

Efficacy of prophylactic treatment with montelukast and montelukast plus add-on loratadine for seasonal allergic rhinitis

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ABSTRACT

Cysteinyl leukotriene and leukotriene receptor occupancy have been linked to several processes in seasonal allergic rhinitis (SAR), including nasal congestion, rhinorrhea, and recruitment of inflammatory cells. We investigated whether add-on loratadine, an antihistamine, might be effective for SAR patients showing unsatisfactory control of symptoms with the leukotriene receptor antagonist (LTRA) montelukast alone. Patients with SAR caused by Japanese cedar pollen (SAR-JCP; mean age, 29.4 years) were given prophylactic montelukast for 1 month before peak JCP dispersal. Patients recorded the severity of the symptoms (sneezing, rhinorrhea, nasal congestion, and ocular symptoms) daily on visual analog scale (VAS). We selected patients with VAS scores of >50 for any of the symptoms just before the peak pollen season (March 2 to March 8) and designated them as "poorly controlled" patients. Then, in the peak JCP season (from March 9), we conducted a randomized, double-blind, placebo-controlled study to determine whether add-on loratadine might be effective for these "poorly controlled" patients. Montelukast alone was effective, as evaluated by improvement of the VAS scores, in 95 of the 137 patients (69.3%). Add-on loratadine significantly decreased the total scores for nasal symptoms ($p < 0.05$), sneezing ($p < 0.05$), and rhinorrhea ($p < 0.05$) when compared with placebo. The symptoms of SAR in two of three SAR-JP patients could be controlled (VAS score[s] under 50) by prophylactic treatment with montelukast alone under the condition of mild JCP dispersal. Furthermore, the effect of add-on antihistamine on sneezing and rhinorrhea was found in selected SAR-JCP patients.

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It has been shown that administration of leukotriene receptor antagonists (LTRAs) significantly suppresses infiltration by eosinophils and presumably contributes to the amelioration of allergic inflammation.^{1,2} Placebo-controlled, multicenter, large-scale, double-blind studies with LTRA for seasonal allergic rhinitis (SAR) have been conducted both in Europe and in the United States. The results showed that LTRAs significantly suppressed the symptom scores for nasal congestion, sneezing, and rhinorrhea and were therefore effective against SAR.^{3–6}

The increasing prevalence of SAR caused by Japanese cedar pollen (SAR-JCP), a commonly encountered condition, has become a major public health problem in Japan. In our latest study, the estimated prevalence rate of SAR-JCP was 39.6% in subjects between 20 and 49 years of age.⁷ The symptoms of SAR-JCP are characteristically more severe than those of SAR in Europe and the United States, because the amount of JCP dispersal is very large.⁸ Therefore, prophylactic treatment is recommended, with oral administration started either almost simultaneously with the start of dispersal of JCP or before the symptoms have developed.^{9,10} Although prophylactic treatment by the inverse agonist effect of antihistamines has been promoted,⁹ it has become increasingly clear with presentation of the various effects of cysteinyl leukotriene, that LTRAs might be more suitable as prophylactic agents against SAR.^{11,12}

In this study, SAR-JCP patients were treated with the LTRA, montelukast, just before the dispersal of JCP. As the first end point, the percentage of patients who could get through the JCP dispersal season with montelukast treatment alone was examined. The second end point was the efficacy of additional administration of loratadine on the symptoms of SAR evaluated in a

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placebo-controlled double-blind study of SAR patients whose symptoms were not satisfactorily controlled by treatment with montelukast alone.

PARTICIPANTS AND METHODS

Participants

The 148 participants in this study comprised 63 men and 85 women with a mean age of 29.4 ± 1.0 years. All subjects were judged as positive by the JCP-specific capsulated hydrophilic carrier polymer radioallergosorbent test (CAP-RAST) score (score not <2 , irrespective of the presence of sensitization by other inhalants) and also positive by the intranasal provocation test with JCP antigen discs and gave a history of suffering from allergic symptoms during the JCP dispersal season in 2009. Patients with the following conditions were excluded: complication by the other nasal diseases, already started on specific immunotherapy, lactating women, pregnancy or possible pregnancy, or other severe complications. Patients were also excluded if they had taken drugs that were discouraged during the study period by the time of the first visit and were therefore unable to discontinue the drugs to allow a washout period of not <2 weeks.

Test Drugs

Montelukast (10 mg) and loratadine (10 mg) were purchased from MSD K.K. (Tokyo, Japan). In the placebo-controlled double-blind study of add-on loratadine, the active drug used was loratadine (10 mg) and 0.1 g of crystal lactose administered in an opaque, colored no. 2 capsule. The placebo used was 0.3 g of crystal lactose administered in identical no. 2 capsules. The test drugs were formulated at the Department of Hospital Pharmacy, University of Fukui Hospital. Six volunteers confirmed that the active drug and the placebo were completely indistinguishable from each other either visually or by taste.

The test drug administrator assigned the drug to the subjects. The test drug was assigned and distributed to each subject at enrollment in the order of the code number of the test drug. The drug name in the label was coded in advance by random allocation of the test drug.

Study Design

The study was conducted from January to April 2010. The study design is presented in Fig. 1. The protocol included four hospital visits. During the first visit, consent for participation in the study and the eligibility criteria for inclusion in the study were confirmed and blood samples were collected. During the second visit (January 25–29), the CAP-RAST results were checked, the drugs were assigned, and the test drug was delivered together with the patient daily symptom record form. The JCP dispersal season in

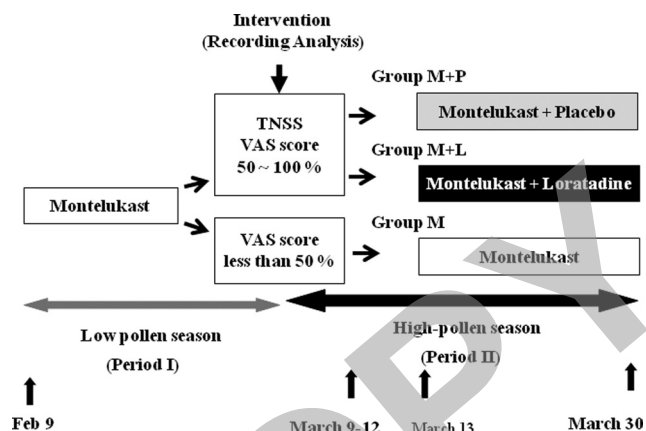


Figure 1. Study design.

2010 was predicted to begin on February 9. Oral montelukast (10 mg/day) once daily at bedtime was prescribed from February 9.

JCP dispersal was measured by a Durham pollen collector,⁹ which was set up in an open space at the University of Fukui. High pollen season was defined as the period when the pollen count in the pollen collector exceeded 100 grains/cm².^{9,13} The requested day of the third visit was e-mailed simultaneously in early March when the pollen dispersal began to increase. Patients with VAS scores of higher than 50 for any of sneezing, rhinorrhea, nasal congestion, or total nasal symptoms within a week before the 3rd visit day were enrolled in a placebo-controlled, double-blind study of add-on loratadine. Patients with VAS scores of lower than 50 in all items were continued on montelukast alone.

The use of drugs other than the test drug was discouraged during the test period. Rescue drugs that were allowed to be used were mometasone furoate nasal spray (MFNS) at the dose of 2 sprays into each nasal cavity once daily (200 μ g) and ketotifen ophthalmic solution at the dose of 1–2 drop(s)/dose and 4 doses/day. Any use of these medications was recorded on the patient daily symptom record form. MFNS was purchased from MSD K.K. Ketotifen ophthalmic solution was purchased from Novartis Pharma K.K. (Tokyo, Japan).

Before enrollment, written informed consent was obtained from each of the participants. The trial was performed in compliance with the Declaration of Helsinki and Good Clinical Practice, with prior approval from the Ethics Committee of the University of Fukui, Fukui, Japan.

Recording and Assessment of the Symptoms

Patients recorded the severity of the following symptoms daily on a VAS: sneezing, rhinorrhea, nasal congestion, and ocular symptoms. Score 0 indicated the absence of the symptom and score 100 indicated the highest severity of the symptoms.^{14,15}

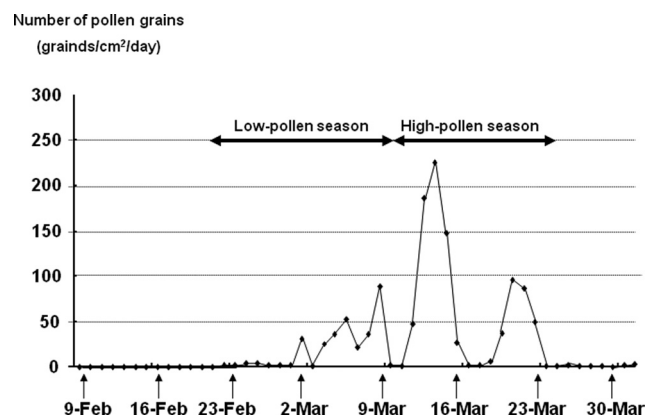


Figure 2. Cedar pollen dispersal status. A count of not $<100/\text{cm}^2$ per day is regarded as peak Japanese cedar pollen dispersal.

Statistical Methods

Data were expressed as the mean $\pm$ standard error. Statistical analyses to assess the significances of differences were performed using the Wilcoxon's signed-rank test.

RESULTS

Primary End Point

In 2010, JCP dispersal was first observed on February 6. The third visit was conducted during the 4-day period of March 9–12. The dispersal status is presented in Fig. 2.

Of the 148 participants, 11 participants, listed later, dropped out during period I: two were infected with influenza, two traveled overseas, six took prohibited drugs, and one could not visit because of a family emergency. All 137 participants who were transferred to period II completed the treatment. On the third visit, the VASs from March 2 to the day of the third visit was checked; 95 of the 137 participants (69.3%) showed VAS scores of <50 for all symptoms. Therefore, they were designated as the montelukast alone (M) group. Forty-two subjects were included in the placebo-controlled double-blind study to examine the effect of add-on use of loratadine. They were divided randomly into the montelukast + loratadine (M + L) group ($n = 21$ subjects) and the montelukast + placebo (M + P) group ($n = 21$). The patient backgrounds of the three groups are presented in Table 1. No significant differences among the groups were found in terms of the patient backgrounds.

Total Nasal Symptom Score

The total nasal symptom score (TNSS) as determined on VAS was significantly higher in the M + L group and M + P group on the day of start of the test on February 9 than that in the M group (Fig. 3). The TNSS in all three groups decreased after oral administration

of montelukast. The mean daily TNSS during the February 9–15 period was 24.0 ± 2.1 in the M group, 44.7 ± 7.5 in the M + L group ($p < 0.05$ versus M group), and 49.8 ± 5.4 in the M + P group ($p < 0.05$ versus M group). In the M + L and M + P groups, the TNSS began to increase after February 25 and reached its peak after March 2. The mean TNSS in the week after March 2 was 31.5 ± 2.1 in the M group, 119.4 ± 8.4 in the M + L group ($p < 0.01$ versus M group), and 121.2 ± 6.9 in the M + P group ($p < 0.01$ versus M group).

Additional oral administration of loratadine was started during the period from March 9 to March 12. The TNSS in the M + L group began to decrease from March 13, the day after the start of loratadine administration in all of the participants: a significant difference was found in comparison with the score in the M + P group (March 13, 87.6 ± 9.0 in the M + L group; 116.4 ± 10.8 in the M + P group; $p < 0.05$), which persisted until March 20. The TNSS began to decrease in the M + P group from March 21 in direct relation to the reduction in JCP dispersal. However, the scores remained higher in the M + P group than in the M group throughout the test period ($p < 0.01$).

In the M group, the TNSS began to increase from March 10. Nevertheless, it was 51.9 ± 3.9 even on March 14, at its peak, which was not markedly different from the scores in mid-February, suggesting that montelukast significantly suppressed the TNSS.

Sneezing Score

The scores for sneezing showed the same time course as the TNSS. The M + P group showed a significantly higher score than the M group from February 9, the day of start of the study, to March 31, the day of end of the study ($p < 0.01$; Fig. 4). In the M + L group, the sneezing score increased from February 20, becoming significantly different from that in the M group ($p < 0.05$). The sneezing score increased to its peak from March 2 in both the M + L group and the M + P group.

In the M + L group, the sneezing score decreased after the start of administration of add-on loratadine. The score was significantly different from that in the M + P group on March 14 (21.8 ± 3.8 in the M + L group; 42.0 ± 6.9 in the M + P group; $p < 0.05$). Subsequently, the significant difference in the sneezing score between the M + L and M + P groups persisted until March 20 ($p < 0.05$). In the M group, no significant difference in the sneezing score was observed.

Rhinorrhea Score

The rhinorrhea scores also showed the same pattern of changes as the TNSS and scores for sneezing (Fig. 5). The rhinorrhea score increased from February 25 in

Table 1 Patient background

	Total Alone	Montelukast + Loratadine	Montelukast + Placebo	Montelukast	Dropout
Case	148	95	21	21	11
Age (yr)	29.4 ± 1.0*	31.1 ± 1.3	26.7 ± 2.4	26.4 ± 2.2	25.5 ± 1.2
Sex (% male)	44.0%	43.2%	33.3%	47.6%	50.0%
CAP-RAST score for Japanese cedar-specific IgE	3.6 ± 0.1*	3.5 ± 0.1	3.9 ± 0.2	3.6 ± 0.2	3.4 ± 0.2
Baseline VAS score#					
TNSS		8.0 ± 0.7	14.9 ± 2.5	16.6 ± 1.8	
Sneezing		5.5 ± 0.9	7.1 ± 1.9	19.5 ± 3.3	
Rhinorrhea		8.9 ± 1.3	18.2 ± 4.2	19.5 ± 3.0	
Nasal congestion		9.5 ± 1.5	19.6 ± 5.6	15.1 ± 3.1	

*Mean ± SE.

#February 9–15.

CAP-RAST = capsulated hydrophilic carrier polymer radioallergosorbent test; TNSS = total nasal symptom score; VAS = visual analog scale.

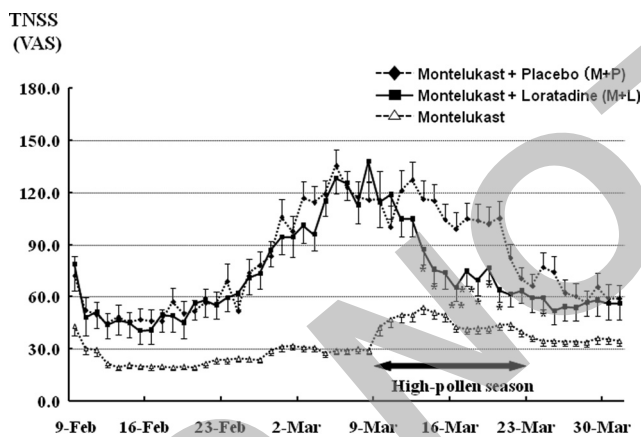
*: $P < 0.05$, **: $P < 0.01$ (M+L vs. M+P)

Figure 3. Changes in the total nasal symptom score.

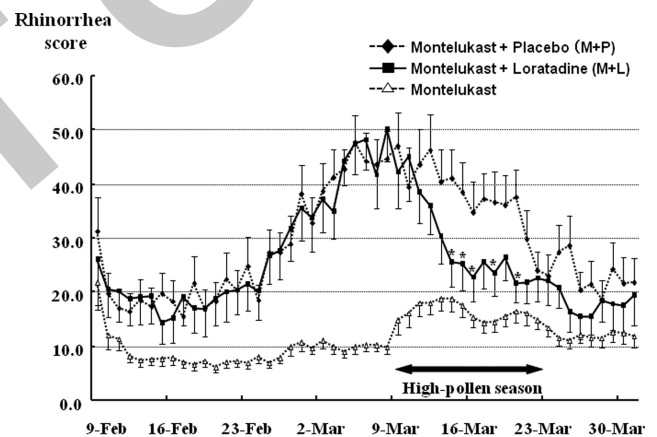
*: $P < 0.05$ (M+L vs. M+P)

Figure 5. Changes in the rhinorrhea score.

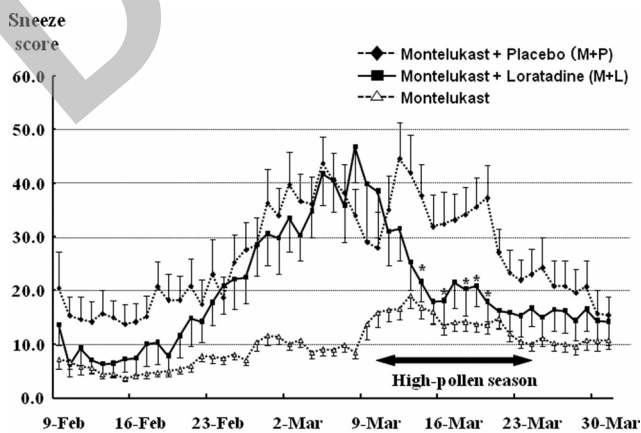
*: $P < 0.05$ (M+L vs. M+P)

Figure 4. Changes in the sneezing score.

both the M + L group and the M + P group. Regarding the weekly peak from March 2, the mean rhinorrhea score was 10.6 ± 1.1 in the M group, 43.1 ± 4.6 in the M + L group ($p < 0.01$ versus M group), and 43.4 ± 3.0 in the M + P group ($p < 0.01$ versus M group).

In the M + L group, the rhinorrhea score began to decrease after the start of administration of loratadine. On the other hand, the score in the M + P group remained high. The score was significantly different between the M + L group and M + P group from March 14 to 21 (25.3 ± 4.9 in the M + L group; 41.1 ± 5.2 in the M + P group; $p < 0.05$). No significant differences between the M + L group and M group were observed from March 14 onward.

The time course of changes in the rhinorrhea score in the M group was similar to that of the score for sneezing.

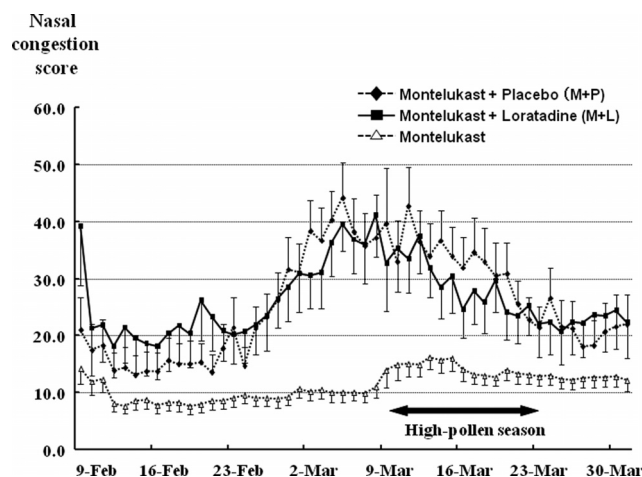


Figure 6. Changes in the nasal congestion score.

Nasal Congestion Score

The nasal congestion score showed a unique time course. The initial score was highest in the M + L group, the score being significantly different from that in the M group ($p < 0.01$; Fig. 6). The score also began to increase in the M + P group from February 20, becoming significantly different from that in the M group ($p < 0.05$). After the start of loratadine administration, the nasal congestion score in the M + L group did not decrease like the sneezing and rhinorrhea scores. No significant difference in the nasal congestion scores, such as that of the sneezing and rhinorrhea scores, was found in the M + L group or the M + P group. Thus, no effect of add-on loratadine was found on the nasal congestion.

In the M group, only a mild increase of the nasal congestion score was recorded at the peak of JCP dispersal.

Ocular Symptom Score

The ocular symptom score in all three groups was low from February 9 to March 31 (data not shown), with no significant differences among the three groups.

Concomitant Use of Drugs

The use of MFNS or ketotifen ophthalmic solution was allowed in accordance with the participant's wishes when the moderate symptoms caused by JCP dispersal were not suppressed by the test drug. MFNS was used from March 9 to 23. The daily use of MFNS in the three treatment groups was extremely low (0.07 dose/day per person) and not significantly different among the three groups. The frequency of use of ketotifen ophthalmic solution was also low in all of the groups (data not shown).

DISCUSSION

This study showed that prophylactic treatment with montelukast could control the nasal symptoms during

the peak pollen season in 69.3% of patients with SAR-JCP. A placebo-controlled double-blind study of add-on loratadine was conducted in the patients whose symptoms could not be satisfactorily controlled by montelukast alone. Loratadine significantly suppressed the TNSS, sneezing score, and rhinorrhea score, suggesting that combined treatment with montelukast + antihistamines elicited an add-on effect in cases that showed poor control with montelukast alone.

The control rate obtained with prophylactic administration of montelukast in SAR-JCP patients was higher than expected. Although we judged that montelukast alone would be effective for suppression of the symptom onset when the VAS scores for the symptoms are not >50 , it remains unclear whether that figure is optimal. However, no participant in the M group requested addition of an antihistamine drug. Therefore, the true efficacy rate might be higher than 70%. Nevertheless, although the mean total JCP dispersal count in Fukui prefecture in the last 10 years was $\sim 2500/\text{cm}^2$, the total JCP dispersal count during the time of this study was as low as $1279/\text{cm}^2$, being less than one-half of the value typically seen each year. It remains doubtful whether 70% efficacy could have been achieved if the total JCP dispersal count had been the same as the usual each year. Further investigation is needed in the future.

An important issue is how to select patients for prophylactic treatment with montelukast. The TNSS before or at the beginning of JCP dispersal may be a crucial criterion. Officially, the first day of JCP dispersal was February 6 in the study year. Nevertheless, it is likely that a small amount of pollen began to be dispersed somewhat earlier, even if it could not be measured by the Durham pollen collector.⁸ It is suspected that montelukast may not be so effective in highly sensitive patients with pollinosis, in whom the symptoms begin to appear even at very low levels of JCP dispersal. Presumably, the symptoms also rapidly increase in severity along with the increase in the amount of JCP dispersal. Then, treatment with an antihistamine or other drugs might become necessary. Apparently, it would not be correct to administer montelukast initially to such patients, in whom conventional prophylactic treatment with antihistamines, *etc.*, may be more appropriate.

Intranasal corticosteroids are recommended for the treatment of AR.¹⁶ However, high percentages of Japanese people do not like the smell or feel of intranasal corticosteroids and do not like spraying something into the nose. Therefore, we only compared oral treatments in this study.

As for studies of the combined effect of LTRA plus an antihistamine, Melzer *et al.* examined the combined effect of montelukast + loratadine in SAR patients and reported significant suppression of all symptoms ex-

aminated in the combined treatment group when compared with that in the respective monotherapy groups.¹⁷ However, in a large-scale study conducted in patients with SAR caused by pollen dispersal in the autumn season, no significant difference was found between the M + L group and the respective monotherapy groups.¹⁸ Recently, a once-daily tablet containing montelukast and loratadine was developed and established to be effective for nasal congestion, with a low incidence of adverse effects.^{19,20}

The design of this study was distinct from that of the previous placebo-controlled, double-blind study. Data from this study proved that the symptoms of SAR were sufficiently suppressed by additional administration of an antihistamine, even in cases showing unsatisfactory response to montelukast alone. Although significant differences were found in this small-scale study, a large-scale study would be needed to establish an optimal combined therapy with an LTRA + antihistamine for SAR-JCP patients.

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