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Original Article

# Population-based open-label clinical effectiveness assessment of the cysteinyl leukotriene receptor antagonist pranlukast

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## Abstract

Although the efficacy of cysteinyl leukotriene receptor antagonists in asthma therapy has been established through controlled clinical trials, there are no data concerning the effectiveness of their use in clinical practice, in which there is no rigid selection based on specific inclusion and exclusion criteria. The aim of the present study was to evaluate the effectiveness of pranlukast in clinical practice. More than 2500 outpatients with mild to severe persistent asthma answered an input questionnaire, which consisted of 33 items assessing asthma symptoms in terms of six activities of daily living during the previous 2 weeks. Of these patients, 1138 received treatment with pranlukast and answered the same questionnaire 4–6 weeks after the start of treatment. In 923 of these 1138 patients, we examined the impact of concomitantly used inhaled steroids, $\beta_2$-adrenergic agonists or sustained-release theophylline on the effectiveness of pranlukast treatment. One hundred and sixty-seven control patients completed the questionnaire twice but did not receive pranlukast treatment. We found a significant decrease in the number of asthma symptoms reported among both the 1138 patients treated with pranlukast and the 167 control patients. However, the magnitude of the decrease in symptoms was significantly ($P < 0.001$) greater with pranlukast treatment. Moreover, pranlukast was equally efficacious in the presence and absence of concomitantly used inhaled steroids, $\beta_2$-adrenergic agonists or sustained-release theophylline. In conclusion, pranlukast was shown to have clinical effectiveness in the treatment of mild to severe persistent asthma symptoms.

**Key words:** asthma, pranlukast, questionnaire, symptom, treatment.

## Introduction

The cysteinyl leukotrienes are potent airway contractile agonists[1–4] that are known to be produced by eosinophils[5–7] and mast cells.[8] They can be recovered from body fluids of patients with asthma during induced[9,10] or spontaneous[11,12] asthma attacks. Cysteinyl leukotriene receptor antagonists have been reported to cause significant inhibition of cold air-,[13] exercise-,[14,15] allergen-[16–18] and aspirin-induced[19–21] asthma. The clinical efficacy of these antagonists in the treatment of mild to moderate asthma has been reported in rigorously controlled studies.[22–25] However, there are no data on the clinical effectiveness of cysteinyl leukotriene receptor antagonists; that is, their use outside the setting of rigidly controlled trials. Because effectiveness influences the use of agents in a practice setting, we administered a questionnaire about asthma symptoms before and after pranlukast administration to more than 1000 outpatients with mild to severe chronic persistent asthma.

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## METHODS

The present study was performed between October 1996 and March 1997 in the Tohoku district (Aomori, Akita, Iwate, Miyagi, Yamagata and Fukushima prefectures) of Japan. Two hundred and twenty-eight medical facilities, ranging from private clinics to university hospitals, participated in the study. Of all patients with mild to severe persistent asthma who regularly attended these facilities, 2516 outpatients answered the first questionnaire at each site. As shown in Table 1, the questionnaire consisted of 33 questions assessing asthma symptoms in terms of six activities of daily living during the previous 2 weeks.

Of the 2516 outpatients who completed the initial questionnaire, 1138 (mean age (± SD) 54.0 ± 17.8 years; 591 males and 547 females) accepted treatment with pranlukast and again answered the same questionnaire 4–6 weeks after the start of treatment. In 923 of the 1138 patients treated with pranlukast, we examined the impact of concomitantly used inhaled steroids, $\beta_2$-adrenergic agonists or sustained-release theophylline on the effectiveness of pranlukast treatment; no subjects were excluded from the study on the basis of medications used. Thus, pranlukast was administered in a practice setting, because the role of post-marketing effectiveness trials should be to inform physicians of the clinical usefulness of administered agents under such conditions and the efficacy of these receptor antagonists has already been recognized by physicians through rigorously controlled studies. In addition, 167 outpatients

**Table 1** Thirty-three item questionnaire administered to patients with mild, moderate or severe persistent asthma at 228 medical facilities in the Tohoku district of Japan

| Circumstances | Item |
|---|---|
| At rising | 1. Cough |
| | 2. Sputum |
| | 3. Wheezing |
| | 4. Precordial oppression |
| | 5. Dyspnea |
| Preparing for the day or moving from place to place | 6. Difficulty putting away bedding |
| | 7. Difficulty breathing when walking fast |
| | 8. Difficulty breathing when walking for a long time |
| | 9. Difficulty breathing when running |
| | 10. Difficulty breathing when going up and down stairs |
| | 11. Ill health on rainy or windy days |
| Outside the home (on the job, at school etc.) | 12. Difficulty breathing during gymnastic class |
| | 13. Chest tightness when laughing loudly |
| | 14. Difficulty breathing during stress |
| | 15. Difficulty breathing in dusty places |
| | 16. Difficulty breathing when exercising lightly |
| At home | 17. Difficulty breathing when carrying heavy items |
| | 18. Difficulty breathing when cleaning the house |
| | 19. Difficulty breathing when holding a child |
| | 20. Difficulty breathing when taking a bath |
| | 21. Difficulty breathing when taking a drink |
| | 22. Difficulty breathing when eating to the point of fullness |
| | 23. Difficulty breathing when playing with pets |
| | 24. Difficulty breathing in the presence of incense or perfume |
| Before sleep | 25. Cough |
| | 26. Sputum |
| | 27. Wheezing |
| | 28. Precordial oppression |
| | 29. Dyspnea |
| During sleep | 30. Difficulty putting down bedding |
| | 31. Inability to sleep well because of difficulty breathing |
| | 32. Trouble falling asleep because of difficulty breathing |
| | 33. Awakening during the night because of difficulty breathing |

(mean age 51.0 ± 15.9 years; 74 males and 93 females) who declined pranlukast treatment and continued to take the same medication answered the second questionnaire after the same interval.

### Statistical analysis

Study subjects were divided into five groups on the basis of the number of symptoms present (i.e. positive questionnaire response to a query) on study initiation; these groups were: (i) 0; (ii) 1–3; (iii) 4–8; (iv) 9–16; and (v) ≥ 17. The Wilcoxon rank sum test was used to examine differences in each group between responses to the first and second questionnaires. Analysis of variance was used to compare responses of patients receiving pranlukast with those of patients not receiving pranlukast and to compare the effectiveness of pranlukast with and without the concomitant use of inhaled steroids, $\beta_2$-adrenergic agonists or sustained-release theophylline.

## Results

As shown in Fig. 1, when subjects were arbitrarily divided into five groups on the basis of the number of symptoms reported, we found a significant improvement not only in the 1138 patients (Fig. 1a) treated with pranlukast for 4–6 weeks but also in the 167 patients (Fig. 1b) who answered the questionnaire on two occasions 4–6 weeks apart without pranlukast treatment. As shown in Fig. 2, the mean (± SEM) number of symptoms reported per person in the pranlukast-treated group was 9.23 ± 0.18 and 4.81 ± 0.39 before and after treatment with pranlukast, respectively. The corresponding numbers in the 167 control patients were 6.25 ± 0.43 and 4.70 ± 0.14 at the time of completion of the first and second questionnaires, respectively. Thus, the decrease in the number of symptoms was significantly greater ($P < 0.001$) in the pranlukast-treated group than in patients not receiving pranlukast.

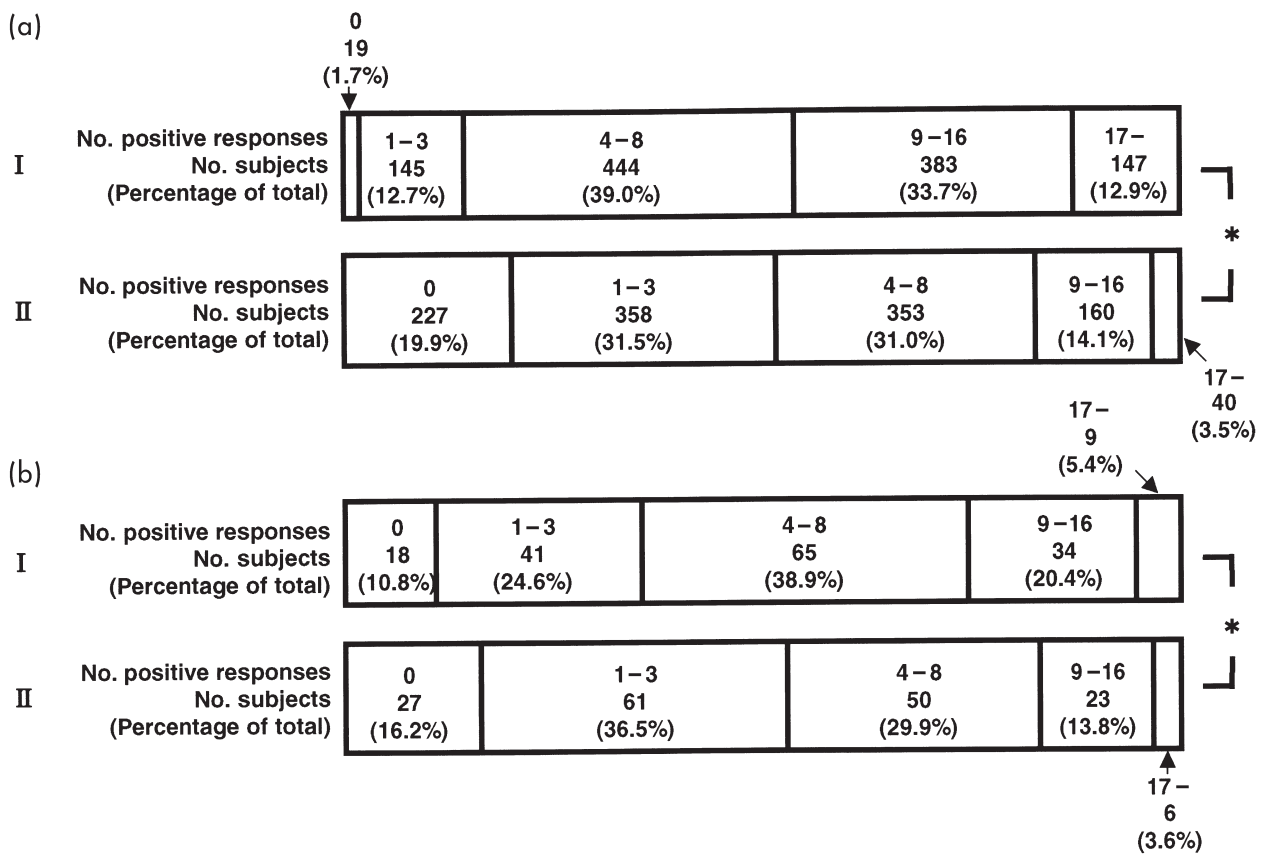


**Fig. 1** Symptom questionnaire results obtained on two occasions 4–6 weeks apart from patients with chronic asthma, 1138 of whom received pranlukast and 167 of whom did not. At the time of administration of the second questionnaire, significant improvement was evident in both (a) pranlukast-treated and (b) non-treated subjects. *$P < 0.001$ (Wilcoxon rank sum test).

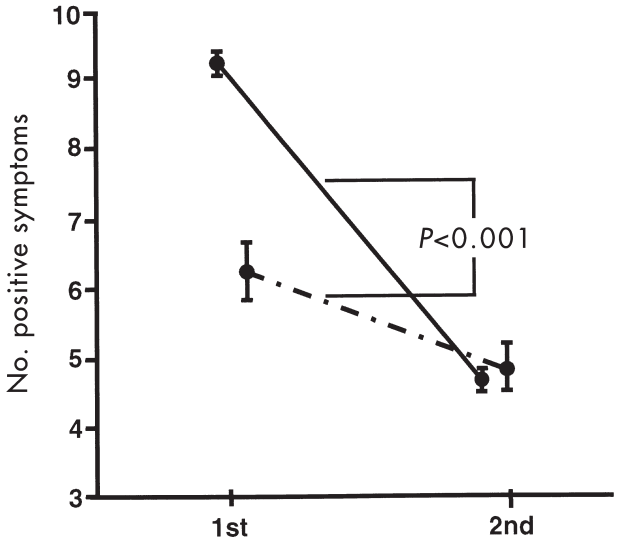


**Fig. 2** Mean (± SEM) number of symptoms in patients with chronic asthma and the time of the first and second questionnaires. Results for 1138 pranlukast-treated patients are indicated by the solid line, while those for 167 non-treated patients are indicated by the dashed line. The decrease in number of symptoms was significantly greater among pranlukast-treated patients compared with non-treated patients ($P < 0.001$).

Figure 3 shows changes in the number of symptoms reported per patient before and after treatment with pranlukast in patients stratified by other asthma medication use. The concomitant use of inhaled steroids (Fig. 3a; $n = 372$), $\beta_2$-adrenergic agonists (Fig. 3b; $n = 602$) or sustained-release theophylline (Fig. 3c; $n = 835$) did not modify the symptomatic response. Irrespective of the concomitant use of one of these three agents, pranlukast treatment significantly ($P < 0.001$) decreased the number of symptoms in all groups. Thus, we found no significant difference in the efficacy of pranlukast with respect to the concomitant use of these three agents.

There were no reported adverse effects of pranlukast, although adverse effects were not included in the outcome measures.

## Discussion

Our data indicate the effectiveness of pranlukast treatment in clinical practice. We found a significantly greater decrease in the number of symptoms reported by 1138 outpatients with mild to severe persistent asthma who

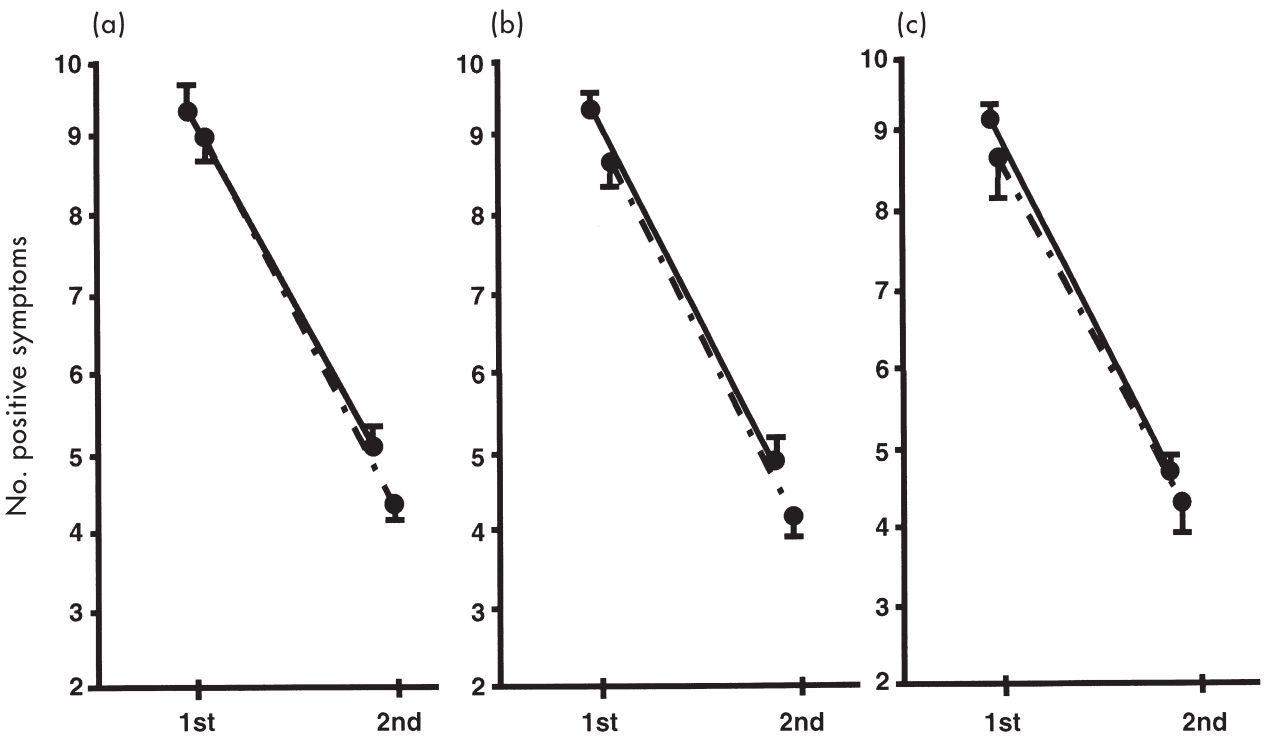


**Fig. 3** Mean (± SEM) numbers of symptoms in pranlukast-treated patients concomitantly taking (a) inhaled steroids ($n = 372$), (b) $\beta_2$-adrenergic agonists ($n = 602$) or (c) sustained-release theophylline ($n = 835$) are indicated by solid lines, while those in pranlukast-treated patients not taking these agents ($n = 551$, 321, and 88, respectively) are indicated by broken lines. Pranlukast was equally effective in the presence and absence of these agents.

were treated with pranlukast, a cysteinyl leukotriene receptor antagonist, compared with control patients, although the control group had fewer symptoms than the treatment group at the time of the first questionnaire. Pranlukast treatment was associated with a decrease in symptoms in all six activities of daily living. Treatment with the drug resulted in a significant decrease in the number of symptoms, irrespective of the concomitant use of inhaled steroids, $\beta_2$-adrenergic agonists or sustained-release theophylline. These findings demonstrate that pranlukast is a useful agent for the relief of asthma symptoms in patients with chronic asthma, regardless of alternative therapy.

The purpose of the present study was to examine the clinical effectiveness of pranlukast in a practice setting on a large number of patients with mild to severe persistent asthma, because clinical usefulness[22–25] of these receptor antagonists has been reported only in rigorously controlled studies. We used a questionnaire to obtain information on both the impact of asthma on the everyday lives of asthmatics[26–28] and on the effects of treatment in a large number of patients. There is no standard method available for widespread use for assessing symptoms that is readily applicable to general practice. Because some of the goals[29] of asthma therapy are to prevent chronic symptoms, to maintain patients' normal activity levels and to meet patients' and families' expectations for care, we designed our questionnaire to enquire about 33 specific issues related to the activities of daily life.

Because our questionnaire about asthma symptoms has not been validated previously, we administered the questionnaire to 167 outpatients, who declined pranlukast treatment but continued to take the same medications, on two occasions 4–6 weeks apart. Although Juniper *et al*.[26] have devised an asthma quality of life instrument, it is not applicable for use in such a clinical practice setting. As shown in Fig. 1, we found a significant decrease in the number of symptoms in these 167 patients, despite the lack of additional treatment. The reason for the improvement in the control group may be that a clinical visit itself improved compliance with medication, that administration of the questionnaire also improved compliance or that symptom scores of the control group were lower than those of the treatment group at the time of the first questionnaire. However, as shown in Fig. 2, the magnitude of the improvement was significantly less marked than that in the pranlukast-treated group. Interestingly, the group who refused pranlukast treatment had fewer asthma symptoms than those who accepted it at the time of the first questionnaire and the final level of symptoms was similar in both groups. Thus, our findings demonstrate that pranlukast significantly decreased asthma symptoms to a minimal level in patients with persistent asthma.

Although inhaled corticosteroids are potent and effective agents currently available for the treatment of mild, moderate or severe persistent asthma, these agents do not completely control asthma. In the present study, we demonstrated that pranlukast treatment significantly decreased the symptoms of asthma, irrespective of the concomitant use of inhaled steroids, $\beta_2$-adrenergic agonists or sustained-release theophylline. It is not surprising that pranlukast improved the clinical condition of asthmatics concurrently using inhaled corticosteroids, because corticosteroids have been reported not to inhibit the production of cysteinyl leukotrienes in both *in vitro*[30,31] and *in vivo* studies.[32] Although the position of this class of drugs in asthma therapy has not been fully established, our findings indicate that pranlukast has clinical effectiveness in the treatment of symptoms in mild to severe persistent asthma. Because the clinical effectiveness would be seen with any leukotriene modifiers, this class of agent is likely to be of value in the global treatment of asthma.

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