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Evaluation of switching low dose inhaled corticosteroid to pranlukast for step-down therapy in well-controlled patients with mild persistent asthma

Running head: Switching low dose ICS to a LTRA

Key words: asthma, step-down therapy, inhaled corticosteroid, leukotriene receptor antagonist, pranlukast hydrate.

Abstract

***Objective*:**

Treatment guidelines for asthma recommend step-down therapy for well-controlled asthma patients. However, the precise strategy for step-down therapy has not been well defined. We investigated whether well-controlled patients with mild persistent asthma can tolerate a step-down therapy of either a reduced dose of inhaled corticosteroid (ICS) or a switch to a leukotriene receptor antagonist (LTRA), pranlukast hydrate.

***Methods*:**

We recruited 40 adult patients with mild persistent asthma that were well-controlled for at least 3 months with a low-dose ICS therapy. The patients were randomly assigned to either an ICS dose reduction or a switch to pranlukast for 6 months.

***Results*:**

FeNO levels in the pranlukast group were significantly increased over that in the ICS group. There were no significant differences between the two groups for lung function, FOT, at the endpoint. The percentage of patients with controlled asthma was 72.2% in the pranlukast group and 90% in the ICS group. No statistically significant

difference between the two groups in the percentages of patients with treatment failure was observed.

***Conclusions*:**

Patients with mild persistent asthma that is well-controlled by a low dose of ICS can be switched to pranlukast safely for at least 6 months. However, 27.8% of the pranlukast group failed to maintain well-control, and FeNO levels increased with the switch to pranlukast at 6 months. This study was been limited by the small sample size and should therefore be considered preliminary. Further studies are needed to investigate the therapeutic efficacy of LTRA monotherapy as a step-down therapy.

Introduction

The Global Initiative for Asthma (GINA) and most other asthma treatment guidelines recommend the use of inhaled corticosteroids (ICS) as the first-line medication for asthma control in patients with persistent asthma of all severities (1). When asthma symptoms have been well-controlled for at least 3 months, the guidelines further recommend a step-down therapy to avoid the adverse effects of the medication. Although some reports on step-down of therapy have been published, most reports involved patients with moderate asthma (2-6). When asthma is controlled with a low-dose of ICS alone, treatment for most patients may be switched to once-daily dosing (7, 8). It has been reported that patients with mild persistent asthma that is well-controlled with the use of twice-daily inhaled fluticasone propionate (FP) can be switched to once-daily FP plus salmeterol without an increase in the rate of treatment failure (9). This report also suggested that a switch to the oral leukotriene receptor antagonist (LTRA), montelukast, was not as effective, although it provided good asthma control. ICS has little effect on the synthesis and action of cysteinyl leukotrienes (LTs), which are inflammatory mediators in asthma. LTRAs have been shown to be beneficial in double-blind, randomized, placebo-controlled trials (10-12). Price D et al. suggested that LTRAs were equivalent to ICS as a first-line therapy and to a long-acting β_2-agonist (LABA) as an add-on therapy in a diverse patient population with asthma (13). Moreover, Tamaoki J et al. reported that the LTRA

pranlukast hydrate can provide further improvements in asthma symptoms and in pulmonary function similar to that of the inhaled corticosteroid beclomethasone dipropionate (BDP) in mild intermittent (step 1) asthma, as defined by the GINA guidelines (1, 14). Thus, in the present study, we investigated whether well-controlled patients with mild persistent asthma treated by ICS can tolerate a step-down therapy with either a reduction in the dose of ICS or by switching to pranlukast.

Methods

Patients. Outpatients with mild persistent asthma aged 20 years or older were enrolled in this study. The diagnosis of asthma was defined on the basis of a compatible clinical history of episodic symptoms with airflow limitation and variation in pulmonary function by monitoring either forced expiratory volume in 1 second (FEV_1) or peak expiratory flow (PEF). The eligible patients whose severity was treatment step 2 were assessed according to the GINA guidelines (1). The included patients also had been treated for at least 3 months with a low-dose of ICS (equivalent to FP 200 μg/day) therapy. Furthermore, those patients with Asthma Control Test (ACT) scores >19 were associated with "well-controlled" or "totally-controlled" asthma. The present study was reviewed and approved by the Juntendo University Research Ethics Committee, and written informed consent was obtained from each patient prior to their participation in the study. This study was registered in the UMIN Clinical Trial Registry (UMIN000001983) on May 19, 2009 (http://www.umin.ac.jp/).

Those patients having any of the following criteria were excluded: a diagnosis of chronic obstructive pulmonary disease (COPD) defined by the GOLD guidelines (15), any current respiratory disorder other than asthma, a history of near fatal asthma, treatment with oral corticosteroids, hospitalization due to asthma in the previous 6 months, treatment with other medications, such as LABA, LTRA, theophylline, and/or anticholinergic agents during the previous 3 months, and hypersensitivity to

pranlukast.

Study design and measurement of clinical parameters. This was a prospective, randomized, controlled, open, two-arm parallel group study. Eligible patients were randomly allocated by the numbered container method to receive either a reduction in the dose of ICS (equivalent to FP 100 μg/day) or a switch to pranlukast. These step-down therapies were followed by a 24-week study period. The primary outcome measure was the percentages of patients with treatment failure, defined as the occurrence of any one of the following events: hospitalization, an urgent medical visit for asthma, need for either dosage re-escalation or additional drugs for asthma as determined by the study physician, and judgment by a physician that the patient should stop treatment for reasons of safety. The patients with treatment failure were also defined as those with uncontrolled asthma. The ACT score, pulmonary function tests, including respiratory resistance and reactance by the forced oscillation technique (FOT) and the fractional exhaled nitric oxide (FeNO) levels were measured every 8 weeks. Other assessment parameters were the number of acute exacerbations, such as the events requiring treatment with a systemic steroid, and number of rescue inhalations of short-acting inhaled beta agonists (SABA). The FeNO levels were measured in accordance with the American Thoracic Society recommendations, at a constant flow of 0.05 L/s against an expiratory resistance of 20 cm water with a chemiluminescence analyzer (NOA 280i, Sievers, Boulder, CO, USA). FOT was

measured using a MasterScreen Impulse oscillometry (Jaeger, Wurzburg, Germany).

Statistical analysis. Data are expressed as the mean ± SD. Sample normality was examined using the Shapiro-Wilk test, and differences in parameters between populations were analyzed for significance using the Student t-test, Mann–Whitney U-test, the chi-square test, and Fisher's exact test as needed. Kaplan-Meier estimates of the cumulative incidence of treatment failure (i.e., patients who needed step-up treatment) were calculated from the date of initiation of step-down therapy to the date of treatment failure. Comparisons between groups were based on the log-rank test according to the treatment (ICS *vs.* pranlukast). Differences were considered to be statistically significant when the *p* values were 0.05 or less. Statistical analyses were performed with the Statistical Package for Social Sciences software (SPSS, Inc., Chicago, IL, USA).

Results

Forty patients with asthma were enrolled in the study (Figure 1). The eligible patients were treated with either a low daily dose (200 μg) of FP or a therapeutically equivalent dose of either BUD or ciclesonide (CIC). The patients were randomly assigned to either the pranlukast group (20 patients) or the other group who received either inhaled 100 μg FP daily or a therapeutically equivalent dose of either BUD or CIC (20 patients). Two patients in the pranlukast treatment group withdrew consent and dropped out of the study (Figure 1). Thus, a per-protocol set (PPS) cohort included 38 patients. Baseline patient characteristics at enrollment and at randomization of the two groups are summarized in Table 1. The male to female ratio was 18: 20, and the mean age was 53.1 ± 15.2 years (range: 21-81 years). The mean duration of asthma was 9.8 ± 11.3 years, while the mean FEV_1% was 77.1 ± 8.0%. No significant differences in the baseline characteristics of the patients were observed in either treatment group. Previous reports suggested that the worsening of allergic rhinitis symptoms in patients with asthma is associated with worsening asthma symptoms (16, 17). In this study, there were no significant differences in the number of patients with atopy, allergic rhinitis, serum positive specific IgE to pollen, and the seasonal pattern of distribution in the study periods in either treatment group (Table 1). During the study period, none of the patients dropped out because of adverse side effects. Intestinal symptoms (soft stool) were reported by 1 patient in the pranlukast group

(Table 2).

The ACT score and the parameters in both the pulmonary function tests and FOT were maintained in almost all of the patients during the study period except for the FeNO levels (Table 3 and Figure 2). At 6 months, the FeNO levels were significantly higher in the pranlukast group than that in the ICS group. At the end of the study, the percentage of patients with controlled asthma was 72.2% in the pranlukast group and 90% in the ICS group (Table 2). Figure 3 shows the Kaplan-Meier plot of the cumulative percentages of patients with treatment failure for the two groups. The most common reason for treatment failure was either a need for dosage re-escalation of ICS or a switch to ICS in symptomatic asthmatic patients. One patient in the ICS group had an unscheduled emergency department visit. One patient in the pranlukast group and one in the ICS group needed systemic use of corticosteroids. However, there were no statistically significant differences between the two groups in the percentages of patients with treatment failure.

Discussion

Asthma treatment guidelines recommend the use of ICS for patients with mild persistent asthma as the first-line controller medication and as the step-down therapy to the minimum dose needed to maintain asthma control (1). These corticosteroids have little effect on either the synthesis or biological actions of cysteinyl LTs which are a family of inflammatory lipid mediators involved in asthma (18). Although the efficacy of LTRAs has been demonstrated as beneficial in double-blind, randomized, placebo-controlled trials (10-12), results of prior mostly double-blind, randomized, controlled trials comparing LTRAs and ICS have suggested that LTRAs have less efficacy than that of ICS for patients with mild persistent asthma (11, 19-21). However, one trial compared LTRAs and ICS when used for patients as a first-line medication and found that LTRAs are equivalent to ICS with regard to the effect on asthma-related quality of life at 2 months in a diverse patient population with asthma, but equivalence was not shown at 2 years (13). Moreover, a study by the American Lung Association Asthma Clinical Research Centers reported that 78.7% of patients with asthma that is well-controlled with the use of ICS (equivalent to FP 200 μg/day) when switched to montelukast remained free of symptoms for 16 weeks, although the switch to montelukast resulted in an increased rate of treatment failure and decreased asthma control (9). In the current study, we demonstrated that patients with mild persistent asthma who are well-controlled with a low dose of ICS (equivalent to FP 200 μg/day)

can be safely switched to a LTRA, pranlukast monotherapy, for 6 months. Although 27.8% of the pranlukast group and 10.0% of the ICS group failed to maintain well-control at 6 months, there was no statistically significant difference between the pranlukast and ICS groups in the percentage of patients with treatment failure. These discrepant findings between previous studies and the current study may be due to either the better control status of our enrolled asthma patients using the low dose of ICS or small sample size which is the most important limitation of this study. This study should therefore be considered preliminary. We suggest that longitudinal studies with a longer period and a larger number of patients are needed to confirm our findings.

Inducible nitric oxide synthase (iNOS) is upregulated in the epithelium and in other cells in the airway of the patients with asthma, and FeNO levels have been advocated as a marker reflecting eosinophilic airway inflammation (22). High FeNO levels are observed in the patients with non-severe asthma (23-27) and decrease in response to treatment with corticosteroids (28, 29). Therefore, measurement of FeNO levels is a relatively simple and non-invasive test for the steroid-naïve asthma patients (30). A previous study demonstrated that pranlukast significantly reduced the eosinophil levels in the sputum from patients with asthma, but it did not reduce the FeNO levels (31). However, FeNO levels decrease with the use of montelukast therapy in asthma patients (32-35). Our study has also shown that ICS could maintain lower

FeNO levels during the study period, but pranlukast was not able to control FeNO levels in some patients. These results and previous reports suggested that pranlukast, but not montelukast, either does not have the potential to reduce FeNO levels or may induce poor adherence to therapy. Moreover, several randomized control trials have prospectively evaluated whether using FeNO levels to guide anti-inflammatory therapy in predominantly mild-to-moderate asthma suggest that an asthma treatment strategy based on the measurement of FeNO levels did not result in a reduction in asthma exacerbations or in the total amount of inhaled corticosteroid therapy, when compared with current asthma guidelines (36-40). However, in asymptomatic asthmatic children, the likelihood of relapse following withdrawal of ICS therapy is greatest in patients whose FeNO levels increase during the 1 month after discontinuation of ICS (41). In this study, although there was a statistically significant difference between the increased FeNO levels in the pranlukast group, the percentages of patients with treatment failure were similar in both treatment groups. These results suggested that further studies with a longer time period and a larger number of patients are required to investigate whether the increased FeNO levels are associated with treatment failure and with uncontrolled asthma and might reflect a future risk in step-down therapy with pranlukast.

Three principal reasons for choosing LTRAs over ICS are cost, safety, and adherence in clinical practice (42-44). A generic version of pranlukast first became

available in Japan, and generic brands of montelukast and zafirlukast are expected to be available in the near future. The LTRAs have a very good safety profile. Indeed, ICS have a few side effects, including hoarseness and oral candidiasis, and a few systemic glucocorticoid effects, such as inhibition of bone growth in children (44). Furthermore, many patients with asthma also have rhinitis and other coexisting allergic conditions in which LTs may contribute to the symptoms (43).

Conclusions

Our study demonstrated that patients with well-controlled, mild persistent asthma who are taking low doses of ICS can be switched safely to pranlukast for at least 6 months. Although there was no statistically significant difference between the pranlukast and ICS groups in the percentages of patients with treatment failure, 27.8% of the pranlukast group failed to maintain well-control, and FeNO levels increased significantly with the use of pranlukast at 6 months. These conclusions have been limited by our small sample size and should therefore be considered preliminary. Future directions include the examination of other LTRAs, larger sample sizes, and longer studies.

Abbreviations: ICS: inhaled corticosteroid, FP: fluticasone propionate, BDP: beclomethasone dipropionate, CIC: ciclesonide, LTs: cysteinyl leukotrienes, LTRA: leukotriene receptor antagonist, FEV_1: forced expiratory volume in 1 second, PEF: peak expiratory flow, FOT: forced oscillation technique, FeNO: fractional exhaled nitric oxide, GINA: Global Initiative for Asthma, LABA: long-acting β_2-agonist, ACT: Asthma Control Test, COPD: chronic obstructive pulmonary disease, PPS: per-protocol set.

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Table 1. Baseline characteristics of the study population.

Table 2. Comparison between groups at the end of the study.

Table 3. Change in parameters from baseline.

$^{*}p < 0.05$ and $^{**}p < 0.01$, significantly different from corresponding values for inhaled corticosteroid (ICS) group.

ACT, Asthma Control Test; FeNO, ractional exhaled nitric oxide; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 second; PEF, peak expiratory flow; MMF, mid-maximal flow rate; R5, resistance at 5 Hz; R20, resistance at 20 Hz.

Figure Legends

Figure 1. Flow of patients in study.

Figure 2. Changes in the Asthma Control Test (ACT) score, the fractional exhaled nitric oxide (FeNO) levels, and the parameters in pulmonary function tests from baseline. Patients with mild persistent asthma received either a reduced dose of inhaled corticosteroid (ICS) (closed circle) or pranlukast (PL) (open circle) at 0 months (ICS n = 20; PL n = 18), 2 months (ICS n = 20; PL n = 18), 4 months (ICS n = 19; PL n = 16), and 6 months (ICS n = 18; PL n = 13). Values are means ± SD; * $p < 0.05$, significantly different from corresponding values for ICS group.

Figure 3. Kaplan-Meier estimates of cumulative percentages of patients with treatment failure.

Figure 1. Harada et al.

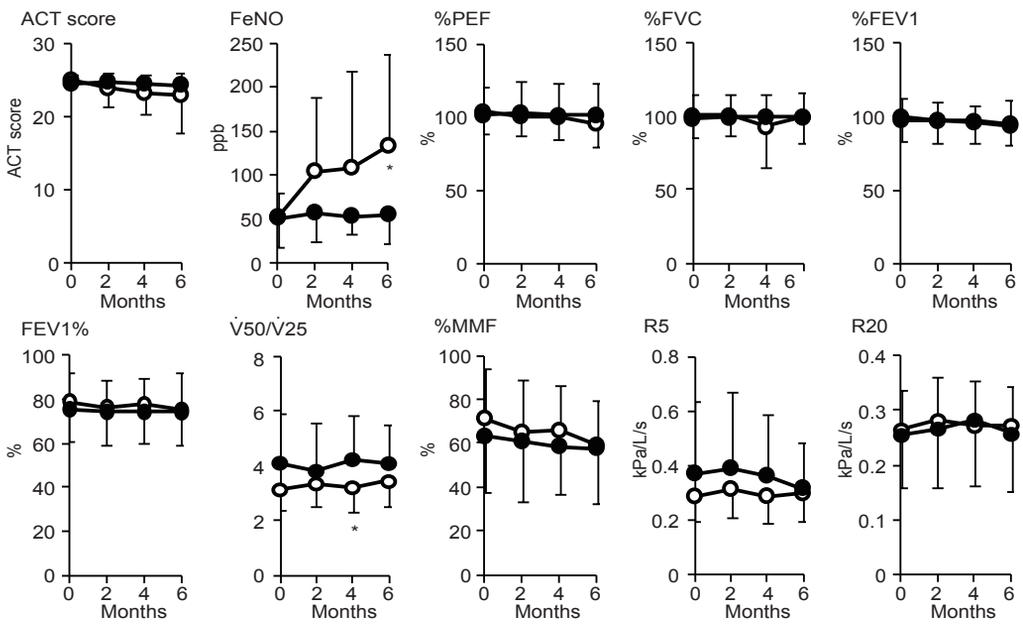

Figure 2. Harada et al.

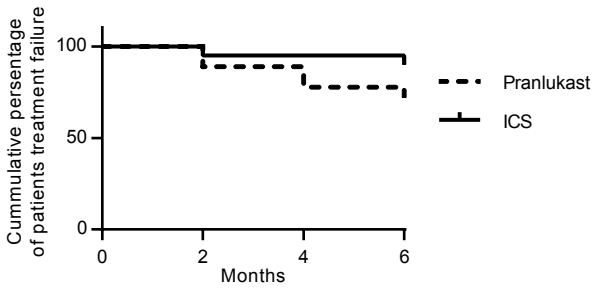

Table 1. Harada et al.

	PL (n = 18)	ICS (n = 20)	*P* value
Age (years)	49.2±14.3	56.5±15.6	0.12
Median (Range)	47.5 (21 – 76)	62.0 (25 – 81)	
Gender; Male / Female	9/9	9/11	0.76
BMI (kg/m^2)	23.1±3.2	21.2±3.4	0.11
Median (Range)	22.5 (18.6 - 30.0)	20.8 (15.6 - 30.8)	
Duration of asthma (years)	8.0±7.1	11.4±14.0	0.97
Median (Range)	5.0 (1 – 24)	4.0 (0 – 47)	
Never smokers	12	15	0.57
Smokers (EX/Current)	6 (5/1)	5 (5/0)	
Atopy/nonatopy	14/4	16/4	1.00
Allergic rhinitis	8	7	0.55

Table 2. Harada et al.

		Pranlukast (n = 18)	ICS (n = 20)	*p* value
ACT total score	Baseline	24.9±0.5	24.4±1.3	0.11
	6 Mo	22.9±5.1	24.3±1.6	0.52
	Change at 6 Mo	-2.00±5.13	-0.21±1.27	0.29
FeNO (ppb)	Baseline	52.3±27.7	51.4±33.0	0.69
	6 Mo	132.9±103.6	55.3±32.1	0.05*
	Change at 6 Mo	85.4±90.6	1.97±28.8	0.005**
FVC (L)	Baseline	3.65±1.13	3.31±0.85	0.47
	6 Mo	3.71±1.12	3.31±0.89	0.27
	Change at 6 Mo	-0.05±0.23	-0.01±0.16	0.96
%FVC (%)	Baseline	100.6±15.0	98.6±16.3	0.58
	6 Mo	99.5±17.8	99.8±16.6	0.89
	Change at 6 Mo	-2.30±6.89	1.61±8.56	0.43
FEV_1 (L)	Baseline	2.88±0.83	2.50±0.74	0.15
	6 Mo	2.78±0.75	2.46±0.78	0.15
	Change at 6 Mo	-0.17±0.22	-0.05±0.13	0.22
%FEV_1 (%)	Baseline	99.9±12.8	97.9±14.3	0.40
	6 Mo	94.1±17.4	95.3±14.7	0.55
	Change at 6 Mo	-5.15±8.84	-1.84±5.91	0.63
FEV_1% (%)	Baseline	79.0±7.6	75.4±8.1	0.09
	6 Mo	75.1±9.2	74.0±8.3	0.63
	Change at 6 Mo	-3.95±4.30	-1.18±2.86	0.22
PEF (L/sec)	Baseline	8.44±2.15	7.29±2.22	0.11
	6 Mo	8.17±2.14	7.37±2.44	0.29
	Change at 6 Mo	-0.49±1.01	-0.01±0.45	0.11
%PEF (%)	Baseline	104.1±14.3	101.7±19.9	0.33
	6 Mo	96.1±16.4	101.8±22.8	0.73
	Change at 6 Mo	-5.86±14.0	-0.26±6.36	0.13
$\dot{V}50/\dot{V}25$	Baseline	3.15±0.74	4.12±1.81	0.07
	6 Mo	3.45±0.89	4.11±1.42	0.18
	Change at 6 Mo	0.39±0.62	-0.02±0.75	0.14
%MMF (%)	Baseline	71.1±22.6	62.9±25.2	0.19
	6 Mo	58.9±20.4	57.6±24.7	0.48
	Change at 6 Mo	-9.46±9.77	-4.40±7.29	0.15
R5 (kPa/L/s)	Baseline	0.29±0.09	0.37±0.26	0.42
	6 Mo	0.30±0.10	0.32±0.17	0.84
	Change at 6 Mo	0.01±0.11	-0.01±0.05	0.78
R20 (kPa/L/s)	Baseline	0.27±0.07	0.26±0.10	0.71
	6 Mo	0.27±0.07	0.26±0.11	0.53
	Change at 6 Mo	0.01±0.08	-0.01±0.06	0.76

Table 3. Harada et al.

	Pranlukast (n = 18)	ICS (n = 20)	*P* value
Hospitalization and visit to an emergency department	0	1	1.00
Side effect	1; soft stool	0	0.48
The frequency of shortness of breath (ACT score), mean	4.4	4.8	0.29
The frequency of asthma symptoms at night or earlier morning (ACT score), mean	4.2	4.9	0.23
The frequency of SABA use (ACT score), mean	4.6	5.0	0.11
Controlled asthma (%)	13 (72.2)	18 (90.0)	0.22
Uncontrolled asthma (%)	5 (27.8)	2 (10.0)	