Journal of Drug Assessment Vol. 3, 2014, 51–59

2155-6660
doi:10.3109/21556660.2014.960969

Article JDA-2014-0004.R1/960969
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Original article

Placebo-controlled study with OHIO chamber of prophylactic pranlukast for children with Japanese cedar pollinosis: TOPIC-J III study

Kei Hosoya
Satoru Masuno
Department of Otorhinolaryngology, Nippon Medical School, Tokyo, Japan

Kazuhiro Hashiguchi
Otorhinolaryngology, Futaba Clinic, Tokyo, Japan

Kimihiro Okubo
Department of Otorhinolaryngology, Nippon Medical School, Tokyo, Japan

Address for correspondence:
Kimihiro Okubo, MD, Chairman, Professor, Department of Otolaryngology, Nippon Medical School, Sendagi 1-1-5, Bunkyo-ku, Tokyo 113-8603, Japan.
Tel.: +81 3-3822-2131 ext 6338;
Fax +81 3-5814-6207;
ent-kimi@nms.ac.jp

Keywords:
Cedar pollinosis – Pranlukast – Nasal symptoms – Pediatric patients – Prophylactic therapy

Accepted: 28 August 2014; published online: 21 October 2014
Citation: J Drug Assess 2014; 3:51–9

Abstract

Objective:
This double-blind, placebo-controlled comparative study was designed to investigate whether pranlukast dry syrup, a leukotriene receptor antagonist, has a protective effect against priming, controlled pollen exposure, and natural pollen exposure in children with Japanese cedar pollinosis.

Research design and methods:
Thirty children aged 12–15 years with Japanese cedar pollinosis (positive skin test for Japanese cedar pollen), who had suffered from pollinosis for at least 2 years and developed severe nasal obstruction when exposed to Japanese cedar pollen, were enrolled in this study. They were randomly allocated to treatment with pranlukast or placebo orally after breakfast and dinner for 8 weeks during the Japanese cedar pollen season. Soon after the start of the pollen season, all subjects underwent a challenge by exposure for 3 h to Japanese cedar pollen (8000 grains/m^3) in an artificial exposure chamber (OHIO chamber).

Clinical trial registration:
The University Hospital Medical Information Network in Japan (UMIN000009840).

Main outcome measures:
The effect of pranlukast was evaluated using self-rating of nasal symptoms by the subjects and measurement of eosinophil cationic protein in nasal discharge specimens.

Results:
Scores for the symptoms of pollinosis were lower in the pranlukast group than in the placebo group during treatment in the priming state, as well as after controlled pollen exposure and natural pollen exposure. Pranlukast significantly improved the score for nasal obstruction, compared with placebo. A correlation was found between changes of the scores for symptoms of pollinosis and changes of the eosinophil cationic protein level.

Conclusions:
These results confirm a protective effect of pranlukast against both priming and challenge (controlled and natural) with Japanese cedar pollen. The present findings suggested that pranlukast dry syrup may be useful for prophylaxis against pollinosis in children.

Introduction

Japanese cedar (JC) pollinosis is a form of seasonal allergic rhinitis peculiar to Japan that was first reported in 1964[1]. It is caused by pollen dispersal in the early spring from Japanese cedar and cypress trees throughout Japan, which

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release a massive amount of pollen. In Japan, the prevalence of JC pollinosis increased by ~10% over 10 years from 16.2% in 1998 to 26.5% in 2008[2,3]. In 2008, the prevalence of JC pollinosis was 33.1–39.1% among adults in each decade from the 20s to the 50s, 31.4% in teenagers and 13.7% in children aged 5–10 years[4]. The prevalence of JC pollinosis in children appears to be much higher than that of allergic rhinitis, which was reported as 10% or less in children aged 6–7 and ~15% in those aged 13–14 years[5,6].

In Japan, the pollen season usually starts in early February and ends between mid-March and early April. JC pollinosis causes nasal and ocular symptoms that can significantly influence the quality-of-life (QoL)[7], and it is important to initiate treatment before or at the start of the pollen season to prevent the development of symptoms. Accordingly, the Japanese guideline for nasal allergy recommends initiation of prophylactic therapy before or early in the pollen season[4].

Leukotrienes dilate vessels in the nasal mucosa[8], increase vascular permeability[9], and promote the migration of inflammatory cells such as eosinophils and macrophages[10–12]. Thus, leukotrienes are important chemical mediators of allergic rhinitis, suggesting that usefulness of leukotriene receptor antagonists (LTRAs)[13–15]. Clinical studies have shown that LTRAs are as effective as antihistamines for pollinosis[16–18]. It has also been reported that initiating prophylactic LTRA therapy before or early in the pollen season can prevent symptoms of pollinosis[19–22].

The LTRA pranlukast is effective for perennial allergic rhinitis in adults[23]. It is also superior to placebo as prophylactic therapy for pollinosis[21,22]. Furthermore, pranlukast has an immediate effect against exposure to pollen in an artificial exposure chamber (OHIO chamber), improving the early and late phases of nasal obstruction[24], and inhibits priming for pollinosis[25]. Moreover, pranlukast dry syrup (PLK-DS) is more effective than placebo for preventing nasal obstruction in children with pollinosis tested in an OHIO chamber[26,27].

Accordingly, this study was performed to determine the efficacy of prophylactic therapy with PLK-DS vs placebo for JC pollinosis in children by investigating the inhibitory effect on priming for pollinosis and on the response to pollen exposure (both controlled exposure in an OHIO chamber and natural exposure during the pollen season).

Materials and methods

Subjects

This study enrolled 30 children with JC pollinosis who met the following inclusion criteria: aged from 10 years to younger than 15 years, class 2–6 when multiple antigen testing was performed to detect specific IgE antibodies for JC pollen in serum, a history of nasal symptoms with nasal obstruction following exposure to JC pollen in an OHIO chamber, development and exacerbation of nasal symptoms with nasal obstruction during the annual JC pollen season, and those determined to be eligible by an investigator or sub-investigator when clinical examination was done before the start of the study. The exclusion criteria were as follows: any lesion of the nasal or ocular mucosa, use of parenteral corticosteroids within 6 months before obtaining informed consent, nasal disease (deviation of the nasal septum, nasal polyps, etc.), systemic disease (asthma, tuberculosis, etc.), a history of anaphylaxis, a history of hypersensitivity to any ingredient of the test drug, current immunotherapy (hyposensitization therapy or allassotherapy), and any other reason that made patients ineligible for this study according to the investigator. We specified two persons who were responsible for patient enrollment (K.H. and S.M). It was also pre-determined that if they could not reach a consensus as to whether to include/exclude a child, an independent researcher (Dr Minoru Gotoh, Nippon Medical School Tama Nagayama Hospital, Tokyo, Japan) would be consulted to make the final decision.

The subjects received a detailed explanation of this study and possible adverse reactions to the test drug, and their parents or guardians provided informed consent. The study was performed at Medical Corporation Shinanokai Samoncho Clinic according to the ethical guidelines in the protocol and the Declaration of Helsinki (2000) after receiving approval from the ethics committee of the clinic. This study was registered with the University Hospital Medical Information Network in Japan (registration No. UMIN000009840).

Study procedures

This was a randomized, double-blind, placebo-controlled clinical trial. The investigational drugs included PLK-DS (10% pranlukast) and placebo, which were confirmed to be indistinguishable from each other. In late January 2013, 30 participants were selected based on the results of skin tests with JC pollen. For the skin test, a skin prick test was performed. When 'the test site showed a wheal of at least 5 mm surrounded by at least 10 mm of erythema', the judgment was positive. According to the schedule shown in Figure 1, the participants received PLK-DS or placebo twice a day (after breakfast and after dinner) for 2 months from February 1, which was expected to be before the start of the JC pollen season, through the peak pollen season until March 31.

'The starting date of the pollen season' is defined as the day when at least 1 pollen grain/cm^2 has been detected for at least 2 days by an automatic pollen measuring device

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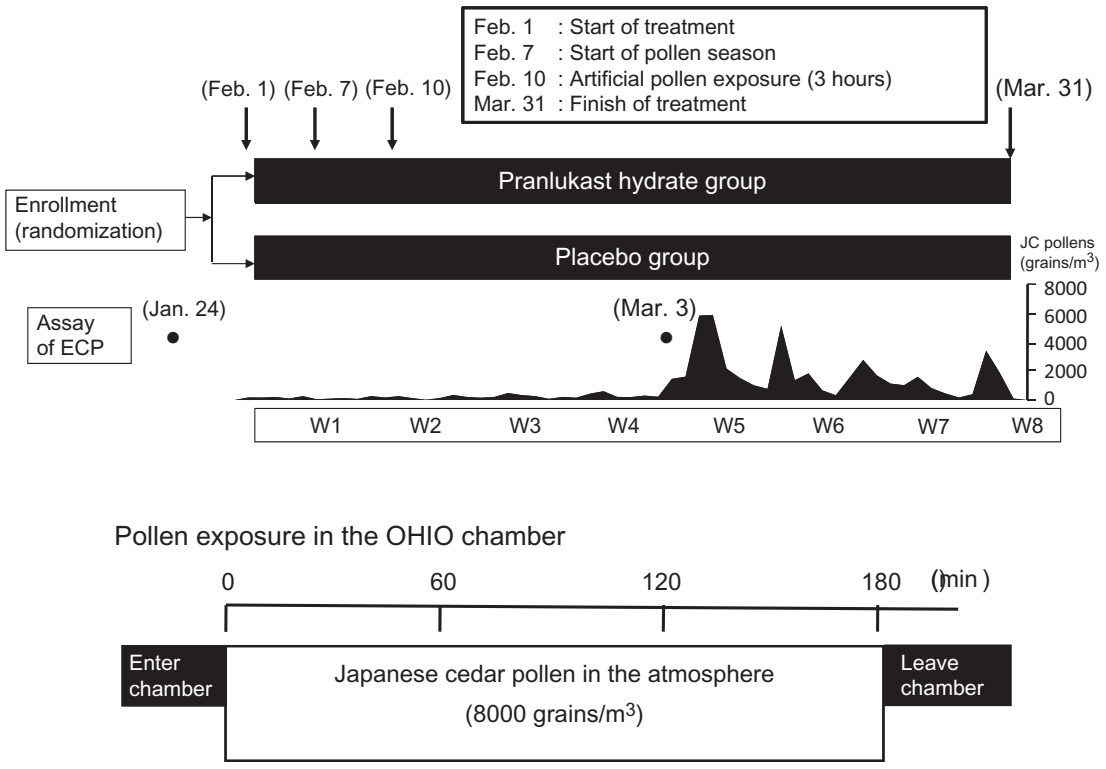

Figure 1. Study schedule. ECP, eosinophil cationic protein; JC, Japanese cedar.

(Durham pollen gathering device) at the Ministry of the Environment. In fact, a very low level of pollen dispersion occurs before the official start of the pollen season, and some patients develop symptoms before the starting date.

Early in the JC pollen season (February 10), subjects were exposed to JC pollen for 3 h in an OHIO chamber (JC pollen count: 8000 grains/m^3)[28–30]. Before the JC pollen season (January 24) and during the pollen season (March 3), eosinophil cationic protein (ECP) was measured in nasal discharge samples as an index of inflammation. Extraction of ECP from nasal discharge samples and measurement were done according to the manufacturer's recommendations (MESACUP ECP Test: Medical & Biological Laboratories Co., Ltd., Aichi, Japan)[27]. Concomitant use of the following drugs was not permitted during treatment with the investigational drug: corticosteroids (oral, inhaled, and topical), antihistamines (oral, inhaled, and topical), anti-allergic drugs, leukotriene antagonists, anti-prostaglandin D_2/thromboxane A_2 drugs, vasoconstrictors, anticholinergics, and other drugs that could affect evaluation of efficacy. However, if a patient developed severe symptoms following the start of the pollen season, rescue medications could be used to treat the symptoms (including Intal Nasal Spray 2%, Intal Ophthalmic Solution 2%, vasoconstrictors, and anticholinergics), provided that the total nasal symptoms score (Table 1) was ≥4 points on the previous day. As rescue medication for severe symptoms while patients were in the OHIO chamber or after leaving the chamber, Intal Nasal Spray 2% and/or Intal Ophthalmic Solution 2% could be used if this was determined to be necessary by an investigator or sub-investigator. Atmospheric JC pollen levels were based on the data published by Nippon Medical School.

Table 1. Nasal symptoms questionnaire.

Sneezing – 'How severe is sneezing?'
0: None/1: Mild/2: Moderate/3: Severe/4: Very severe
Nasal discharge – 'How severe is running nose?'
0: None/1: Mild/2: Moderate/3: Severe/4: Very severe
Nasal obstruction – 'How severe is nasal obstruction?''
0: None/1: Mild/2: Moderate/3: Severe/4: Very severe

Evaluation

Nasal symptoms were recorded in the nasal allergy diary before sleeping every day from February 1 to March 31. On the day after controlled pollen exposure in the OHIO chamber, symptoms were also recorded in the morning and at noon. The most severe symptoms during each period were recorded in the diary.

In the nasal allergy diary, the severity of each symptom (sneezing, nasal discharge, and nasal obstruction) was

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assigned a score from 0–4[24]. The weekly mean scores were calculated from February 1 for each symptom and for all three symptoms combined (total score), and changes from the mean score of Week 1 (including the first day of the pollen season and before controlled exposure in the OHIO chamber) were determined for each of the subsequent weeks. ECP levels were compared at two times, which were before the start of the JC pollen season and during the pollen season.

Statistical analysis

Data were analyzed with a two-sided U-test and the Wilcoxon test, and $p \leq 0.05$ was accepted as the level of significance. Statistical analysis was performed using SAS version 8.02 (SAS Institute Inc., Cary, NC).

Results

JC pollen season

The JC pollen season started on February 7 (7 days after commencing treatment) (Figure 1). In February, the daily JC pollen count was relatively low. However, the count increased during Week 5 and was at least 2000 grains/m^3 in each week up to Week 8 (end of the study).

Patient demographic profile

Of the 30 patients enrolled, 25 completed this study and five were excluded due to insufficient data in the nasal allergy diary (Table 2). Among the 25 patients, 13 received PLK-DS (six boys and seven girls; mean age: 13.77 ± 1.17 years) and 12 received placebo dry syrup (four boys and eight girls; mean age: 13.67 ± 0.98 years). There was no significant difference of nasal symptom scores between the two groups in Week 1, and both groups had mild symptoms at that time (Table 3).

Table 2. Patient characteristics at baseline.

	Pranlukast hydrate group	Placebo group
No. of patients	13	12
Sex		
Male	6 (46.2%)	4 (33.3%)
Female	7 (53.8%)	8 (66.7%)
Age, years		
12	3 (23.1%)	1 (8.3%)
13	1 (7.7%)	5 (41.7%)
14	5 (38.5%)	3 (25%)
15	4 (30.8%)	3 (25%)
Mean ± SD	13.77 ± 1.17	13.67 ± 0.98
CAP-RAST		
Class 3	0	1 (8.3%)
Class 4	0	1 (8.3%)
Class 5	1 (7.7%)	1 (8.3%)
Class 6	12 (92.3%)	9 (75%)

Table 3. Mean symptom scores in the first before pollen exposure in the OHIO chamber.

	Pranlukast hydrate group (mean ± standard error)	Placebo group (mean ± standard error)	U-test
Sneezing	0.582 ± 0.222	0.583 ± 0.205	$p = 1.000$
Rhinorrhea	1.110 ± 0.255	0.893 ± 0.248	$p = 0.566$
Nasal obstruction	1.011 ± 0.261	0.667 ± 0.239	$p = 0.393$
Total nasal symptoms	2.703 ± 0.603	2.143 ± 0.606	$p = 0.369$

Nasal symptoms

Sneezing

In Week 2, subjects were exposed to JC pollen in the OHIO chamber. Subsequently, the sneezing score increased significantly in the placebo group, while there was no significant increase in the PLK-DS group. From Week 3 to Week 7, the sneezing score showed a significant increase in both groups (Figure 2).

Nasal discharge

In Week 2 (OHIO chamber), the nasal discharge score increased significantly in the placebo group, while there was no significant increase in the PLK-DS group. In addition, the placebo group had a significantly higher nasal discharge score compared with the PLK-DS group. In Weeks 3 and 4 (before the peak of the pollen season), there was a significant increase of the score in the placebo group, but not in the PLK-DS group. Between Weeks 5 and 7 (peak pollen season), a significant increase of the score was observed in both groups (Figure 3).

Nasal obstruction

In the placebo group, a significant increase of the nasal obstruction score continued from Week 2 (OHIO chamber) to Week 7 of the JC pollen season. On the other hand, there was no significant increase of the score in the PLK-DS group from Week 2 to Week 8 (end of the study) (Figure 4).

Total score

In the placebo group, the total nasal symptoms score was significantly increased between Week 2 (OHIO chamber) and Week 7 (peak pollen season). In the PLK-DS group, there was no significant increase between Week 2 and Week 4 (before the peak pollen season), although a

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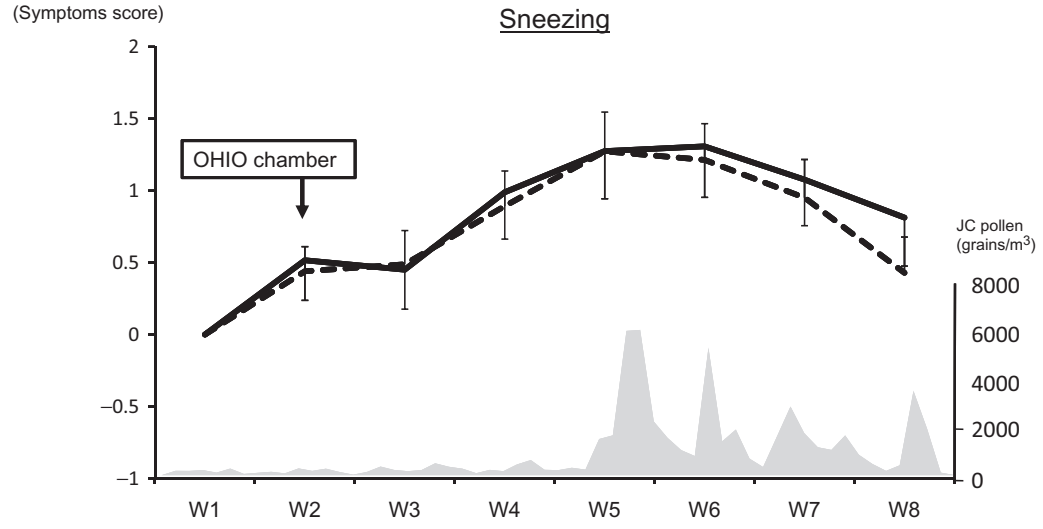
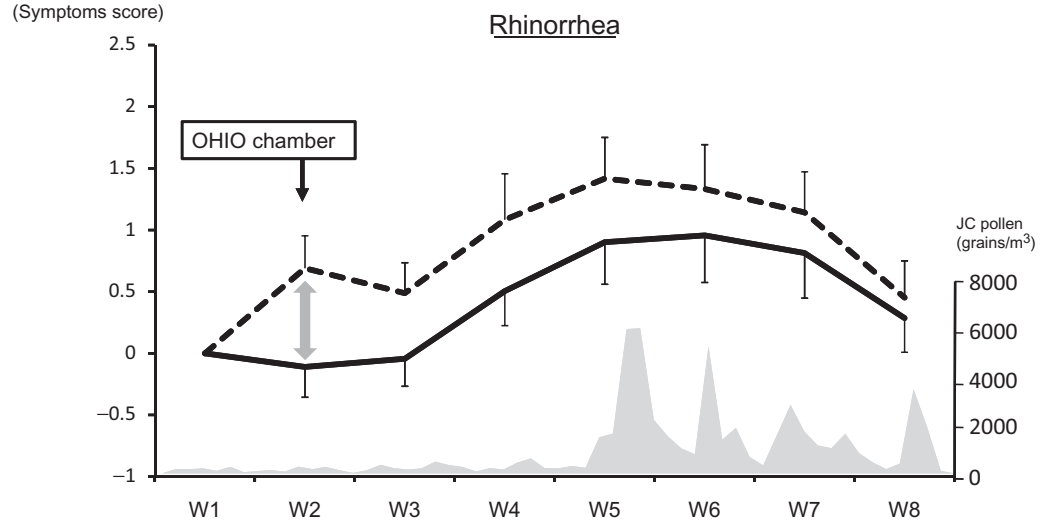


p-value (Wilcoxon test)	Placebo group (vs. W1)	0.041	0.084	0.003	<0.001	0.002	0.001	0.122
	Pranlukast hydrate group (vs. W1)	0.092	0.137	0.008	0.001	0.003	0.004	0.027
p-value (*U*-test)	Placebo group vs. Pranlukast hydrate group	0.764	0.723	1.000	1.000	0.978	1.000	0.313

Figure 2. Weekly mean sneezing scores. The solid line and dashed line represent the pranlukast hydrate group and the placebo group, respectively. $\boxed{p = 0.01}$: significant, $p = 0.1$: not significant. JC, Japanese cedar.



p-value (Wilcoxon test)	Placebo group v(vs. W1)	0.022	0.044	0.016	0.004	0.007	0.013	0.232
	Pranlukast hydrate group (vs. W1)	0.501	0.765	0.111	0.031	0.029	0.045	0.553
p-value (*U*-test)	Placebo group vs. Pranlukast hydrate group	0.021	0.077	0.201	0.211	0.242	0.605	0.462

Figure 3. Weekly mean rhinorrhea scores. The solid line and dashed line represent the pranlukast hydrate group and the placebo group, respectively. $\boxed{p = 0.01}$: significant, $p = 0.1$: not significant. JC, Japanese cedar.

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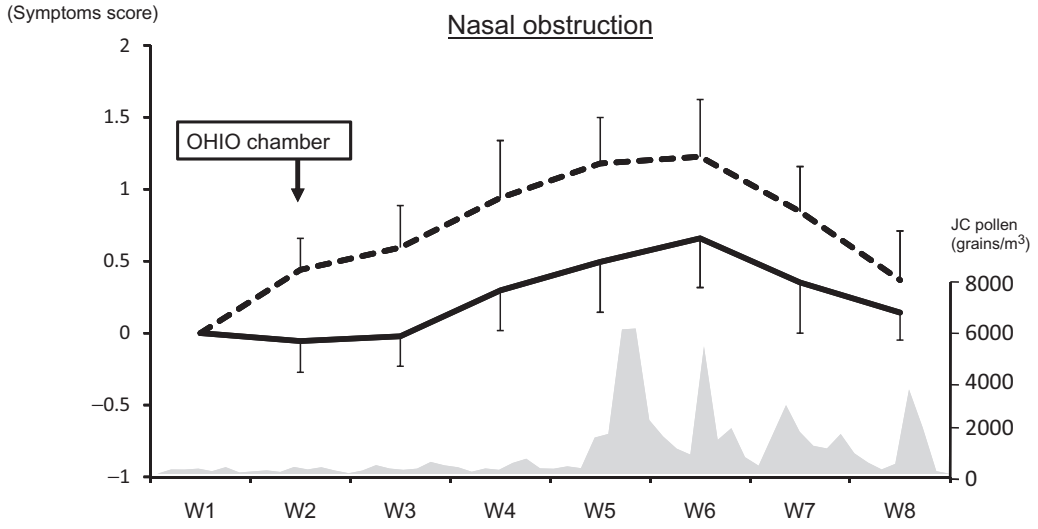

p-value (Wilcoxon test)	Placebo group (vs. W1)	0.045	0.047	0.016	0.005	0.007	0.023	0.287
	Pranlukast hydrate group (vs. W1)	0.751	0.959	0.354	0.241	0.070	0.445	0.464
p-value (*U*-test)	Placebo group vs. Pranlukast hydrate group	0.173	0.063	0.091	0.103	0.327	0.231	0.785

Figure 4. Weekly mean nasal obstruction scores. The solid line and dashed line represent the pranlukast hydrate group and the placebo group, respectively. $p = 0.01$: significant, $p = 0.1$: not significant. JC, Japanese cedar.

significant increase of the score was observed during Weeks 5–7 (peak pollen season) (Figure 5).

Changes of ECP

In the placebo group, the ECP level in nasal discharge increased significantly from 11.46 ± 0.33 μg/L before the start of the pollen season (January 24) to 12.97 ± 0.60 μg/L during the peak pollen season (March 3) ($p = 0.042$, Wilcoxon test). On the other hand, the PLK-DS group showed no significant increase of ECP in nasal discharge (from 10.86 ± 0.89 μg/L to 11.52 ± 1.08 μg/L; $p = 0.455$, Wilcoxon test) (Figure 6).

Use of rescue drugs

Rescue drugs were hardly used during the early pollen season (W1–4). The number of days when a dosage of 0.5 drops/day was exceeded was 0 days for Intal Nasal Solution 2% in both the placebo group and the pranlukast dry syrup group. For Intal Ophthalmic Solution 2%, a dosage of 0.5 drops/day was exceeded on 0 days in the placebo group and 1 day in the pranlukast dry syrup group. During the late pollen season (W5–8), there was a slight increase in use, with a dosage of 0.5 drops/day, for Intal Nasal Solution 2% being exceeded on 0 days in the placebo group and 1 day in the pranlukast dry syrup group. For Intal Ophthalmic Solution 2%, the dosage of 0.5 drops/day was exceeded on 2 days in the placebo group and 3 days in the pranlukast dry syrup group.

Discussion

The main findings of the present study were as follows: First, prophylactic administration of PLK-DS to children with JC pollinosis demonstrated an inhibitory effect on priming in the early part of the pollen season. Second, prophylaxis with PLK-DS reduced the symptoms caused by exposure to JC pollen in an OHIO chamber during the early part of the pollen season. In particular, PLK-DS prophylaxis reduced nasal discharge and nasal obstruction after controlled exposure to JC pollen in the OHIO chamber. Third, prophylaxis with PLK-DS inhibited an increase of ECP in nasal discharge specimens during the peak pollen season. These findings indicated that PLK-DS prophylaxis was effective for reducing symptoms of pollinosis and nasal inflammation in children with JC pollinosis.

We previously reported that PLK-DS was effective in children who were exposed to pollen using the OHIO chamber[26]. In that study, we measured ECP levels in nasal discharge specimens at the end of pollen exposure,

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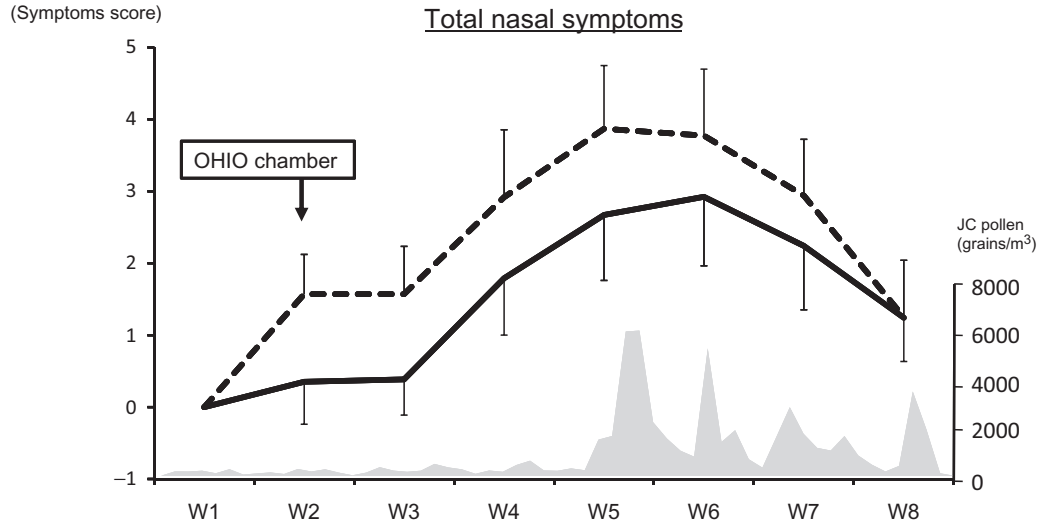

p-value (Wilcoxon test)	Placebo group (vs. W1)	0.020	0.026	0.012	0.003	0.003	0.004	0.134
	Pranlukast hydrate group (vs. W1)	0.839	0.403	0.080	0.011	0.070	0.020	0.068
p-value (*U*-test)	Placebo group vs. Pranlukast hydrate group	0.165	0.242	0.242	0.301	0.430	0.663	0.849

Figure 5. Weekly mean total nasal symptoms scores. The solid line and dashed line represent the pranlukast hydrate group and the placebo group, respectively. $\boxed{p = 0.01}$: significant, $p = 0.1$: not significant. JC, Japanese cedar.

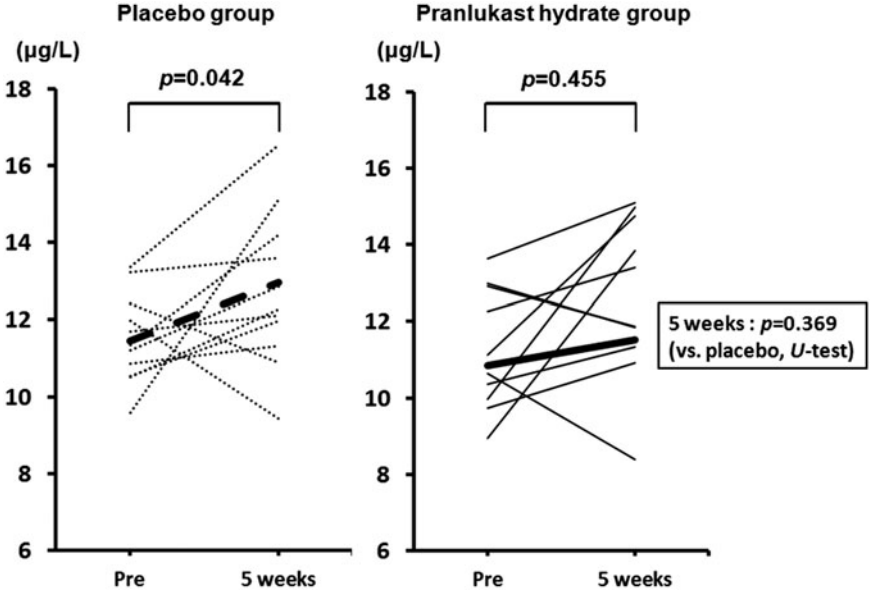

Figure 6. Changes of eosinophil cationic protein.

and found that PLK-DS inhibited an increase of ECP[27]. Although we demonstrated that PLK-DS suppressed inflammation and pollinosis symptoms, that study was not performed during the pollen season and did not confirm the effect of the drug on natural exposure to pollen. Also, prophylactic therapy is important in children as well as in adults, hence we considered it important to determine the efficacy of PLK-DS prophylaxis in children with pollinosis.

The pathogenesis of allergic rhinitis is considered to involve minimal chronic inflammation[31,32]. It is thought that repeated exposure to low levels of antigens causing no

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symptoms leads to chronic inflammation of the nasal mucosa. In fact, repeated out-of-season exposure of patients with seasonal allergic rhinitis to 1/100 of the antigen dose causing symptoms has been shown to increase histamine and ECP levels in nasal discharge[33]. It was also reported that symptom returned to baseline by 6 weeks after the pollen season, but the levels of interleukin-1, leukotriene, and ECP in nasal discharge remained high[34]. Assuming that patients have minimal chronic inflammation, we consider that initiation of prophylactic therapy with anti-inflammatory agents either before or early in the pollen season is a logical method to reduce the deterioration of symptoms and QoL during the pollen season.

The present placebo-controlled study demonstrated that PLK-DS prophylaxis is useful for children with pollinosis. As has been reported in adults[20–22], the nasal symptoms scores (especially for nasal obstruction) of the PLK-DS group were significantly lower than those of the placebo group. Since use of PLK-DS as prophylactic therapy in children with pollinosis delays the onset of nasal symptoms as it does in adults[22] and, thus, delays the deterioration of QoL and the need for symptomatic medication, this drug appears to be appropriate for prophylaxis because of its anti-inflammatory effect.

A limitation of this study was the small sample size, which was probably the reason for the few significant differences between the PLK-DS and placebo groups. Because the maximum number of patients who could fit in the pollen exposure chamber used in this study was 15 and it was important to test all subjects under similar conditions during the pollen season, we limited the number of subjects for this study. In the future, a larger multi-center, placebo-controlled, double-blind study should be performed to confirm the usefulness of PLK-DS as prophylactic therapy for JC pollinosis in children. Another limitation was that the dropout rate was rather high. The five dropouts were due to insufficient entries in the nasal allergy diary. Patients were instructed to make daily entries in this diary before bedtime about the most serious symptoms of that day. The method of evaluation was to calculate the weekly mean score and determine the change from the mean score of the first week. If entries were missed, it could have been possible to calculate the mean value from the remaining data. However, the severity of pollinosis is highly dependent on the amount of pollen dispersed in the atmosphere, and this varies from day to day. We, therefore, considered it inappropriate to calculate the mean score when data were missing.

Conclusion

In children with JC pollinosis, we demonstrated an inhibitory effect of PLK-DS on priming in the early pollen season, as well as inhibition of symptoms caused by controlled exposure to pollen and symptoms during the pollen season. PLK-DS was also shown to suppress an increase of ECP in nasal discharge, indicating an anti-inflammatory effect. The present findings suggested that pranlukast dry syrup may be useful for prophylaxis against pollinosis in children.

Transparency

Declaration of funding
There was no funding for this study.

Declaration of financial/other relationships
The authors have no specific relationships to declare. JDA Peer Reviewers have no relevant financial relationships to disclose.

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