th edn. Tokyo: Life Science Medica, 2002 (in Japanese).
2. Konno A. [Investigation of evaluation of various treatment against pollinosis based on scientific evidence.] *The report of Japanese Ministry of Health and Welfare scientific research for sensory organ impairment and immunoallergy.* 2001 (in Japanese).
3. Okuda M. Epidemiology of Japanese cedar pollinosis throughout Japan. *Ann. Allergy Asthma Immunol.* 2003; **91**:288-296.
4. Kawaguchi T, Hoshiyama Y, Watanabe Y. Cost of cedar pollinosis. *The Allergy in Practice* 2001;**273**:178-182 (in Japanese).
5. Okubo K, Gotoh M, Shimada K *et al.* Fexofenadine improves the quality of life and work productivity in Japanese patients with seasonal allergic rhinitis during the peak cedar pollinosis season. *Int. Arch. Allergy Immunol.* 2005;**136**:148-154.
6. Ishizaka T, Ishizaka K. Activation of mast cells for mediator release through IgE receptors. *Prog. Allergy.* 1984;**34**: 188-235.
7. Presta LG, Lahr SJ, Shields RL *et al.* Humanization of an antibody directed against IgE. *J. Immunol.* 1993;**151**: 2623-2632.
8. MacGlashan DW Jr, Bochner BS, Adelman DC *et al.* Down-regulation of FcεRI expression on basophils during in vivo treatment of atopic patients with anti-IgE antibody. *J. Immunol.* 1997;**158**:1438-1445.
9. Beck LA, Marcotte GV, MacGlashan D Jr, Togias A, Saini S. Omalizumab-induced reductions in mast cell FcεRI expression and function. *J. Allergy Clin. Immunol.* 2004; **114**:527-530.
10. Kolbinger F, Saldanha J, Hardman N, Bendig MM. Humanization of a mouse anti-human IgE antibody: a potential therapeutic for IgE-mediated allergies. *Protein Engineering* 1993;**6**:971-980.
11. Heusser CH, Wagner K, Bews JPA *et al.* Demonstration of the therapeutic potential of non-anaphylactogenic anti-IgE antibodies in murine models of skin reaction, lung function and inflammation. *Int. Arch. Allergy Immunol.* 1997;**113**:231-235.
12. Casale TB, Bernstein L, Busse WW *et al.* Use of an anti-IgE humanized monoclonal antibody in ragweed-induced allergic rhinitis. *J. Allergy Clin. Immunol.* 1997;**100**:110-121.
13. Ädelroth E, Rak S, Haahtela T *et al.* Recombinant humanized mAb-E25, an anti-IgE mAb, in birch pollen-induced seasonal allergic rhinitis. *J. Allergy Clin. Immunol.* 2000; **106**:253-259.
14. Casale TB, Condemi J, LaForce C *et al.* Effect of omalizumab on symptoms of seasonal allergic rhinitis. A randomized controlled trial. *JAMA* 2001;**286**:2956-2967.
15. Chervinsky P, Casale T, Townley R *et al.* Omalizumab, an anti-IgE antibody, in the treatment of adults and adolescents with perennial allergic rhinitis. *Ann. Allergy Asthma Immunol.* 2003;**91**:160-167.
16. Milgrom H, Fick RB, Su JQ *et al.* Treatment of allergic asthma with monoclonal anti-IgE antibody. *N. Engl. J. Med.* 1999;**341**:1966-1973.
17. Soler M, Matz J, Townley R *et al.* The anti-IgE antibody omalizumab reduces exacerbations and steroid requirement in allergic asthma. *Eur. Respir. J.* 2001;**18**:254-261.
18. Busse W, Corren J, Lanier BQ *et al.* Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. *J. Allergy Clin. Immunol.* 2001;**108**:184-190.
19. Milgrom H, Berger W, Nayak A *et al.* Treatment of childhood asthma with anti-immunoglobulin E antibody(omalizumab). *Pediatrics* 2001;**108**:1-10.
20. Hochhaus G, Brookman L, Fox H *et al.* Pharmacodynamics of omalizumab: implications for optimised dosing strategies and clinical efficacy in the treatment of allergic asthma. *Curr. Med. Res. Opin.* 2003;**19**:491-498.
21. Prussin C, Griffith DT, Boesel KM, Lin H, Foster B, Casale TB. Omalizumab treatment downregulates dendritic cell FcRεI expression. *J. Allergy Clin. Immunol.* 2003;**112**:1147-1154.
22. Chang TW. The pharmacological basis of anti-IgE therapy. *Nature Biotechnology* 2000;**18**:157-162.
23. Shields RL, Whether WR, Zioncheck K *et al.* Inhibition of allergic reactions with antibody to IgE. *Int. Arch. Allergy Immunol.* 1995;**107**:308-312.
24. Coyle AJ, Wagner K, Bertrand C, Tsuyuki S, Bews J, Heusser C. Central role of immunoglobulin (Ig) E in the reduction of lung eosinophil infiltration and T helper 2 cell cytokine production : inhibition by a non-anaphylactogenic anti-IgE antibody. *J. Exp. Med.* 1996; **183**:1303-1310.
25. Kuehr J, Brauburger J, Zielen S *et al.* Efficacy of combination treatment with anti-IgE plus specific immunotherapy in polysensitized children and adolescents with seasonal allergic rhinitis. *J. Allergy Clin. Immunol.* 2002;**109**:274-280.