

Beneficial Effects of Leukotriene Receptor Antagonists in the Prevention of Cedar Pollinosis in a Community Setting

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■ Abstract

Background: In recent years, many countries have experienced an increase in the prevalence of allergic rhinitis. No effective approach is currently available to prevent the onset of symptoms in allergic individuals. Pranlukast, a leukotriene receptor antagonist with a good safety and efficacy record for the management of allergic inflammation, may be appropriate for early intervention in the management of pollinosis.

Objective: To investigate the efficacy of pranlukast as an early intervention in the control of cedar pollinosis.

Methods: In a double-blind comparative study, pranlukast (n=102) or placebo (n=91) was administered to cedar pollinosis patients immediately before the start of the dispersion season and continued for 4 weeks. Subsequently, pranlukast was administered to all patients for 2 weeks until the end of the cedar pollen dispersion season (mid-March). All patients were carefully monitored for severity of nasal symptoms, symptom scores, medication scores, symptom-medication scores, and quality of life (QOL).

Results: Compared with placebo, therapy with pranlukast before and during the dispersion of cedar pollen in these patients significantly improved nasal symptoms (paroxysmal sneezing, rhinorrhea, and nasal congestion), symptom scores, and symptom-medication scores. The drug also significantly reduced deterioration of QOL, and improved nasal symptoms and QOL throughout the dispersion period.

Conclusion: Administering pranlukast immediately before the beginning of cedar pollen dispersion is effective in reducing symptoms of allergic rhinitis throughout the dispersion period.

Key words: Allergic rhinitis. Cedar pollinosis. Early intervention. Leukotriene receptor antagonist.

■ Resumen

Antecedentes: En los últimos años, muchos países han experimentado un aumento en la prevalencia de la rinitis alérgica. No está disponible actualmente ningún abordaje eficaz para prevenir el comienzo de los síntomas en los individuos alérgicos. Pranlukast, un antagonista del receptor de los leucotrienos con buena seguridad y récord de eficacia para el manejo de la inflamación alérgica podría ser apropiado como intervención precoz en el manejo de la polinosis.

Objetivo: Investigar la eficacia del pranlukast como intervención precoz en el control de la polinosis por cedro.

Métodos: En un estudio doble ciego comparativo, se administró pranlukast (n=102) o placebo (n=91) a pacientes con polinosis por cedro inmediatamente antes de comenzar la polinización del cedro y continuaron durante 4 semanas. Posteriormente, se administró pranlukast a todos los pacientes durante 2 semanas hasta el final de la época de polinización del cedro. De todos los pacientes se controló cuidadosamente la gravedad de los síntomas nasales, la puntuación de los síntomas, la puntuación de la medicación, puntuación de síntomas-medicación y la calidad de vida (CV).

Resultados: Comparado con el placebo, la terapia con pranlukast antes y durante la polinización del cedro en estos pacientes mejora significativamente los síntomas nasales (estornudos paroxísticos, rinorrea y congestión nasal), la puntuación de síntomas, y la puntuación de síntomas-medicación. El fármaco también redujo significativamente el deterioro de la CV, y mejoró los síntomas nasales y la CV durante todo el período de polinización.

Conclusión: La administración de pranlukast inmediatamente antes y en el comienzo de la polinización del cedro es eficaz en la reducción de síntomas de la rinitis alérgica durante toda la época de polinización.

Palabras clave: Rinitis alérgica. Polinosis por cedro. Intervención precoz. Antagonista del receptor de leucotrienos.

Introduction

Recent observations suggest a significant worldwide increase in the prevalence of allergic rhinitis and cedar pollinosis [1]. In Japan, extensive dispersion of cedar pollen has also led to increased incidence of pollinosis, and it is estimated that over 16% of the population are now affected by cedar pollinosis [2,3]. Seasonal dispersion of cedar pollen normally starts in early February in the south Kanto area (Chiba and Tokyo), peaks from late February to early March, and terminates in the middle of March. The status and magnitude of pollen dispersion in Japan is determined by the Ministry of the Environment, and an annual forecast of the initiation date and the probable pollen count is made available to the public in January. Pollen counts in Japan are generally determined using the gravimetric method with a Durham sampler (Nishiseiki Co. Ltd., Funabashi, Japan), whereas in Western countries the volumetric method with a Burkard sampler (Burkard Manufacturing Co. Ltd., Rickmansworth, United Kingdom) is used. Direct comparison of the counts using both methods is difficult, and counts are often influenced by local meteorological conditions and the type of pollen. In a study conducted in the Chiba prefecture in 2005, the amount of pollen in the air counted with a Burkard sampler was about 12 times higher than that detected with a Durham sampler [4].

Rhinitis tends to be severe in patients with cedar pollinosis and is often associated with significant impairment of quality of life (QOL). Early intervention in such patients may be beneficial and greatly influence the severity and outcome of symptoms during the peak pollen season. Such approaches are recommended in the Clinical Guidelines for the Management of Allergic Rhinitis in Japan [3].

Leukotriene receptor antagonists have proven to be effective in the treatment of nasal congestion [5,6]. These drugs also reduce allergic inflammation by inhibiting eosinophil secretion in the airway [7-9]. Recent studies have shown that leukotriene receptor antagonists are as effective as antihistamines for the treatment of allergic rhinitis, without the sedative side effects frequently observed with antihistamines. It has been suggested that leukotriene receptor antagonists are less effective than nasal corticosteroids [10-12], which effectively reduce sneezing, rhinorrhea, and nasal obstruction. However, adherence is sometimes poor in Japan, because patients prefer oral medication. Leukotriene receptor antagonists are suitable for early intervention because of their anti-allergic inflammatory effects and safety. In Japan, pranlukast is the only leukotriene receptor antagonist currently recommended

for use in the treatment of allergic rhinitis [13]. Therefore, we conducted a double-blind placebo-controlled comparative study of the efficacy of early intervention with pranlukast in patients with cedar pollinosis.

Methods

Participants

The study population consisted of patients with cedar pollinosis who lived in the south Kanto area from February to March 2007. Age ranged from 20 to 65 years and participants met the following inclusion criteria: a positive allergen-specific skin test (wheal diameter ≥ 10 mm) to a standardized cedar pollen extract (Torii Pharmaceutical Co. Ltd., Tokyo, Japan) and a serum cedar pollen-specific immunoglobulin (Ig) E levels score of ≥ 2 by the CAP radioallergosorbent test (CAP-RAST; SRL, Tokyo, Japan). The exclusion criteria were as follows: complications including nasal polyps and chronic sinusitis; continuous use of antihistamines, antiallergic drugs, or nasal corticosteroid drops; immunotherapy; pregnancy, women of childbearing potential, and nursing mothers; and other patients deemed inappropriate for the study by the investigator. Informed written consent was obtained from participants after they received a detailed explanation of the study and of the possible side effects. The study adhered to the Ethical Guidelines for Clinical Studies and Good Clinical Practice (GCP), and the Declaration of Helsinki (revised in 2000).

Study Protocol

Specially designed capsules containing 112.5 mg of pranlukast hydrate per capsule or placebo capsules were used. Participants were selected in late January based on a skin test for cedar pollen to confirm the presence of cedar pollinosis. The study was initiated before the beginning of cedar pollen dispersion, which was forecast to be in early February, and administration of pranlukast or placebo was started according to the study schedule outlined in Figure 1. Two capsules were administered bid (after breakfast and dinner) for 4 weeks (double-blind comparative study period). Subsequently, all patients took pranlukast for an additional 2 weeks (pranlukast administration period). A total of 193 subjects completed the study (Table). The pranlukast group included 102 patients (57 males and 45 females; mean age, 36.5 years). Of these, about 28.4% had perennial allergic rhinitis. The placebo group included 91 patients (49 males and 42 females; mean age, 36.1

Table. Baseline Characteristics of the Patients

	Pranlukast Group n=102	Placebo Group n=91
Mean (SD) age, y	36.5 (11.6)	36.1 (12.1)
Female sex (%)	45 (44.1)	42 (46.2)
Mean duration of cedar pollinosis, y	9.7	9.4
Type of allergic rhinitis		
Cedar pollinosis with perennial symptoms	29	25
Cedar pollinosis only	73	66
Additional allergy history		
History of asthma symptoms	2	5
Current asthma symptoms	0	0
History of allergic conjunctivitis	102	91
Cedar pollen RAST score, mean (SD)	3.9 (0.9)	4.0 (1.2)
Cedar pollen skin test score, mean (SD)	2.0 (0.8)	1.9 (0.7)
Peak of daily total nasal symptoms score in the last pollen season	5.2	5.0

Abbreviation: RAST, radioallergosorbent test.

years; perennial allergic rhinitis in 27.5%). The symptoms of perennial allergic rhinitis were mild, and none of the enrolled patients required treatment. There were no significant differences in sex, age, age at onset, duration of disease, or frequency of complications between the 2 groups.

For assignment of participants to the 2 study groups, limited randomization was performed in subgroups of 6 patients with no differences in sex or age, and 3 participants in each subgroup were assigned to the pranlukast group or to the placebo group.

Other antihistaminic drugs were administered concomitantly as follows: in the last 2 weeks of the double-blind comparative period, an oral antihistamine (loratadine), nasal vasoconstriction drops (tetrahydrozoline hydrochloride), or chemical mediator release-suppressing eye drops (sodium cromoglycate) was administered for eye and nasal symptoms based on the patient's self-judgment of symptom severity. In the pranlukast administration period, the same drugs and a nasal corticosteroid spray (fluticasone propionate) were permitted depending on symptom severity, as described in the Clinical Guidelines for the Management of Allergic Rhinitis in Japan [3]. Use was also based on patient self-judgment.

Pollen Counts

Cedar pollen dispersion was measured using a gravimetric method with a Durham sampler.

Symptom Scoring

Each participant completed the Japanese rhinoconjunctivitis QOL questionnaire (JRQLQ) survey form 4 times every 2 weeks [14-16]. Participants also kept a nasal allergy diary record. Symptoms, medication, and symptom-medication scores were based on daily nasal allergy diary records using

the following criteria. For nasal symptoms, the severity of paroxysmal sneezing (number of sneezes per day), runny nose (number of times participants blew their nose per day), nasal congestion, and the degree of interference with daily life were evaluated on a 5-point scale (0-4) based on the Clinical Guidelines for the Management of Allergic Rhinitis in Japan [3], as follows: 0, no sensation; 1, mild; 2, moderate; 3, severe; and 4, extremely severe. Episodes of sneezing and nose blowing (rhinorrhea) per day were rated from 0 to 4 as follows: 0, none; 1, 1-5 episodes; 2, 6-10 episodes; 3, 11-20 episodes; and 4, >21 episodes. Eye itching and watering were evaluated using a 5-point scale. Eye itching was rated as follows: 0, none; 1, itching but not necessary to scratch; 2, scratching occasionally; 3, scratching frequently; and 4, more frequently. Eye watering was rated as follows: 0, none; 1, not necessary to wipe; 2, wiping sometimes; 3, wiping frequently; and 4, more frequently. The medication score was based on the required amounts of the 4 concomitant drugs according to Japanese practice guidelines. The following scores were applied each day of the pollen season: 0, if no intake of concomitant medication; 1, one oral antihistamine, nasal vasoconstriction drops, or chemical mediator release-suppressing eye drops; 2, nasal corticosteroid spray. For each patient, the medication scores and the symptom-medication scores (by adding the symptom scores to the medication scores) were calculated. The QOL scores were also evaluated on a 5-point scale (0-4). The symptom-medication score was used as the primary outcome parameter and other criteria were used as secondary outcome parameters.

Statistics

Data were analyzed using 2-tailed tests at a significance level of 5%, the chi-square test, Fisher exact test, 2-sample *t* test, and

paired *t* test. The analysis was performed using SAS v. 8.02 (Cary, North Carolina, USA).

Results

Pollen Counts

Cedar pollen started to disperse in the study region on February 6th (day 3 of drug administration) and the first week included 2 days before and 5 days after pollen dispersion began. Pollen counts of $>50/\text{cm}^2/\text{d}$ occurred almost daily for about 3 weeks from February 19th (week 3 of drug administration) to March 9th. The pollen count then decreased to $<50/\text{cm}^2/\text{d}$ and was almost undetectable on March 20th (Figure 1).

Nasal Symptom Score

The nasal symptom score in the pranlukast group increased by less than 0.48 (<0.5), and was significantly lower (Figure 2). The sneezing scores in the placebo group increased by more than 0.63 (≥ 0.5) between week 3 and week 5, compared to the scores observed initially in week 1; however, the severity of sneezing in the pranlukast group was significantly milder than in the placebo group during weeks 3, 4, and 5. Compared to week 1, the rhinorrhea score increased by ≥ 0.5 from weeks 3 to 6 in the placebo group and by ≥ 1 in week 4, whereas the increase was lower (<0.5) in the pranlukast group. The severity of rhinorrhea in the pranlukast group was significantly milder than that observed in the placebo group in week 4. The nasal congestion score increased by ≥ 0.5 in weeks 4 and 5 in the placebo group, compared to week 1, and exceeded 1,

whereas the score increased by <0.5 throughout the study in the pranlukast group, although it did not exceed 1. No significant increase was observed in the score at week 4 in the pranlukast group compared to week 1. The severity of nasal congestion in the pranlukast group was significantly milder than in the placebo group in weeks 4 and 5, as shown in Figure 2.

Symptom Scores, Medication Scores, and Symptom-Medication Scores

The symptom score increased by ≥ 0.5 from week 2 to week 6 in the placebo group and by ≥ 1 in week 4, compared to week 1, whereas the increase was <0.5 in the pranlukast group. The score in the pranlukast group was significantly lower than that in the placebo group in weeks 4 and 5 (Figures 3 and 4). The medication scores showed that the oral antihistamine was used significantly more often in the placebo group in weeks 3 and 4 and that the nasal vasoconstrictor was used significantly more often in the placebo group in week 4. The symptom-medication score increased by ≥ 2 in weeks 4 and 5 in the placebo group, compared to week 1, whereas the increase was <2 in the pranlukast group. In week 4 the symptom-medication score in the pranlukast group was significantly lower than in the placebo group. Regarding eye symptoms, there was no significant difference in eye itching or watering between the placebo and pranlukast groups (data not shown). The score for the degree of interference with daily life increased by ≥ 0.5 from week 3 to week 5 in the placebo group, compared to week 1, whereas the increase was <0.5 in the pranlukast group. The score in the pranlukast group was significantly lower than in the placebo group in week 4 (Figure 4).

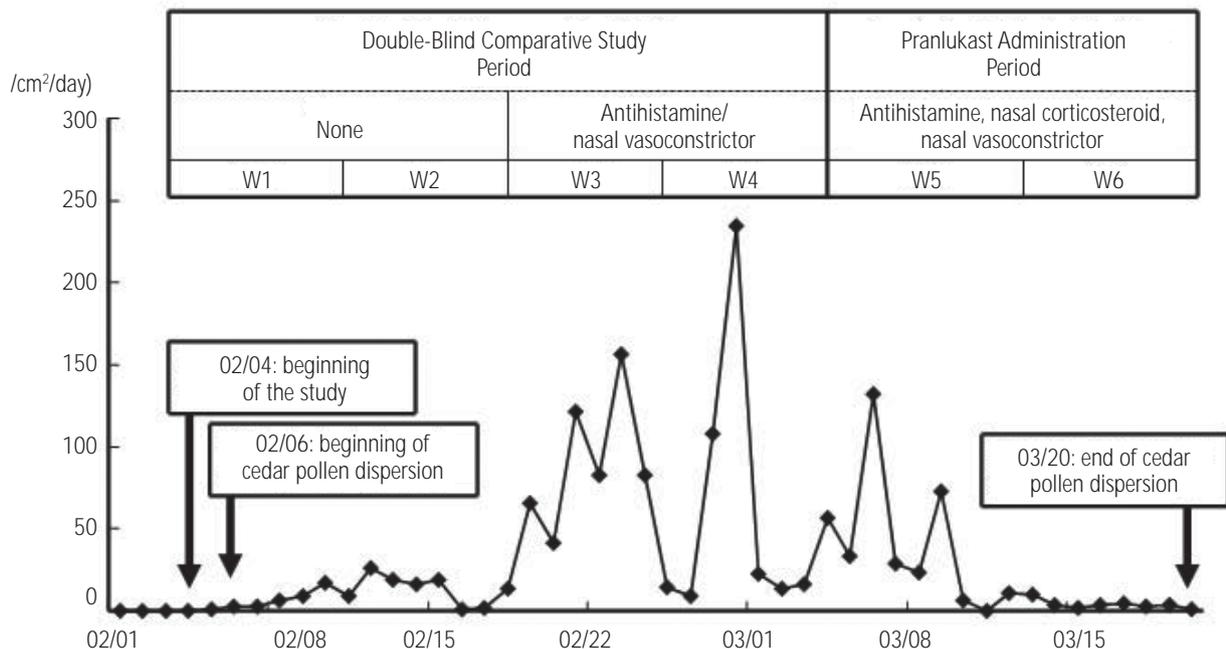


Figure 1. The study schedule and the 2007 cedar pollen counts.

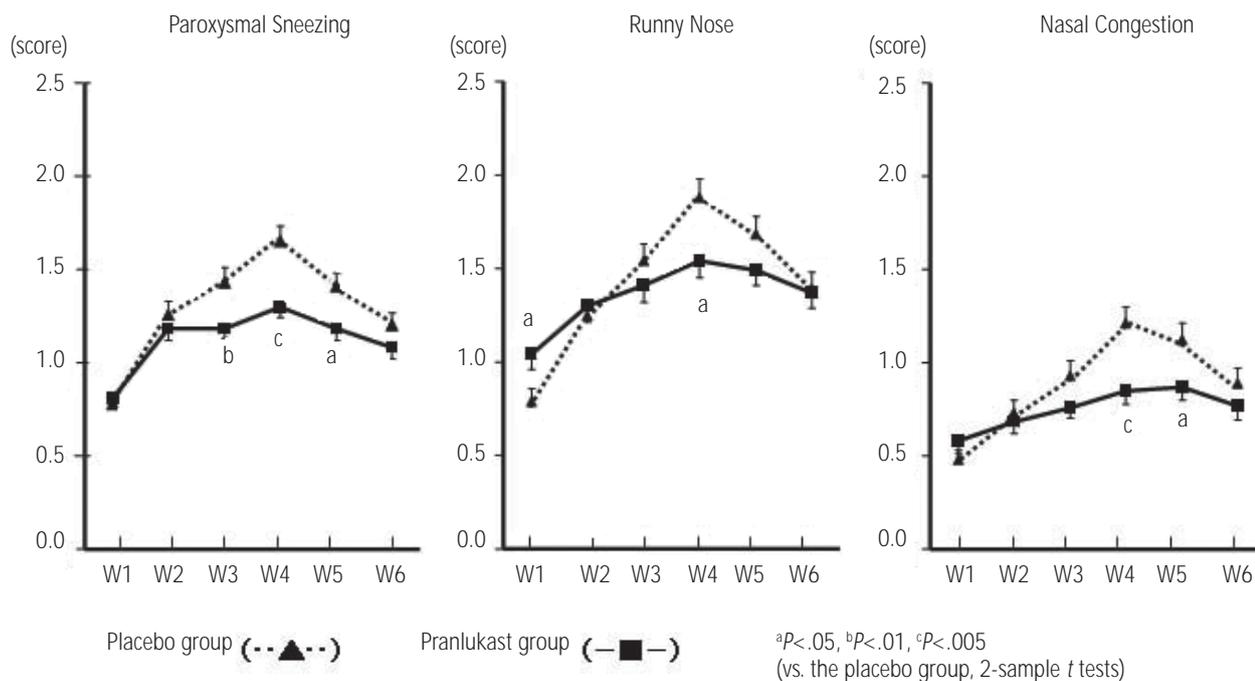


Figure 2. Effects on nasal symptoms.

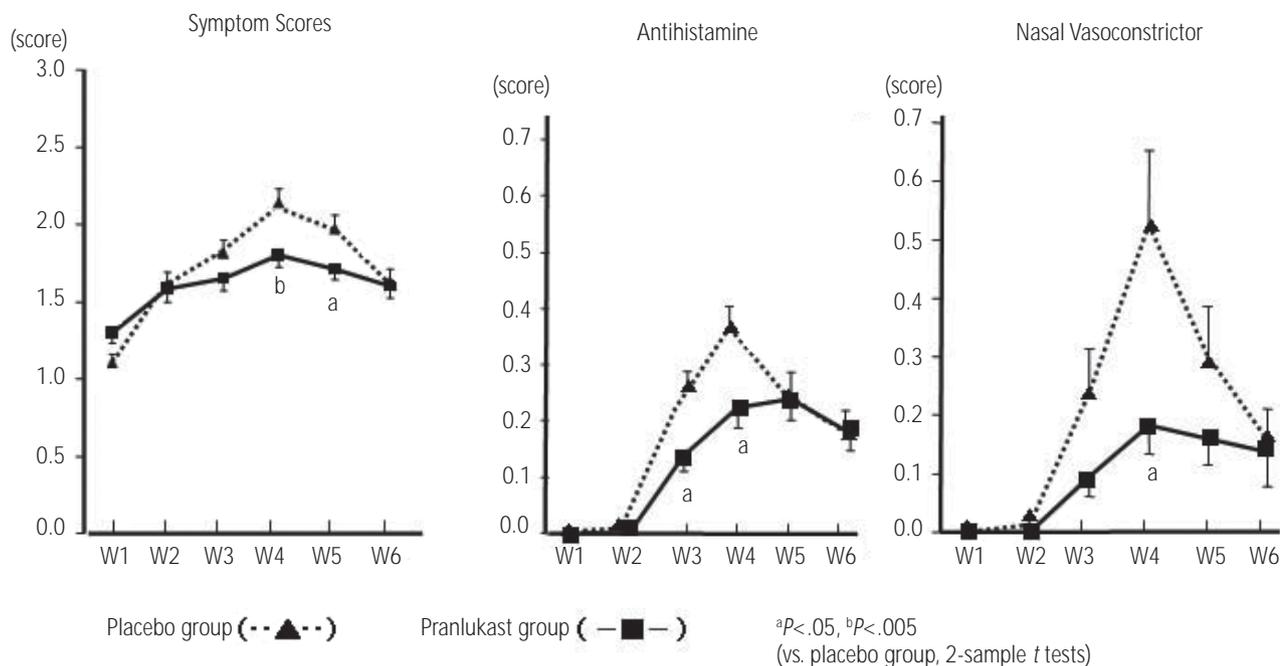


Figure 3. Symptom scores and medication scores.

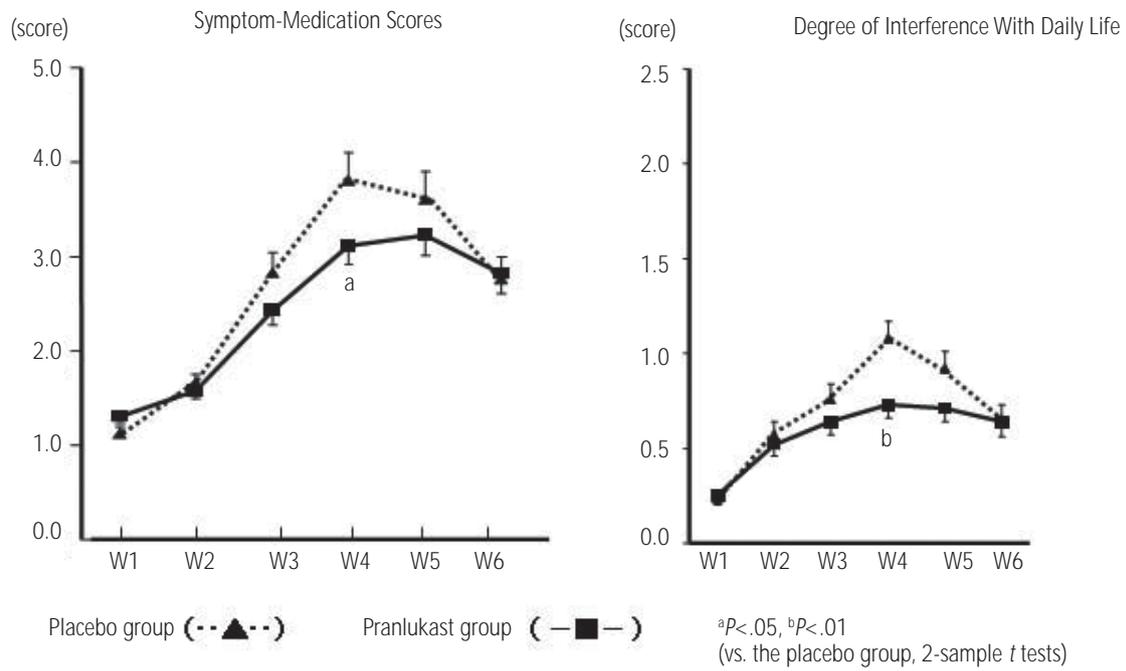


Figure 4. Symptom-medication scores and the degree of interference with daily life.

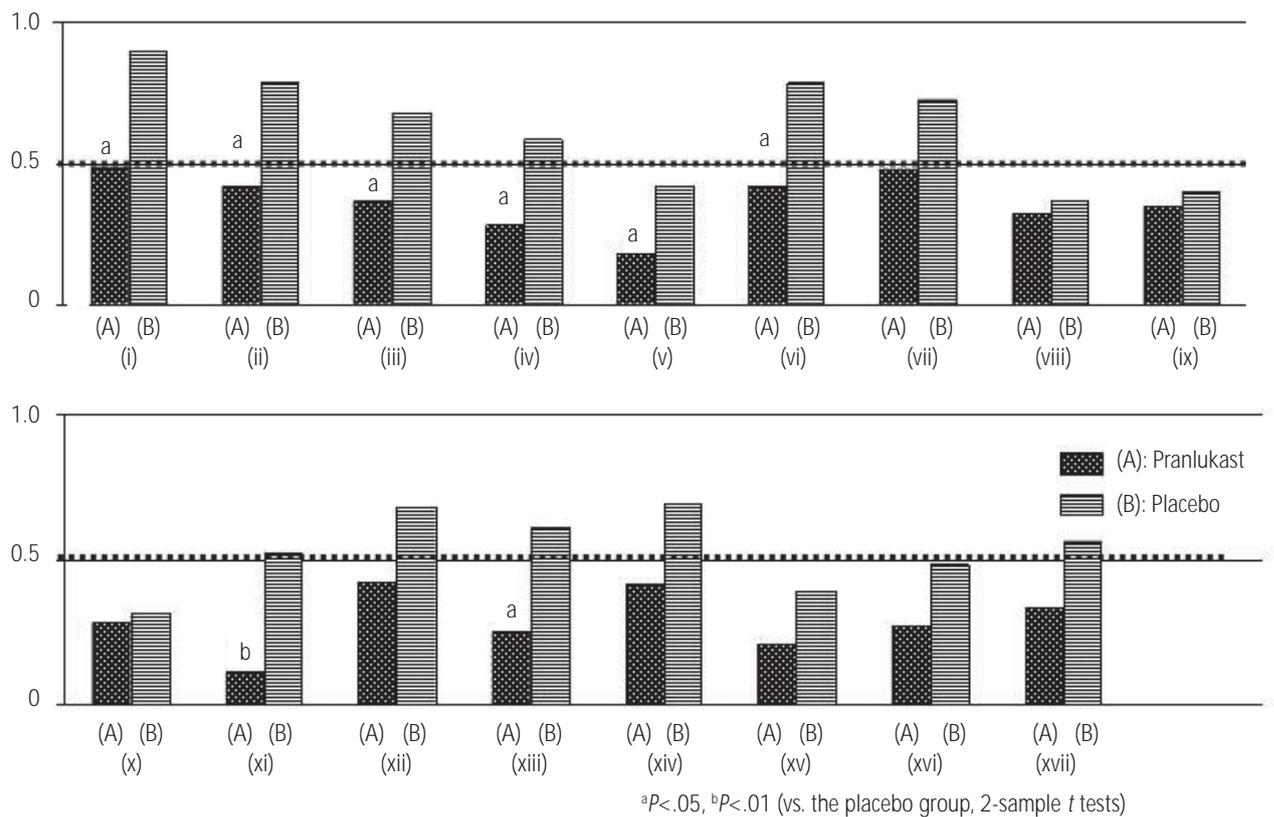


Figure 5. Change in QOL scores at 4 weeks from baseline (at 0 weeks).

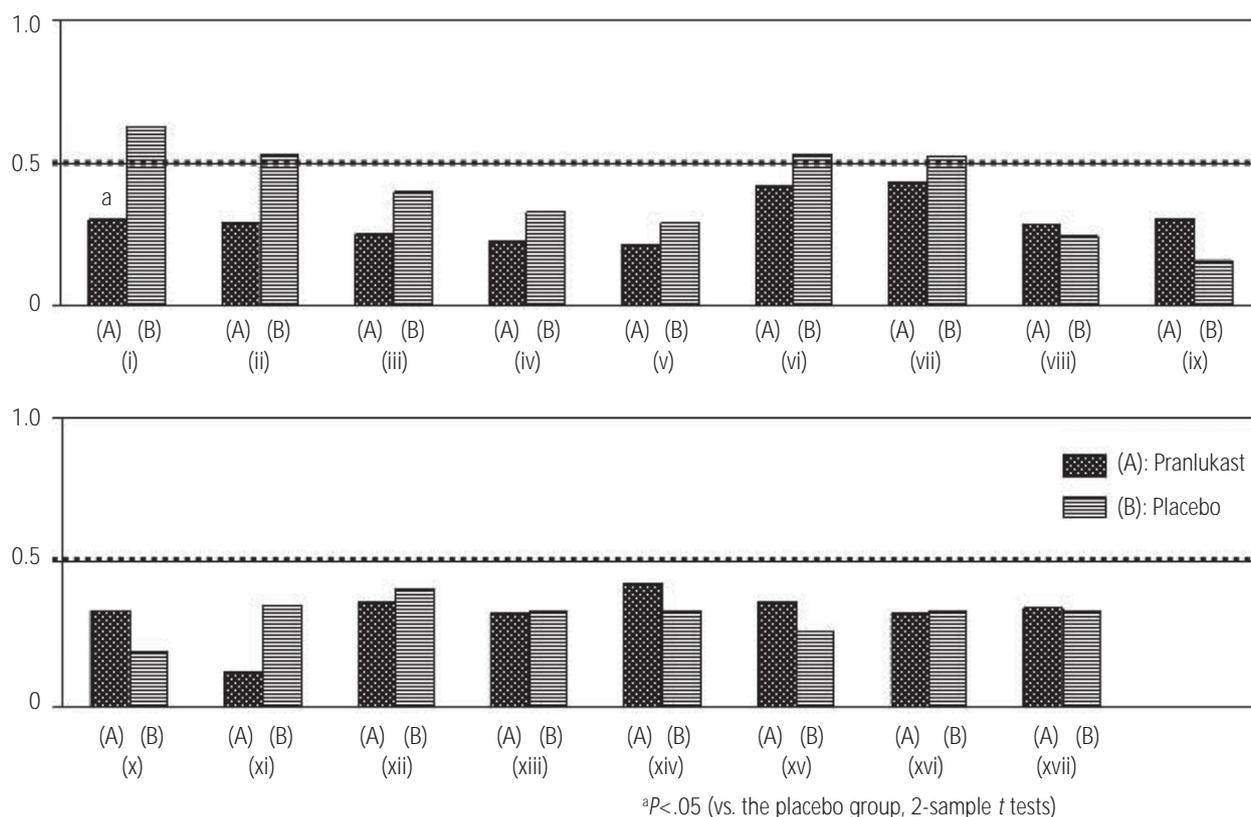


Figure 6. Change in QOL scores at 6 weeks from baseline (at 0 weeks).

Quality of Life

QOL scores were determined using the JRQLQ questionnaire. The total QOL score after 4 weeks of drug administration was significantly lower in the pranlukast group. In the placebo group, the QOL scores for 11 out of a total of 17 items on the JRQLQ increased by ≥ 0.5 at week 4 compared to week 0 (Figure 5). The QOL scores for all 17 items improved at week 6 (the end of the cedar pollen dispersion period) and did not increase by ≥ 0.5 at week 6 compared to week 0, before the pollen season in the pranlukast group (Figure 6). However, in 4 items (reduced productivity at work/home/school; poor concentration; limitation to participating in outdoor activities; and limitation to leaving one's house) in the placebo group, the scores were still ≥ 0.5 ; therefore, the improvement was limited. In particular, there was no significant increase in impaired sleeping scores following initiation of pranlukast, and sleep was not disturbed in the pranlukast group throughout the study.

Side Effects

Pranalukast was safe and no significant side effects were noted. However, in 2 cases, mild diarrhea was observed on day 16 of administration. In 1 case, the diarrhea stopped when administration was interrupted for 2 days. No further problems

occurred when administration was restarted. In the other case, abdominal pains occurred on day 16 of drug administration. However, administration of the drug was continued and the symptom disappeared 2 days later.

Discussion

Recent randomized controlled trials comparing leukotriene receptor antagonists with antihistamines or nasal corticosteroids in patients with pollinosis have shown that the use of leukotriene receptor antagonists significantly improved the nasal symptoms score. The effectiveness of such therapy was determined in part by pollen levels in the community [11,17]. Earlier studies have shown that leukotriene receptor antagonists are as effective as oral antihistamines alone, but significantly inferior to nasal corticosteroids [12,18-20]. The results of the present study were similar.

Our results show only limited improvement in nasal symptoms and impaired QOL scores in patients treated with placebo for the first 4 weeks of pollen dispersion, even after combined administration of pranlukast with nasal corticosteroids and antihistamines. In addition to the expected symptom control during the initial period (when the pollen count was still low and associated with mild symptoms and

moderate hyperreactivity of the nasal mucosa), the effects of early intervention with pranlukast persisted during the whole season, including during peak pollen dispersion.

The lasting effects of pranlukast during peak pollen dispersion reported here may be due to its anti-inflammatory properties. Allergic inflammation in the airway is induced by leukotriene, and this leads to eosinophilic infiltration and degranulation during active inflammation, stimulation of type 2 helper T-cell production, and proliferation and hyperplasia of goblet cells and mucus glands, resulting in hypersecretion [7-9]. Cysteinyl leukotriene receptor antagonists such as pranlukast have potent inhibitory effects on the inflammatory cascade [21-23].

The antihistamine used in this study, loratadine, acts quickly with a very low sedative effect, and was administered on demand; however, exacerbation was still observed in the placebo group. It has been shown that treatment with antihistamines only during peak cedar pollen dispersion results in a poor outcome [3]. Various anti-inflammatory effects of antihistamines have been shown in vitro and in animal studies, but have yet to be clarified clinically beyond H₁-receptor antagonism [24]. Similarly, lasting effects of an antihistamine were not obtained in the present study.

Nasal corticosteroids are generally very effective in preventing or reducing rhinorrhea and sneezing, as well as in reducing the severity of nasal obstruction. Thus, intranasal corticosteroids provide significant resolution of these symptoms and are advantageous for early intervention. However, adherence to intranasal corticosteroids is sometimes poor [25], since many patients prefer to use oral medication. A comparative study with leukotriene receptor antagonists and corticosteroids in patients with allergic rhinitis may further clarify these important issues. Allergen-specific immunotherapy has been evaluated and shown to be an effective approach to modifying the course of allergic rhinitis [26,27]. The combination of early intervention with drugs and specific immunotherapy may be beneficial for the management of pollinosis.

These observations show that administration of pranlukast in cedar pollinosis patients initiated just before and continued during the entire pollen dispersion season in high-risk communities is effective in improving clinical symptoms and quality of life. The efficacy of early intervention with pranlukast must be compared with that of other drugs, while taking into account the cost-benefit ratio.

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