

Therapeutic Effect of Montelukast, a Cysteinyl Leukotriene Receptor 1 Antagonist, on Japanese Patients with Seasonal Allergic Rhinitis

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ABSTRACT

Background: Secretion of nasal discharge was enhanced and airway-resistance in the nasal cavity was augmented, resulting in nasal congestion, when leukotrienes were administered to the nasal mucosa. These results indicate that leukotrienes play an important role in the pathogenesis of allergic rhinitis.

Methods: A double-blind clinical study was carried out to evaluate the efficacy and the safety of montelukast, a cysteinyl leukotriene receptor 1 antagonist, 5 mg, 10 mg or placebo orally administered once daily at bedtime for 2 weeks, to Japanese patients with seasonal allergic rhinitis. The composite nasal symptom scores (average over the 2-week treatment period) were compared among the montelukast 5 mg and 10 mg groups with the placebo group.

Results: The composite nasal symptom score significantly improved in the montelukast 5 mg and 10 mg groups compared with the placebo group. The administration of montelukast 5 mg or 10 mg once daily was well tolerated and the safety profiles were similar to those of the placebo. There were no significant differences in the incidences of adverse experience or drug-related adverse experience among the montelukast 5 mg, 10 mg groups and the placebo group.

Conclusions: Both montelukast 5 mg and 10 mg doses show clinically meaningful efficacy for the treatment of patients with seasonal allergic rhinitis and the safety profiles of those are comparable to that of the placebo.

KEY WORDS

cysteinyl leukotriene receptor, dose-response relationship, montelukast, rhinitis allergic, seasonal

INTRODUCTION

Allergic rhinitis is a type-I allergic disorder of nasal mucosa as characterized by nasal symptoms such as sneezing, nasal discharge and nasal congestion, while allergic reactions are triggered in the nasal mucosa when aspirating antigens in the air (house-dust, mite, and cedar pollen, etc.) through the nose.¹ The incidence of allergic rhinitis has been estimated to be approximately 10%–20%² (pollinosis: 10%–15%) and the incidences have been rising in Japan. Symptomatically, allergic rhinitis is broadly classified into two phases, i.e., immediate phase and delayed phase.

During the immediate phase, allergic rhinitis is characterized by three symptoms such as sneezing, nasal discharge and nasal congestion, while nasal congestion is the major complaint in the delayed phase.

Cysteinyl leukotrienes (CysLT) and related substances are lipid-mediators secreted from inflammatory cells. Granulocytes, primarily consisting of eosinophils, are elevated in nasal discharge secreted from patients with allergic rhinitis as accompanied by increases in leukotrienes (LTs).³ In addition, it has been reported that secretion of nasal discharge was enhanced and airway-resistance in the nasal cavity was augmented, resulting in nasal congestion, when

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Table 1 Patient demographics and other baseline characteristics

Treatment-groups	Placebo	Montelukast 5 mg	Montelukast 10 mg
Number of subjects (Efficacy assessment)	314	318	310
Gender			
Male	112 (35.7) †	109 (34.3)	114 (36.8)
Female	202 (64.3)	209 (65.7)	196 (63.2)
Age (Years) ‡			
Mean±SD	36.3±9.5	37.2±9.7	36.4±9.8
Body weight (kg) ‡			
Mean±SD	59.7±11.6	59.0±11.0	59.6±11.9
Disease type			
Seasonal	251 (79.9)	249 (78.3)	242 (78.1)
Seasonal+Perennial	63 (20.1)	69 (21.7)	68 (21.9)
Duration of illness (Years) ‡			
Mean±SD	13.6±7.1	14.8±8.7	14.1±7.8
Specific IgE-antibodies			
Only cedar ≥ 2	139 (44.3)	129 (40.6)	126 (40.6)
≥ 2 types: ≥ 2 antibodies	175 (55.7)	189 (59.4)	184 (59.4)
Skin test			
Negative	56 (17.8)	59 (18.6)	65 (21.0)
Positive	248 (79.0)	248 (78.0)	236 (76.1)
Indeterminable	10 (3.2)	11 (3.5)	9 (2.9)
Baseline symptomatic scores (Mean±SD)			
Composite nasal symptom scores	1.53±0.45	1.54±0.46	1.52±0.43
Daytime nasal symptom scores	1.86±0.48	1.87±0.50	1.83±0.45
Nighttime nasal symptom scores	1.19±0.55	1.20±0.54	1.20±0.54

† Number of patients (%).

‡ ANOVA was used to test homogeneity of age, body weight and duration of illness, while the chi-square test was used for other patient characteristics.

LTs were administered to the nasal mucosa experimentally.⁴ These results indicate that LTs play a clinically meaningful role in the pathogenesis of allergic rhinitis.

Montelukast is a cysteinyl leukotriene receptor 1 (CysLT₁) antagonist that has been developed primarily intended for the treatment of bronchial asthma.¹ Montelukast has been marketed for adult and pediatric patients with bronchial asthma since 1997, and is currently marketed in a number of countries. Since montelukast has been expected to be effective not only for the treatment of bronchial asthma but also for improvement of symptoms associated with allergic rhinitis based on its mechanisms of actions, its clinical development was initiated as a medication for allergic rhinitis. The clinical studies of montelukast have been performed overseas in patients with seasonal and perennial allergic rhinitis and its usefulness was demonstrated.⁵

In Japan, we conducted a double blind clinical study in patients with seasonal allergic rhinitis using montelukast 5-mg and 10-mg tablets as well as the placebo tablets in order to develop a new medication for allergic rhinitis as characterized by “easy to use”, “highly effective” and “very safe”. In conclusion, we

have demonstrated the efficacy and the safety of montelukast in Japanese patients with seasonal allergic rhinitis in the present study.

METHODS

PATIENTS

The demographics and the other baseline characteristics of 945 patients (942 patients for efficacy analysis) treated with montelukast 5 mg, 10 mg or placebo, are described in Table 1. Patients were treated as out patients at 24 institutions. The patients were seasonal allergic rhinitis patients who fulfilled the inclusion criteria listed as follows: (1) quantitative analysis of specific IgE antibody (UniCAP-RAST) revealed scores = 2 points (containing antibodies against pollen scattered between February and April, 2003); (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 two criteria fulfilled for symptoms^{6,7} [(1) total scores of daytime nasal symptoms (sneezing attacks, nasal discharge and nasal congestion during the day) = 4 points per day, as an average (total = 12 points) and (2) total scores of nighttime nasal symptoms (difficulties in falling into sleep, nasal congestion at night, and degree 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.

Adopted from the Practical Guideline for the Management of Allergic Rhinitis in Japan, 2002 edition (the Fourth Revised Edition)⁷.

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.

awakening at night) = 2 points per day, as an average (total = 6 points)] (Tables 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 before the run-in period such as anti-histamines, leukotriene receptor antagonists, anti-thromboxane A₂ drugs, chemical mediator release inhibitors, Th2 cytokine inhibitors, corticosteroids (topical and systemic), vasoconstrictors, parasympathetic nerve blockers (anti-cholinergic), biological preparations (histamine-containing immunoglobulin), tranquilizers (anti-depressants, anti-psychotics, and CNS suppressants), and the other drugs with similar pharmacological activities to the above-mentioned drugs (herbal medications that are expected to have anti-allergic action, but common cold medication can be used when necessary). Bronchial asthma patients with uncontrolled mild to moderate symptoms and patients with severe bronchial asthma were excluded from the study.

STUDY DESIGN

The study was a double blind, randomized, placebo-controlled, multi-center dose-finding study, con-

ducted during the spring season in 2004. The study period consisted of a four-day run-in period and two-week treatment period. The treatment period was determined by the previous overseas results that montelukast reached its almost maximal therapeutic effect, compared with placebo within 2 weeks.⁵ The patients were randomized in a 1 : 1 : 1 ratio to receive either montelukast 5 mg, 10 mg, or placebo groups. Montelukast sodium 5-mg and 10-mg tablets and the matching placebo tablets (Banyu Pharmaceutical Co., Ltd.) were orally administered once daily at bedtime for two weeks. 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 without violating any of the exclusion criteria, were enrolled after the informed consent to participate in this study was obtained. Nasal symptoms based on physical examinations and rhinitis-diaries were checked at every 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, daily mean of the composite nasal symptom scores (CNSS) (average of nasal symptom scores during the daytime and the night-

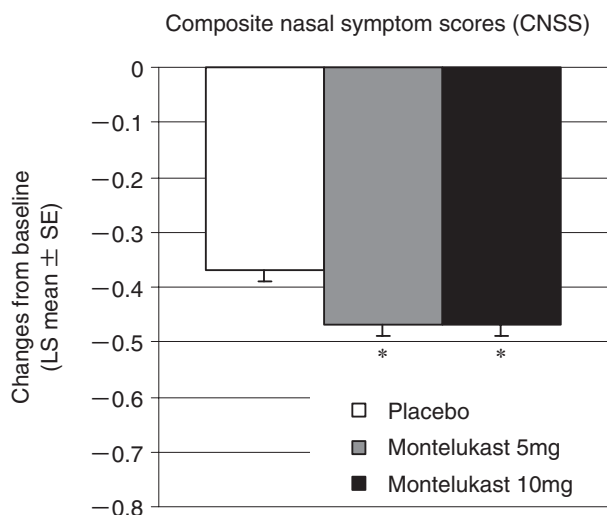


Fig. 1 Mean change from baseline in the composite nasal symptom scores for the 2-week treatment period. * $p < 0.01$.

time) over a 2 week treatment period, were compared with those during the 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). In addition, patient and investigator impressions were assessed with regards to the efficacy. The use of CNSS, DNSS and NNSS as the primary and secondary endpoints has 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 the baseline over 2 weeks in the CNSS between the treatment groups were performed using an analysis of covariance (ANCOVA) model which contains the treatment group and the study site as factors and the baseline as a covariate. A step-down procedure was used in the between-group comparison. The onset of action was evaluated via comparisons of montelukast with the placebo using the same ANCOVA model at Day 3, Day 2 and Day 1 in a step-down procedure. The patient and investigator impres-

sions were analyzed (the percentage of “much improved” and “improved”) using a logistic regression model via a step-down procedure.

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

RESULTS

A total of 945 patients was randomized (316, 319 and 310 patients for placebo, montelukast 5 mg and 10 mg groups, respectively), and 917 patients completed the study, while 28 patients (9, 12 and 7 patients for placebo, montelukast 5 mg and 10 mg groups, respectively) discontinued the study. Among them, 943 patients were eligible for safety analysis, excluding two patients (one for the placebo group due to the informed consent withdrawal and another for the montelukast 5 mg group due to not visiting the study site). In addition, 942 patients were eligible for efficacy analysis, excluding one patient (the placebo group). The patient characteristics for efficacy analysis are summarized in Table 1. There were no clinically significant differences of the baseline patient characteristics among the three treatment groups.

EFFICACY ANALYSIS

The changes from the baseline (LS mean $\pm$ SE) in the CNSS over 2 weeks for each treatment group are shown in Figure 1. The LS mean changes from the baseline in the CNSS over 2 weeks were -0.37, -0.47 and -0.47 points for the placebo, montelukast 5 mg and 10 mg groups, respectively, demonstrating significant improvements in montelukast (5 mg and 10 mg) compared with the placebo ($P = 0.001$ for both groups). There was no significant difference between montelukast 5 mg and 10 mg groups.

The change from the baseline (LS mean $\pm$ SE) in the DNSS over 2 weeks for each treatment group is shown in Figure 2. The LS mean changes from the baseline in the DNSS over 2 weeks were -0.33, -0.43 and -0.44 points for the placebo, montelukast 5 mg and 10 mg groups, respectively, demonstrating significant improvements in montelukast (5 mg and 10 mg) compared with the placebo ($P = 0.002$ and $P = 0.004$, respectively).

As for each component of the nasal symptom scores, the change from the baseline (LS mean) in the daytime nasal congestion scores over 2 weeks were -0.31, -0.42 and -0.44 points for the placebo, montelukast 5 mg and 10 mg groups, respectively, demonstrating significant improvements in montelukast (5 mg and 10 mg) compared with the placebo ($P = 0.004$ and $P = 0.011$, respectively).

The changes from the baseline (LS mean) in the mean nasal discharge scores for the 2-week treatment period were -0.33, -0.46 and -0.44 points for the placebo, montelukast 5 mg and 10 mg groups, re-

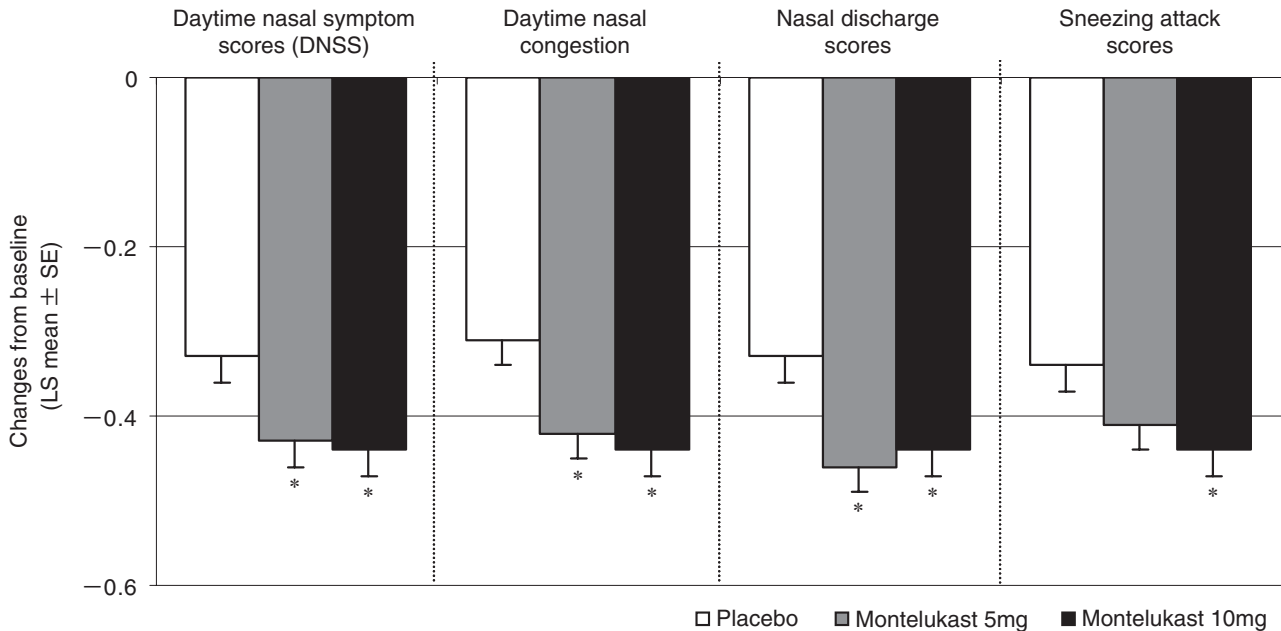


Fig. 2 Mean change from baseline in symptom scores of the daytime nasal symptoms during 2-week treatment period. * $p < 0.01$.

spectively, demonstrating significant improvements in montelukast (5 mg and 10 mg) compared with the placebo ($P = 0.010$ and $P = 0.003$, respectively).

The changes from the baseline (LS mean) in the mean sneezing scores for the 2-week treatment period were -0.34, -0.41 and -0.44 points for the placebo, montelukast 5 mg and 10 mg groups, respectively, demonstrating significant improvements in montelukast 10 mg compared with the placebo ($P = 0.013$). There was no significant difference between the placebo and montelukast 5 mg groups ($P = 0.073$).

Thus, there were no significant differences in any of the efficacy parameters above between montelukast 5 mg and 10 mg groups.

The change from the baseline (LS mean) in the NNSS over 2 weeks for each treatment group is shown in Figure 3. The changes from the baseline (LS mean) in the NNSS over 2 weeks were -0.40, -0.50 and -0.51 for the placebo, montelukast 5 mg and 10 mg groups, respectively, demonstrating significant improvements in montelukast (5 mg and 10 mg) compared with the placebo ($P = 0.002$ and $P = 0.003$, respectively).

The changes from the baseline (LS mean) in the nighttime nasal congestion scores over 2 weeks were -0.49, -0.63 and -0.62 points for the placebo, montelukast 5 mg and 10 mg groups, respectively, demonstrating significant improvements in montelukast (5 mg and 10 mg) compared with the placebo ($P = 0.007$ and $P = 0.003$, respectively).

The changes from the baseline (LS mean) in the mean scores of difficulties in falling into sleep at night for the 2-week treatment period were -0.43, -0.51 and -0.54 points for the placebo, montelukast 5 mg and 10 mg groups, respectively, demonstrating significant improvements in montelukast (5 mg and 10 mg) compared with the placebo ($P = 0.004$ and $P = 0.027$, respectively).

The changes from the baseline (LS mean) in the mean scores of extent of awakening at night for the 2-week treatment period were -0.30, -0.37 and -0.38 points for the placebo, montelukast 5 mg and 10 mg groups respectively, demonstrating significant improvements in montelukast (5 mg and 10 mg) compared with the placebo ($P = 0.013$ and $P = 0.016$, respectively).

The changes from the baseline (LS mean) in the mean scores of Composite nasal congestion score for the 2-week treatment period were -0.52, -0.53 and -0.40 points for the placebo, montelukast 5 mg and 10 mg groups respectively, demonstrating significant improvements in montelukast (5 mg and 10 mg) compared with the placebo ($P = 0.003$ and $P = 0.002$, respectively).

Thus, there were no significant differences in any of the efficacy parameters above between montelukast 5 mg and 10 mg groups.

There was significant difference in the impression rates of patient impressions only between montelukast 10 mg group and the placebo group (montelukast 10 mg group: $P = 0.036$, montelukast 5 mg

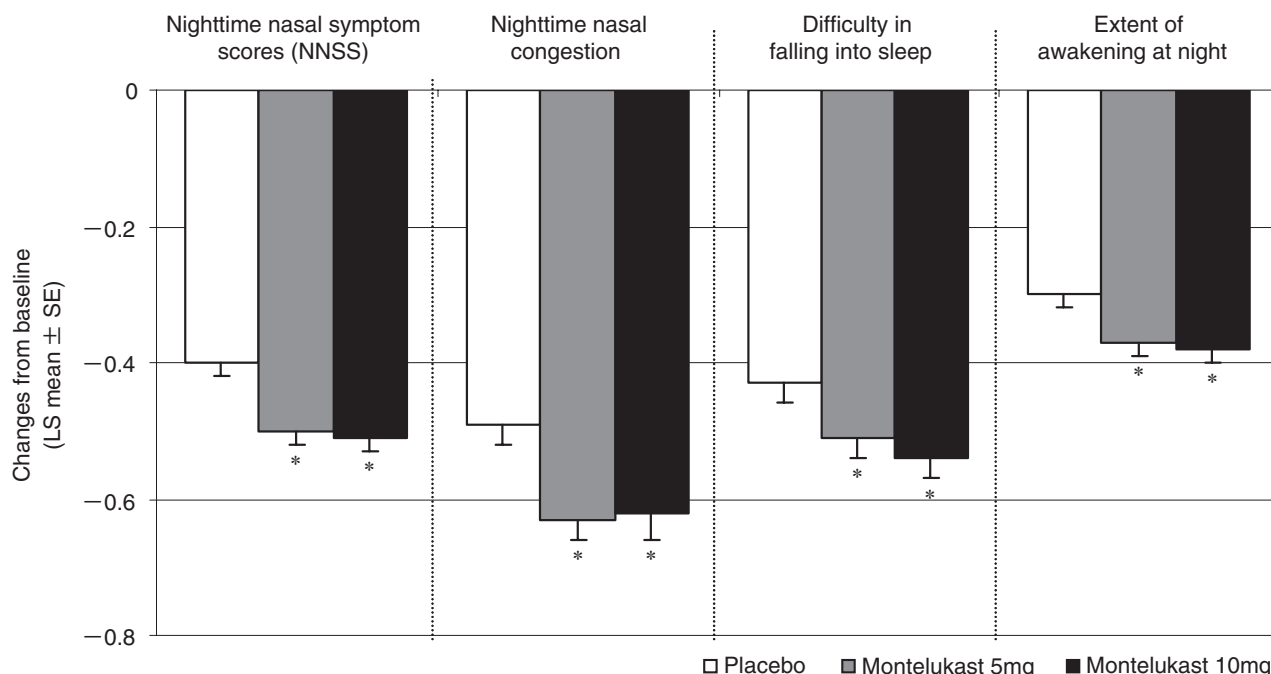


Fig. 3 Mean change from baseline in symptom scores of the nighttime nasal symptoms during the 2-week-treatment period. * $p < 0.01$.

group: $P = 0.144$).

There was no significant difference in the impression rates of investigator impressions between the montelukast 10 mg group and the placebo group ($P = 0.250$). Thus, the impression rates of investigator impressions between the montelukast 5 mg group and the placebo group were not compared.

ANALYSIS OF THE ONSET OF ACTION

To assess the time of onset of action of montelukast, the changes from the baseline in the CNSS, DNSS and NNSS at Day 1, 2 and 3 in the montelukast groups were compared with those of the placebo group (Fig. 4). There were significant between-group differences in the CNSS and DNSS in the montelukast 10 mg group compared with the placebo group from Day 1 ($P < 0.05$). Similarly, there were significant differences in the NNSS between the montelukast 10 mg group and the placebo group from Day 2 ($P < 0.01$). In addition, there were significant differences in the CNSS between the montelukast 5 mg group and the placebo group from Day 2 ($P < 0.05$), while there were significant differences in the DNSS between the montelukast 5 mg group and the placebo group from Day 3. However, there was no significant difference in the NNSS between the montelukast 5 mg group and the placebo group.

SAFETY ANALYSIS

There were no clinically meaningful differences be-

tween the treatment groups in the incidence of clinical and laboratory adverse experiences (AE). The incidences of AE were 26.3%, 29.9% and 26.5% for clinical AE and 6.0%, 7.2% and 9.0% for laboratory AE in the placebo, montelukast 5 mg and 10 mg groups, respectively. There was also no significant difference in the incidence of drug-related clinical or laboratory AE among the three groups. The incidences of drug-related AE were 4.1%, 4.7% and 4.2% for clinical AE and 3.2%, 1.9% and 5.8% for laboratory AE in the placebo, montelukast 5 mg and 10 mg groups, respectively. There were no serious AE and no fatalities.

"Headache", "constipation", "thirst" and "somnolence" were common drug-related AE occurring in more than 2 cases (approximately 1%) in any of the three groups. All drug-related clinical AE were mild or moderate. In addition, one patient terminated the study due to the drug-related AE, severe "pruritus" and "nausea", in the montelukast 5 mg group. The patient recovered thereafter.

"Blood bilirubin increased", "blood triglycerides increased", "urinary occult blood positive" and "protein urine present" were drug-related laboratory AE occurring in more than 2 cases (approximately 1%) assigned to at least one of the three groups. All drug-related laboratory AE were transient in the montelukast-treated groups, and all of them recovered or improved without any treatment.

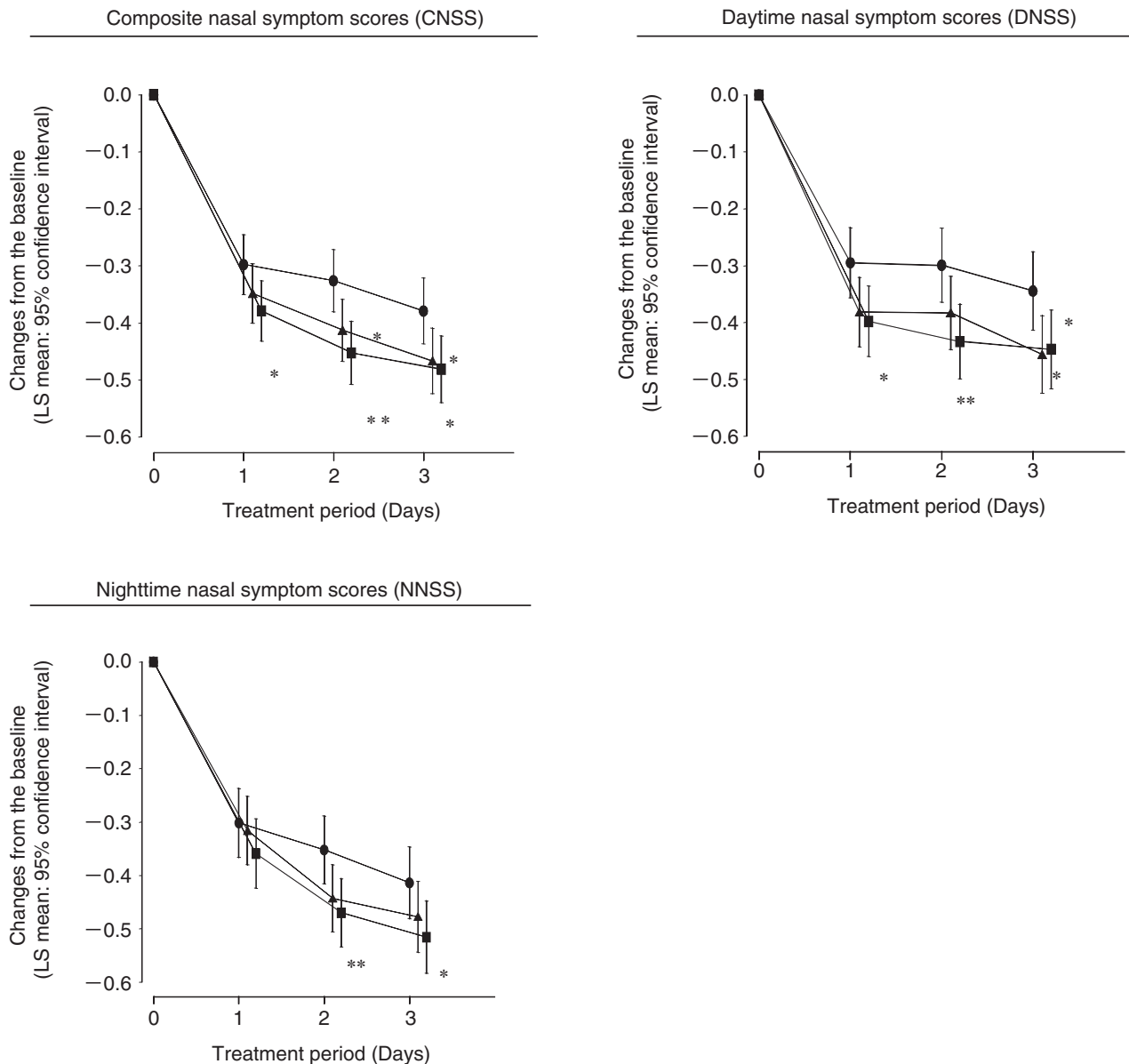


Fig. 4 Mean change from baseline in the composite, the daytime and the nighttime nasal symptom scores through Day 1 to Day 3 (LS mean and its 95% confidence interval). ●: Placebo Group ▲: Montelukast 5-mg group ■: Montelukast 10-mg group. * $P < 0.05$, ** $P < 0.01$ (Comparison versus placebo group).

DISCUSSION

Steroid preparations and leukotriene antagonists have been used for the treatment of allergic rhinitis, in particular, as medications for nasal congestion.⁷ In this study, montelukast once daily treatment has been indeed demonstrated to be efficacious for treatment of nasal congestion. Montelukast alleviated not only nasal congestion but also general symptoms associated with allergic rhinitis, including sneezing and nasal discharge. This may be attributable to its anti-inflammatory activity besides antagonistic actions against leukotriene receptors located in surrounding

blood vessels.

Montelukast can be expected to be used as a treatment for nasal congestion by its mechanism of airflow resistance improvement in the nasal cavity, which has been demonstrated in non-clinical and clinical studies.^{8,9} Anti-histamines, anti-allergic agents, corticosteroids (nasal drops) and vasoconstrictors are used for the treatment of allergic rhinitis at present. Therapeutic agents except for corticosteroid partially showed therapeutic effects on sneezing and nasal discharge, but not on nasal congestion. In addition, it is difficult for elderly patients to take inhaled corticosteroids in the delivery technique. Thus, simple

oral administration of montelukast, a cysteinyl leukotriene receptor antagonist, is considered to have an advantage in therapeutic effect on nasal congestion in addition to sneezing and nasal discharge. Both the montelukast 5 mg 10 mg groups showed significant improvement compared with placebo for many secondary endpoints including the Composite nasal symptoms score in the present study.

The primary endpoint of the CNSS was improved significantly in both montelukast 5 mg and 10 mg groups compared with the placebo group. The between-group difference in the changes from the baseline (LS mean) between montelukast (5 mg and 10 mg) and the placebo was -0.11 points, suggesting that the efficacy of montelukast in Japanese patients was comparable with the results of clinical studies conducted overseas in non-Japanese patients with seasonal allergic rhinitis.^{5,10-14} Several efficacy parameters, including the DNSS and the NNSS, also improved to some extent in both the montelukast 5 mg and 10 mg groups, compared with the placebo group, which were similar to the CNSS.

In this study, we investigated time needed for exerting the efficacy and found that the CNSS improved to some extent in the montelukast 10 mg group, starting on Day 1. The CNSS improved to some extent, starting on Day 2 in the montelukast 5 mg group. Taken together, these results demonstrated that montelukast exerts fast acting pharmacological effects which were similar to the results in the previous study.¹⁵ The early onset of action could be beneficial to allergic rhinitis patients.

Patient impressions (improved or better) and frequency of sneezing (mean scores for the 2-week treatment period) improved to some extent only in the montelukast 10 mg group, but not in the montelukast 5 mg group, as compared with the placebo group.

When the efficacy was analyzed according to the baseline symptoms severity subgroup, the CNSS improved to some extent only in the montelukast 10 mg group, as compared with the placebo group, among patients with severe symptoms (the CNSS ≥ 1.5 points as an average and the NNSS ≥ 1.0 point as an average during the run-in period) (data not shown), although the montelukast 5 mg and 10 mg groups showed similar efficacy in the primary endpoint. The study was conducted in the spring of 2004 when annual pollen-amount was approximately 1/5 of that seen in usual years in Japan. Taking the pollen-amount into consideration, the data suggest that montelukast may be clinically useful for treating seasonal allergic rhinitis at a dose of 10 mg in patients with severe symptoms. It has been also reported that the incidence of complications with allergic rhinitis was 59.4% in adult patients and 79% in pediatric patients with bronchial asthma in Japan.¹⁶

We investigated the safety, based on the incidence

of clinical and laboratory adverse experiences, and there were no significant or clinically meaningful differences in the incidence of adverse experiences and drug-related adverse experiences among the three groups. With regard to laboratory AE, there were no significant differences in the incidence of adverse experiences and drug-related adverse experiences among the three groups. No serious adverse experiences occurred in any of the three groups. All drug-related adverse experiences were transient in the montelukast-treated groups, and all of them recovered or showed a trend of recovery. These results demonstrated the clinical usefulness of montelukast from the standpoint of safety. In addition, there was no difference in the safety profiles between montelukast (5 mg and 10 mg) and the placebo groups, demonstrating that montelukast was well tolerated and safe in patients with allergic rhinitis following its administration for two weeks. Thus, montelukast once daily is one of the therapeutic alternatives for allergic rhinitis, and useful not only for the treatment for nasal congestion but also for improving allergic symptoms in general.

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