

# Clinical evaluation of response to long-term treatment with Pranlukast in patients with bronchial asthma

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**Summary.** *Background:* Short-term treatment with pranlukast, a leukotriene receptor antagonist, has shown to be effective for the management of asthma. The effectiveness and safety of long-term treatment with pranlukast remains to be established.

*Objectives:* The aim of this study was to determine the effects of pranlukast on morning peak expiratory flow rates (PEFRs), the diurnal variation of these values, and disease severity.

*Methods:* Fifteen men with bronchial asthma were studied for 5 years. During the first year, the subjects were treated with a bronchodilator; some also received inhaled and oral corticosteroids. During the next 4 years, the subjects received pranlukast in addition.

*Results:* Mean PEFR increased after the start of treatment with pranlukast. The increase in PEFR occurred later in subjects with more severe disease. Diurnal variation of PEFR was unchanged, but subsequently decreased. The condition of all subjects improved, but the greatest improvement was obtained in patients with mild to moderate asthma.

*Conclusions:* Long-term treatment with pranlukast is effective for the management of bronchial asthma, particularly in patients with mild to moderate disease. Our results suggest that the effectiveness of antiasthmatic drugs should be evaluated over a period of years, rather than on a short-term basis.

**Key words:** bronchial asthma, leukotriene receptor antagonist, pranlukast

## Introduction

Pranlukast, a selective receptor antagonist of the cysteinyl leukotrienes C<sub>4</sub>, D<sub>4</sub>, and E<sub>4</sub> [1,2], is effective against mild to moderate bronchial asthma [3-7] as well as against moderate to severe asthma [8,9]. Many studies have shown that short-term treatment with pranlukast improves both the signs and symptoms of asthma [3-9], but few have assessed the response to long-term treatment [10]. We retrospectively studied the safety and effectiveness of pranlukast in adults with bronchial

asthma who received the drug for 4 years, following a 1-year observation period.

## Methods

The subjects were 15 men with bronchial asthma (mean age, 55.3 years) treated at the outpatient clinic of our hospital. Nine patients had atopic asthma and 6 non-atopic asthma. Three patients had nasal allergy, and one

Table 1. Clinical Characteristics of Patients

n=	15
Mean age: years (range)	55.3 (29-74)
Sex: Male/Female	15/0
Mean asthma duration: years (range)	23.0 (7-72)
Mean age at asthma onset: years (range)	33.5 (2-57)
Atopic status: Atopic/Non-atopic	9/6
Asthma severity:	
Step 1 (mild)	2
Step 2 (mild)	2
Step 3 (moderate)	4
Step 4 (severe)	7
Asthma medications used:	
Inhaled $\beta_2$ -adrenergic agents	9
Inhaled corticosteroids	14
Oral corticosteroids	9
Oral $\beta_2$ -adrenergic agents	5
Oral theophylline	14

had atopic dermatitis. During the first year, the subjects received inhaled and oral  $\beta_2$ -adrenergic agents (fenoterol, procaterol), oral sustained-release theophylline, inhaled corticosteroids (beclomethasone), and oral corticosteroids (prednisolone) (Table 1). No patient had previously received pranlukast. Disease severity was assessed according to The Guidelines for Prevention and Management of Asthma, 1998, issued by the Study Group for Immunity and Allergy, Japanese Ministry of Health, Labor and Welfare [11]. Baseline disease severity was classified as Step 1 (actual peak expiratory flow rate [PEFR]/predicted PEFR $\times$ 100%: >80%) in 2 patients, Step 2 (70-80%) in 2, Step 3 (60-70%) in 4, and Step 4 (<60%) in 7. The subjects were initially observed for 1 year. They were then additionally given 450 mg/day of pranlukast for 4 years. PEFRs and treatment details were recorded for 5 years.

During treatment with pranlukast, 14 patients regularly received inhaled steroids and 9 regularly received oral steroids; bronchodilators given during the observation period were continued (Table 1). We compared mean values for PEFR, the day time variation of PEFR (morning and evening), and the doses of inhaled and oral steroids between the observation period (year 1) and each year of the 4-year treatment period to examine changes in these variables. Mean values during each year of treatment were also compared. Changes in disease severity were monitored throughout the study.

The statistical significance of differences in mean values was assessed with the use of paired t-tests. P values of less than 0.05 were considered to indicate statistical significance.

## Results

**Peak Expiratory Flow Rates:** Mean percent PEFRs (actual value/predicted value) during years 1, 2, 3, and 4 of treatment with pranlukast were significantly higher than the mean percent PEFR during the observation period (Figure 1). The mean PEFR during year 2 of pranlukast treatment was significantly higher than that during year 1. The mean PEFR during year 3 of pranlukast treatment was significantly higher than that during year 2. Mean PEFRs during years 3 and 4 of pranlukast treatment did not decrease, indicating no change in the response to treatment. There was no significant difference in mean PEFR between year 3 and year 4 of pranlukast treatment.

PEFRs were also examined according to disease severity (Figure 2). In the Step 2 and Step 3 groups, the mean PEFRs during years 1, 2, 3, and 4 of treatment with pranlukast were significantly higher than the values during the observation period. In the Step 2 group, the mean PEFR during year 3 of pranlukast treatment was significantly higher than that during year 1 of treatment. In the Step 3 group, the mean PEFRs during years 2 and 3 of pranlukast treatment were significantly higher than those during years 1 and 2, respectively. In the Step 1 and Step 4 groups, the mean PEFRs during years 2, 3, and 4 of pranlukast treatment were significantly higher than the mean PEFR during the observation period. In addition, the mean PEFR during year 2 of pranlukast treatment was significantly higher than that during year 1 of pranlukast treatment.

**Diurnal variation:** The mean diurnal variation of PEFR during year 1 of pranlukast treatment was similar to that during the observation period (Figure 3). In contrast, the mean diurnal variations of PEFR during years 2, 3, and 4 of pranlukast treatment were significantly smaller than the value during the observation period and that during year 1 of pranlukast treatment, indicating that pranlukast continued to be effective.

The diurnal variation of PEFR was also examined according to disease severity (Figure 4). In the Step 1 group, mean diurnal variations during years 1 and 2 of pranlukast treatment were significantly smaller than those during the observation period. In the Step 2 and Step 3 groups, mean diurnal variations during years 2, 3, and 4 of pranlukast treatment were significantly lower than the values during the observation period and after 1 year of pranlukast treatment. In the Step 4 group, the mean diurnal variation during year 4 of pranlukast treatment was significantly smaller than that during the observation period, whereas the mean diurnal variation during year 2 of pranlukast treatment was significantly larger than that during year 1 of pranlukast treatment.

**Dose of steroid:** The dose of inhaled steroids required by the patients was examined according to the severity of asthma (Figure 5). In the Step 1 group, the mean dose of inhaled steroids during year 4 of pranlukast

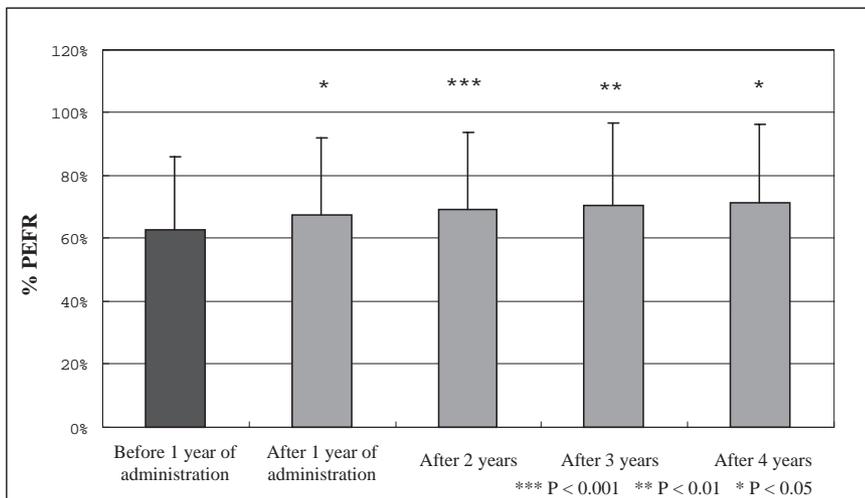


Figure 1. PEFR in all subjects before and after 1, 2, 3, and 4 years of pranlukast treatment.

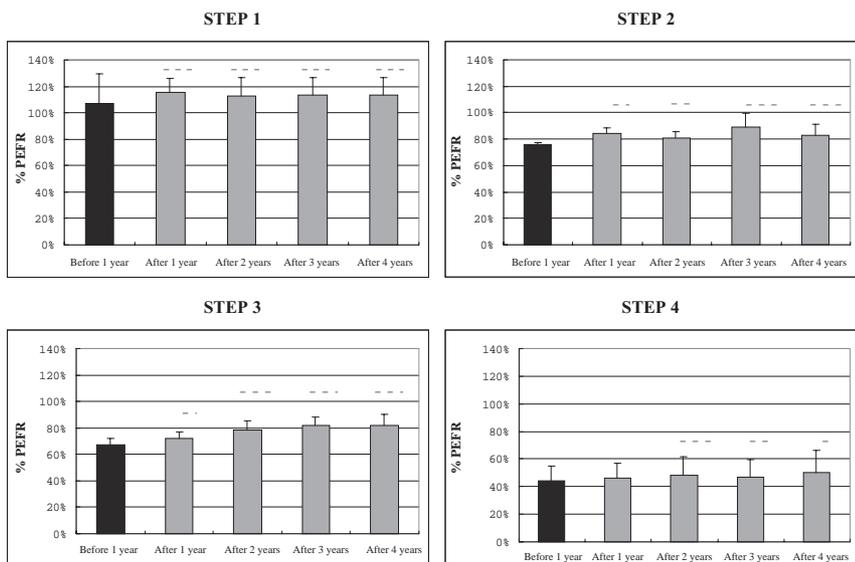


Figure 2. Mean PEFR according to disease severity.

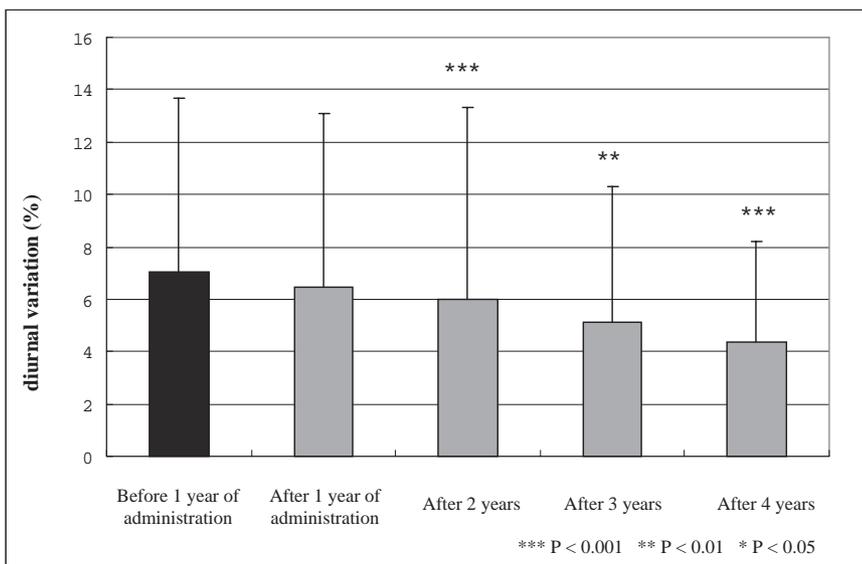


Figure 3. Mean diurnal variations of PEFR in all subjects before and during 1, 2, 3, and 4 years of pranlukast treatment.

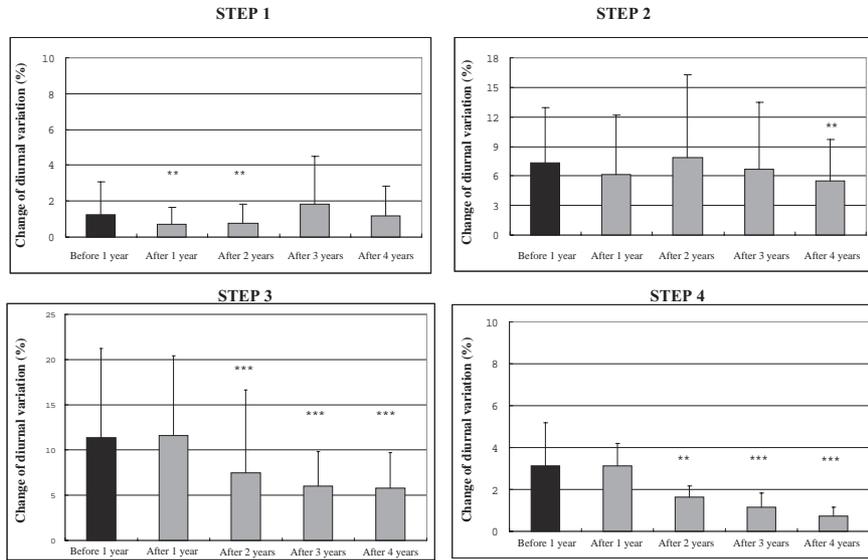


Figure 4. Means diurnal variations of PEFr according to disease severity.

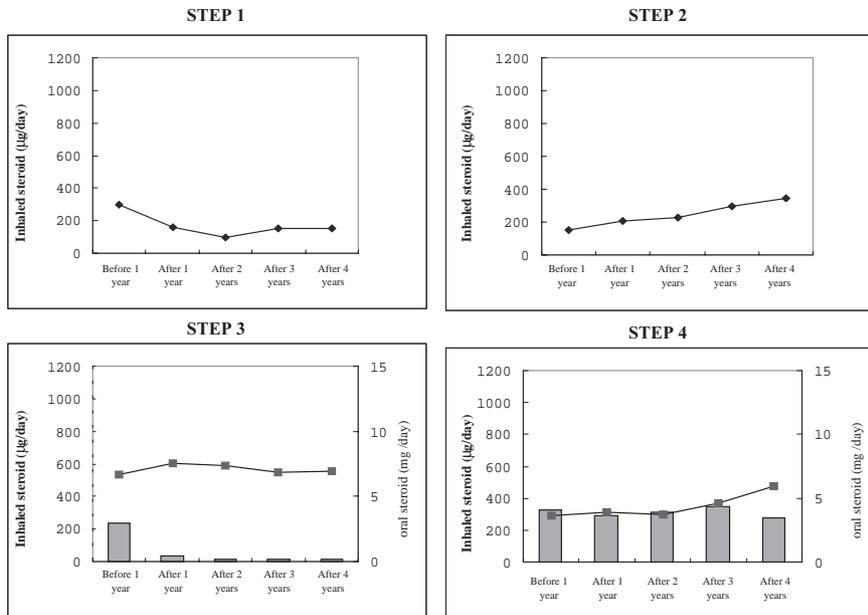


Figure 5. Mean corticosteroid dose according to disease severity.

treatment (150 mg/day) was significantly lower than that during the observation period (300 mg/day). In the Step 2 group, the mean dose of inhaled steroids during year 4 of pranlukast treatment (350 mg/day) was higher than that during the observation period (210 mg/day). In the Step 3 group, the mean dose of inhaled steroids increased transiently, but the dose at study endpoint was similar to that during the observation period. The mean dose of oral steroids required during year 4 of pranlukast treatment (0.9 mg/day) was significantly lower than that during the observation period (3.0 mg/day) because these drugs were discontinued by 2 of the 3 patients. In the Step 4 group, the dose of inhaled steroids increased; the dose of oral steroids during year 4 of pranlukast treatment (3.5 mg/day) was slightly but not significantly lower than that

during the observation period (4.1 mg/day). One of the 6 patients who were receiving oral steroids discontinued their use. The administered dose of inhaled beclomethasone dipropionate (BDP) was estimated to be twofold that of inhaled fluticasone propionate (FP).

**Concomitantly Used Anti-asthmatic Agents**

**Beta-2 agonists:** Oral beta-2 agonists were given to 5 patients. The dose was not changed during the study. Tulobuterol patches were additionally used in 2 patients in the Step 4 group. Inhaled beta agonists were discontinued in 1 patient in the Step 1 group, and the dose was reduced in 2 patients in the Step 3 group. Six of the patients in the Step 4 group received inhaled beta-agonists.

Table 2. Concomitantly used anti-asthmatic agents.

	Patients No.	Glucocorticoids		$\beta$ 2-agonists		Sustained-release theophylline	Anti- cholinergic agents
		Oral	Inhaled	Oral/Patch	Inhaled		
STEP 1	1	-	○	-	-	⊙	-
	2	-	○	-	⊙	○	-
STEP 2	3	-	△→▲FP	△	-	○	⊙
	4	-	△	△	-	-	-
STEP 3	5	△	○	-	△	○	⊙
	6	⊙	△	△	△	△	-
	7	○	△FP	-	○	○	-
	8	-	△→▲FP	-	○	△	-
STEP 4	9	⊙	△FP	△	-	△	○
	10	-	■	-	△	△	-
	11	△	△→▲FP	■TULO	△	△	-
	12	△	△→▲FP	-	△	△	-
	13	△	△→▲FP	△	△	△	■
	14	○	△→▲FP	■TULO	△	○	■
	15	△	△→▲FP	-	△	△	△

⊙: discontinued ○: dose reduced △: dose unchanged ▲: dose increased ■ added

FP: Fluticasone propionate TULO: Tulobuterol patch

**Sustained-release theophylline:** Sustained-release theophylline was discontinued in 1 patient in the Step 1 Group, and the dose was reduced in 1 patient each in the Step 1, 2, and 4 groups and in 2 patients in the Step 3 group.

**Anti-cholinergic agents:** Anticholinergic agents were discontinued in 1 patient each in the Step 2 and 3 groups, and the dose was reduced in 1 patient in the Step 4 group. Anticholinergic agents were additionally given to 2 patients in the Step 4 group (Table 2).

**Changes in Disease Severity:** Disease severity during the observation period was compared with that during year 4 of pranlukast treatment (Figure 6). By the end of the study, the condition of both patients originally in the Step 2 group had improved, and disease severity

was reclassified as Step 1 in 1 patient. Of the 4 patients originally in the Step 3 group, disease severity was reclassified as Step 1 in 2 patients and Step 2 in another 2 by the end of the study. Of the 7 patients originally in the Step 4 group, the condition of 2 patients improved; disease severity was reclassified as Step 2 in 1 and Step 3 in 1. The other 5 patients remained in the Step 4 group. These results indicated an improvement in all severity groups, with the most marked improvement in patients with mild to moderate disease (Steps 1, 2, and 3).

#### Adverse Effects

No adverse effects were reported during the 4 years of treatment with pranlukast.

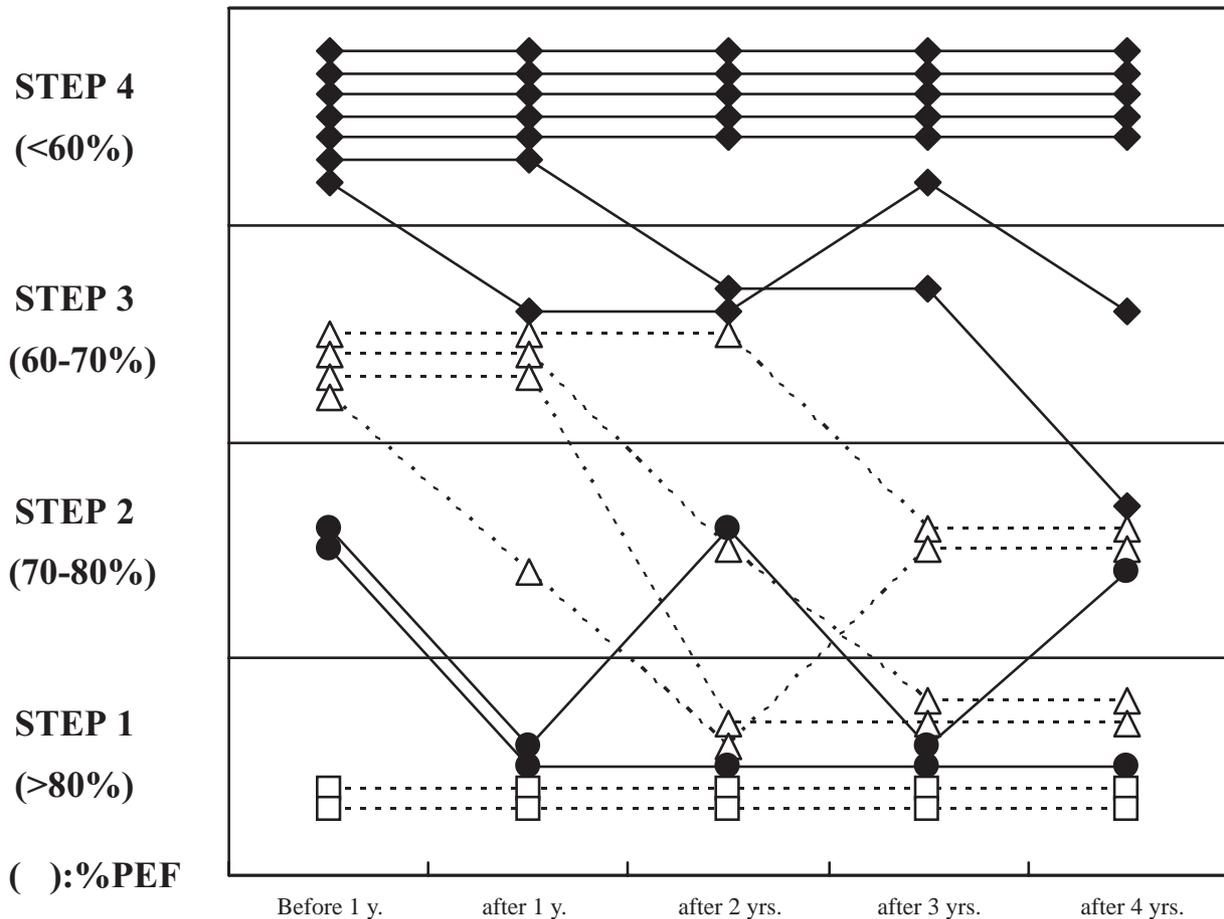


Figure 6. Disease severity before and during 1, 2, 3, and 4 years of pranlukast treatment.

## Discussion

Cysteinyl leukotrienes are linked to the pathogenesis of bronchial asthma [12-14]. They play important roles in mucus secretion in human airways [15], increased vascular permeability [16,17], granulocytic infiltration into asthmatic airways [18], alteration of airway hyperreactivity, promotion of remodeling, and bronchial smooth muscle constriction [19,20].

Although inhaled steroids are considered the most useful anti-inflammatory drugs for the long-term management of bronchial asthma, leukotriene modifiers such as pranlukast have been shown to improve clinical symptoms and respiratory function with a better safety profile. Our results indicate that long-term treatment with pranlukast is safe, effectively controls asthma, and helps reduce disease severity. Pranlukast may therefore suppress exacerbations of asthma as well as prevent decreased responsiveness to treatment.

The severity of the disease decreased during 4 years' treatment with pranlukast, regardless of age, baseline severity, and the presence or absence of atopy. The PEFR

significantly increased, and diurnal variations of PEFR decreased, irrespective of disease severity at baseline.

Previous studies have shown that pranlukast is effective in the management of mild to moderate asthma [3-7] as well as moderate to severe asthma [8,9]. Our results support these previous findings. The PEFR of the patients who had Step 1 disease at baseline gradually increased, despite decreased use of inhaled steroids. The PEFR in the patients with a baseline severity of Step 3 also progressively improved, with decreased use of oral steroids and no change in the dose of inhaled steroids. The PEFR in patients with Step 2 severity at baseline also increased, and both patients in this group showed improvement in disease severity. However, the dose of inhaled steroids in the Step 2 group increased, perhaps because treatment was switched from BDP to FP in 1 patient during year 3 of pranlukast treatment. FP was continued during year 4 of pranlukast administration. Because the PEFR increased and disease severity decreased during year 1 of pranlukast treatment in this patient, the improvement in asthma status is primarily attributed to pranlukast and not to the increased dose of

inhaled steroids used. In the Step 4 group, the mean dose of inhaled steroids was lower than that in the Step 3 group because 1 patient in the former group did not receive BDP treatment until year 4. The increase in the dose of inhaled steroids in years 3 and 4 of pranlukast treatment in the Step 4 group is attributed to the fact that 5 patients switched from BDP to FP, similar to the Step 2 group. The patients were switched to FP because FP was introduced in Japan during the study and was considered to be more effective than BDP, particularly in Step 4 patients. The inhaled steroid dose converted into the equivalent dose of BDP therefore seems to have increased, but the dose of concomitantly used oral steroids could be reduced.

Among the 13 patients who had a baseline severity of Step 2 or higher (excluding the 2 Step 1 patients), disease severity improved by at least one step as compared with baseline in 4 patients (2 with Step 2, 1 with Step 3, and 1 with Step 4) after 1 year of pranlukast treatment, 7 patients (1 with Step 2, 4 with Step 3, and 2 with Step 4) after 2 years, 7 patients (2 with Step 2, 4 with Step 3, and 1 with Step 4) after 3 years, and 7 patients (1 with Step 2, 4 with Step 3, and 2 with Step 4) after 4 years. Of the 13 patients with baseline disease severity of Step 2 or higher, 6 (1 of the 2 with Step 2 disease and 5 of the 7 with Step 4 disease) showed no improvement in the step classification of disease severity (Figure 6). These results suggest that the effectiveness of pranlukast should not be evaluated after only 1 or 2 months of treatment. Increased PEFs and decreased disease severity were maintained during 4 years of treatment with pranlukast, and no adverse reactions occurred. We therefore conclude that long-term treatment with pranlukast is safe and effective.

Finally, not all patients showed clinical improvement in response to treatment with pranlukast, suggesting that there may be responders and non-responders to antagonists of cysteinyl leukotriene receptors [21]. Non-response to such drugs may be related to genetic polymorphism. In the future, identification of patients most likely to benefit from pranlukast might be facilitated by analysis of leukotriene receptor polymorphism.

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