

Cedar and Cypress Pollinosis and Allergic Rhinitis: Quality of Life Effects of Early Intervention with Leukotriene Receptor Antagonists

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Key Words

Pollinosis • Cedar pollen • Cypress pollen • Leukotriene receptor antagonist

Abstract

Background: Allergic rhinitis involves inflammation of the nasal passages. The use of nasal steroids is generally very effective in providing significant symptom relief. However, compliance for their use is sometimes poor. **Methods:** To examine the efficacy of early intervention (before pollen dispersal) with oral cysteinyl leukotriene receptor antagonists (LTRA) on pollinosis in patients with allergy to cedar and Japanese cypress pollens, groups of subjects were treated with LTRA or a placebo for 4 weeks at the beginning of the cedar pollen dispersal season. Subsequently, all patients received nasal steroid therapy concomitantly with LTRA throughout the remaining period of the pollen dispersal season. The effects of such early treatment with LTRA on pollinosis were investigated using symptom scores from an allergy diary and quality of life (QOL) scores. **Results:** Sneezing and nasal congestion scores were significantly lower in the LTRA-pretreated subjects than observed in the placebo-pretreated patients between weeks 4 and 6 and weeks 3 and 5, respectively. QOL scores improved significantly in all domains after

concomitant therapy with nasal steroids. The percent improvement in the nasal congestion score after the concomitant therapy was significantly higher in the LTRA group (69%) than in the placebo group (41%). **Conclusion:** Significant differences observed in symptoms and in QOL effects between LTRA- and placebo-pretreated patients and the absence of major adverse effects noted in these studies suggest that early intervention with LTRA is beneficial and safe and should be considered in the management of pollinosis-associated allergic rhinitis.

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Introduction

Allergic rhinitis is a type I allergic disease mediated by specific IgE antibody responses. The disease develops as inflammation associated with early infiltration with eosinophils and other pro-inflammatory cells into the nasal mucosa. The pathogenesis of later phases of allergic rhinitis exhibits many characteristics similar to bronchial asthma [1, 2]. Dust mite allergens are responsible for at least 90% of cases of perennial allergic rhinitis. Arboreal pollens, including that of cedar and Japanese cypress, are also important causes of rhinitis, especially in Japan [3–

5]. Cedar forests cover nearly 18% of the total land area of Japan, while Japanese cypress is concentrated in the Kanto region and the western part of the country. Both cedar and Japanese cypress produce enormous amounts of pollen which is dispersed over many kilometers and reaches major cities, including Tokyo and Osaka, causing widespread pollinosis. Cedar pollen dispersal precedes Japanese cypress pollen dispersal, and approximately 70% of patients with cedar pollinosis are also allergic to Japanese cypress pollen. Cedar pollen dispersal starts in early February and reaches a peak between late February and early March, and this is followed by the dispersal of Japanese cypress pollen, which reaches a peak from late March to early April, with some variation due to changes in the climate each year [6]. The pollen dispersal season lasts for more than 10 weeks in and around the area of Chiba.

Outside the pollen dispersal season, patients with cedar and Japanese cypress pollinosis who do not have rhinitis caused by other allergens in general exhibit normal nasal mucosa with few or no symptoms. Repeated exposure to pollen induces allergic inflammation and increases hypersensitivity of the nasal mucosa, and early intervention against mild pollinosis just after the start of the pollen dispersal season may have a significant effect on the severity of symptoms when pollen dispersal is at its peak. In Japan, the Ministry of the Environment makes a detailed prediction of the date around which cedar pollen dispersal is likely to start, making it easy to assess the effects of early intervention in patients with pollinosis due to cedar and Japanese cypress.

Leukotriene receptor antagonists (LTRA) have been shown to be effective in controlling nasal inflammation [7, 8] by their ability to inhibit eosinophil secretion in the airway [9, 10]. Recent studies have shown that LTRA are as effective as antihistamines but less effective than nasal steroids [11–13]. Nasal steroids reduce sneezing, nasal secretion as well as nasal obstruction. However, the compliance for use of nasal steroids is sometimes poor [14] and their market share is much smaller than that for other oral anti-allergic medications in Japan, because patients seem to prefer such non-sensory attribute, painless route of administration [15, 16].

LTRA do not exert any central nervous system depression or adrenal suppressive effects and may be more suitable for early interventional use especially in patients with milder symptoms. In order to determine the effects of early intervention with LTRA on cedar and Japanese cypress pollinosis, we conducted a double-blind, placebo-controlled trial in subjects allergic to both pollens. Either LTRA or placebo was administered to subjects im-

mediately before the start of the pollen dispersal season and continued throughout the pollen season. All subjects received nasal steroids after the initial treatment with LTRA. Symptom and quality of life (QOL) scores were monitored during the pollen and before the dispersal season and after concomitant therapy with nasal steroids and LTRA.

Subjects and Methods

Subjects

The study population comprised 60 subjects (30 males and 30 females), ranging in age from 20 to 65 years, who were otherwise healthy, but who had a clinical history of moderate/severe Japanese cedar and cypress pollinosis for at least 3 consecutive cedar and cypress pollen seasons. The subjects lived in and around Chiba City where the pollen spread would be expected to be consistent. The diagnosis of cedar and cypress pollinosis was based on clinical history, positive allergen-specific skin tests (wheal diameter ≥ 10 mm) to a standardized cedar pollen extract (Torii Pharmaceutical Co., Tokyo, Japan), and a serum cedar and cypress pollen-specific IgE level score ≥ 2 by a CAP radioallergosorbent test (SRL Inc., Tokyo, Japan). Exclusion criteria were complication of moderate/severe perennial allergic rhinitis with a need for treatment, a history of severe asthma, use of anti-allergic drugs within 4 weeks, and a prior history of any allergen-specific immunotherapy, including for cedar pollen. Pregnant women or those at risk of pregnancy were also excluded. The study was conducted at Chiba University Hospital in compliance with the Ethical Guidelines for Clinical Studies and Good Clinical Practice and the Declaration of Helsinki (2000 revision). The Ethics Committee of Chiba University approved the protocol, and written informed consent was obtained from each subject prior to his or her participation in the study.

Methods

Capsules containing 112.5 mg of pranlukast hydrate or placebo were used in the study. The study schedule is shown in figure 1. Prior to the study, patients were interviewed regarding their medical history and underwent the skin test for cedar pollen extract and a CAP radioallergosorbent test in late January 2007 to measure specific serum antibodies against cedar and Japanese cypress pollen. Administration of LTRA or placebo was initiated before the start of the cedar pollen dispersal season, which had been forecast to be in early February. Two capsules were administered orally twice a day after breakfast and dinner for 4 weeks (hereafter referred to as 'pretreatment' period). During the latter 2 weeks of this period, subjects were allowed to use an antihistamine (loratadine, 1 capsule per day), other nasal vasoconstriction drops (tetrahydrozoline hydrochloride, maximum 2 drops to each nasal cavity per day and less than 7 days successively), or disodium cromoglycate eye drops (maximum 4 drops to each eye) at their own discretion, based on the severity of symptoms. Subsequently, all subjects took nasal steroids (fluticasone propionate) and LTRA for 4 weeks (main dispersal treatment period) in accordance with ARIA [2] and the Practical Guidelines for the Management of Allergic Rhinitis in Japan [4], again based on the severity of symptoms.

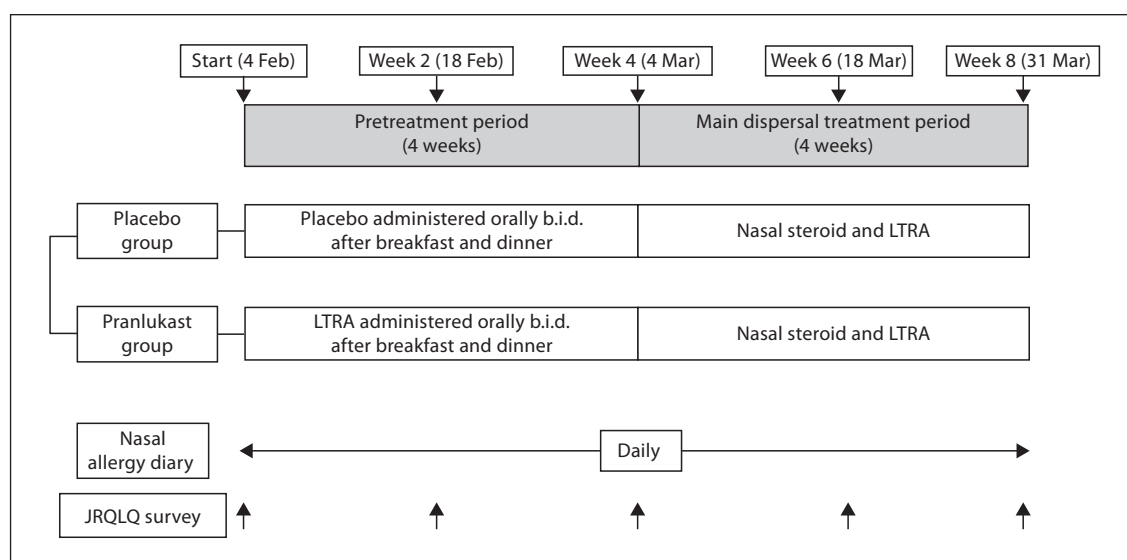


Fig. 1. Study schedule. b.i.d. = Twice daily.

Table 1. Severity of nasal symptoms

Parameter	Severity				
	++++	+++	++	+	–
Paroxysmal sneezing, times/day	≥21	11–21	6–10	1–5	0
Runny nose (nose blowing frequency) times/day	≥21	11–21	6–10	1–5	0
Nasal congestion	complete congestion, all day	very severe nasal congestion with frequent oral breathing	severe nasal congestion with occasional oral breathing	no oral breathing but nasal congestion	none

Adapted from the Practical Guideline for the Management of Allergic Rhinitis in Japan, 2005 [5].

Some subjects ($n = 30$) received LTRA throughout the study period (LTRA group). However, a group of other subjects ($n = 30$) received placebo during the pretreatment period and LTRA during the main treatment period (placebo group). The sample size was determined based on previous studies of LTRA on the change and variance of clinical symptoms [17]. A nasal allergy diary was written daily, and Japan Rhinoconjunctivitis Quality of Life Questionnaire (JRQLQ) survey sheets [18, 19] were completed every 2 weeks until completion of the study. For assignment of subjects to groups, limited randomization was performed in subgroups of 6 age- and sex-matched subjects each, of whom 3 were assigned to the LTRA group and 3 were assigned to the placebo group. A controller who was not directly involved in the study was responsible for group allocation. A group allocation number was given to each subject. This information was closely guarded by the controller and by 1 member of the ethical committee not directly involved in the study.

During the study period, all study subjects recorded their use (dose and frequency) of permitted concomitant medications (listed above) in a nasal allergy diary. Use of other drugs considered unlikely to affect the study was also allowed.

Cedar and Japanese cypress pollen dispersal was measured with a Durham sampler installed on the roof top of one of the buildings in the School of Medicine, Chiba University.

Nasal symptoms, eye symptoms, symptom scores, medication scores and symptom-medication scores were evaluated from the nasal allergy diary using the following criteria. For nasal symptoms, the severity of paroxysmal sneezing (number of sneezes per day), runny nose (number of times of blowing the nose per day), nasal congestion, and the degree of interference with daily life were evaluated on a 5-point scale (0–4) using a modified Okuda classification [4, 20] (table 1). Symptom scores for classification of the severity of nasal symptoms were calculated using the same classification. The daily total nasal symptom score was expressed

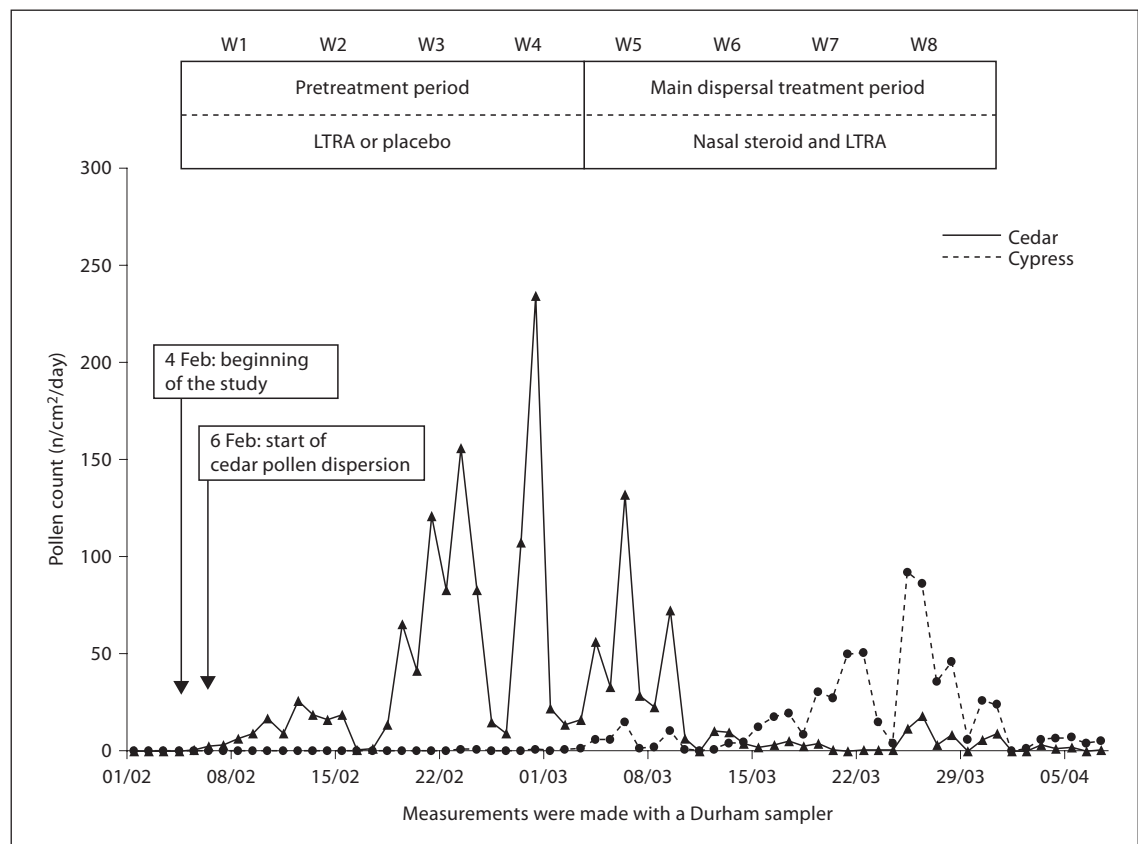


Fig. 2. Dispersal of cedar and Japanese cypress pollen in 2007 and study schedule.

as the highest score of nasal symptoms. For eye symptoms, itching and watering were evaluated using a 4-point scale. The use of other medications was also scored and recorded according to the characteristics of the drug and the duration of usage, based on the following guidelines: anti-histamines, mast cell stabilizers and vasoconstrictors scored as 1, topical nasal steroids scored as 2, and the symptom-medication score was determined by adding the symptom score and the medication score. The score for each QOL item was also evaluated on a 5-point scale (0–4). In addition, the percent improvement in nasal symptoms was analyzed and expressed as the ratio of the patients who had improved nasal symptoms ≥ 1 in week 8 at the end of the study compared with week 4 before the concomitant therapy with nasal steroids. The symptom-medication score was used as the primary outcome parameter and other items were used as secondary parameters.

Statistical Analysis

After completion of the study (clinical and laboratory), a biostatistician who had not been involved in carrying out the clinical trial, analyzed the data. After completing the analysis, the allocation identification numbers for the active and placebo groups were accessed. Data comparisons were performed using 2-tailed tests at a significance level of 5%, using a χ^2 test, the Fisher exact test, the Mann-Whitney U test, a 2-sample t test, a paired t test, and the Wilcoxon test in SAS version 8.02 (SAS Inc., Cary, N.C., USA).

Results

Dispersal of Cedar and Japanese Cypress Pollen

Measurements with a Durham sampler (fig. 2) indicated that 6 February was the start of the cedar pollen dispersal season, based on a pollen count of $\geq 1/\text{cm}^2/\text{day}$. After 19 February, a pollen count $\geq 20/\text{cm}^2/\text{day}$ was obtained on most days, which dropped to $< 10/\text{cm}^2/\text{day}$ after 10 March, marking the end of the dispersal season. Japanese cypress pollen was observed in the middle of March and reached a count of $> 20/\text{cm}^2/\text{day}$ on most days after 19 March until dispersal ended in early April.

Subjects

Four subjects withdrew from the study for personal reasons, and not because of any adverse effects. All other subjects exhibited full compliance with the study protocol. Thus, a total of 56 subjects were included for complete evaluation. The LTRA group comprised 29 subjects (mean age 36.1 years and cedar pollen RAST score 3.9). The placebo group comprised 27 subjects (mean age 33

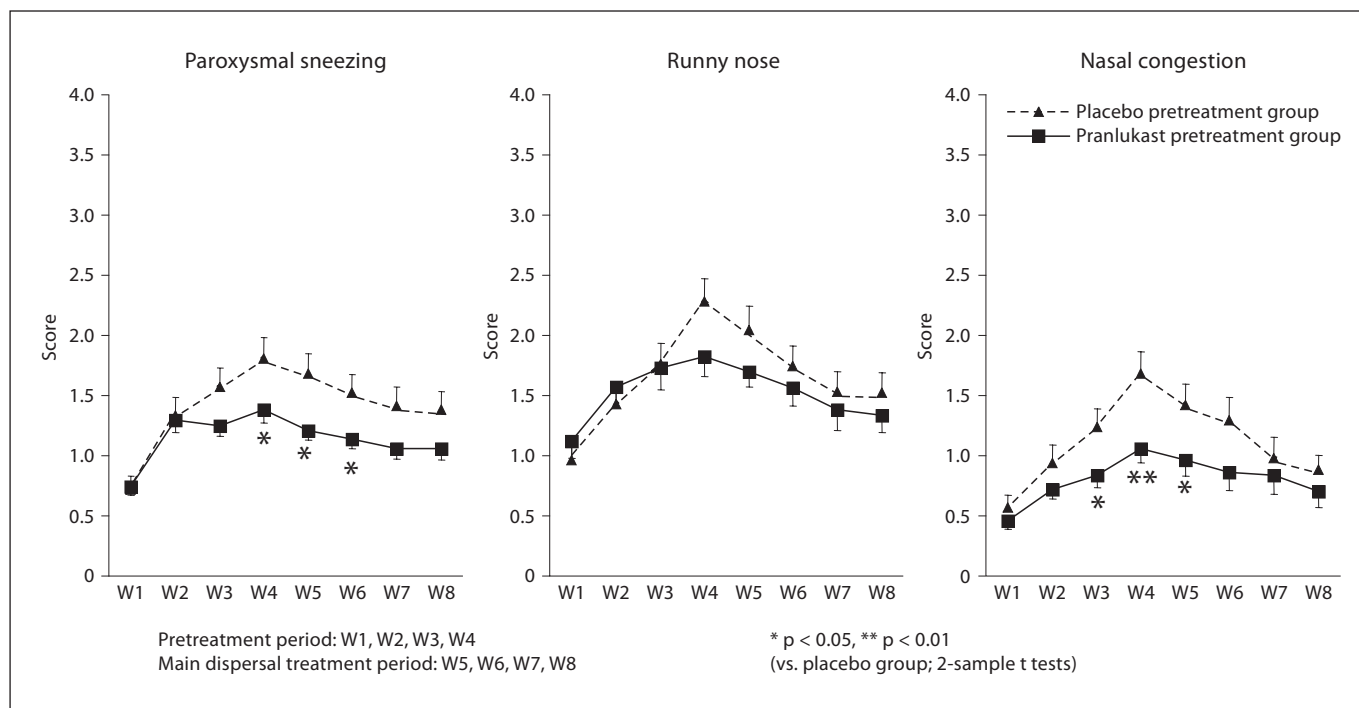


Fig. 3. Mean weekly score for each nasal symptom.

years and cedar pollen RAST score 3.5). There were no significant differences between the 2 study groups for age at disease onset, disease duration, or any subsequent complications.

Treatment Effects

The mean nasal symptom scores for each week of the pollen season are shown in figure 3. In both groups, symptoms worsened as cedar pollen dispersal increased and then improved after week 5, after the start of nasal steroid drops. In the LTRA group, nasal symptoms were mild from week 3 until the end of the study, and sneezing and nasal congestion scores were significantly lower in the LTRA group than in the placebo group between weeks 4 and 6 and weeks 3 and 5, respectively.

The total nasal symptom score increased in both groups from the start of the cedar pollen dispersal season and decreased in week 5, after the use of nasal steroids at the peak of the cedar dispersal season (fig. 4). Mean symptom scores were significantly lower in the LTRA group than in the placebo group in weeks 4 and 5 (fig. 4). Medication and symptom-medication scores also increased following the start of cedar pollen dispersal and decreased in week 5, after the start of nasal steroid therapy. These scores were lower in the LTRA group than in

the placebo group during the pretreatment period, although the differences were not significant (data not shown). There were no significant differences in eye itching or watering scores between the groups (data not shown).

The degree of interference with daily life increased in both groups following the onset of cedar pollen dispersal and decreased in week 5 following the start of nasal steroid therapy. The score in the LTRA group was significantly lower than that in the placebo group in week 4 (fig. 4).

A comparative analysis of the improvement in nasal symptom score in week 8 (at the end of the study) and in week 4 (before the concomitant therapy with nasal steroids) is shown in table 2. The percent improvement in nasal congestion was significantly higher in LTRA-pretreated patients (69.0%) than in placebo-pretreated patients (40.7%).

JRQLQ Scores

For 17 QOL items, each mean QOL score generally increased by ≥ 0.5 points after pollen dispersal (data not shown) and improved for all items after the start of concomitant therapy at week 5 with nasal steroid drops (fig. 5). Although scores for all items in the LTRA group

Fig. 4. Symptom scores and the degree of interference with daily life.

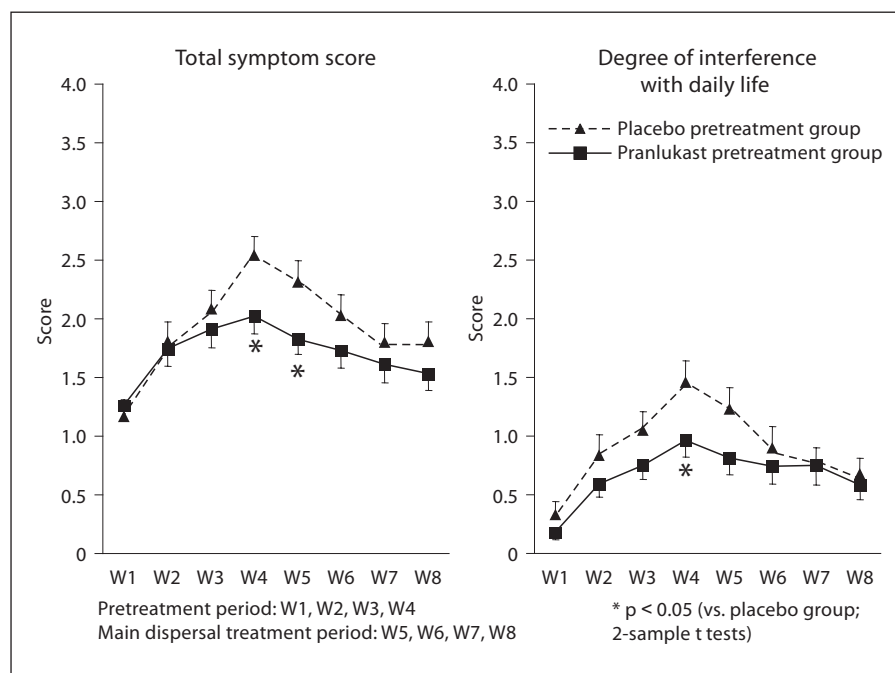
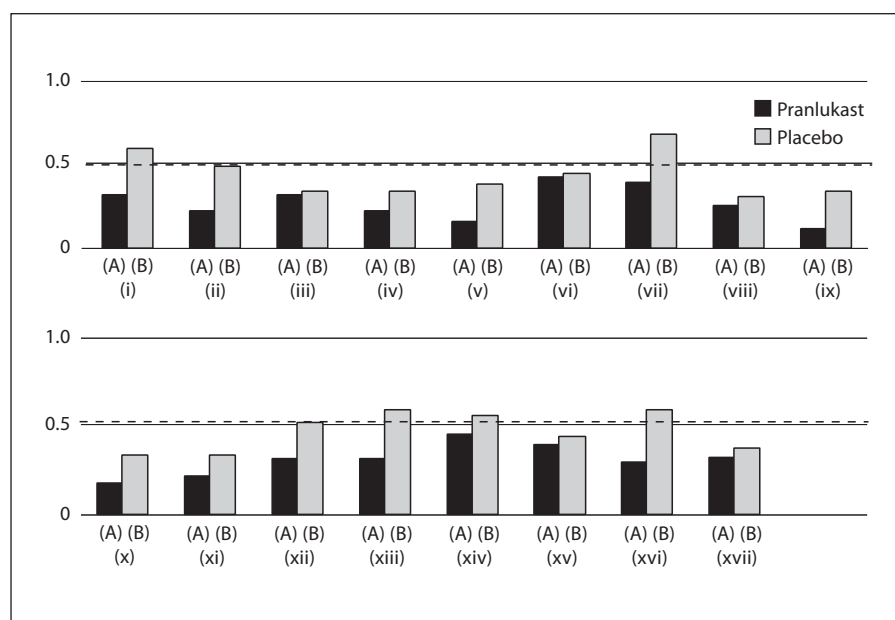


Fig. 5. QOL items at week 8 versus week 0. (i) = Reduced productivity at work/home/school; (ii) = poor mental concentration; (iii) = reduced thinking power; (iv) = impaired reading book/paper; (v) = reduced memory loss; (vi) = limitation of outdoor life (e.g., sports, picnic); (vii) = limitation of going out; (viii) = hesitation visiting friends 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; (xvii) = unhappiness.



did not increase by 0.5 points at week 8 compared with week 0 (before pollen dispersal), scores for 7 items (interference with study, work and housework; poor concentration; interference with going out; malaise; fatigue; frustration; depressed feeling) in the placebo group still increased by ≥ 0.5 points at week 8.

These 17 QOL items were categorized into 6 domains (daily life; outdoor activities; social life; physical exercise; mental life; sleep) and scores were compared among domains (table 3). Mean QOL scores generally increased with cedar pollen dispersal when compared between week 4 and week 0, and scores increased by ≥ 0.5 points

Table 2. Improvement in nasal symptom score at week 8 compared with week 4

	Improved ≥1 point	Improved <1 point	χ^2 test ¹
Runny nose			
Pranlukast	16 (55.2)	13 (44.8)	0.977
Placebo	15 (55.6)	12 (44.4)	
Sneezing			
Pranlukast	16 (55.2)	13 (44.8)	0.803
Placebo	14 (51.9)	13 (48.1)	
Nasal congestion			
Pranlukast	20 (69.0)	9 (31.0)	0.034
Placebo	11 (40.7)	16 (59.3)	

Data are number of patients, with percentages in parentheses.

¹ The number of the patients who had an improved score of ≥1 point in the pranlukast-pretreated group was compared with that in the placebo-pretreated group.

for 5 of the 6 domains excluding sleeping problem in the LTRA group and for 5 domains excluding social functioning in the placebo group. After the start of nasal steroid therapy at week 5, scores in all 5 domains which had increased by ≥0.5 points at week 4 exhibited significant improvement at week 8 in the LTRA-treated group. The sleep problem and social functioning domains were not significantly aggravated at week 8 under Japanese cypress pollen dispersal when compared with week 0.

In contrast, in the placebo group, scores for 4 domains (social functioning; sleep problem; physical problems; emotional function) did not manifest significant improvement when evaluated during week 8 when compared with the scores observed at week 4 (before nasal steroid therapy). All domains exhibited a still significant increase at week 8 when compared with the scores observed at the beginning of the study (week 0).

Overall QOL condition scores also increased after pollen dispersal in both LTRA- and placebo-treated groups. After the use of nasal steroids, significant improvement was observed at week 8 in the LTRA-treated group but not in the placebo group compared with the scores at week 4.

Use of Concomitant Medications and Safety

Antihistamines and nasal vasoconstrictor drugs were used less frequently by the subjects in the LTRA group in the latter 2 weeks of the pretreatment period than in the

Table 3. QOL score by JRQLQ (domains)

	Week	Pranlukast mean ± SE	Placebo mean ± SE
Versus week 0			
Usual daily activities	0	0.25 ± 0.08	0.13 ± 0.06
	4	0.97 ± 0.15***	0.87 ± 0.14***
	8	0.48 ± 0.10*	0.56 ± 0.14*
Outdoor activities	0	0.14 ± 0.05	0.19 ± 0.07
	4	1.02 ± 0.19***	1.20 ± 0.19***
	8	0.53 ± 0.14**	0.74 ± 0.18**
Social functioning	0	0.10 ± 0.04	0.06 ± 0.03
	4	0.69 ± 0.14***	0.53 ± 0.13***
	8	0.28 ± 0.09	0.38 ± 0.11**
Sleep problem	0	0.17 ± 0.07	0.19 ± 0.09
	4	0.59 ± 0.14**	0.81 ± 0.15***
	8	0.38 ± 0.10	0.52 ± 0.13*
General physical function	0	0.21 ± 0.08	0.13 ± 0.07
	4	1.00 ± 0.16***	0.96 ± 0.20***
	8	0.52 ± 0.12*	0.69 ± 0.18**
Emotional function	0	0.14 ± 0.05	0.06 ± 0.04
	4	0.78 ± 0.16***	0.74 ± 0.15***
	8	0.05 ± 0.14*	0.55 ± 0.15**
Overall QOL condition	0	1.07 ± 0.19	0.81 ± 0.13
	4	2.48 ± 0.15***	2.26 ± 0.19***
	8	1.45 ± 0.17	1.41 ± 0.16*
Versus week 4			
Usual daily activities	4	0.97 ± 0.15	0.87 ± 0.14
	8	0.48 ± 0.10***	0.56 ± 0.14*
Outdoor activities	4	1.02 ± 0.19	1.20 ± 0.19
	8	0.53 ± 0.14**	0.74 ± 0.18**
Social functioning	4	0.69 ± 0.14	0.53 ± 0.13
	8	0.28 ± 0.09***	0.38 ± 0.11
Sleep problem	4	0.59 ± 0.14	0.81 ± 0.15
	8	0.38 ± 0.10	0.52 ± 0.13
General physical function	4	1.00 ± 0.16	0.96 ± 0.20
	8	0.52 ± 0.12***	0.69 ± 0.18
Emotional function	4	0.78 ± 0.16	0.74 ± 0.15
	8	0.05 ± 0.14*	0.55 ± 0.15

* p < 0.05, ** p < 0.01, *** p < 0.001 (2-sample t test).

placebo group; however, the differences were not significant (data not shown). The compliance for the use of LTRA and nasal steroids during the whole study period did not differ between the groups. However, an adverse event was reported by 1 patient in the LTRA group who experienced abdominal pain on day 16, but this resolved 2 days later and did not prevent continuation of study drug administration.

Discussion

In the present studies, the symptoms of allergic rhinitis increased predictably in the placebo group of subjects. However, many JRQLQ scores also worsened even in the LTRA group at the height of the pollen dispersal season. Therefore, pretreatment with LTRA alone did not appear to result in significant relief of nasal symptoms, and additional nasal steroid therapy in accordance with the standard guidelines was required to induce significant symptom relief [2, 4]. During the later phases of the cedar pollen dispersal season, symptoms and QOL scores exhibited improvement following the initiation of nasal steroid therapy in both LTRA and placebo-pretreated groups. However, differences between the groups in scores for sneezing and nasal congestion were still statistically significant. Subsequently, the symptoms in both groups improved and there were no significant differences in scores between the 2 groups. These findings are considered to reflect the effects of nasal steroid therapy. However, the degree of improvement in nasal congestion scores in week 8 at the end of the study compared with week 4 just before the concomitant therapy with nasal steroids was significantly higher in the LTRA-pretreated group than in the placebo-pretreated group.

QOL scores are considered to be more sensitive markers of clinical improvement than symptom scores derived from an allergy diary [21–23]. All QOL scores improved significantly in the LTRA group after the initiation of concomitant therapy with nasal steroids. The QOL items were categorized into 6 domains (daily life; outdoor activities; social life; physical exercise; mental life; sleep). Scores for the first 5 domains and the overall condition were significantly improved in the LTRA group after the initiation of concomitant nasal steroid therapy. Sleep was not significantly affected in the Japanese cypress pollen dispersal season. In contrast, in the placebo group, domain scores for social life, physical exercise, mental life and sleep (which was disturbed in the Japanese cypress pollen dispersal season in the placebo group) did not improve even after concomitant therapy with nasal steroid, and daily life and overall condition scores demonstrated delayed improvement compared with the LTRA group.

In Japan, pollen counts are typically measured using the gravimetric method with a Durham sampler, in contrast to Western countries in which a Burkard sampler is typically used. In a study in Chiba Prefecture in 2005, the amount of air-borne pollen counted with a Burkard sampler was about 12 times greater than that counted with a Durham sampler [24]. For Durham sampler measure-

ments, a count of 1–10/cm²/day is defined as low dispersal and >20/cm²/day is considered high dispersal. In this study (2007), cedar pollen dispersal was detected by a Durham sampler at the beginning of February. The count was >20/cm²/day on many days after 19 February and then returned to <10/cm²/day after 10 March, after which dispersal ended. Japanese cypress pollen was detected at the end of February, had a count of >20/cm²/day on many days after 19 March, with dispersal ending in early April.

Symptoms of allergic rhinitis are generally mild immediately after the start of the pollen dispersal season, but hypersensitivity-induced inflammation of the nasal mucosa is produced by repeated exposure to pollen. Such exposure results in enhanced expression of adhesion molecules, increased infiltration of the nasal mucosa by inflammatory cells, hyperpermeability of epithelial cells, and an increased neural sensory response [1, 2, 25]. Even in the LTRA group, many JRQLQ scores increased by ≥ 0.5 points at the height of the pollen dispersal season. With standard therapy using nasal steroids for severely affected patients, the QOL scores in the LTRA group were still lower than those in the placebo group. In the placebo group, nasal steroid therapy produced a smaller improvement in QOL scores.

The observations reported here and other earlier studies have suggested that LTRA are extremely safe and do not result in any major adverse effects, such as anticholinergic activity, local irritation or adrenal suppression. In this study, mild abdominal pain was reported by 1 patient, but no causal relationship with LTRA was detected.

Nasal steroids are generally very effective and provide a significant resolution of symptoms. Nasal steroids might be advantageous for early intervention; however, the compliance is sometimes poor, since many patients prefer to use oral medication, particularly in Japan [14, 15].

Although the number of patients enrolled in the study was limited and a comparative study with LTRA and steroids in a large scale will be needed to evaluate the effectiveness, based on the information summarized here, it is proposed that the use of LTRA is safe and might be appropriate for pretreatment before the appearance and establishment of clinical symptoms early in the course of the cedar pollen season.

Acknowledgements

We thank Dr. Minoru Okuda, Dr. Minoru Gotoh, Dr. Akiyoshi Konno and Dr. Peary L. Ogra for their helpful comments and suggestions, and Dr. Hidenori Suzuki and Dr. Tatsuyuki Kakuma for their support as the respective study controller and study biostatistician.

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