

Pranlukast dry syrup inhibits symptoms of Japanese cedar pollinosis in children using OHIO Chamber

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ABSTRACT

Pranlukast (PLK) is a leukotriene receptor antagonist (LTRA) that has been approved for treatment of asthma in patients of all ages and allergic rhinitis (AR) in adults but not for AR in children in Japan. This randomized, double-blind, placebo-controlled, crossover study used an artificial exposure chamber (OHIO Chamber) to investigate the efficacy and safety of PLK in children from 10 to 15 years old with seasonal AR (SAR) due to Japanese cedar (JC) pollen. Eighty-four subjects were enrolled and randomized to the treatment arm and 74 were included in the per protocol set. Subjects received either PLK dry syrup (DS) or placebo for 1 week. They were challenged with JC pollen in the OHIO Chamber for 3 hours. Total nasal symptom scores (TNSSs) were recorded every 30 minutes during the exposure. PLK DS treatment suppressed the TNSS changes from baseline significantly when compared with placebo. The difference in the least square means in TNSS between the PLK DS-treated group and placebo group was -0.37 (95% CI, -0.54 , -0.20) with a value of $p < 0.0001$, showing that PLK DS significantly suppressed the nasal symptoms. Regarding specific nasal symptoms, PLK DS significantly suppressed sneezing, nasal discharge, and nasal obstruction. The effect of PLK DS on nasal obstruction was most prominent, with significant improvement relative to placebo beginning 60 minutes after the start of exposure. No serious adverse events were reported during the study. In this study, PLK DS is effective and safe for treatment in children with SAR.

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Allergic rhinitis (AR) is a chronic and prevalent disease, affecting not only adults but also school-age children in developed countries.¹ Airborne antigens, such as dust-mite allergens and Japanese cedar (JC) pollen, are significant contributors to AR in Japan. The recent increase in the prevalence rate of JC pollinosis has been significant, with approximately 26% of

the Japanese population affected.² The main symptoms are sneezing, nasal discharge, and nasal obstruction, which are not life-threatening but can be difficult to tolerate when more severe. These symptoms decrease patients' quality of life³ and reduce work and school performance in adults and children, respectively.^{4–7} Nasal obstruction, which can cause sleep disturbance, is the most bothersome symptom both in adults and in children.^{8–10}

Cysteinyl leukotrienes (CysLTs) C_4 , D_4 , and E_4 are metabolic products of arachidonic acid generated from not only mast cells but also eosinophils and basophils during allergic reactions, and they bind the CysLT₁ and CysLT₂ receptors.^{11,12} They cause bronchoconstriction, increase vascular permeability, and stimulate mucous glands, which induces tissue edema and hypersecretion.¹² In the human nasal mucosa, CysLT₁ receptors are expressed in the vascular endothelium and interstitial cells in the inferior turbinate as well as in leukocytes such as eosinophils, mast cells, macrophages, and neutrophils.¹³ Thus, CysLTs are major mediators in the pathogenesis of AR and contribute to its symptoms of sneezing, nasal discharge, and nasal obstruction.¹⁴ Treatment with CysLTs receptor antagonists (LTRAs) is considered to be effective in the management of AR.¹⁵

Pranlukast (PLK) was the first CysLT₁ antagonist to be approved in Japan for the treatment of asthma in

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adults and children and AR in adults.^{16,17} To our knowledge, no randomized, placebo-controlled studies have been published that assess the efficacy and safety of PLK or any other CysLT₁ antagonists in the treatment of AR in children, although a pediatric formula has been developed for pediatric use in asthma.¹⁸

The aim of this study was to investigate the efficacy and safety of PLK dry syrup (DS) in the treatment of seasonal AR (SAR) due to JC pollen in school-age children whose symptoms were induced in an artificial pollen exposure chamber (OHIO Chamber).

METHODS

Study Populations

Children who had JC pollinosis and were between the ages of 10 and 15 years were recruited in this study. The inclusion criteria were as follows: height of ≥ 130 cm and weight of ≥ 25 and < 65 kg; allergic symptoms, particularly nasal obstruction, during the pollen season for at least 2 years with a positive multiple antigen simultaneous test (class, ≥ 2) or positive skin test for JC pollen antigen; absence of abnormal findings on physical or blood examinations; and the ability to record symptoms in a diary.

The exclusion criteria were as follows: acute rhinitis, chronic rhinitis, congestive rhinitis, atrophic rhinitis, rhinosinusitis with purulent nasal discharge, nasal disease (nasal polyps and/or deviated nasal septum), nasal deformity, or adenoid hypertrophy that would interfere with evaluating the efficacy of the drug; allergic symptoms due to other allergens during the study period; severe allergic diseases including asthma, atopic dermatitis, and drug allergy; and surgery, including laser surgery, for the purpose of treating AR. Subjects who were considered ineligible by the physician in charge were excluded as well.

The following medications were prohibited throughout the study periods: antihistamines, LTRAs, oral or local steroids, biological preparations, anticholinergics, β_2 -stimulants, decongestants for nasal use, and herbal medicine for allergies.

This study was conducted in conformity with Good Clinical Practice guidelines and the Declaration of Helsinki of 1995 (as revised in Seoul in 2008). The study protocol was reviewed and approved by an independent Institutional Review Board of the Shinanozaka Clinic (Tokyo, Japan). Informed consent was obtained from the parent or the legal guardian of all subjects and informed assent was obtained from all the subjects before participation in the study.

Study Design and Protocol

This was a single-center, randomized, placebo-controlled, crossover comparative study conducted in the nonpollen season, from December 2010 to February 6,

2011. The study was completed before JC pollen started to disperse (February 15).

The study periods, shown in Fig. 1, consisted of observation (single-blind) and treatment periods (double blind), in which the subjects were exposed to a fixed concentration (8000 grains/m³) of JC pollen for 3 hours in a temperature- and humidity-controlled pollen exposure chamber (OHIO Chamber) as described elsewhere.^{19,20}

Each subject was instructed to grade and record the severity of their nasal obstruction in the OHIO Chamber every 30 minutes according to the severity criteria shown in Table 1. Every 30 minutes, subjects reported the number of times they sneezed and blew their noses. These results were evaluated using severity scoring criteria,² ranging from 0 to 4 as shown in Table 2. The total nasal symptoms score (TNSS) was the sum of the three recorded nasal scores.

During the observation period, which took place 1–4 weeks before first administration of the study drug, informed assent and consent were obtained from all subjects and their parents. Subjects were examined to confirm that they met the inclusion criteria and did not fulfill any of the exclusion criteria. The screening exposure in the OHIO Chamber was performed after subjects took placebo for 1 week in a single-blind fashion, to ensure they would respond adequately to the pollen stimulation and not respond to placebo treatment. Subjects were enrolled in the study only if one nasal symptom score was at least 1 point worse on one occasion during exposure compared with each score recorded before entering the chamber.

Eligible subjects were enrolled in the double-blind treatment period and randomized to receive PLK DS or identical placebo twice daily for 1 week (period 1) followed by a washout period of 7 days, and then crossed over to the other treatment period (period 2) for 7 days. The actual drug contained PLK DS and refined sucrose in a sachet. The external appearance of placebo was indistinguishable from that of the actual drug. The dosage of the study drug was determined based on each subject's weight according to the optimal dose of PLK DS used for pediatric asthma (about 7 mg/kg per day).²¹ Subjects were exposed to pollen in the OHIO Chamber at a concentration of 8000 grains/m³ for 3 hours on the last day of each treatment period (periods 1 and 2). The use of rescue drugs was not allowed during the treatment periods.

Efficacy

The TNSS was the sum of the subjects' self-rated scores of the three nasal symptoms (sneezing, nasal discharge, and nasal obstruction).

The primary efficacy endpoint was the sum of the mean score of each of the nasal symptom scores during exposure.

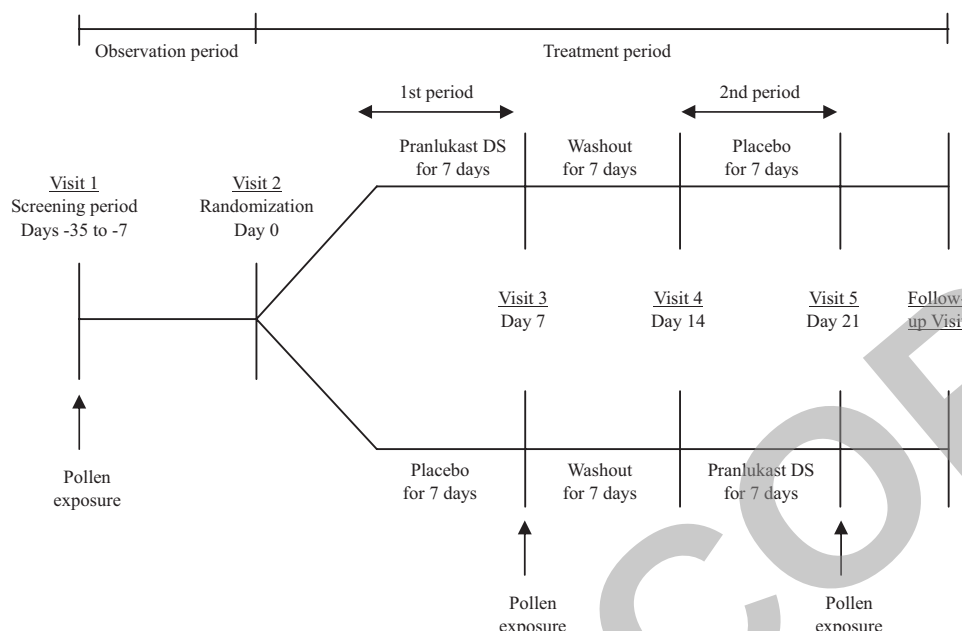


Figure 1. Study schedule. The study periods consisted of observation and treatment periods. The screening exposure in the OHIO Chamber was performed after subjects received placebo treatment for 1 week, to determine whether they would respond adequately to the pollen stimulation and not respond to placebo treatment. One inclusion criterion was that at least one nasal symptom score was at least 1 point worse during exposure than before subjects entered the chamber. Eligible subjects were enrolled in the treatment period and randomized to receive pramlukast dry syrup (PLK DS) or placebo for 1 week (period 1) followed by a washout period of 7 days, and then crossed over to the other treatment period (period 2) for 7 days. Subjects were exposed to pollen in the OHIO Chamber for 3 hours on the last day of each treatment period (periods 1 and 2).

Table 1 Severity of nasal obstruction

Severity	++++ (score 4)	+++ (score 3)	++ (score 2)	+ (score 1)	– (score 0)
	Completely obstructed	Severe nasal blockage causing prolonged oral breathing	Severe nasal blockage causing occasional oral breathing	Nasal blockage without oral breathing	No symptoms

Altered partially from the Japanese guidelines for allergic rhinitis² and the severity of nasal obstruction was judged during each 30-min period during exposure.

Table 2 Severity of sneezing and nasal discharge

Severity	++++ (score 4)	+++ (score 3)	++ (score 2)	+ (score 1)	– (score 0)
Sneezing	≥21 Times	20–11 Times	10–6 Times	5–1 Times	Below +
Nasal discharge	≥21 Times	20–11 Times	10–6 Times	5–1 Times	Below +

Sneezing: The number of times the subject sneezed during each 30-min period during exposure.

Nasal discharge: The number of times the subject blew his/her nose during each 30-min during exposure.

The secondary efficacy endpoints were the mean scores of each nasal symptom score during exposure and the TNSS and each nasal symptom score at each measurement point.

Safety

Safety was evaluated throughout the period of the study. All subjects were asked about their health status and any adverse reactions during the study period.

Statistical Analysis

Efficacy analyses were conducted using the per protocol set population, which included all randomized subjects who received study drugs and completed the entire study protocol.

Analysis of the primary efficacy endpoint, the ability of PLK DS to suppress the symptoms induced in the OHIO Chamber, was performed using an analysis of

Table 3 Subject characteristics

Parameter	Category	No. (%) of Patients
All		84
Gender, <i>n</i> (%)	Male	38 (45.2)
	Female	46 (54.8)
Age (yr)	mean $\pm$ SD	12.5 $\pm$ 1.6
	Range	10–15
Height (cm)	mean $\pm$ SD	154.20 $\pm$ 9.52
	Range	131.3–175.8
Weight (kg)	mean $\pm$ SD	44.18 $\pm$ 8.41
	Range	27.2–64.3
Severity*, <i>n</i> (%)	Mild	—
	Moderate	11 (13.1)
	Severe	44 (52.4)
	Most severe	29 (34.5)

*Severity was diagnosed based on the Japanese guidelines for allergic rhinitis.²

covariance model with treatment group, period, and sequence as factors and TNSS before entering into the OHIO Chamber as covariates in the model. Analysis of the secondary efficacy endpoint was also performed using an analysis of covariance model with treatment group, period, and sequence as factors and TNSS or each nasal symptom score before entering into the OHIO Chamber as covariates in the model. The 95% CI and the difference in the least square means were calculated.

Safety analyses included all randomized subjects who received at least one dose of study medication during a treatment period in double-blind fashion and was performed using the McNemar test.

The two-tailed significant level was 5% for the analysis of efficacy and safety.

RESULTS

A total of 215 children were recruited. Eighty-four subjects were enrolled and 74 completed the study. Four subjects discontinued the study because of acute upper respiratory disease, two for personal reasons, three for protocol deviation, and one based on the decision of a doctor in charge. The characteristics of subjects are shown in Table 3.

The time course of changes in TNSS during exposure is shown in Fig. 2. Beginning 30 minutes after the start of exposure (except for 60 and 150 minutes), at each measurement point the mean of the TNSS in the PLK DS group, adjusted by the TNSS before entering into the OHIO Chamber, was significantly lower than scores in the placebo group.

The mean TNSS score over the exposure time was 1.17 and 1.55 for the PLK DS-treated group and the placebo group, respectively (Table 4). The difference in

the least square means for TNSS between the PLK DS-treated group and placebo group was -0.37 (95% CI, -0.54 , -0.20), with a value of $p < 0.0001$, showing that PLK DS significantly suppressed the nasal symptoms induced by pollen exposure.

The time courses of the changes in each symptom during exposure are shown in Figs. 3, 4, and 5. PLK DS significantly suppressed sneezing, nasal discharge, and nasal obstruction. The effect of PLK DS on nasal obstruction was most prominent; this symptom showed a significantly lower score when compared with placebo beginning 60 minutes after the start of exposure.

The scores for sneezing and nasal discharge in the PLK DS-treated group were lower than those in the placebo group, with significant differences at measurement time points of 120 and 180 (sneezing) and 90 minutes (nasal discharge).

The differences in the least square means for the PLK DS and placebo groups were -0.06 (95% CI, -0.12 to -0.00) with a value of $p = 0.0339$ for sneezing, -0.08 (95% CI, -0.14 to -0.02) with a value of $p = 0.0133$ for nasal discharge, and -0.25 (95% CI, -0.36 to -0.14) with a value of $p < 0.0001$ for nasal obstruction (Table 4).

Safety

No serious side effects were found in this study and the safety profile was similar in both groups. Eight subjects reported side effects, four (4.8%) in the PLK DS group and four (4.9%) in the placebo group (Table 5). There was no significant difference between side effect prevalence in the two groups ($p = 1.0000$).

All side effects were mild and resolved without treatment.

DISCUSSION

The effectiveness and safety of PLK in capsule formulation has been demonstrated in randomized, double-blind trials in adult patients with asthma and AR.^{16,17,22,23} Although the efficacy of its DS formulation has been evaluated in pediatric patients aged >1 year with asthma,²¹ there have been no published randomized clinical studies on the treatment of pediatric AR. To our knowledge, this is the first randomized, double-blind, placebo-controlled, crossover study to demonstrate the efficacy of PLK DS on SAR and also the first trial using an allergen exposure chamber including school-age children in the world. This study showed that 1 week of PLK DS therapy was significantly superior to placebo in reducing the TNSS and suppressed not only sneezing and nasal discharge, but also nasal obstruction during pollen exposure. The safety profile was similar between PLK DS and placebo.

Although the number of SAR patients <10 years old is increasing in Japan,² we restricted the subjects' age range to between 10 and ≤ 15 years in this allergen exposure study because of ethical considerations. Children and

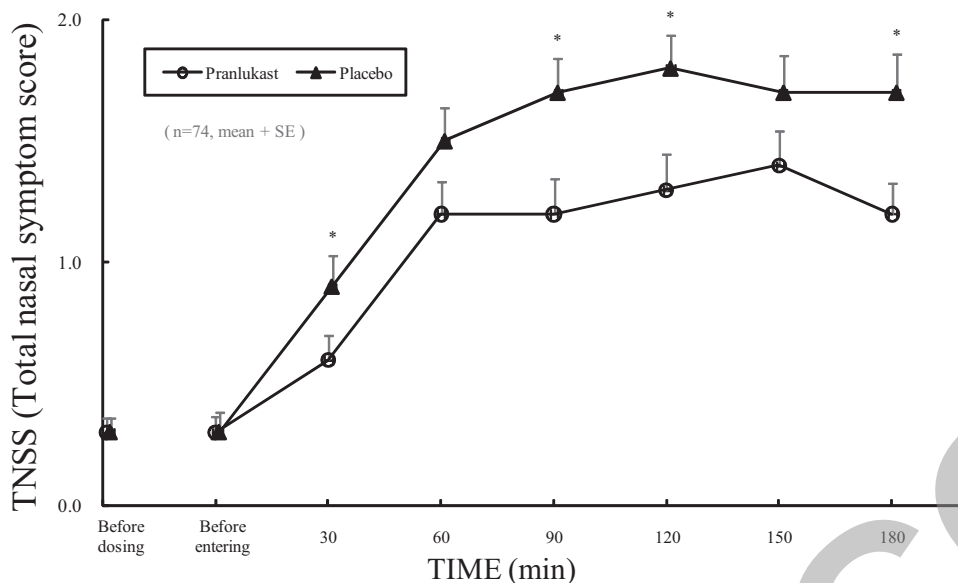


Figure 2. Time course of the total nasal symptom score (TNSS). The mean of the TNSS, adjusted by the TNSS before subjects entered the OHIO Chamber, is significantly lower in the pranlukast dry syrup (PLK DS) group than in the placebo group, beginning 30 minutes after the start of exposure (except 60 and 150 minutes; * $p < 0.05$).

Table 4 Summary statistics and difference of least square means for the nasal symptom score

Parameter		PLK DS (n = 74)	Placebo (n = 74)
Total nasal symptom score	Mean ± SD	1.17 ± 0.95	1.55 ± 0.98
	LS mean difference from placebo and 95% CI	-0.37 (-0.54, -0.20)	
	ANCOVA	p < 0.0001	
Sneezing score	Mean ± SD	0.18 ± 0.26	0.24 ± 0.29
	LS mean difference from placebo and 95% CI	-0.06 (-0.12, -0.00)	
	ANCOVA	p = 0.0339	
Nasal discharge score	Mean ± SD	0.30 ± 0.34	0.39 ± 0.37
	LS mean difference from placebo and 95% CI	-0.08 (-0.14, -0.02)	
	ANCOVA	p = 0.0133	
Nasal obstruction score	Mean ± SD	0.69 ± 0.58	0.92 ± 0.64
	LS mean difference from placebo and 95% CI	-0.25 (-0.36, -0.14)	
	ANCOVA [‡]	p < 0.0001	

ANCOVA = analysis of covariance; LS = least square; PLK DS = pranlukast dry syrup.

adults differ in terms of drug metabolism because of developmental differences in relevant organs. Pharmacokinetic profiles of PLK, however, are similar in children and adults²⁴ and also similar among children with different diseases.²⁵ The PLK DS dosage of about 7 mg/kg per day twice daily used in this study is valid because it is converted from the adult dose as a reference and is also used for the treatment of pediatric asthma in Japan.¹⁸ PLK DS is therefore a potentially effective treatment not only for children with SAR aged between 10 and ≤15 years, but also for those <10 years old.

A multicenter, double-blind, comparative study with epinastine for perennial AR showed that PLK was significantly more effective than epinastine in relieving total nasal symptoms, especially in reducing nasal obstruction.²² One small study of treatment for adults with SAR showed the superiority of PLK in the reduction of nasal

symptom scores and significant suppression of nasal obstruction when compared with a second-generation antihistamine.²⁶ Therefore, PLK was at least as effective as some second-generation antihistamines for adults with AR in terms of total nasal symptoms and nasal obstruction.

The result of our study was consistent with that of the allergen challenge study conducted by Keskin *et al.*,²⁷ who showed the superiority of montelukast, another LTRA, in significant suppression of nasal obstruction in children with grass pollen-induced AR. Additionally, our study indicated that PLK DS was effective for not only nasal obstruction but also sneezing and nasal discharge in children with SAR, as also shown in studies of adults with SAR.^{28–31}

The efficacy of LTRAs in children with AR seems to be equivalent to that in adults with AR. Application of LTD₄

Figure 3. Time course of the sneezing score. The mean of the sneezing score, adjusted by the sneezing score before subjects entered the OHIO Chamber, is significantly lower in the pranlukast dry syrup (PLK DS) group than in the placebo group at 120 and 180 minutes after the start of exposure (* $p < 0.05$).

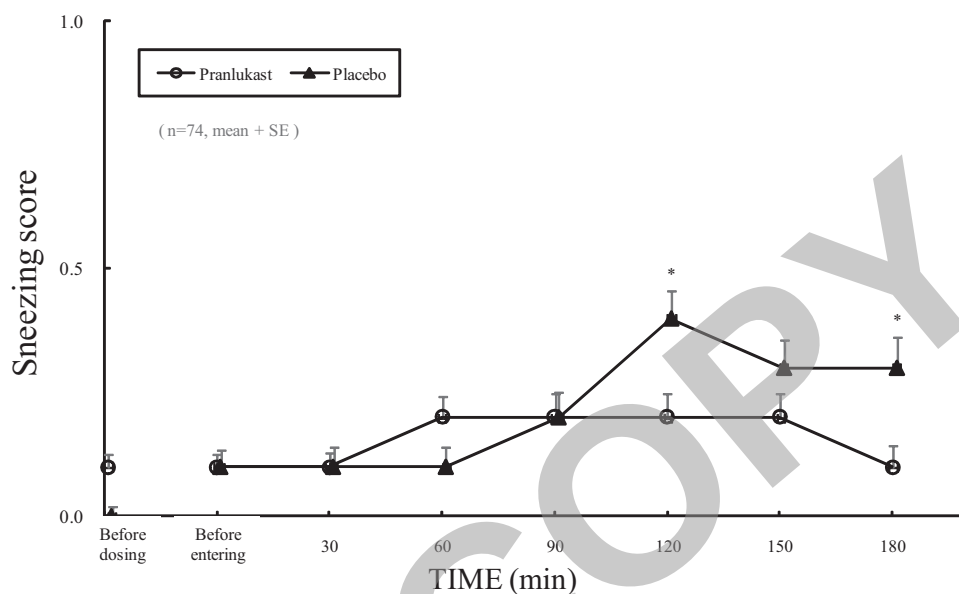
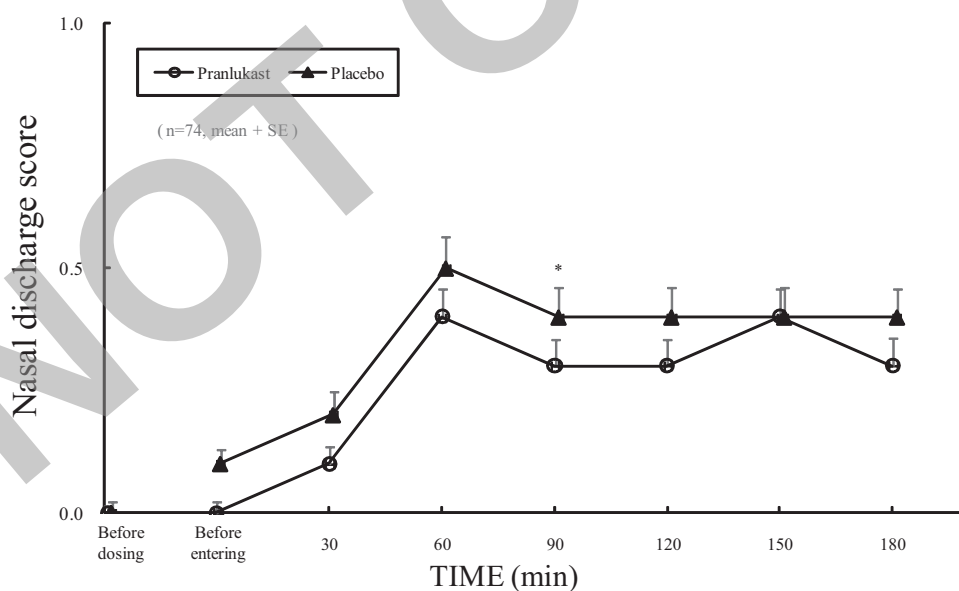


Figure 4. Time course of the nasal discharge score. The mean of the nasal discharge score, adjusted by the nasal discharge score before subjects entered the OHIO Chamber, is significantly lower in the pranlukast dry syrup (PLK DS) group than in the placebo group at 90 minutes after the start of exposure (* $p < 0.05$).



directly to the nasal mucosa in adult patients with AR significantly increased nasal secretion.³² CysLTs might therefore have the ability to stimulate mucous glands, resulting in hyper-rhinorrhea during allergen exposure. Although CysLTs do not directly stimulate the sensory nerves that induce sneezing, a reduction in sneezing has been shown in clinical trials of adult patients with AR. The mechanism underlying this suppression of sneezing has not been identified.

Although several pediatric studies demonstrated the efficacy of PLK DS in the treatment of asthma,²⁴ there is no literature on pediatric patients with JC pollinosis in Japan. One reason is because it is difficult to conduct a double-blind, placebo-controlled study of pediatric SAR patients in pollen season may be the challenge of obtaining precise self-ratings of subjects' nasal symptoms, es-

pecially nasal obstruction, and compliance in keeping an allergy diary every day. Data on severity of sneezing and nasal discharge could substitute for that on the frequency of sneezing and nose blowing, but nasal obstruction is a subjective symptom that may be difficult for children to recognize and self-rate in daily life. We therefore decided to conduct this study using the OHIO Chamber, in which subjects were exposed to constant concentrations of JC pollen in a stable environment. A precise evaluation of subjects' nasal symptoms was obtained by chamber staff observing from outside the chamber throughout the exposure.

AR is known to have a large negative impact on school performance and daily life, such as impaired learning or sleep disturbance.^{8,33,34} Obstructive sleep apnea syndrome (OSAS) is a sleep disorder that affects approxi-

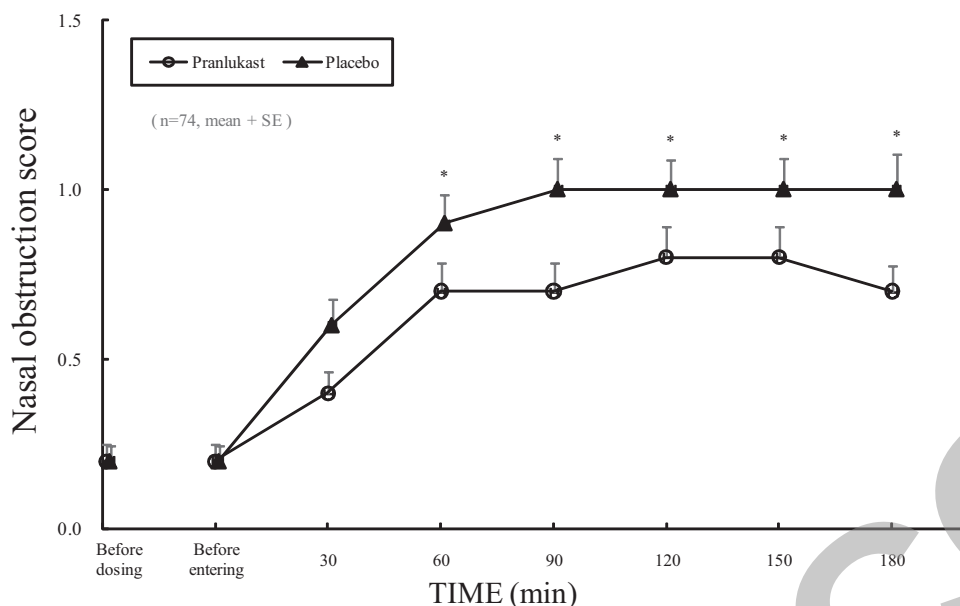


Figure 5. Time course of the nasal obstruction score. The mean of the nasal obstruction score, adjusted by the nasal obstruction score before subjects entered the OHIO Chamber, is significantly lower in the pramlukast dry syrup (PLK DS) group than in the placebo beginning 60 minutes after the start of exposure (* $p < 0.05$).

Table 5 Summary of safety

	PLK DS ($n = 83$)	Placebo ($n = 82$)	McNemar Test
Patients with adverse events regardless of relationship to study drug	12 (14.5%)	10 (12.2%)	$p = 1.0000^* \text{ NS}$
Patients with side effects	4 (4.8%)	4 (4.9%)	$p = 1.0000^* \text{ NS}$

There was no significant difference between PLK DS and placebo administration in terms of adverse events regardless of relationship to study drug and side effects.
 $*p \geq 0.05$.
 NS = not significant, PLK DS = pramlukast dry syrup.

mately 2% of all children.³⁵ Although AR is a risk factor for pediatric OSAS, increased upper airway resistance due to nasopharyngeal lymphoid (adenoid) hypertrophy is its most common cause.^{36,37} Interestingly, a recent study demonstrated that LT and their receptors were increased in adenotonsillar tissue in children with OSAS, and that LTRA treatment induced significant reductions in adenoid size and sleep disturbances.³⁸ Kaditis *et al.* examined the expression pattern of CysLT₁ receptor, CysLT₂ receptor, and T lymphocytes, and proposed that the expression of CysLT₁ and CysLT₂ receptor in tonsillar tissue during childhood might be the result of allergic sensitization and could promote sleep disturbances by causing pharyngeal lymphoid tissue enlargement.³⁹ Therefore, an antagonist action with PLK on the CysLT₁ receptor in adenoid tissue results in a reduction in adenoid size.

The report of 4-week PLK administration in 12 patients with perennial AR demonstrated a marked suppression of eosinophil infiltration in the PLK-treated patients.⁴⁰ This pharmacological action might also have contributed to the improvement of nasal symptoms a few hours after

the onset of pollen exposure in our study, since 1-week administration of PLK DS might suppress the eosinophil infiltration in autocrine fashion.

In conclusion, this is the first study to demonstrate the efficacy of PLK DS for the treatment of children with SAR exacerbated by exposure to JC pollen in an OHIO Chamber. Treatment with PLK DS twice daily for 1 week resulted in significant relief of the nasal symptoms of SAR induced by exposure to JC pollen in an OHIO Chamber. Additional studies in the natural condition are needed, but our results support the use of PLK DS in treating SAR in children in clinical settings as in adults. No serious adverse events were observed, and adverse effect profiles were similar between PLK DS- and placebo-treated groups in this study.

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REFERENCES

1. Bousquet J, Kkhaltaev N, Cruz AA, et al. Allergic Rhinitis and Its Impact on Asthma (ARIA) 2008 update (in collaboration

- with the World Health Organization, GA(2)LEN and AllerGen). *Allergy* 63(suppl 86):8–160, 2008.
2. Okubo K, Kurono Y, Fujieda S, et al. Japanese guideline for allergic rhinitis. *Allergol Int* 60:171–189, 2011.
 3. Leynaert B, Neukirch C, Liard R, et al. Quality of life in allergic rhinitis and asthma. A population-based study of young adults. *Am J Respir Crit Care Med* 162:1391–1396, 2000.
 4. Blaiss MS. Allergic rhinitis and impairment issues in schoolchildren: A consensus report. *Curr Med Res Opin* 20:1937–1952, 2004.
 5. Burton WN, Conti DJ, Chen CY, et al. The impact of allergies and allergy treatment on worker productivity. *J Occup Environ Med* 43:64–71, 2001.
 6. Blaiss MS. Allergic rhinitis: Direct and indirect costs. *Allergy Asthma Proc* 31:375–380, 2010.
 7. Lamb CE, Ratner PH, Johnson CE, et al. Economic impact of workplace productivity losses due to allergic rhinitis compared with select medical conditions in the United States from an employer perspective. *Curr Med Res Opin* 22:1203–1210, 2006.
 8. Craig TJ, McCann JL, Gurevich F, et al. The correlation between allergic rhinitis and sleep disturbance. *J Allergy Clin Immunol* 114(suppl):S139–S145, 2004.
 9. Meltzer EO, Blaiss MS, Derebery MJ, et al. Burden of allergic rhinitis: Results from the Pediatric Allergies in America survey. *J Allergy Clin Immunol* 124(suppl):S43–S70, 2009.
 10. Meltzer EO, Nathan R, Derebery J, et al. Sleep, quality of life, and productivity impact of nasal symptoms in the United States: Findings from the Burden of Rhinitis in America survey. *Allergy Asthma Proc* 30:244–254, 2009.
 11. Figueroa DJ, Borish L, Baramki D, et al. Expression of cysteinyl leukotriene synthetic and signalling proteins in inflammatory cells in active seasonal allergic rhinitis. *Clin Exp Allergy* 33: 1380–1388, 2003.
 12. Peters-Golden M, Gleason MM, and Togias A. Cysteinyl leukotrienes: Multi-functional mediators in allergic rhinitis. *Clin Exp Allergy* 36:689–703, 2006.
 13. Shirasaka H, Kanaizumi E, Watanabe K, et al. Expression and localization of the cysteinyl leukotriene 1 receptor in human nasal mucosa. *Clin Exp Allergy* 32:1007–1012, 2002.
 14. Peters-Golden M, and Henderson WR Jr. The role of leukotrienes in allergic rhinitis. *Ann Allergy Asthma Immunol* 94:609–618, 2005.
 15. Shirasaka H. Cysteinyl leukotriene receptor CysLT1 as a novel therapeutic target for allergic rhinitis treatment. *Expert Opin Ther Targets* 12:415–423, 2008.
 16. Fujimura M, Sakamoto S, Kamio Y, et al. Effect of a leukotriene antagonist, ONO-1078, on bronchial hyperresponsiveness in patients with asthma. *Respir Med* 87:133–138, 1993.
 17. Okuda M, Unno T, Wada T, et al. Clinical study of leukotriene antagonist ONO-1078 (pranlukast hydrate), on perennial allergic rhinitis. A double-blind, dose finding study (late phase II study) [in Japanese]. *Otologia Fukuoka* 43:631–657, 1997.
 18. Mikawa H, Baba M, and Nakashima M. Clinical usefulness of a leukotriene antagonist; pranlukast dry syrup on pediatric bronchial asthma in multi-center comparative double-blind clinical study with oxatamide dry syrup [in Japanese]. *Rinsho Iyaku* 13:423–456, 1997.
 19. Hashiguchi K, Tang H, Fujita T, et al. Validation study of the OHIO Chamber in patients with Japanese cedar pollinosis. *Int Arch Allergy Immunol* 149:141–149, 2009.
 20. Hashiguchi K, Tang H, Fujita T, et al. Preliminary study on Japanese cedar pollinosis in an artificial exposure chamber (OHIO Chamber). *Allergol Int* 56:125–130, 2007.
 21. Mikawa H, and Baba M. Efficacy and safety of a leukotriene antagonist; ONO-1078 dry syrup, on pediatric bronchial asthma–dose finding study in a multi-center, open trial [in Japanese]. *Rinsho Iyaku* 13:395–342, 1997.
 22. Okuda M, Kataura A, Togawa K, et al. Clinical evaluation of Leukotriene antagonist; ONO-1078 (pranlukast hydrate), on perennial allergic rhinitis: A double-blind, comparative study with epinastine hydrochloride (Phase III study) [in Japanese]. *Otologia Fukuoka* 44:47–72, 1998.
 23. Gotoh M, Suzuki H, and Okubo K. Delay of onset of symptoms of Japanese cedar pollinosis by treatment with a leukotriene receptor antagonist. *Allergol Int* 60:483–489, 2011.
 24. Keam SJ, Lyseng-Williamson KA, and Goa KL. Pranlukast: A review of its use in the management of asthma. *Drugs* 63:991–1019, 2003.
 25. Nakade S, Ueda S, Ohno T, et al. Population pharmacokinetics of pranlukast hydrate dry syrup in children with allergic rhinitis and bronchial asthma. *Drug Metab Pharmacokinet* 21:133–139, 2006.
 26. Sagara H, Yukawa T, Kashima R, et al. Effects of pranlukast hydrate on airway hyperresponsiveness in non-asthmatic patients with Japanese cedar pollinosis. *Allergol Int* 58:277–287, 2009.
 27. Keskin O, Alyamac E, Tuncer A, et al. Do the leukotriene receptor antagonists work in children with grass pollen-induced allergic rhinitis? *Pediatr Allergy Immunol* 17:259–268, 2006.
 28. Okubo K, and Baba K. A double-blind non-inferiority clinical study of montelukast, a cysteinyl leukotriene receptor 1 antagonist, compared with pranlukast in patients with seasonal allergic rhinitis. *Allergol Int* 57:383–390, 2008.
 29. Philip G, Malmstrom K, Hampel FC, et al. Montelukast for treating seasonal allergic rhinitis: A randomized, double-blind, placebo-controlled trial performed in the spring. *Clin Exp Allergy* 32:1020–1028, 2002.
 30. Sasaki K, Okamoto Y, Yonekura S, et al. Cedar and cypress pollinosis and allergic rhinitis: Quality of life effects of early intervention with leukotriene receptor antagonists. *Int Arch Allergy Immunol* 149:350–358, 2009.
 31. van Adelsberg J, Philip G, LaForce CF, et al. Randomized controlled trial evaluating the clinical benefit of montelukast for treating spring seasonal allergic rhinitis. *Ann Allergy Asthma Immunol* 90:214–222, 2003.
 32. Okuda M, Watase T, Mezawa A, et al. The role of leukotriene D4 in allergic rhinitis. *Ann Allergy* 60:537–540, 1988.
 33. Simons FE. Learning impairment and allergic rhinitis. *Allergy Asthma Proc* 17:185–189, 1996.
 34. Walker S, Khan-Wasti S, Fletcher M, et al. Seasonal allergic rhinitis is associated with a detrimental effect on examination performance in United Kingdom teenagers: Case-control study. *J Allergy Clin Immunol* 120:381–387, 2007.
 35. Ali NJ, Pitson DJ, and Stradling JR. Snoring, sleep disturbance, and behaviour in 4–5 year olds. *Arch Dis Child* 68:360–366, 1993.
 36. Katz ES, and D'Ambrosio CM. Pediatric obstructive sleep apnea syndrome. *Clin Chest Med* 31:221–234, 2010.
 37. Lipton AJ, and Gozal D. Treatment of obstructive sleep apnea in children: Do we really know how? *Sleep Med Rev* 7:61–80, 2003.
 38. Goldbart AD, Goldman JL, Veling MC, et al. Leukotriene modifier therapy for mild sleep-disordered breathing in children. *Am J Respir Crit Care Med* 172:364–370, 2005.
 39. Kaditis AG, Ioannou MG, Chaidas K, et al. Cysteinyl leukotriene receptors are expressed by tonsillar T cells of children with obstructive sleep apnea. *Chest* 134:324–331, 2008.
 40. Ueda T, Takeno S, Furukido K, et al. Leukotriene receptor antagonist pranlukast suppresses eosinophil infiltration and cytokine production in human nasal mucosa of perennial allergic rhinitis. *Ann Otol Rhinol Laryngol* 112:955–961, 2003. □

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