In the present study, the QOL of Japanese cedar pollinosis patients was evaluated, in comparison with a placebo control, using the 'Japanese Allergic Rhinitis QOL Standard Questionnaire' (JRQLQ) after administration of 60 mg fexofenadine HCl, twice daily for 14 days.

METHODS

Patients

The subjects were male and female Japanese cedar pollinosis patients (hereafter called 'patients') aged from 20 to 56 years. Cedar pollinosis symptoms had to have been present for more than 2 years and cedar pollen-specific IgE was class 2 or above. Patients who lived or worked in the metropolitan area were favored as study subjects. In addition, the total symptom score (TSS; comprising sneezing, runny nose, nasal congestion, itchy eyes and watery eyes) was at least 4 and at least two of the five symptoms were of greater than moderate severity on the starting day of administration.

The following patients were excluded from the study: patients whose symptoms had developed before the cedar pollen season, patients with complications of nasal diseases that could have an effect on the evaluation of efficacy (perennial allergic rhinitis, acute and chronic rhinitis etc.), patients who planned to go to Hokkaido, Okinawa or abroad, and others whom the physician-in-charge judged unfit as study subjects.

Prior to participation in the present study, written consent was obtained from all patients after the physician-in-charge had explained the study in person to the patients. In addition, the study was conducted with the approval of the Institutional Review Board of Nippon Medical School.

Study design

The present study was a randomized, double-blind comparison study against a placebo control, performed at a single institution.

After obtaining patient consent, screening was performed to confirm compliance with the subject selection and exclusion criteria and to examine the physical condition of each individual. Screening included patient background, physician's examination, clinical laboratory analysis (hematology, blood biochemistry, serology and urinalysis), physical examination, and electrocardiogram (12 lead electrocardiogram). The physician-in-charge determined the eligibility of each patient as a subject in the present study based on the results of screening. The pre-observation period was 7 days before the start of administration of the trial drug, during which time the physician's examination, rhinoscopy and blood collection were performed. Following completion of the pre-observation period, patients were assigned at random to receive test drug or placebo and administration was started. A fexofenadine HCl 60 mg tablet (fexofenadine group) or placebo tablet (placebo group) was administered twice a day, once in the morning and once in the evening, for 14 days (Fig. 1).

Patients were asked to record in the patient diary pollinosis symptoms (sneezing, runny nose, nasal congestion, itchy eyes, watery eyes and interference with daily life) and compliance with the drug administration schedule.

The physician-in-charge examined each patient a total of five times: at screening, during the pre-observation period, on the starting day of drug administration and 1 and 2 weeks after the start of drug administration. The baseline data were those at the start of drug administration and the end-points were data obtained 2 weeks after the start of test drug administration.

Patients were asked to fill out the JRQLQ questionnaire[2] at the start of the pre-observation period, on the starting day of drug administration and at the times of hospital visits, 1 and 2 weeks after the start of drug administration (Fig. 2). In addition, patients were asked to make an entry in the patient diary every day from the start of the pre-observation period until the day after the completion of drug administration.

During the study period, any concurrent use of drugs that could influence the evaluation of efficacy was prohibited. However, when drugs had to be used, as judged by the physician-in-charge, the drugs used were recorded in the survey form.

Evaluation items

The JRQLQ

The JRQLQ, which was used as the primary standard for evaluation, is composed of three parts: nasal and eye symptoms (JRQLQ I), a QOL-related questionnaire (JRQLQ II) and an overall face scale.

The nasal and eye symptoms included the six categories of runny nose, sneezing, nasal congestion, itchy nose, itchy eyes and watery eyes. Each subject evaluated symptoms on a five-point scale, which included 0 for no symptoms, 1 for mild, 2 for moderately severe, 3 for severe and 4 for very severe symptoms. Mean scores for

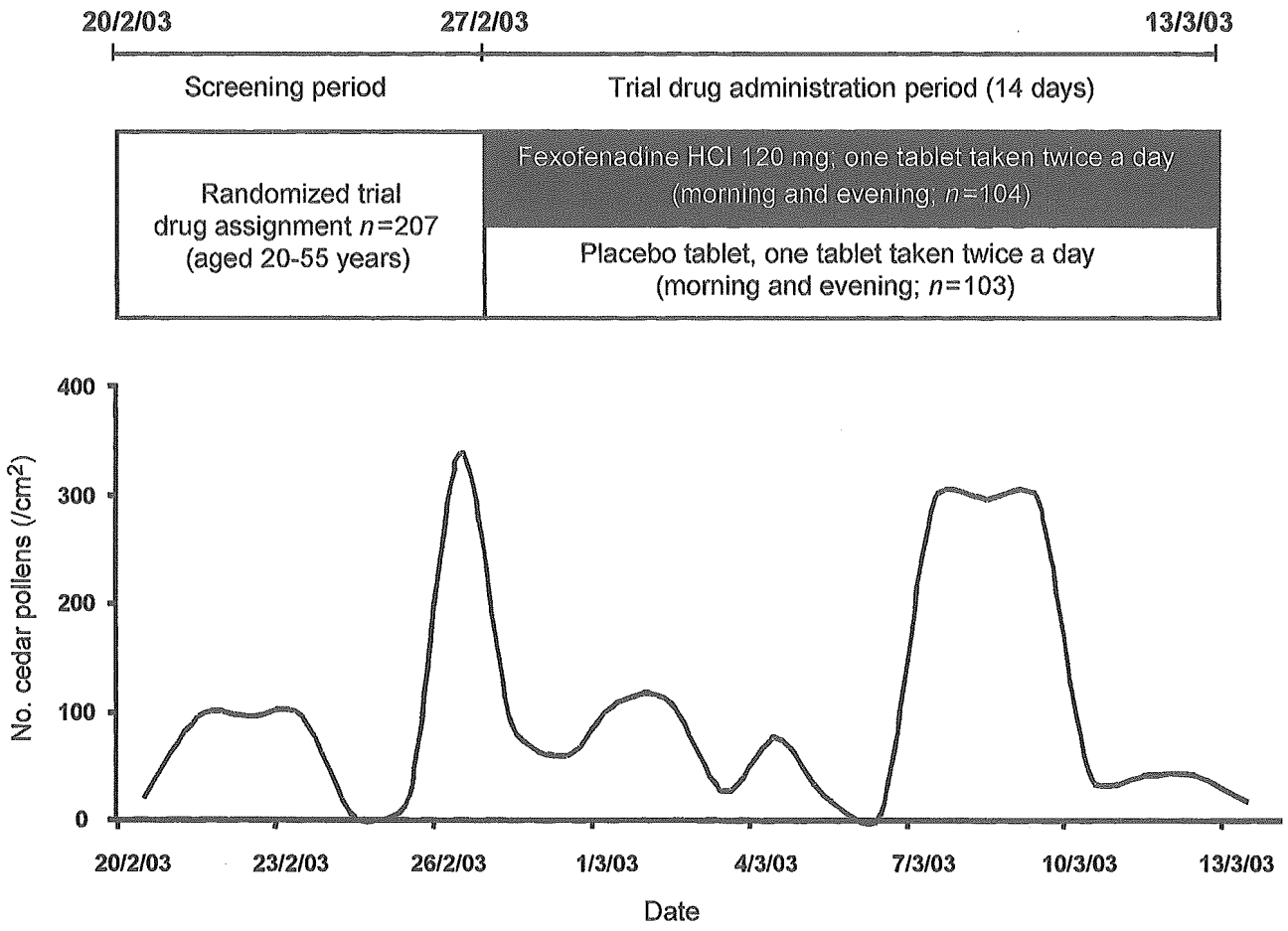


Fig. 1 Study design.

these six categories were determined as the mean nasal and eye symptom scores (JRQLQ I).

The QOL-related questionnaire included 17 items concerning: (i) reduced productivity at work/home/school; (ii) poor mental concentration; (iii) reduced thinking power; (iv) impaired reading book/paper; (v) reduced memory loss; (vi) limitation of outdoor life (e.g. sports, picnic); (vii) limitation of going out; (viii) hesitation visiting friend or relatives; (ix) reduced contact with friends or others by telephone or conversation; (x) not an easy person to be around; (xi) impaired sleeping; (xii) tiredness; (xiii) fatigue; (xiv) frustration; (xv) irritability; (xvi) depression; and (xvii) unhappiness. Each item was evaluated on a five-point scale as 0 for no significant problem, 1 for a mild problem, 2 for moderately severe, 3 for severe and 4 for very severe (Fig. 2). Mean scores for these categories were determined as the mean QOL-related questionnaire scores (JRQLQ II). In addition, these categories were divided into six domains, including 'usual daily activities' for items i–v, 'outdoor activities' for items vi and vii, 'social functioning' for items viii to x, 'sleep problem' for item xi, 'general physical problems' for items xii and xiii, and 'emotional function' for items xiv to xvii. The mean score for each domain was calculated for analysis.

Overall face scale, including overall symptoms, condition and feelings, was evaluated on a scale from 0 for 'happy' to 4 for 'crying' for the past 1–2 weeks.[2]

The present study evaluated the mean score for each domain in the QOL-related questionnaire as well as JRQLQ I, JRQLQ II and overall face scale.

Allergy diary

In the allergy diary, each item from a list including sneezing (number of attacks in a day), runny nose (number of incidences of nose blowing per day), nasal congestion, itchy eyes and watery eyes was evaluated on

Japanese Rhino-conjunctivitis Quality of Life Questionnaire (JRQLQ No1)

To patients with allergic rhinitis (including pollinosis)

These days, the aim of medical treatment is not just to cure disease but also to give patients a better quality of life. The purpose of this survey is to determine to what extent your rhinitis interferes with your life and whether it would be improved by treatment. As with all medical treatment, the information you provide in this survey will remain strictly confidential.

You may find some of the following questions difficult to answer, but just answer to the best of your ability.

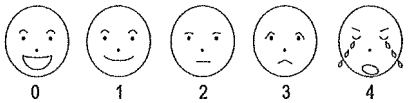
I Tick the box that best describes the severity of the worst nasal and eye symptoms you have experienced in the past 1–2 weeks.

Nasal and eye symptoms	0, No symptoms	1, Mild	2, Moderate	3, Severe	4, Very severe
Runny nose	☐	☐		☐	☐
Sneezing	☐	☐		☐	☐
Blocked nose (nasal congestion)	☐	☐		☐	☐
Itchy nose	☐	☐		☐	☐
Itchy eyes	☐	☐		☐	☐
Watery eyes	☐	☐		☐	☐

II Tick the box that best describes the worst extent to which the symptoms in I above have interfered with your quality of life in the past 1–2 weeks. If any of the items listed under Quality of life below definitely do not relate to the symptoms in I (nose, eye), then there is no need to tick a box for that particular item.

Quality of life	0, No	1, Yes, slightly	2, Yes, moderately	3, Yes, greatly	4, Yes, very greatly
1. Reduced productivity at work/home	☐	☐		☐	☐
2. Poor mental concentration	☐	☐		☐	☐
3. Reduced thinking power	☐	☐		☐	☐
4. Impaired reading book/newspaper	☐	☐		☐	☐
5. Reduced memory loss	☐	☐		☐	☐
6. Limitation of outdoor life (e.g. sport, picnics)	☐	☐		☐	☐
7. Limitation of going out	☐	☐		☐	☐
8. Hesitation visiting friend or relatives	☐	☐		☐	☐
9. Reduced contact with friends or others by telephone or conversation	☐	☐		☐	☐
10. Not an easy person to be around	☐	☐		☐	☐
11. Impaired sleeping	☐	☐		☐	☐
12. Tiredness	☐	☐		☐	☐
13. Fatigue	☐	☐		☐	☐
14. Frustration	☐	☐		☐	☐
15. Irritability	☐	☐		☐	☐
16. Depression	☐	☐		☐	☐
17. Unhappiness	☐	☐		☐	☐

III Please circle the number of the face that best describes your general state (including your symptoms, life and emotion) in the past 1–2 weeks.



● Do not fill out the following.

To be completed by physician

Patient's name: Medical record no: Age: yr Sex: M F

Name of medical institution: Physician's name: Date:

Diagnosis:
SAR: (Antigen:) Treatment (prevention, drug, immunology therapy, operation)
PAR: (Antigen:) Treatment (prevention, drug, immunology therapy, operation)
Non-Allergy: (Disease:) Treatment ( )

QOL score: None 0, Mild 1, Moderate 2, Severe 3, Very severe 4.
Total QOL score
Score by QOL category: ☐ 1–5 points daily life ☐ 6–7 points out-door ☐ 8–10 points social ☐ 11 points sleep ☐ 12, 13 points body ☐ 14–17 points psycho-life
*Please write the names of drugs used if possible

Score: None: 0 points Mild: 1 point Moderate: 2 points Severe: 3 points Very severe: 4 points

Fig. 2 Japanese Allergic Rhinitis Standard Quality of Life Questionnaire (JRQLQ no. 1).

a scale from 0 for the most mild to 4 for the most severe. The total scores for sneezing, runny nose, nasal congestion, itchy eyes and watery eyes were calculated as the TSS for statistical analysis. The severity in the season was compared between the fexofenadine and placebo groups.

Safety

All unfavorable signs and symptoms observed during the period of administration of the test drug were classified as adverse events, regardless of the presence or absence of a causal relationship to the test drug.

The safety items evaluated included analysis of data obtained during the study period (clinical laboratory analysis, physical examination and physician's examination) and symptoms experienced during the study period (only adverse events reported at the physician's examinations, but not those described in the allergy diary).

Statistical analysis

Continuous variables and categorical variables were analyzed by the Mann–Whitney *U*-test and Chi-squared test, respectively, for characteristics related to patients' background (age, sex, address, occupation and work place).

Changes in JRQLQ scores from baseline were analyzed by analysis of covariance (ANCOVA), with the treatment group as the main effect and the baseline values as the covariate. For TSS, the statistical significance between two groups was examined using the Mann–Whitney *U*-test.

RESULTS

Patient population

Of a total of 250 subjects screened, 210 were randomized to receive treatment; 104 received fexofenadine HCl 60 mg b.i.d. (fexofenadine group) and 103 received placebo b.i.d. (placebo group). All 207 randomized subjects completed the 2 week study period.

Overall, 207 subjects were enrolled in the Intent-to-Treat (ITT) population (patients who received at least one dose of treatment and completed a baseline and not less than one valid QOL assessment): 104 subjects in the fexofenadine group and 103 in the placebo group. There were no differences between the two treatment groups in terms of demographic characteristics (Table 1). The mean age of subjects in the fexofenadine group was 32.7 years compared with 34.2 years in the placebo group. The majority of patients were male (60% fexofenadine group; 56% placebo group). There were almost equal numbers of students (47% fexofenadine group; 45% placebo group) and non-students (53% fexofenadine group; 55% placebo group).

Baseline JRQLQ scores were comparable between the two treatment groups (Table 2). The mean QOL-related questionnaire score (JRQLQ II) was 1.00 in the fexofenadine group and 0.89 in the placebo group, showing that patients were greatly troubled by pollinosis symptoms. Individual JRQLQ domain scores at baseline indicated that patients were less troubled by their symptoms in relation to their social functioning and were more troubled in their usual daily activities, outdoor activities and by general physical problems.

Table 1 Patient characteristics at baseline (Intent-to-Treat population)

Characteristic	Fexofenadine HCl 60 mg b.i.d (n = 104)	Placebo (n = 103)	P
Mean (±SD) age (years)	32.7 ± 9.8	34.2 ± 9.8	0.631*
Sex			
Total	104	103	
No. males (%)	62 (60)	58 (56)	0.674†
No. females (%)	42 (40)	45 (44)	
Occupation			
No. students (%)	48 (47)	45 (45)	0.769†
No. non-students (%)	55 (53)	56 (55)	

*Wilcoxon test.

†Chi-squared test.

Table 2 Baseline Japanese Allergic Rhinitis Standard Quality of Life Questionnaire (JRQLQ) scores (Intent-to-Treat population)

Scores	Fexofenadine HCl 60 mg b.i.d (n = 104)	Placebo (n = 103)	P (Wilcoxon test)
Nasal and eye symptoms	1.60 ± 0.73	1.60 ± 0.73	0.864
QOL-related questionnaire	1.00 ± 0.86	0.89 ± 0.73	0.557
Scores by domain			
Usual daily activities	1.19 ± 1.0	0.96 ± 0.8	0.123
Outdoor activities	1.03 ± 1.0	1.08 ± 1.0	0.682
Social functioning	0.66 ± 0.8	0.64 ± 0.7	0.75
Sleep problem	0.93 ± 0.9	0.83 ± 0.9	0.285
General physical problems	1.12 ± 1.1	0.96 ± 1.0	0.495
Emotional function	0.96 ± 1.0	0.87 ± 0.9	0.993
Condition of past 1 or 2 weeks	2.46 ± 0.9	2.45 ± 0.9	0.961

Data are the mean ±SD.

QOL, quality of life.

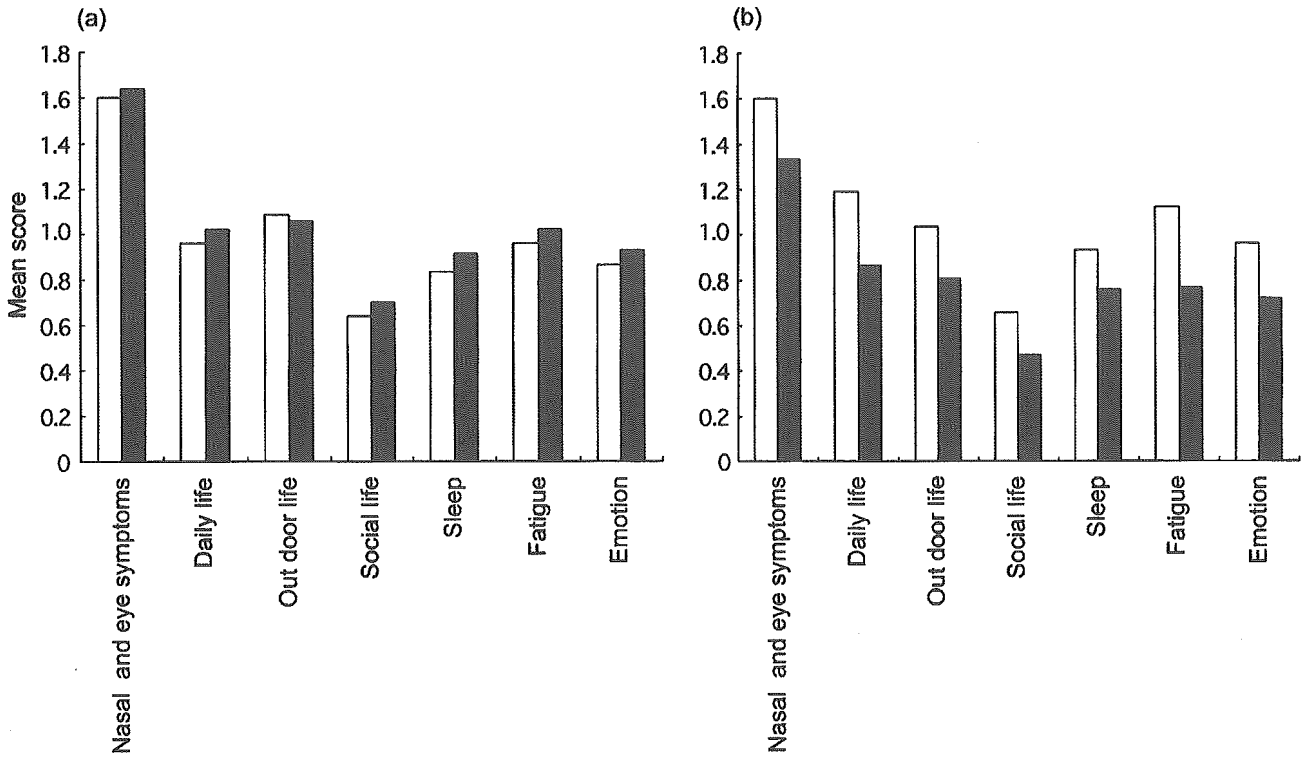


Fig. 3 Mean Japanese Allergic Rhinitis Standard Quality of Life Questionnaire (JRQLQ) scores at baseline (□) and at the end of the 2 week administration period (■) for (a) placebo and (b) fexofenadine HCL 120 mg (60 mg b.i.d.).

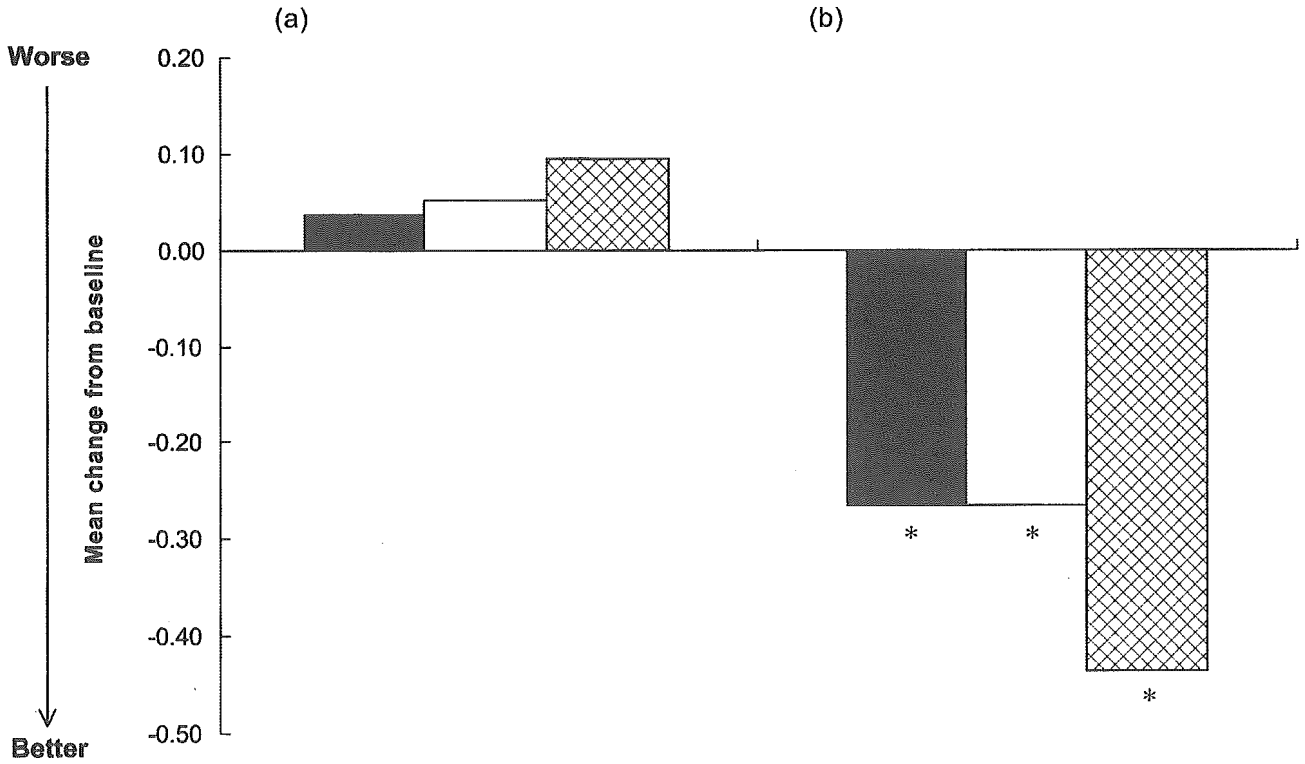


Fig. 4 Mean changes in scores from baseline (■, nasal and eye symptoms; □, quality of life-related questionnaire; ⊠, overall face scale) following 2 week administration of (a) placebo or (b) fexofenadine HCL 120 mg (60 mg b.i.d.). *$P < 0.001$ compared with placebo.

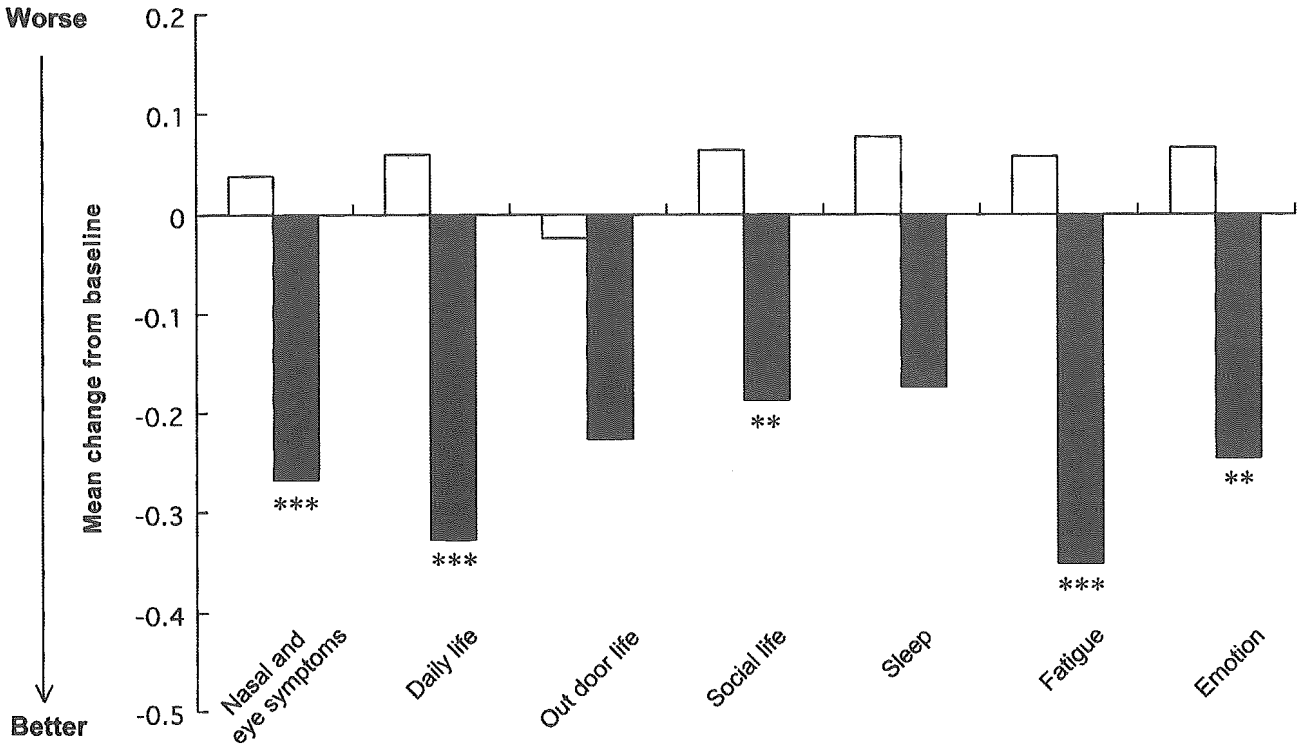


Fig. 5 Mean changes in scores from baseline (domains in the quality of life-related questionnaire) following 2 weeks administration of placebo (□) or fexofenadine HCL 120 mg (60 mg b.i.d.; ■). Changes in nasal and eye symptoms, which are shown in Fig. 4, are shown as a reference. $^{**}P < 0.01$, $^{***}P < 0.001$ compared with placebo.

Outcome

Quality of life

Mean scores in each domain are shown for JRQLQ I and JRQLQ II in Fig. 3. Scores of all domains, except outdoor activities, decreased or worsened in the placebo group, whereas all showed an improvement in the fexofenadine group.

Significant improvements in scores from baseline were clearly seen in the fexofenadine group for JRQLQ I, JRQLQ II and the overall face scale ($P < 0.001$; Fig. 4). In addition, with regard to each domain of JRQLQ II, a significant improvement in scores was observed for usual daily activities ($P < 0.001$), social functioning ($P = 0.002$), general physical problems ($P < 0.001$) and emotional function ($P = 0.002$) in the fexofenadine group (Fig. 5). Scores for outdoor activities ($P = 0.055$) and sleep problems ($P = 0.064$) tended to improve, albeit not significantly, in the fexofenadine group.

In JRQLQ II by domain in each week, there was a significant improvement in the first week for all the domains in the fexofenadine group. No significant change was seen in the fexofenadine group for outdoor activities ($P = 0.055$) and sleep problems ($P = 0.064$) in the second week (end-point), which could have been due to changes in the pollen count (Fig. 6).

Symptom severity

The daily TSS (total score of sneezing, runny nose, nasal congestion, itchy eyes and watery eyes), as calculated from the subject diary, significantly improved in the fexofenadine group from the first day after administration compared with the placebo group. This improvement was sustained at the peak pollen count, showing improvement every day throughout the administration period (Fig. 7).

Safety

No serious adverse events were reported throughout the study period. There was no significant difference in the number of adverse events between the two groups ($P = 0.568$). A high white blood cell count and headache occurred most frequently.

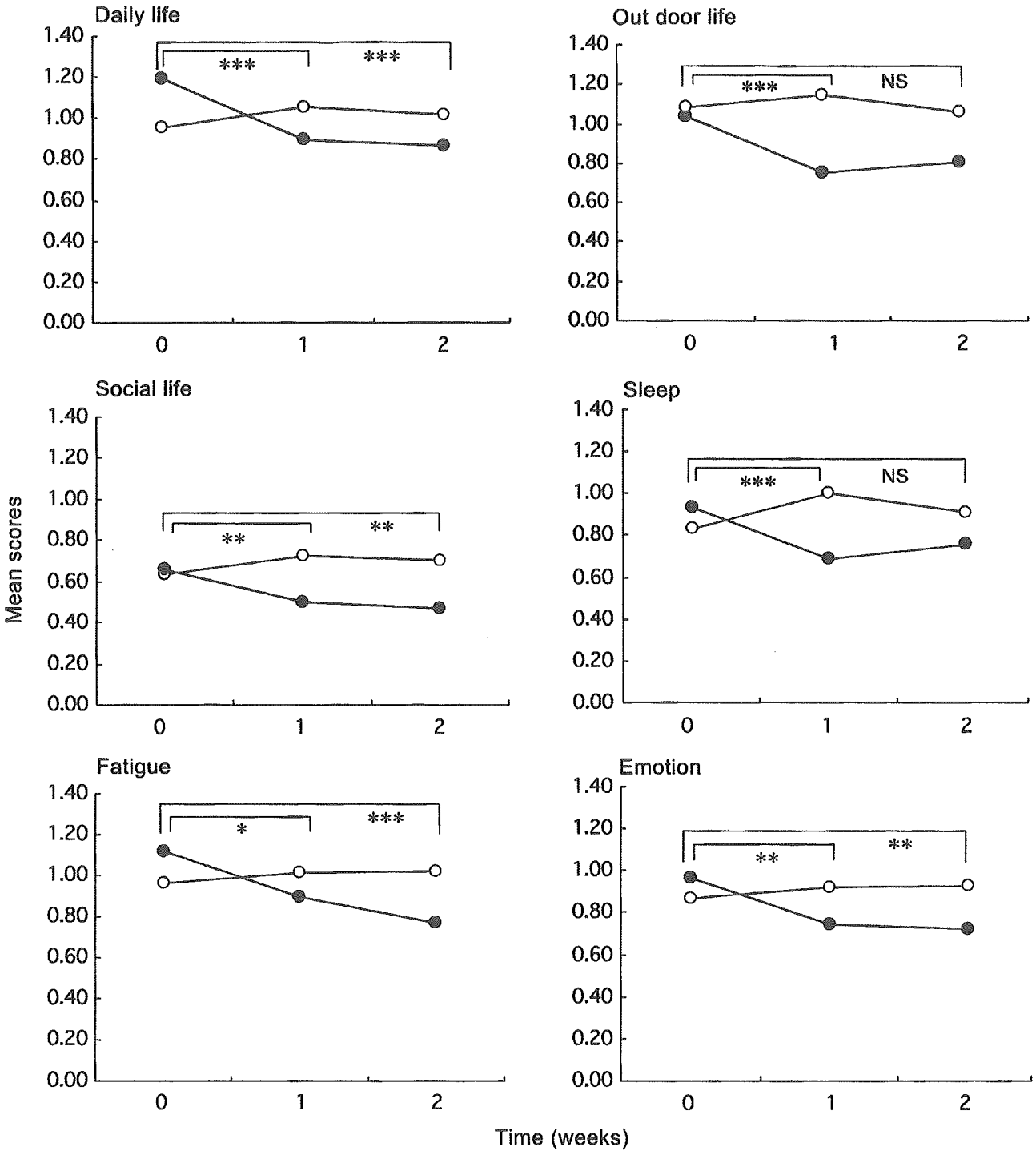


Fig. 6 Changes in quality of life-related questionnaire domains from baseline to end-point following 2 weeks administration of placebo (O) or fexofenadine HCL 120 mg (60 mg b.i.d.; ●). $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ compared with placebo. The starting day of administration (baseline), 1 week after the start of administration and 2 weeks after the start of administration (end-point) are indicated on the graphs as 0, 1 and 2 weeks, respectively.

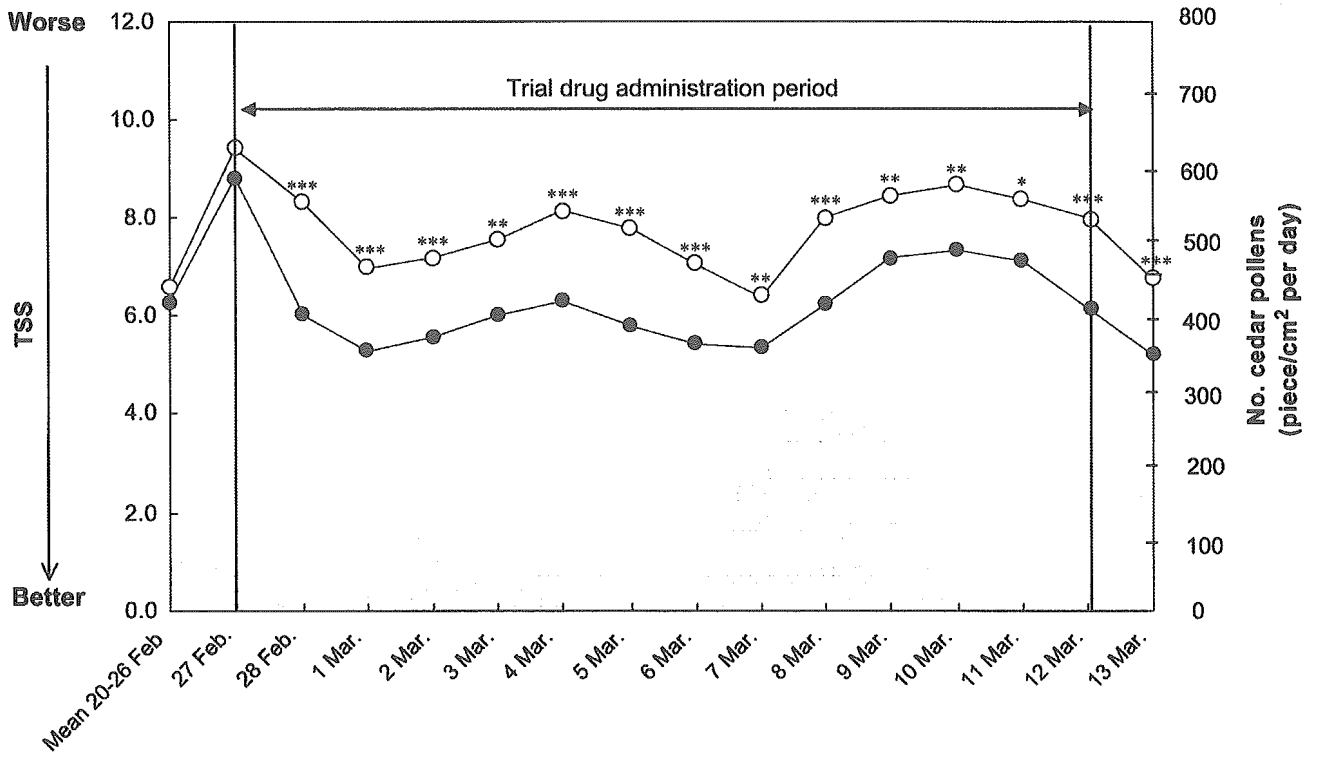


Fig. 7 Total symptom score (TSS) in subject diary and pollen counts following 2 weeks administration of placebo (O) or fexofenadine HCL 120 mg (60 mg b.i.d.; ●). The TSS included sneezing, nasal discharge, nasal congestion, itchy eyes and watery eyes. The number of cedar pollens throughout the 2 week period is indicated by the shaded area on the graph. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ compared with placebo.

Discussion

Allergic rhinitis has been regarded as a 'life style disease' that interferes with daily life rather than as a 'chronic disease'. This is based on the fact that allergic rhinitis is not a life-threatening disease but, rather, it worsens QOL. The World Health Organization defines QOL as an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns.[3] To determine whether an improvement or deterioration of QOL has taken place, oral and written questionnaires are administered. Among the questionnaires that are currently used mainstream methods of surveying, some (SF-36 etc.) are not specific to particular diseases and examine general health status, whereas others examine QOL specific to a disease. From a survey using SF-36, Fukuroku *et al.*[3] reported that among nasal symptoms in perennial allergic rhinitis, nasal congestion was the one that interfered most severely with the QOL. The Juniper questionnaire is the only one specific to allergic rhinitis and is regarded as the standard questionnaire in the US and Europe.[4] Using this questionnaire, it has been reported that there is a correlation between the severity of disease and the QOL score of patients.[5]

We have recently developed and validated a Japanese original standardized questionnaire for allergic rhinitis.[6] The findings of the present study demonstrate that fexofenadine HCl 60 mg b.i.d. significantly improved the overall QOL and total symptom score in Japanese subjects with pollinosis compared with placebo during the 2 week treatment period. This improvement in QOL was associated with significant symptom relief in the fexofenadine treatment group. Furthermore, fexofenadine-treated subjects experienced significant improvement in nasal and eye symptoms, usual daily activities, social functioning, general physical problems and emotional function. These significant improvement scores ranged from 0.19 to 0.35 in the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ). This improvement rate is not consistent with the Juniper theory of 0.5.[7]

The results presented here are consistent with those published previously, in which fexofenadine significantly

improved QOL in pollinosis and chronic indiopathic urticaria (CIU) patients.[8–11] Tanner *et al.* assessed the impact of fexofenadine HCl 60 mg b.i.d. on patients' QOL in a pooled analysis of two placebo-controlled trials in patients with pollinosis.[8] A significant ($P = 0.05$) improvement in overall RQLQ score was reported for patients receiving fexofenadine HCl 60 mg b.i.d. compared with placebo.[8] In a more recent study, van Cauwenberge *et al.*[11] assessed the impact of once-daily administration of fexofenadine HCl 120 mg, loratadine 10 mg or placebo on patients' QOL in the treatment of pollinosis. A total of 509 pollinosis patients aged 12–75 years completed the QOL assessment (RQLQ). For all treatment groups (fexofenadine, loratadine and placebo), there was a significant improvement from baseline in overall QOL ($P < 0.0001$); however, the improvement in the fexofenadine group was significantly greater than that obtained in either the loratadine ($P = 0.03$ for fexofenadine *vs* loratadine) or placebo ($P = 0.005$ for fexofenadine *vs* placebo) groups. In addition, fexofenadine was significantly better than either loratadine or placebo in reducing overall mean 24 h reflective symptom scores for itchy, watery or red eyes and nasal congestion from baseline ($P = 0.05$), whereas the effect of loratadine on these two symptom scores did not differ from that of placebo.[11] Furthermore, in patients with CIU, fexofenadine HCl 60 mg b.i.d. significantly improved overall QOL compared with placebo.[9] These results corroborate the findings presented here that fexofenadine improved overall QOL in Japanese subjects with pollinosis.

The present clinical study demonstrated the usefulness of the recently validated JRQLQ instruments in assessing QOL in a Japanese patient population with pollinosis during the peak cedar pollinosis season. The JRQLQ, as a measure of QOL, will soon be adopted as an outcome measure for clinical trials in the Japanese population.[12] The results presented here support the use of the JRQLQ questionnaire for assessing the impact of pollinosis symptoms on QOL.

Conclusions

In conclusion, the present clinical study showed that fexofenadine HCl 60 mg b.i.d. significantly improves QOL in Japanese patients with pollinosis during the peak cedar pollenosis season, using a recently validated Japanese instrument.

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CASE REPORT

Sublingual Immunotherapy for Japanese Cedar Pollinosis

Minoru Gotoh[1] and Kimihiro Okubo[2]

ABSTRACT

Background: Although subcutaneous immunotherapy may cure allergic diseases, it is not commonly used in Japan because of the pain and risk of anaphylactic shock. Sublingual immunotherapy(SLIT)overcomes these limitations and although it is the most advanced form of local immunotherapy for clinical application, it is not used in Japan nor has it been extensively studied.

Methods: After obtaining approval from the Ethics Committee of Nippon Medical School and informed consent from five patients with cedar pollinosis(one man, four women ; age range, 38–66 years), administration of a therapeutic extract was started in July 2001 or later(mean treatment period, 13.4 months). The clinical efficacy of SLIT and its influence on the quality of life, as measured by the Japanese Allergic Rhinitis QOL Standard Questionnaire, and the incidence of side effects were evaluated in 2003.

Results: Between February and April the mean severity score was 1.44 in the patients undergoing SLIT and 1.86 in the patients undergoing pharmacotherapy, and the respective mean QOL total scores during the season were 3.82 and 10.0. Neither systemic nor local side effects occurred during SLIT.

Conclusions: SLIT is safe and effective for Japanese cedar pollinosis.

KEY WORDS

allergic rhinitis, Japanese Allergic Rhinitis QOL Standard Questionnaire(JRQLQ), Japanese cedar pollinosis, quality of life, sublingual immunotherapy(SLIT)

INTRODUCTION

Subcutaneous injection immunotherapy is a painful procedure and has the risk of anaphylactic shock as a side effect, which is why it is not commonly used in Japan. To overcome these limitations, patients in Europe and the United States can undergo local immunotherapy in which the antigen is administered to the nasal, intestinal or tracheal mucosa, and of these, sublingual immunotherapy (SLIT) is the most advanced clinical application. Placebo-control studies of SLIT against house dust,[1-3] grass,[4-7] weeds[8] and *Parietaria* [9,10] have demonstrated a marked improvement in clinical symptoms after immunotherapy compared with placebo, and a significantly lower incidence of side effects than with injection immunotherapy. In Japan, immunotherapy consists of subcutaneous injection only and local immunotherapy is not used in clinical practice. Other than our pilot study,[11] SLIT has not been investigated in Japan. In the present study conducted in 2003 we evaluated the clinical efficacy of SLIT, its influence on the quality of life (QOL) and the incidence of side effects in patients with cedar pollinosis.

CLINICAL SUMMARY

SUBJECTS

After the protocol was approved by the Ethics Committee of Nippon Medical School and informed consent was given by five patients with cedar pollinosis (one man, four women ; age range, 38–66 years(Table 1)), administration of a therapeutic extract was started.

The main antigen was cedar and none of the patients had other allergic diseases or double sensitization with other antigens that would influence the evaluation of the treatment response during the cedar pollen season. Treatment was started in July 2001 or later, and clinical efficacy was evaluated in April 2003 (mean treatment period, 13.4 months).

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Table 1 Profile of patients

	SLIT	Pharmacotherapy
Age (mean)	47.3	45.0
Sex		
female	4	4
male	1	1
Duration of SLIT (mean)	13.4 months	
Severity		
Mild	0	0
Moderate	2	4
Severe	3	1

Table 2 Schedule of sublingual administration

	1st week 1 : 50000	2nd week 1 : 5000	3rd week 1 : 500	4th week 1 : 500
1st day	1 drop	1 drop	1 drop	20 drops
2nd day	2 drops	2 drops	2 drops	
3rd day	3 drops	3 drops	4 drops	
4th day	4 drops	4 drops	8 drops	
5th day	6 drops	6 drops	12 drops	20 drops
6th day	8 drops	8 drops	16 drops	
7th day	10 drops	10 drops	20 drops	

The pharmacotherapy group consisted of five patients with cedar pollinosis who consulted the outpatient clinic of the Department of Otorhinolaryngology at Nippon Medical School Hospital during the same period (one man, four women ; age range, 36–53 years (Table 1)).

METHODS

Japanese cedar antigen extract (1 : 20) (Hollister-Stier Laboratories LLC, Spokane, WA, USA) was diluted prior to use, but because it is not standardized, there are no data about its major allergen content. In our preliminary study, the concentration of the major Japanese cedar pollen allergen, Cry j 1, was regarded as being 7.7–16.5 μg/ml.[12] Crumbs containing the antigen extract were placed under the tongue for approximately 2 min and then spat out ('sublingual spit-out'). The subjects attended the outpatient clinic, weekly from week 1 to week 3 and then fortnightly from week 4 of treatment, where they obtained the therapeutic extract and administered it at home in increasing doses (Table 2).

Clinical Symptoms (Nasal Symptom Score)

Nasal allergic symptoms were evaluated from patient diaries and symptom/severity scores were calculated according to the Japanese Practice Guideline for Allergic Rhinitis (4th edition).[13] The most severe status was scored as 4, severe status as 3, moderate status as 2, and mild status as 1 (Table 3).

Medication Score

In the drug therapy group, the various medications were also scored according to the guideline[13] as follows : first- or second-generation antihistamines and mast cell stabilizers, 1 point ; topical steroids, 2 points ; vasoconstrictor or anticholinergic nasal drop preparations, 1 point ; antihistaminic eye drop preparations, 1 point ; steroid eye spray preparations, 2 points ; the period during which the dose is increased, 0.5 points ; the maintenance dose, 1 point ; and mixed preparation of an antihistaminic agent and betamethasone, 3 points (Table 4).

Evaluation of QOL

We evaluated changes in the subjects' QOL during the cedar pollen season using the Japanese Allergic Rhinitis QOL Standard Questionnaire (JRQLQ ; 2002),[14] which has three parts : (I) nasal/ocular symptoms, (II) 17 questions about QOL and (III) a comprehensive evaluation (face scale).

The QOL questions investigated issues in six domains ('daily life', 'outdoor life', 'social life', 'sleep', 'fatigue' and 'emotion'), such as 'interference with study, work, or housework', 'lack of concentration', 'decline in thinking power', 'inconvenience with reading and newspapers', 'debilitating memory loss', 'interference with outdoor activities such as sports, picnic, etc', 'limitation on going out', 'interference with social activities', 'interference with conversation/telephone conversation', 'embarrassment from presumed public attention', 'sleep disorder', 'feeling of weariness', 'fatigue', 'nervousness', 'frustrated', 'gloominess' and 'lack of satisfaction with daily life'. Responses were evaluated using five grades.

PATHOLOGICAL FINDINGS

In 2003, the amount of cedar pollen in Chiyoda-ku, central Tokyo, was 3,622 grains/cm^2, which was similar to the annual average (according to a survey conducted by the Bureau of Public Health Tokyo Metropolitan Government).

CHANGES IN CLINICAL SYMPTOMS (NASAL SYMPTOM SCORE)

As shown in Table 5 the mean symptom scores in the SLIT group for sneezing, nasal discharge, nasal obstruction, and ocular symptoms between February and April were 1.07, 1.30, 0.56, and 0.39, respectively. All scores were highest in March and rapidly returned to the February values in April. The respective mean symptom scores in the pharmacotherapy group were 1.07, 1.76, 1.01, and 0.80 (Table 5). All scores were highest in March, as in the SLIT group, but in April there was a prolonged interval until symptoms were relieved.

The mean severity scores between February and April were 1.44 in the SLIT group and 1.86 in the pharmacotherapy group (Table 6).

Table 3 Criteria for symptom score and severity score

Grade	No. of sneezing attacks per day	No. of nose blows per day	Nasal obstruction
Most severe (4 points)	>20	>20	Complete (all day)
Severe (3 points)	11-20	11-20	Severe (considerable amount of mouth breathing required)
Moderate (2 points)	6-10	6-10	Marked (frequent mouth breathing)
Mild (1 point)	1-5	1-5	Present (no mouth breathing)
No symptoms (0 point)	0	0	None

Table 4 Criteria for medication score

1st, 2nd generation anti-histamines, mast cell stabilizers	1 point
Topical steroids	2 points
Decongestant, anti-cholinergic agents	1 point
Ocular anti-histamines	1 point
Ocular steroids	2 points
Specific immunotherapy	
During step up	0.5 points
During maintenance dose	1 point
Oral steroids and anti-histamines	3 points

CHANGES IN THE MEDICATION SCORE

The mean medication scores between February and April were 0.21 in the SLIT group and 1.85 in the pharmacotherapy group(Table 7).

CHANGES IN THE QOL

The mean QOL total scores during the pollen season were 3.82 in the SLIT group and 10.0 in the drug therapy group(Table 8).

SIDE EFFECTS

Neither systemic nor local side effects occurred during SLIT.

DISCUSSION

The mechanism of action for SLIT, or for conventional allergen immunotherapy, is still unclear, but for allergen-specific immunotherapy, reduction of effector cells[15,16] and blocking antibody[17-20] have been the conventional theories. Recently, however, it has become widely accepted that immunotherapy may modify the T cell response to natural allergens because of T cell anergy and/or immune deviation.[21-24] For SLIT in particular, allergen administered to the oral mucosa accumulates in the submandibular lymph node, in which the immune response occurs[25] and peaks at approximately 2 h after administraton.[26] Of the local immunotherapy modalities, SLIT is the most effective with a lower incidence of side effects, which complies with the WHO position paper on allergen immunotherapy requiring a new route of administration, such as local immunotherapy, and treatment that does not cause anaphylaxis, such as peptide therapy.[27] However, only subcutaneous immunotherapy is used for Japanese cedar pollinosis and other than our pilot study,[11] and the present report, SLIT is an unknown treatment.

Approximately 13% of the Japanese population are affected by Japanese cedar pollinosis[28] and the proportion of severe status patients is higher than with grass or ragweed pollinosis, which are the representative conditions in other countries, and the symptoms persist for about 3 months, becoming a social issue. When the amount of pollen increases, patients show more severe symptoms, and the number of severe status patients is greatest in mid-March(late season)when the pollen count reaches its peak. Substantial antigen exposure enhances the antigen-antibody reaction in the airways (airway hypersensitivity), which is the mechanism involved in severe pollinosis, and immunotherapy with antigen-specific effects may control the exacerbation of the symptoms in the latter half of the cedar pollen season by inhibiting antigen-related enhancement of nasal mucosal hypersensitivity. In the present study, SLIT both inhibited the exacerbation of symptoms in the latter half of the season and reduced their severity throughout the season. Furthermore, there were neither local nor systemic side effects, as reported elsewhere for other antigens.

SLIT for cedar pollinosis is a new therapy and in the future SLIT may by indicated for patients with nasal allergy caused by other allergens such as house dust mites or animal dander through improvement of the administration schedule and establishing the dose at which the most potent effects are achieved. Therefore, a multicenter study involving a large number of patients should be conducted.

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Table 5 Monthly mean change in symptom score

		Feb.	Mar.	Apr.	Mean of 3 months
Score of sneezing	Pharmacotherapy	0.44	1.35	1.36	1.07
	SLIT	0.84	1.48	0.87	1.07
Score of nasal discharge	Pharmacotherapy	1.02	2.19	2.00	1.76
	SLIT	0.91	1.79	1.16	1.30
Score of nasal obstruction	Pharmacotherapy	0.48	1.37	1.15	1.01
	SLIT	0.31	0.86	0.49	0.56
Eye symptom score	Pharmacotherapy	0.46	1.14	0.76	0.80
	SLIT	0.26	0.68	0.21	0.39

Table 6 Monthly mean change in severity score

		Feb.	Mar.	Apr.	Mean of 3 months
Severity score	Pharmacotherapy	1.14	2.25	2.13	1.86
	SLIT	1.11	1.92	1.26	1.44

Table 7 Monthly mean change in medication score

		Feb.	Mar.	Apr.	Mean of 3 months
Medication score	Pharmacotherapy	1.49	1.90	2.13	1.85
	SLIT	0.07	0.43	0.12	0.21

Table 8 Monthly mean change in QOL score

		Feb.	Mar.	Apr.	Mean of 3 months
QOL score	Pharmacotherapy	6.0	16.8	7.2	10.0
	SLIT	1.67	5.8	3.82	3.82

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Fexofenadine Improves the Quality of Life and Work Productivity in Japanese Patients with Seasonal Allergic Rhinitis during the Peak Cedar Pollinosis Season

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Key Words
Fexofenadine · Japanese cedar pollinosis · Quality of life · Seasonal allergic rhinitis · Work productivity

Abstract
Background: Although currently in its infancy, quality of life (QOL) research in Japan is rapidly expanding and is expected to become a standard outcome measure in clinical trials. In Japan, QOL has not previously been assessed in patients with allergic rhinitis (AR); we report the first clinical study applying the recently validated Japanese translations of the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) and Work Productivity and Activity Impairment-Allergy Specific (WPAI-AS) Questionnaire to assess the effects of the oral antihistamine, fexofenadine, on QOL and work productivity due to cedar pollinosis. ***Patients and Methods:*** A randomized, double-blind, placebo-controlled, single-site study was conducted during the peak cedar pollinosis season in Japan. After a 7-day run-in period, subjects were randomized to receive fexofenadine HCl 60 mg twice daily (bid) or placebo for 2 weeks. ***Results:*** Overall, 206 Japanese subjects with AR were included in the intention-to-treat population (fexofenadine, n = 104, and placebo, n = 102). Fexofenadine statistically significantly improved overall QOL compared with placebo ($p = 0.005$) and improvements were reported in the RQLQ domains: activities ($p = 0.047$), practical problems ($p = 0.003$), nasal symptoms ($p = 0.003$) and eye symptoms ($p \leq 0.001$). Clinically significant improvements in practical problems, eye symptoms and activity limitations, exceeding the 0.05 level, were observed with fexofenadine. These improvements in QOL were associated with significant symptom relief ($p < 0.001$ vs. placebo). Improvements in impairment at work were also reported with fexofenadine. ***Conclusion:*** In Japan, this is the first clinical study to show that fexofenadine HCl (60 mg b.i.d.) improves overall QOL and work productivity in patients with seasonal AR using validated Japanese instruments.

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Introduction

Allergic rhinitis (AR) is a very common disorder with a reported prevalence of 10–20% in Japan [1]. Japanese cedar *(Cryptomeria japonica)* pollen is the most common and potent seasonal allergen in Japan causing allergic pollinosis. The prevalence of cedar pollinosis is estimated to be approximately 12 or 13% in the Japanese population

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[2]. Although AR is not a life-threatening illness, the clinical symptoms associated with AR can significantly disrupt patients' quality of life (QOL) and impair daily living activities such as work productivity or school performance [3, 4]. Given the burden of the symptoms of AR on patients' well-being, effective treatments should improve patients' QOL, and QOL should be included as an outcome measure in clinical trials assessing the overall effectiveness of treatment.

In Japan, QOL research is in its infancy, however, it is rapidly expanding and may soon be adopted as an outcome measure for clinical trials assessing the overall effectiveness of treatments for AR. The Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) and Work Productivity and Activity Impairment-Allergy Specific (WPAI-AS) Questionnaire, originally developed in English, measure the impact of AR symptoms on QOL and patient productivity [5–7]. For use in different ethnic populations, cross-cultural validation of the translated questionnaires is required; therefore the RQLQ and WPAI-AS Questionnaires were translated into Japanese and validated for use in a Japanese population [8, 9].

The mainstay of treatment for Japanese patients with AR is oral antihistamines [10]. These agents have been shown to effectively relieve the clinical symptoms of AR such as sneezing; itchy nose, palate and/or throat; rhinorrhea, and itchy, watery and/or red eyes. Fexofenadine is a potent, selective, non-sedating, H_1-receptor antagonist with proven efficacy in the relief of clinical symptoms of AR, including nasal congestion [11–18]. In addition to its anti-allergic effects, fexofenadine has anti-inflammatory properties at clinically relevant concentrations [19–21]. Furthermore, health outcome studies have shown that fexofenadine HCl 60 mg twice daily (b.i.d.) significantly improves patient-reported QOL and decreases work impairment [22]; however, these studies have not been performed in Japan where problems from cedar pollinosis are significant.

Here we present results from the first study assessing the effect of fexofenadine HCl 60 mg b.i.d. on QOL and work/school productivity in Japanese patients with seasonal AR (SAR), using the recently validated translations of the RQLQ and WPAI-AS Questionnaires.

Patients and Methods

Study Population

The study population consisted of male and female SAR subjects, aged 20–55 years. For study participation, subjects had to demonstrate a positive Japanese cedar-pollen-specific IgE test (> class 2 severity), have cedar pollinosis symptoms for 2 or more years and reside within the urban area of Tokyo (to ensure equivalent exposure to pollen). Subjects were also required to have a total symptom score (TSS; sneezing, nasal discharge, nasal blockage and itching eyes) >4 with two or more individual symptoms rated higher than moderate on the 1st day of study treatment.

Subjects were excluded from the study if they had experienced symptoms before the beginning of the Japanese cedar pollinosis season, had complications of nasal disease (perennial allergic nasal disease, vasomotor rhinitis, acute or chronic non-allergic rhinitis, acute/chronic sinusitis, or infective rhinosinusitis, infective rhinitis), were traveling abroad during the study period or were deemed ineligible for participation by the investigator (due to cognitive impairment, for example).

Study Design

This was a randomized, double-blind, placebo-controlled study that was conducted at the Waseda Clinic in Tokyo, Japan. The study consisted of an initial screening visit, a 7-day run-in period and a 14-day treatment period (fig. 1).

Upon completion of the run-in period, subjects were randomly assigned to receive either oral fexofenadine HCl 60 mg b.i.d. or placebo b.i.d. for 14 days. Subjects were instructed to take their study treatment in the morning and evening. At the clinic, all subjects were required to complete the Japanese versions of RQLQ and WPAI-AS Questionnaires during the run-in period, on the 1st day of study drug administration and after 2 weeks of study treatment.

The study was designed and monitored in accordance with the principles of Good Clinical Practice, as set out in the Declaration of Helsinki and its amendments. Written informed consent was obtained from all study participants. Ethical approval was obtained from the institutional review board of the participating center.

Study Instruments

Quality of life was assessed using the Japanese version of the RQLQ, which measures the effects of AR symptoms on seven domains: activities, sleep, no nose/eye symptoms, practical problems, nasal symptoms, eye symptoms and emotional function. Each question was scored using a 7-point scale (0 = not troubled to 6 = extremely troubled). Domain scores were expressed as a mean of all items within the domain, and the overall RQLQ score was calculated by taking the mean across all items. A change in RQLQ domain scores >0.50 was interpreted as a clinically meaningful minimally important difference [23]. Performance impairment due to allergy symptoms was assessed using the Japanese translation of the WPAI-AS instrument, which has been validated to measure generic and allergy-specific performance impairment in work and classroom productivity and regular activity [9]. WPAI-AS scores were expressed as impairment percentages and scores ranging from 0 to 100%, with higher scores reflecting greater impairment and greater loss of productivity.

Outcomes

The primary outcome measure was the change from baseline in the overall QOL score over the entire 2-week treatment period. Secondary outcomes were the change from baseline in each of the seven RQLQ domains, and WPAI-AS scores including percent work/classroom impairment, percent work/classroom time missed due to AR symptoms, overall work/classroom impairment and regular daily activity impairment.

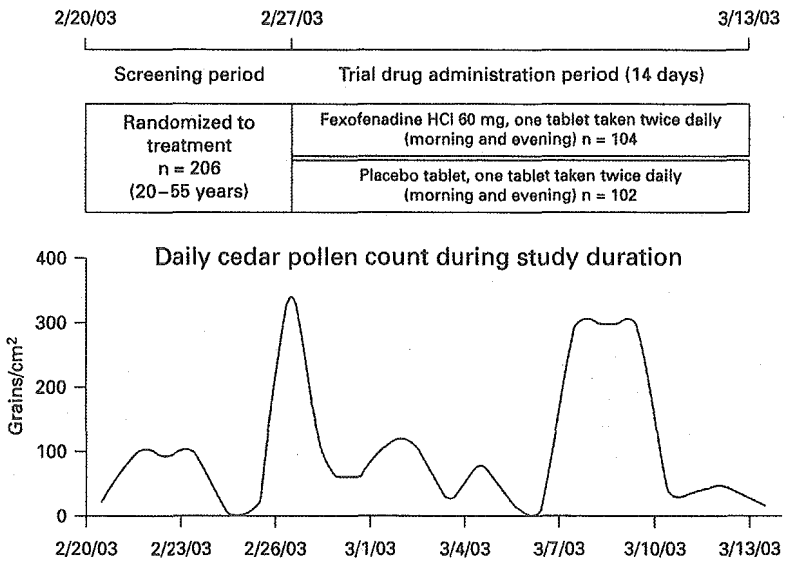

Fig. 1. Study design.

Symptom Assessments

Throughout the run-in and treatment periods, subjects completed symptom diaries to subjectively rate the severity of their individual allergy symptoms. The TSS was defined as the sum of the five individual symptom scores: (1) sneezing; (2) nasal discharge; (3) nasal blockage; (4) itchy eyes, and (5) watery eyes. Patients assessed each symptom using a five-point scale: 0 = absent; 1 = mild; 2 = moderate; 3 = severe, and 4 = very severe. The baseline TSS was calculated as the mean of the daily TSS scores during the run-in period, and the treatment TSS was calculated as the mean of the daily TSS scores during the treatment period.

Statistical Analysis

The study was powered (90%) to detect a 0.5-point difference in the overall QOL score of the RQLQ compared to baseline, at a 5% significance level, assuming a standard deviation of 1.23. A sample size of 258 subjects was required for the study. Analyses were performed on the intention-to-treat (ITT) population, which comprised those subjects who received at least one dose of study treatment and completed a baseline assessment and at least one other valid QOL assessment.

The statistical analysis focused on assessing significant differences between fexofenadine HCl 60 mg b.i.d. and placebo b.i.d. in the RQLQ and the WPAI-AS scores using general linear models, adjusting for covariates, at a significance level of 0.05. Secondary statistical analyses evaluated improvements in the individual scale scores of the RQLQ and WPAI-AS during treatment using general linear models. Changes in TSS were analyzed using a t test with significance declared at the 0.05 level.

Results

Baseline Characteristics

A total of 250 subjects were screened and 210 were randomized to receive treatment during the peak cedar pollinosis season (February and March 2003). The mean cedar pollen count during the entire study duration was 101.2 grains/cm^2 (maximum = 295.1 grains/cm^2, minimum = 4.3 grains/cm^2; fig. 1).

Of the 210 subjects randomized, 3 subjects did not complete any health-related QOL questionnaire, and 1 subject received rescue medication, and they were, therefore, not included in the analysis presented here. Overall, 206 subjects were included in the ITT population; 104 subjects in the fexofenadine HCl 60 mg b.i.d. group, and 102 subjects in the placebo group. All 206 randomized subjects completed the 2-week study period.

There were no differences between the two treatment groups for demographic characteristics (table 1). The mean age of the patients in the fexofenadine group was 32.7 years versus 34.3 years in the placebo group. The majority of patients were male (60% fexofenadine; 57% placebo), most were working (76% fexofenadine; 87% placebo) and few were taking classes (18% fexofenadine; 15% placebo).

Baseline RQLQ scores were comparable between the two treatment groups (table 2). The mean overall QOL score was 1.8, showing that patients were troubled by AR

symptoms. Individual RQLQ domain scores at baseline indicated that patients were less troubled by their symptoms during sleep and more troubled in practical problems, activities and nasal symptom domains.

Using the WPAI-AS Questionnaire, all subjects reported high levels of activity impairment (42.4% fexofenadine; 39.0% placebo) at baseline (table 2). Similarly, overall work impairment (39.5% fexofenadine; 36.7% placebo), impairment while working (39.1% fexofenadine; 36.6% placebo) and overall classroom impairment (33.0% fexofenadine; 31.4% placebo) levels were high (table 2).

Table 1. Baseline characteristics by treatment group (ITT population)

Characteristics		Fexofenadine HCl 60 mg b.i.d. n = 104	Placebo n = 102
Age, years (mean ± SD)		32.7±9.8	34.3±9.9
Patients			
Gender	Male	62 (60%)	58 (57%)
	Female	42 (40%)	44 (43%)
Working	Yes	79 (76%)	89 (87%)
	No	25 (24%)	13 (13%)
Taking classes	Yes	19 (18%)	15 (15%)
	No	85 (82%)	87 (85%)

Outcomes

Quality of Life. Fexofenadine HCl 60 mg b.i.d. was statistically superior to placebo in improving overall QOL in Japanese subjects with SAR ($p = 0.005$). Figure 2 shows mean changes from baseline in overall QOL scores in the fexofenadine HCl group compared with placebo at the end of the 2-week study treatment period. Additionally, the fexofenadine group reported significantly greater improvements than the placebo group for four of the seven RQLQ domains: activities ($p = 0.047$), practical problems ($p = 0.003$), nasal symptoms ($p = 0.003$) and eye symptoms ($p \leq 0.001$). Furthermore, significant improvements in practical problems, eye symptoms and activity limitations, exceeding the levels considered to reflect clinically important changes (>0.5) [23], were also observed in the fexofenadine group (table 3).

Impairment (WPAI-AS). Fexofenadine HCl also resulted in statistically significant improvements in 'impairment at work' due to allergy symptoms over the entire 2-week treatment period. Overall work impairment decreased by 5.5% in the fexofenadine group, which was significantly different to the 3.4% increase in the placebo group ($p = 0.016$; fig. 3). In addition, 'impairment while working' due to allergy symptoms significantly decreased by 5.6% in the fexofenadine group and increased by 3.2% in the placebo group ($p = 0.019$). There were no significant differences between the two treatment groups for the percentage of work time missed. The activity impairment scores in the fexofenadine group demonstrated significant

Table 2. RQLQ and WPAI-AS scores at baseline (%; ITT population)

	Fexofenadine HCl 60 mg b.i.d.		Placebo	
	mean ± SD	n	mean ± SD	n
Overall QOL	1.8±1.0	104	1.8±1.0	102
Activities	2.3±1.2	103	2.2±1.1	102
Sleep	1.0±1.0	104	1.0±1.1	102
No nose/eye symptoms	1.4±1.2	104	1.4±1.1	102
Practical problems	2.7±1.3	104	2.7±1.3	102
Nasal symptoms	2.3±1.1	104	2.2±1.3	102
Eye symptoms	1.8±1.3	104	1.8±1.1	102
Emotional function	1.6±1.3	104	1.7±1.1	102
Activity impairment	42.4±26.9	104	39.0±23.4	102
Work time missed	1.1±4.5	79	0.3±1.7	89
Impairment at work	39.1±27.6	79	36.6±25.8	89
Overall work impairment	39.4±27.9	79	36.7±25.9	89
Class time missed	3.1±8.1	18	0.0±0.0	15
Classroom impairment	29.4±26.8	19	31.4±32.8	14
Overall classroom impairment	33.0±26.9	18	31.4±32.8	14

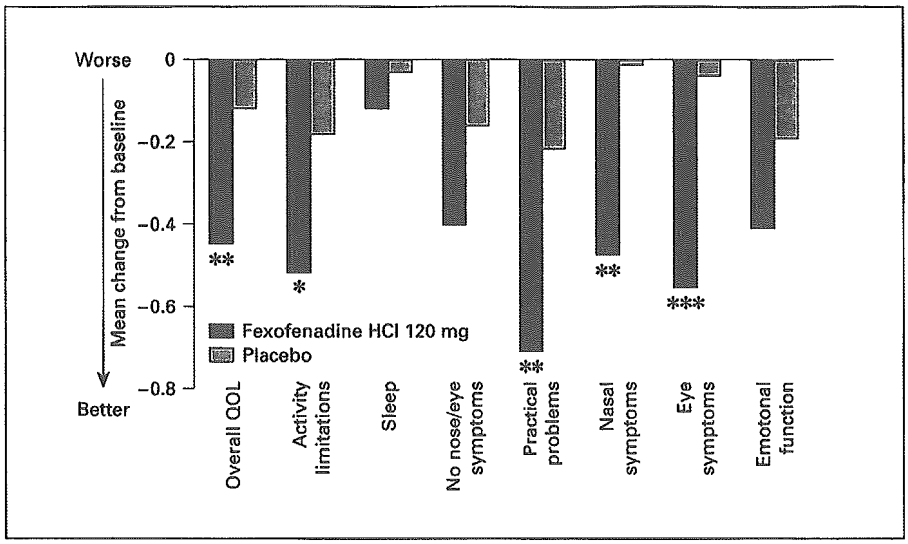

Fig. 2. Changes in overall RQLQ and individual RQLQ domains (baseline vs. study end). * $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.0001$, vs. placebo.

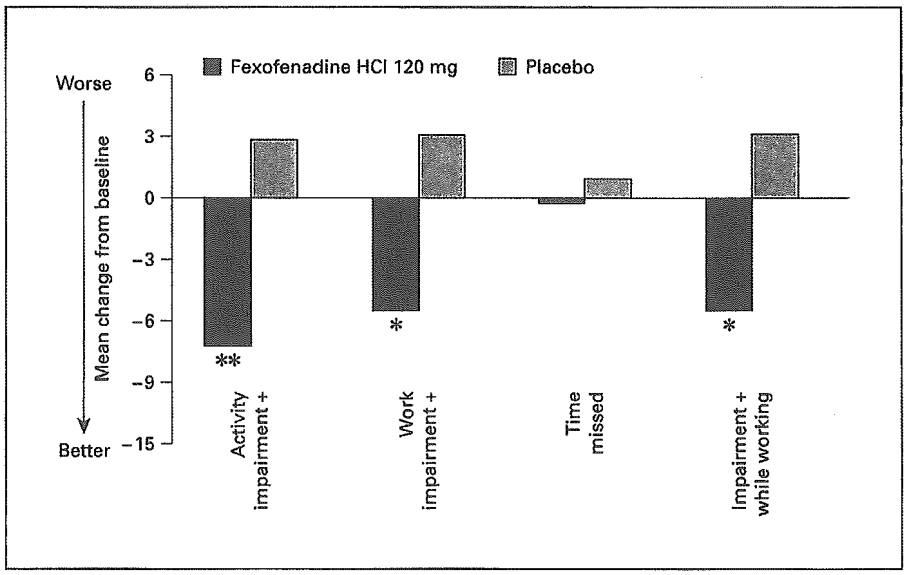

Fig. 3. Changes in work and activity impairment (baseline vs. study end). * $p \leq 0.05$, ** $p \leq 0.01$, vs. placebo.

reductions compared with the placebo group ($p = 0.0027$), since in the placebo group increases in impairment were observed. Concerning overall classroom impairment, there were no significant differences between fexofenadine and placebo.

Symptom Severity. The baseline TSS was comparable between the two treatment groups: 6.6 and 6.9 for the fexofenadine and placebo groups, respectively. At the end of the treatment period, subjects in the fexofenadine group reported significantly greater reductions in their TSS than those receiving placebo (end of treatment TSS: 6.1 vs. 7.7 for fexofenadine and placebo, respectively; $p < 0.001$).

Table 3. Mean change in scores from baseline for RQLQ domains (ITT population)

RQLQ domains	Fexofenadine HCl 60 mg b.i.d., n = 104	Placebo n = 102	p
Activities	−0.52	−0.18	0.0467
Sleep	−0.12	−0.03	–
No nose/eye symptoms	−0.40	−0.16	–
Practical problems	−0.72	−0.22	0.0034
Nasal symptoms	−0.48	−0.01	0.0032
Eye symptoms	−0.56	−0.04	0.0006
Emotional function	−0.41	−0.19	–
Overall QOL	−0.45	−0.12	0.0052

Discussion

In Japan, Japanese cedar *(C. japonica)* pollen is the most common and potent seasonal allergen causing allergic pollinosis with a prevalence of approximately 12 or 13% in the Japanese population [2]. In addition to controlling the bothersome clinical symptoms of AR such as itching, sneezing, runny nose and watery red eyes, effective antihistamine therapy should also result in improvements in patients' QOL and allow them to perform normal daily activities. We report here the first clinical study to use the validated Japanese translations of the RQLQ and WPAI-AS in Japan to demonstrate improvements in QOL and work productivity in patients with cedar pollinosis with a newer-generation antihistamine.

The findings presented here demonstrate that fexofenadine HCl 60 mg b.i.d. statistically significantly improved the overall QOL in Japanese subjects with SAR compared with placebo during the 2-week treatment period. Although statistically significant changes were observed in all RQLQ domains, clinically relevant changes were reported in several domains. Fexofenadine-treated subjects experienced improvements in the baseline symptoms (bothersome), practical problems, eye symptoms and activity limitations, exceeding the levels considered to reflect clinically important changes (>0.5) [23]. Furthermore, the improvement in QOL was associated with significant symptom relief in the fexofenadine treatment group.

Allergic rhinitis is a condition that induces work absenteeism and a reduction in work productivity. Importantly, it has been reported that the use of sedating antihistamines causes a further decrease in work productivity [24]. Although this was a small study, the results presented here demonstrate that fexofenadine is associated with improved patient function as shown by statistically significant reductions in impairment scores due to allergy in daily activities and at work. In the placebo group, the overall scores increased from baseline for work-related impairment items, suggesting that work productivity continued to decline over the 2-week placebo treatment period. These findings suggest that fexofenadine may reduce indirect health care costs by increasing work productivity; therefore, it may be a cost-effective therapy. In Japan in 2004, given an average working day of 8 h on an hourly wage of 2,000 yen [25] and that the difference reported here in overall work impairment between the two treatment groups was 8.9%, these findings could be translated into a saving of approximately 1,420 yen/day. In a month, this would be equivalent to 28,400 yen or almost USD 260, based on the assumption that there are 20 working days per month. However, cost-effectiveness studies are warranted to further assess these benefits.

The results discussed here are consistent with those previously published, in which fexofenadine statistically significantly improved QOL in patients with SAR and chronic idiopathic urticaria [13, 22, 26, 27]. For example, Tanner et al. [22] assessed the impact of fexofenadine HCl 60 mg b.i.d. on patients' QOL in a pooled analysis of two placebo-controlled trials in patients with SAR. Statistically significant ($p \leq 0.05$) improvements in overall RQLQ scores were reported for patients receiving fexofenadine HCl 60 mg b.i.d. compared with placebo [22]. In a more recent study, van Cauwenberge et al. [13] assessed the impact on patients' QOL following once-daily administration of fexofenadine HCl 120 mg, loratadine 10 mg or placebo in the treatment of SAR. A total of 509 patients aged 12–75 years completed the QOL assessment (RQLQ). For all treatment groups (fexofenadine, loratadine and placebo), there was a statistically significant improvement in overall QOL compared to baseline ($p < 0.0001$); however, the improvement in the fexofenadine group was significantly greater than that obtained in both loratadine ($p \leq 0.03$) and placebo groups ($p \leq 0.005$). In addition, fexofenadine was statistically significantly better than both loratadine and placebo in reducing overall mean 24-hour reflective symptom scores for itchy, watery or red eyes and nasal congestion from baseline ($p \leq 0.05$), whereas loratadine was not different from placebo on these two symptom scores [13]. Furthermore, in patients with chronic idiopathic urticaria, fexofenadine HCl 60 mg b.i.d. statistically significantly improved overall QOL compared with placebo, as assessed using the Dermatology Life Quality Index Questionnaire [26]. These results corroborate the findings presented here with fexofenadine improving overall QOL in Japanese subjects with SAR.

Although changes in classroom impairment measures were not statistically significant compared with those at work, the relatively small population of students included in this study may explain these findings. Further studies are, therefore, needed in larger adolescent/student populations to assess improvements in classroom activities. However, it has previously been shown that fexofenadine treatment is associated with statistically significant improvements in the percentage of classroom time missed and classroom impairment ($p < 0.05$) [22].

In Japan, QOL has not previously been assessed in patients with AR and this is the first clinical study to demonstrate the usefulness of the recently translated and validated RQLQ and WPAI-AS instruments in assessing