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ORIGINAL ARTICLE

A Double-Blind Non-inferiority Clinical Study of Montelukast, a Cysteinyl Leukotriene Receptor 1 Antagonist, Compared with Pranlukast in Patients with Seasonal Allergic Rhinitis

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ABSTRACT

Background: During the course of development of montelukast, a cysteinyl leukotriene receptor 1 antagonist, for treatment of seasonal allergic rhinitis, a double-blind, non-inferiority study was carried out to evaluate the efficacy and safety of montelukast 5 mg and 10 mg compared with pranlukast 450 mg, which has a similar mechanism of action.

Methods: Montelukast 5 mg, 10 mg or pranlukast 450 mg and the corresponding placebo were orally administered to patients with seasonal allergic rhinitis three times a day for 2 weeks. Non-inferior efficacy of montelukast 5 mg and 10 mg to pranlukast 450 mg was investigated by the change from the baseline in the composite nasal symptoms scores over the 2-week treatment period.

Results: Montelukast 5 mg, 10 mg once daily and the pranlukast 450 mg/day showed significant improvements in the change from the baseline in the composite, daytime and nighttime nasal symptom scores, and the improvement lasted for 2 weeks. Montelukast 5 mg and 10 mg were non-inferior to pranlukast 450 mg in the change from the baseline in the composite nasal symptoms scores. The incidence rates of adverse experiences and drug-related adverse experiences were not significantly different among the three treatment groups.

Conclusions: The results indicate that administration of montelukast 5 mg and 10 mg once daily are potent alternatives for the treatment of seasonal allergic rhinitis and demonstrated that the efficacy and the safety profiles are comparable with pranlukast 450 mg/day.

KEY WORDS

comparative double blind study, cysteinyl leukotriene receptor, montelukast, pranlukast, seasonal allergic rhinitis

INTRODUCTION

Montelukast sodium (montelukast) is a cysteinyl leukotriene receptor 1 ($CysLT_1$) specific antagonist that has been developed primarily for the treatment of bronchial asthma.[1] Montelukast is used for adult and pediatric patients with bronchial asthma in a number of countries including Japan. Cysteinyl leukotrienes (CysLT) and the related substances are physiologically active chemical mediators that also play an important role in the pathogenesis of allergic rhinitis. Since montelukast has been expected to be effective not only for the treatment of bronchial asthma but also for improving symptoms associated with allergic rhinitis based on its mechanisms of actions, its clinical development was initiated. It has been reported that pranlukast hydrate (pranlukast), a selective antagonist against $CysLT_1$ receptors like montelukast,

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Table 1 Patient demographics and other baseline characteristics

Treatment group	Montelukast 5 mg	Montelukast 10 mg	Pranlukast
Efficacy assessment	461	454	456
Gender			
Male	219 (47.5)	209 (46.0)	211 (46.3)
Female	242 (52.5)	245 (54.0)	245 (53.7)
Age (years)			
Mean ± SD	33.8 ± 10.3	34.9 ± 10.4	34.3 ± 9.5
Body weight (kg)			
Mean ± SD	60.5 ± 11.5	59.9 ± 11.2	59.6 ± 9.9
Disease type			
Seasonal	289 (62.7)	299 (65.9)	305 (66.9)
Seasonal + Perennial	172 (37.3)	155 (34.1)	151 (33.1)
Duration of allergic rhinitis (years)			
Mean ± SD	13.2 ± 7.5	13.7 ± 7.1	13.5 ± 7.7
Specific IgE-antibodies			
Only cedar ≥ 2	211 (45.8)	212 (46.7)	225 (49.3)
≥ 2 types: ≥ 2 antibodies	250 (54.2)	242 (53.3)	231 (50.7)
Baseline symptoms scores (Mean ± SD)			
Composite nasal symptom scores	2.00 (0.55)	2.03 (0.56)	2.02 (0.58)
Daytime nasal symptom scores	2.41 (0.59)	2.43 (0.60)	2.44 (0.61)
Nighttime nasal symptom scores	1.59 (0.66)	1.63 (0.65)	1.60 (0.69)

Number of patients (%).

was efficacious for alleviating nasal congestion, nasal discharge and sneezing in rhinitis patients.[2] It has been stated in the Practical Guideline for the Management of Allergic Rhinitis in Japan[3,4] that leukotriene receptor antagonists are effective primarily for the treatment of moderate to severe nasal congestion-type allergic rhinitis. In particular, they are more efficacious against nasal congestion than the second-generation antihistamines and are as effective as the second-generation antihistamines against sneezing and nasal discharge.[3,4] At present, pranlukast is the only leukotriene receptor antagonist that has been approved for allergic rhinitis, and it has been also known that pranlukast exerts antagonistic actions against leukotriene (LT) C_4, D_4 and E_4 receptors.[2]

Clinical studies of montelukast have been conducted overseas in patients with seasonal and perennial allergic rhinitis and its usefulness was demonstrated.[5] As a result, its indications and usage for allergic rhinitis have been granted in a number of countries. Also, the incidence of complications of allergic rhinitis in patients with bronchial asthma is fairly high[6] and morbidity has been rising in Japan. The clinical development of montelukast has been initiated in an attempt to determine indications and usage for allergic rhinitis, and in the previous study conducted in patients with seasonal allergic rhinitis[7] using placebo as a control drug, it has been already demonstrated that montelukast was effective and safe for oral administration of montelukast 5 mg or 10 mg once daily at bedtime for two weeks. Thus, we conducted a double blind non-inferiority study of montelukast using pranlukast, as a control drug with a similar leukotriene receptor antagonist to evaluate the efficacy and the safety of montelukast in patients with seasonal allergic rhinitis.

METHODS

PATIENTS

The demographics and other baseline characteristics of 1375 patients (1371 patients for efficacy analysis), treated with montelukast 5-mg, 10-mg tablets (Banyu Pharmaceutical Co., Ltd.), or pranlukast 112.5-mg capsules (Ono Pharmaceutical Co., Ltd.) are described in Table 1. Patients were treated as out patients at 19 institutions. The seasonal allergic rhinitis patients who fulfilled the inclusion criteria are listed as follows: (1) quantitative analysis of specific IgE antibody (UniCAP-RAST) revealed scores ≥2 points (IgE antibody containing antibodies against pollen scattered between February and April, 2004); (2) a past history of typical seasonal allergic rhinitis at least for the past two years; (3) age: between 15 and 65 years (male or female); (4) the following three criteria fulfilled for symptoms.[3,4] [(1) daytime nasal congestion scores ≥2 points per day, as an average (total ≥6 points), (2) total scores of daytime nasal symptoms (sneezing attack, nasal discharge and nasal congestion during the daytime) ≥4 points per day, as an average (total ≥12 points) and (3) total scores of

Table 2 Severity of daytime nasal symptoms (DNSS)

Types	Severity				
	++++	+++	++	+	−
Sneezing	= 21 times	11−20 times	6−10 times	1−5 times	None
Nasal discharge (Frequencies)	= 21 times	11−20 times	6−10 times	1−5 times	None
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

If scored, ++++: 4-points, +++: 3-points, ++: 2-points, +: 1-point, −: 0-point.

Daytime symptoms: after rising until bedtime.

Adapted from the Practical Guideline for the Management of Allergic Rhinitis in Japan, 2002 edition (the Fourth Revised Edition).[5]

Table 3 Severity of nighttime nasal symptoms (NNSS)

Types	Severity				
	++++	+++	++	+	−
Difficulty in falling asleep	Unable to sleep at all	Very bad	Bad	Slightly bad	Not at all
Nasal congestion at night	Severe nasal congestion with persistent oral-breathing	Persistent nasal congestion with oral-breathing	Nasal congestion occasionally bothered	Nasal congestion (+), but not bothering	No nasal congestion
Awakening at night	= 4 times	3 times	2 times	Once	None

If scored, ++++: 4-points, +++: 3-points, ++: 2-points, +: 1-point, −: 0-point.

Nighttime symptoms: after bedtime until rising the following morning.

nighttime nasal symptoms (difficulties in falling into sleep, nasal congestion at night, and degree of awakening at night) ≥ 2 points per day, as an average (total ≥ 6 points)] (Table 2, 3). The study was performed when the patients fulfilled these two inclusion criteria. The patients with nasal disorders that might interfere with the efficacy assessment, or those using drugs that might interfere with the efficacy assessment were excluded from the study. Patients who used any drug that might affect efficacy assessment in the study within 2 weeks prior to the observation period such as anti-histamines, leukotriene receptor antagonists, anti-thromboxane A_2 drugs, chemical mediator release inhibitors, Th2 cytokine inhibitors, corticosteroids (topical and systemic), vasoconstrictors, parasympathetic nerve blockers (anticholinergic), biological preparations (histamine-containing immunoglobulin), tranquilizers (antidepressants, anti-psychotics, and CNS suppressants), and other drugs with similar pharmacological activities to the above-mentioned drugs (herbal medications that are expected to have anti-allergic patients with uncontrolled mild to moderate symptoms). Patients with severe bronchial asthma were also excluded from the study.

DOSAGE AND ADMINISTRATION

Montelukast sodium 5-mg/10-mg tablets and the corresponding placebo tablets were administered orally once daily (one tablet per day) at bedtime for two weeks. Pranlukast hydrate 112.5-mg capsule, a control drug, and the corresponding placebo capsule were administered orally twice daily, after breakfast (2 capsules) and after dinner (2 capsules).

STUDY DESIGN

The study was a multiple center, randomized, double blind non-inferiority study, compared with pranlukast and conducted during the spring season of 2005. The study period consisted of a 4-day run-in period and a two-week treatment period. The treatment period was determined by the previous overseas results that showed that montelukast reached its almost maximal therapeutic effect, compared with placebo within 2 weeks.[5] The patients were randomized to a 1 : 1 : 1 ratio to receive either montelukast 5 mg, 10 mg, or pranlukast 450 mg groups (total six patients in one block) by the permuted-block method. The study protocol was approved by each institutional review board, and all patients gave written informed consent to participate. The patients who fulfilled the inclusion criteria were enrolled after the informed consent to

Table 4 Composite nasal symptom scores (CNSS)

Treatment group	N	Mean Scores		Changes from baseline				
		Baseline	Post-treatment	Mean	SD	LS mean	95% Confidence interval	*P* value†
Montelukast 5 mg group	461	2.00	1.80	− 0.20	0.58	− 0.19	(− 0.25, − 0.14)	0.000
Montelukast 10 mg group	454	2.03	1.83	− 0.20	0.59	− 0.19	(− 0.25, − 0.13)	0.000
Pranlukast 450 mg group	456	2.02	1.80	− 0.22	0.59	− 0.20	(− 0.26, − 0.14)	0.000

†Mean for the 2-week treatment period compared with the baseline value (based on ANCOVA model which contains the treatment group, study site and day of randomization as factors and the baseline as a covariate).

Table 5 Comparison of composite nasal symptom scores (CNSS) between the treatment groups

Comparison between groups	Difference in changes (LS mean)	95% confidence interval for differences†
Montelukast 10 mg group − Pranlukast 450 mg group	0.01	(− 0.0587, 0.0788)
Montelukast 5 mg group − Pranlukast 450 mg group	0.01	(− 0.0619, 0.0752)
Montelukast 10 mg group − Montelukast 5 mg group	0.00	(− 0.0651, 0.0719)

†Δ=0.085. Non-inferiority was tested via a stepped down procedure.

participate in this study was obtained. Nasal symptoms based on physical examinations and rhinitis-diaries were checked at each patient visit. Clinical and laboratory examinations were performed to assess the safety at the time of initiation of the therapy and at week-2 of treatment or at the time of discontinuation.

EVALUATION OF EFFICACY AND SAFETY

As a primary endpoint, the daily means of the composite nasal symptom scores (CNSS) (average of nasal symptom scores during the daytime and the nighttime) over the 2 week treatment period, were compared with those during the run-in period. As secondary endpoints, the following symptoms were investigated: (1) daytime nasal symptoms scores (DNSS) (mean score of nasal congestion, nasal discharge and sneezing), (2) nighttime nasal symptoms scores (NNSS) (mean score of severity of nasal congestion at night, difficulty in falling asleep and degree of awakening at night), (3) composite nasal congestion scores (mean of nasal congestion scores during the day and at night). The patient's and investigator's impressions (both assessed by a 6-point rating scale) were assessed with regard to the efficacy. The use of CNSS, DNSS and NNSS as the primary and secondary endpoints have been recommended in the Guidance for Industry, Allergic Rhinitis: Clinical Development for Programs for Drug Products (FDA CDER, www.fda.gov/cder/guidance/2718dft.htm, last updated on March 08, 2001).

Clinical and laboratory adverse experiences were investigated. The drug-related adverse experiences were also evaluated.

STATISTICAL ANALYSIS

The full analysis set (FAS) was defined as the primary efficacy analysis population. Comparison of the change from baseline over 2 weeks in the CNSS between treatment groups was performed using an analysis of covariance (ANCOVA) model which confains the treatment group, study site and day of randomization as factors and the baseline as a covariate. Non-inferiority of montelukast to pranlukast was evaluated using the two-sided 95% upper confidence limit of the between-group difference in LS (least square) means of the change from the baseline in the CNSS (non-inferiority margin, Δ = 0.085). A step-down procedure was used in demonstrating the non-inferiority (i.e. if non-inferiority is demonstrated in montelukast 10 mg then montelukast 5 mg is evaluated). The patient's and investigator's impressions were analyzed (the percentage of 'much improved' and 'improved') using a Pearson's chi-square test with step-down procedure. Significance level in this study is two-sided 5%.

The incidences of adverse experiences (AE) and drug related AE as well as their 95% confidence intervals were calculated, and these were compared using Fisher's exact test.

RESULTS

A total of 1375 patients were randomized (462, 457 and 456 patients for the montelukast 5 mg, 10 mg and

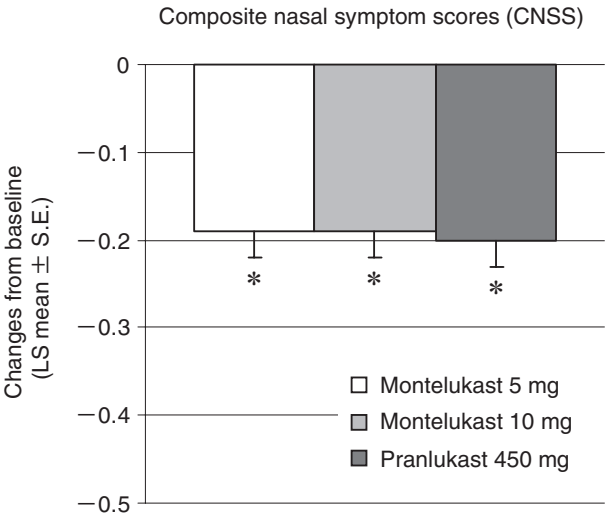

Fig. 1 Mean of composite nasal symptom Scores for the 2-week treatment period. * $p < 0.05$ compared with baseline.

pranlukast 450 mg groups, respectively), and 1371 patients completed the study, and were subjected to FAS for efficacy analysis, while 4 patients (one and three patients for montelukast 5 mg and 10 mg, respectively) discontinued the study. All 1375 patients were subjected to the safety analysis. The demographics and other baseline characteristics of the 1371 patients included in the efficacy analysis were described in Table 1. There were no clinically significant differences of the baseline patient characteristics among the three groups.

EFFICACY ANALYSIS

As shown in Figure 1 and described in Table 4, 5, the change from the baseline (LS mean ± SE) in the CNSS over 2 weeks for each treatment group is shown in Figure 1. The LS mean changes from the baseline in the CNSS over 2 weeks were –0.19, –0.19 and –0.20 points for the montelukast 5 mg, 10 mg and pranlukast 450 mg, respectively, demonstrating significant improvements compared to the baseline ($P <$ 0.001 for all three groups).

The difference in LS mean for the change between the two groups (montelukast 10 mg – pranlukast 450 mg) was 0.01 point with a 95% confidence intervals (CI) (–0.0587, 0.0788) point. Since the 95% upper confidence limit of the difference was less than the non-inferiority margin (Δ = 0.085), the non-inferiority of montelukast 10 mg to pranlukast 450 mg was demonstrated. In addition, there was no significant difference between montelukast 10 mg and pranlukast 450 mg.

Similarly the between-group difference (montelukast 5 mg – pranlukast 450 mg) was 0.01 point with a 95% CI (–0.0619, 0.0752) point. Thus, the non-inferiority of montelukast 5 mg to pranlukast 450 mg was demonstrated. In addition, there was no significant difference among the three groups.

The changes in the mean DNSS and DNSS constituents for the 2-week treatment period from the baseline (LS mean ± SE) are shown in Figure 2. The changes in the mean DNSS for the 2-week treatment period from the baseline (LS mean) were –0.17, –0.16 and –0.20 points for the montelukast 5 mg, 10 mg and pranlukast 450 mg groups, respectively, demonstrating significant improvements compared to the baseline ($P <$ 0.001 for all three groups).

As for each component of the nasal symptom scores, the changes in the mean daytime nasal congestion scores for the 2-week treatment period from the baseline (LS mean) were –0.29, –0.26 and –0.31 points for the montelukast 5 mg, 10 mg and pranlukast 450 mg groups, respectively, demonstrating significant improvements compared to the baseline ($P <$ 0.001 for all three groups).

The changes in the mean nasal discharge scores for the 2-week treatment period from the baseline (LS mean) were –0.07, –0.07 and –0.10 points for the montelukast 5 mg, 10 mg and pranlukast 450 mg groups, respectively, demonstrating significant improvements compared to the baseline for the montelukast 10 mg and pranlukast 450 mg groups (P = 0.046 and P = 0.010 for montelukast 10 mg and pranlukast 450 mg groups, respectively), although there was no significant difference between the montelukast 5 mg group and the baseline.

The changes in the mean sneezing attack scores for the 2-week treatment period from the baseline (LS mean) were –0.14, –0.16 and –0.19 points for the montelukast 5 mg, 10 mg and pranlukast 450 mg groups, respectively, demonstrating significant improvements compared to the baseline ($P <$ 0.001 for all three groups).

The changes in the mean NNSS and NNSS constituents for the 2-week treatment period from the baseline (LS mean ± SE) are shown in Figure 3. The changes in the mean NNSS were –0.23, –0.22 and –0.21 points for the montelukast 5 mg, 10 mg and pranlukast 450 mg groups, respectively, demonstrating significant improvements compared to the baseline ($P <$ 0.001 for all three groups).

As for each component, the changes in the mean nighttime nasal congestion scores for the 2-week treatment period from the baseline (LS mean) were –0.31, –0.27 and –0.29 points for the montelukast 5 mg, 10 mg and pranlukast 450 mg groups, respectively, demonstrating significant improvements compared to the baseline ($P <$ 0.001 for all three groups).

The changes in the mean difficulty scores (to fall into sleep) for the 2-week treatment period from the baseline (LS mean) were –0.25, –0.27 and –0.23 points for the montelukast 5 mg, 10 mg and pranlukast 450 mg groups, respectively, demonstrating significant improvements compared to the baseline ($P <$

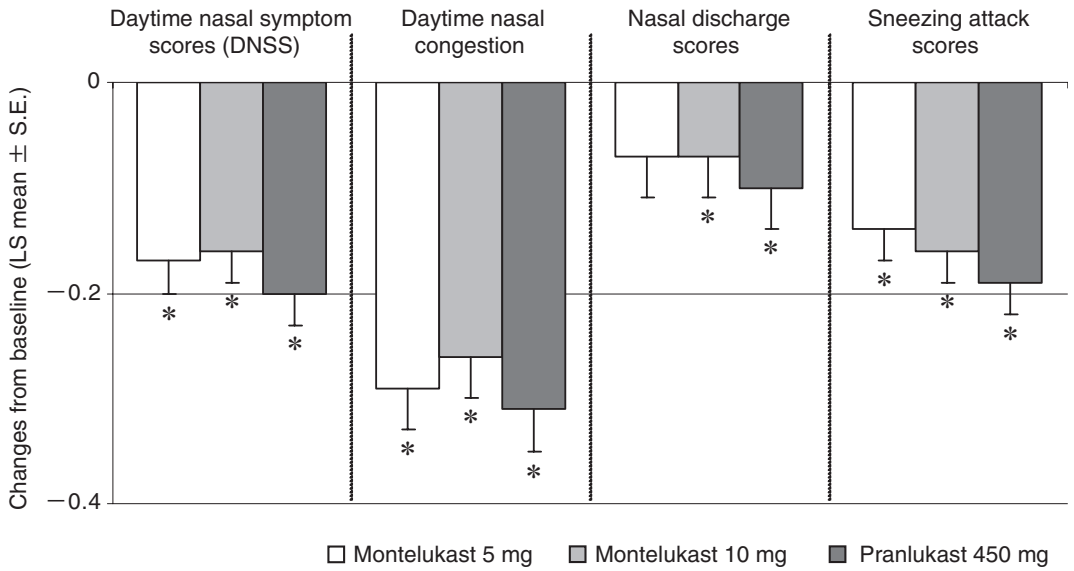

Fig. 2 Mean of daytime nasal symptom scores for the 2-week treatment period.
* $p < 0.05$ compared with baseline.

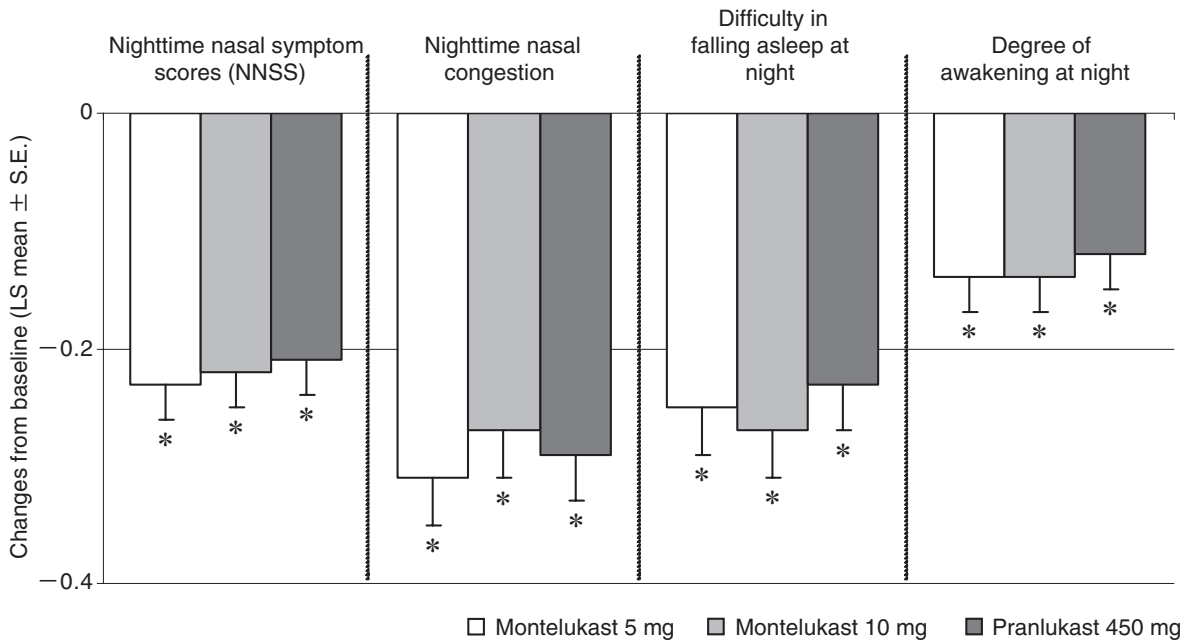

Fig. 3 Mean of nighttime nasal symptom scores for the 2-week treatment period.
* $p < 0.05$ compared with baseline.

0.001 for all three groups).

The changes in the mean scores (to assess degree of awakening at night) for the 2-week treatment period from the baseline (LS mean) were –0.14, –0.14 and –0.12 points for the montelukast 5 mg, 10 mg and pranlukast 450 mg groups, respectively, demonstrating significant improvements compared to the baseline ($P < 0.001$ for all three groups).

In addition, there was no significant difference in the mean scores of all the parameters during the daytime and at night for the 2-week treatment period between the montelukast 5 mg and 10 mg groups. The scores in the montelukast 5 mg and pranlukast 450 mg groups were not compared because there was no significant difference between montelukast 10 mg and pranlukast 450 mg groups.

Furthermore, there was no significant difference in the rates of patient's and investigator's impression be-

tween the montelukast 10 mg group and pranlukast 450 mg group ($P = 0.379$ and $P = 0.907$, respectively). Thus, the rates of patient's and investigator's impression between the montelukast 5 mg group and pranlukast 450 mg group were not compared.

SAFETY ANALYSIS

There was no significant difference in the incidence of AE among the montelukast 5 mg, 10 mg and pranlukast 450 mg groups. The incidences of AE were 24.9%, 24.3% and 23.5% for clinical AE and 2.8%, 2.9% and 5.5% for laboratory AE in the montelukast 5 mg, 10 mg and pranlukast 450 mg groups, respectively. The incidences of drug-related AE were 4.8%, 4.2% and 3.7% for clinical AE and 2.4%, 2.0% and 3.5% for laboratory AE in the montelukast 5 mg, 10 mg and pranlukast 450 mg groups, respectively. There was also no significant difference in the incidence of clinical AE or drug-related clinical AE of the montelukast 5 mg and 10 mg groups compared with the pranlukast 450 mg group. Although the incidence of laboratory AE was significantly lower in the montelukast 5 mg and 10 mg groups compared with the pranlukast 450 mg group ($P < 0.05$), there was no difference in the incidence of the drug-related laboratory AE among the groups.

"Nasopharyngitis" and "headache" were AE that occurred in more than 3% in any of the three groups. In addition, "diarrhea", "thirst" and "somnolence" were drug-related AE that occurred in more than 1% in any of the three groups. Each one patient in the montelukast 5 mg and 10 mg groups discontinued the study due to "diarrhea", and they were rated as serious drug-related AE. These two patients recovered shortly after discontinuation of the study and the physicians-in-charge judged that there was no clinical problem. All other symptoms were mild in intensity, and there was no clinically problematic finding. There was no difference in the safety profile between the montelukast 5 mg and 10 mg groups.

DISCUSSION

In the present study, we have conducted a double blind non-inferiority study of montelukast, compared with pranlukast to evaluate the efficacy and safety of montelukast in patients with seasonal allergic rhinitis. We selected pranlukast as a control drug because pranlukast exerts its pharmacological actions through the same mechanisms as montelukast and it is the only drug that has been approved for allergic rhinitis and it has been widely used in the clinical setting in Japan.[2] In terms of the primary endpoints, the CNSS, non-inferiority of montelukast 10 mg and montelukast 5 mg to pranlukast 450 mg was demonstrated. With regard to the other endpoints, there was no difference among the three treatment groups, the nasal symptoms improved to a comparable extent in all three groups. Taken together, these results have demonstrated that the efficacy of montelukast lasts for two weeks in patients with allergic rhinitis and that montelukast is as effective as pranlukast.

Montelukast and pranlukast have been expected to improve nasal congestion, based on their mechanisms of actions, and in the present study, both drugs indeed improved nasal congestion as well as the other symptoms associated with allergic rhinitis, including sneezing attacks and nasal discharge. With regard to its efficacy against nasal congestion, it has been stated in the Practical Guideline for the Management of Allergic Rhinitis in Japan (2005 Edition) that leukotriene receptor antagonists are effective primarily for treatment of moderate to severe "nasal congestion-type" allergic rhinitis.[3] We also confirmed the efficacy of leukotriene antagonists for improving nasal congestion. A multi-center, randomized, double blind, comparative study of pranlukast was conducted, using epinastine hydrochloride as a control drug,[8] and it has been reported that pranlukast was efficacious in patients whose major complaint was nasal congestion. In addition, it has been reported that pranlukast was also effective against sneezing and nasal discharge.[8] A multi-center, randomized, double blind study of montelukast was conducted overseas, using loratadine as a control drug,[9] and montelukast was shown to be effective for improving nasal congestion and also for improving the nasal symptoms at night. In the present study, we obtained comparable results.

In the present study, the changes in the CNSS from the baseline (LS mean) were –0.19 for both montelukast 10 mg and montelukast 5 mg, smaller than that obtained in the previous study (–0.47).[5] Since the amounts of pollen scattered during the study period in this study were approximately 20 times higher than those reported in the pollen reports[10] in the previous study,[7] the result was attributable to differences in the amounts of pollen scattered during the study period. In addition, montelukast 10 mg improved the nasal symptoms numerically better than montelukast 5 mg (data not shown). The results were similar to those reported in the previous study.[5] Thus, when symptoms become severe due to a large quantity of pollen scattered, these results suggest that montelukast may be more effective at a daily dose of 10 mg.

We investigated the safety of the study drugs, mainly based on the incidence rates of adverse experiences (AE) and drug-related AE (clinical and laboratory tests findings). There were no significant differences in the incidence of clinical AE and drug-related AE among the three groups. Thus, montelukast was well tolerated and as safe as pranlukast at daily doses of 5 mg and 10 mg for two weeks, and there was no difference in the safety profiles between montelukast and pranlukast. In addition, there was no AE that occurred anew in adult patients with allergic rhinitis in

Japan.

In conclusion, the results of the present study indicate that montelukast is efficacious and safe for the treatment of seasonal allergic rhinitis, alleviating overall symptoms, including nasal congestion, sneezing and nasal discharge, as seen in the clinical studies conducted overseas.[11-15]

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