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ORIGINAL ARTICLE

Effects of the Addition of Beta2-agonist Tulobuterol Patches to Inhaled Corticosteroid in Patients with Asthma

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ABSTRACT

Background: Whether the additive effects of the tulobuterol patch (TP), the world's first transdermal beta2-agonist preparation, are useful in asthma patients receiving inhaled corticosteroid (ICS) is unclear. To examine the add-on effects of TP on bronchial hyperresponsiveness and reduction of the percentage of sputum eosinophils, and to compare add-on effects of TP, slow-release theophylline (SRT), and a leukotriene receptor antagonist (LTRA) in patients with asthma receiving ICS.

Methods: Study 1: We randomly allocated 24 patients with asthma receiving ICS alone in equal numbers to either control treatment (ICS alone at conventional doses) or TP treatment (ICS at conventional doses plus TP at 2 mg/day). Following a 2-week observation period, patients received the allocated drug regimens for 4 weeks. Methacholine challenge test and measurement of percentage of eosinophils in hypertonic saline-induced sputum were performed before and after the treatment period. Study 2: We compared add-on effects of TP, SRT, and LTRA in 65 patients with asthma receiving ICS alone, using spirometry and peak expiratory flow (PEF). Participants in these studies had experienced decrease in morning PEF to <80% of the predicted value at least twice a week.

Results: Study 1: In the TP group, improvement of bronchial hyperresponsiveness and decrease in percentage of sputum eosinophils both indicated a statistically significant difference ($p < 0.01$, and $p < 0.05$, respectively). These findings were not observed in the control group. Study 2: forced expiratory volume in 1 second (FEV_1) and PEF markedly increased after treatment with TP compared with treatment with SRT or LTRA.

Conclusions: These findings suggest that TP can be used as a long-term add-on controller for patients with asthma receiving ICS.

KEY WORDS

airway inflammation, bronchial asthma, bronchial hyperresponsiveness, inhaled corticosteroids, tulobuterol patch

INTRODUCTION

Bronchial asthma is a chronic disease associated with allergic airway inflammation, and causes airflow obstruction, bronchial hyperresponsiveness, and airway remodeling as it progresses. The most important target in the long-term treatment of asthma control is allergic airway inflammation, and consensus has been reached worldwide that inhaled corticosteroids (ICS) are useful as first-line controllers for long-term management of bronchial asthma. However, the efficacy of ICS plateaus at high doses, and adverse reactions to high-dose ICS can be critical.[1] Many patients with asthma do not respond well to ICS alone and experience deterioration in the respiratory function in the morning, also known as 'morning dip'. It has been re-

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ported that the addition of another controller to a regimen of ICS regimen at regular doses is more beneficial than increasing the dosage of corticosteroid for treating such patients.[2-7] In global guidelines for the treatment of asthma, such as those provided by the Global Initiative for Asthma (GINA) and the US National Institutes of Heath (NIH), long-acting inhaled beta2-agonists, such as salmeterol, are positioned as first add-on controllers for inhaled corticosteroids because of their excellent improvement of airflow obstruction.[8,9] In addition, slow-release theophylline preparations have attracted interest because they exhibit anti-inflammatory as well as bronchodilator effects.[10,11] Leukotriene receptor antagonists have been demonstrated to be clinically beneficial in many countries, and have been confirmed to inhibit airway infiltration by eosinophils.[7,12]

The tulobuterol patch (Abbott Japan, Tokyo, Japan), the world's first transdermal beta2-agonist preparation, was developed in Japan, and uses a transdermal drug delivery system that can maintain effective blood levels of tulobuterol for 24 hours when applied to the skin once daily. Its adhesive layer is stable when attached to a mildly fat-soluble and basic surface, and serves as a drug container because its reservoir system retains tulobuterol as crystals. With this system, the concentration of soluble tulobuterol in the adhesive layer is stably maintained for a long period of time, and the patch releases tulobuterol continuously into the skin to which it adheres.[13] Since currently available oral beta2-agonists reach peak blood concentrations within 3 hours of administration, patients with asthma who take this before bed cannot achieve maximum bronchodilation in the early morning. In addition, oral beta2-agonists often cause generalized, clinically significant adverse drug reactions such as tremor and palpitations due to steep increases in blood drug concentration. However, the tulobuterol patch overcomes these disadvantages by including a special transdermal drug delivery system. According to guidelines for treatment and control of asthma in Japan, the tulobuterol patch is a useful long-acting beta2-agonist.[14] Tamura *et al.* have reported that the tulobuterol patch exerts dose-related, add-on effects in patients receiving ICS.[15]

In the present study, to clarify the usefulness of the tulobuterol patch as an add-on controller for patients receiving ICS for long-term management of asthma, we examined the add-on effects of the tulobuterol patch in morning peak expiratory flow (PEF), bronchial hyperresponsiveness (BHR), and percentage of sputum eosinophils in patients receiving ICS. In addition, we compared the add-on effects of the tulobuterol patch, slow-release theophylline, and a leukotriene receptor antagonist in patients receiving ICS clinically.

METHODS

STUDY 1

The participants were adult, non-smoking patients with stable bronchial asthma with minimal or no symptoms who visited the Department of Allergology of Mazda Hospital regularly, had received ICS for at least 6 months before the study, received ICS alone for asthma treatment (fluticasone propionate $\geq$200 μg/day) without other controllers during the 4-week period preceding the study, had experienced a decrease in morning PEF to <80% predicted value at least twice a week, and for whom treatment with short-acting inhaled beta2-agonists had improved morning PEF by $\geq$15%. Patients who had undergone systemic administration of corticosteroids during the preceding 4-week period, had signs/symptoms of viral infection during this study, and those with conditions such as COPD, possibly hindering evaluation of drug treatment, were excluded.

Using the envelope method, eligible patients, who were matched by dose of ICS (fluticasone propionate at 200 μg/day, 400 μg/day, or 800 μg/day), were randomly allocated to either control treatment (with ICS at conventional doses) or tulobuterol patch treatment (ICS at conventional doses plus tulobuterol patch at 2 mg/day in the evening) for each ICS dose. The envelopes were opened by an independent pharmacist involved in neither the diagnosis nor treatment of the patients evaluated. Table 1 shows the characteristics of the enrolled patients. Although treatment with 800 μg/day of fluticasone propionate alone appeared to be non-standard, in patients who exhibited a good course with treatment with 800 μg/day of fluticasone propionate and another controller and who wished to discontinue the combined controller, treatment with 800 μg/day of fluticasone propionate alone was selected.

Following a 2-week observation period, patients received the allocated drug regimens for 4 weeks, and underwent PEF monitoring during the observation and treatment periods to evaluate changes in morning PEF. Methacholine challenge testing, measurement of percentage sputum eosinophils, and spirometry were performed before the treatment period and after a 2-day washout period following the treatment period. PEF was measured using a mini-Wright peak flow meter (Clemente Clarke International Ltd., Harlow, Essex, UK). PEF was predicted using Tsukioka's equation, and percentage of measured to predicted PEF (% PEF) was calculated.[16] Bronchial responsiveness was evaluated by methacholine challenge.[17] Methacholine chloride (Sigma Chemical Co., St. Louis, MO, USA) was dissolved in physiological saline to obtain two-fold-increasing concentrations (0.04 to 20 mg/mL). Saline or methacholine solution was inhaled from a Devilbiss 646 Nebulizer (Devilbiss Co., Somerset, PA, USA) at 5 L/minute. Nebulizer

Table 1 Characteristics of patients in the study 1

Characteristic	No.	
	Tulobuterol patch group	Control group
No.	12	12
Sex, male/female	4/8	4/8
Age (years)	48.7 ± 4.5† (29-71)	50.2 ± 4.4† (24-70)
FVC, % predicted value	100 ± 2.7† (74-130)	95 ± 4.4† (75-130)
FEV_1, % predicted value	85 ± 2.5† (66-100)	84 ± 4.4† (65-107)
FEV_1/FVC (%)	73 ± 0.7† (64-86)	75 ± 1.7† (68-85)
Type, extrinsic/intrinsic	8/4	9/3
Severity, Step 1/2/3/4	0/4/4/4	0/4/4/4
Inhaled corticosteroid, FP 200/400/800 (μg/day)	4/4/4	4/4/4

† Mean ± SE (range). FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 second; FP, fluticasone propionate.

output was 0.28 mL/2 minute. After a 2-minute inhalation of saline or methacholine solution by tidal breathing wearing a nose clip, spirometry was performed (Chestac-11; Chest MI, Tokyo, Japan). After changes in forced expiratory volume in 1 second (FEV_1) following saline inhalation were confirmed to be below 10%, two-fold-increasing concentrations of methacholine solution were successively administered until a decrease of 20% or more in FEV_1. Values were semi-logarithmically plotted, and the methacholine concentration producing 20% decrease in FEV_1 ($PC20\text{-}FEV_1$) was calculated as an index of bronchial hyperresponsiveness (BHR). Sputum specimens to determine percentage sputum eosinophils were induced by inhalation of increasing concentrations of hypertonic saline (0.9, 1.8, 3, 4, and 5%), and patients were encouraged to cough deeply after each inhalation. Cell plugs in sputum were separated from saliva and Wright-Giemsastained to count inflammatory cells. Eosinophil percentages were determined by counting 900 cells by light-microscopy.[18]

Written informed consent was obtained from all patients after explanation of the study's purpose. The study protocol was approved by the Mazda Hospital Ethics Committee.

Methacholine $PC20\text{-}FEV_1$ values are presented as geometric means with the geometric standard error of the mean (GSEM) expressed as a factor, while baseline FVC and FEV_1 values are presented as arithmetic means with standard errors of the mean (SEM). Values of %PEF and percentages of eosinophils are presented as arithmetical means with SEM.

Categorical data were examined by the chi-square test or Mann-Whitney U-test. Wilcoxon's signed-rank sum test was used for bronchial responsiveness, percentage sputum eosinophils, spirometry findings, and morning PEF. p values of <0.05 (two-tailed) were considered to indicate a statistically significant difference.

STUDY 2

The participants in this study were adult, nonsmoking patients with stable bronchial asthma who visited the Department of Allergology of Mazda Hospital regularly, who had received inhaled corticosteroids for at least 6 months before the study, who were receiving inhaled glucocorticosteroid alone for treatment of asthma (fluticasone propionate at $\geq$200 μg/day or beclomethasone dipropionate at $\geq$200 μg/day) without other controllers during the 4-week period preceding the study, and who had experienced a decrease in morning peak expiratory flow (PEF) to <80% of the expected value at least twice a week. Since no criteria for asthmatic signs/symptoms other than PEF were included, many patients in Study 2 were nearly completely asymptomatic. Patients who had received systemic administration of corticosteroids during that period, who exhibited signs/symptoms of viral infection during the preceding 4-week period, or who had conditions such as COPD which might hinder evaluation of the efficacy of drug treatment were excluded from the study.

Eligible patients were randomly allocated to the following 4 groups using the envelope method: a control group (inhaled corticosteroids at conventional doses alone), a pranlukast group (inhaled corticosteroids at conventional doses plus the leukotriene receptor antagonist pranlukast at 450 mg/day, divided into 2 doses, morning and evening), a slow-release theophylline group (inhaled corticosteroids at conventional doses plus the slow-release theophylline agent Uniphyl® at 400 mg/day in the evening), or a tulobuterol patch group (inhaled corticosteroids at conventional doses plus a tulobuterol patch at 2 mg/day in the evening). The envelopes were opened by an independent pharmacist involved in neither the diagnosis nor the treatment of the patients evaluated. Table 2 shows the clinical characteristics of the patients enrolled in the study.

Following the 2-week observation period, the patients received the allocated drug regimens for 4 weeks, and underwent spirometry before and after the 4-week treatment period to evaluate changes in morning PEF. PEF was measured using a Mini-

Table 2 Characteristics of patients evaluated in the study 2

Factor		Group C	Group P	Group U	Group T
Age (years)	-19	1	0	0	0
	20-29	1	1	0	1
	30-39	1	1	3	4
	40-49	4	5	3	3
	50-59	4	7	6	4
	60-69	3	1	3	1
	70-	1	2	1	4
Sex, female/male		10/5	12/5	5/11	11/6
Type, intrinsic/extrinsic		4/11	5/12	6/10	5/12
Duration (years)	-5	5	4	5	6
	6-10	4	5	6	6
	11-20	5	5	3	1
	21-30	1	3	2	3
	31-40	0	0	0	1
	41-50	0	0	0	0
Inhaled corticosteroids					
BDP 200-400 μg/day		3	3	3	2
BDP 400-800 μg/day		1	2	4	2
BDP≥800 μg/day		1	1	1	0
FP 200-400 μg/day		6	3	0	5
FP 400-800 μg/day		3	6	4	5
FP≥800 μg/day		1	2	4	3

Abbreviations: Group C, control group; Group P, pranlukast group; Group U, slow-release theophylline group; Group T, tulobuterol tape group; BDP, beclomethasone dipropionate; FP, fluticasone propionate.

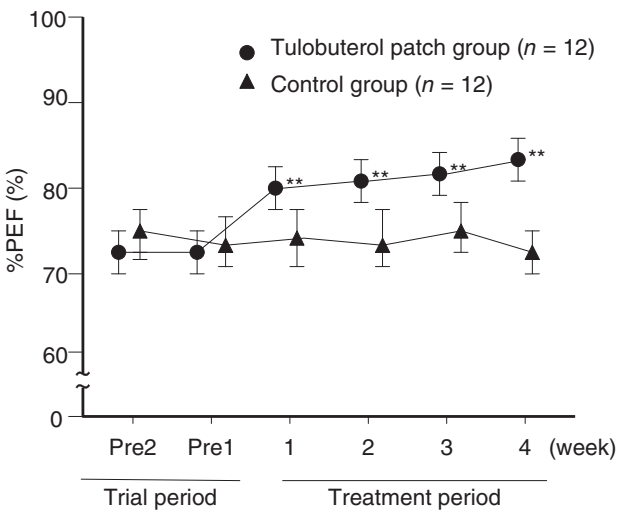

Fig. 1 Changes in % predicted value of morning peak expiratory flow (PEF) before to during the four-week treatment period in the tulobuterol patch and control groups. Values are presented as means and standard errors of the mean (SEM). $^{**}p < 0.01$ vs (Pre 2 and Pre1)/2.

Wright peak flow meter (Clemente Clarke International Ltd., Harlow, Essex, UK). PEF was predicted using Tsukioka's equation, and the ratio of percentage measured to predicted PEF (%PEF) was calculated.[16]

Written informed consent was obtained from all patients who participated in this study after explanation of the purpose of the study. The study protocol was approved by the Ethics Committee of Mazda Hospital.

For statistical analysis, categorical patient characteristics were examined using the chi-square test. Within- and between-group comparisons of pulmonary function test results were performed using Wilcoxon's signed-rank sum test and the Mann-Whitney U test, respectively. *P* values of less than 0.05 (two-tailed) were considered to indicate a statistically significant difference.

RESULTS

STUDY 1

Clinical characteristics and conditions noted during the observation period for the 24 patients subject to analysis are shown in Table 1. There were no significant ($p < 0.05$) biases in the distribution of patients among groups for any background factor.

Mean %PEF in the tulobuterol patch group was 72.5 ± 2.2% during the observation period, 80.0 ± 1.8% at week 1 of treatment, 80.5 ± 2.2% at week 2 of treatment, 81.4 ± 2.4% at week 3 of treatment, and 82.9 ± 1.9% at week 4 of treatment. The %PEF thus improved

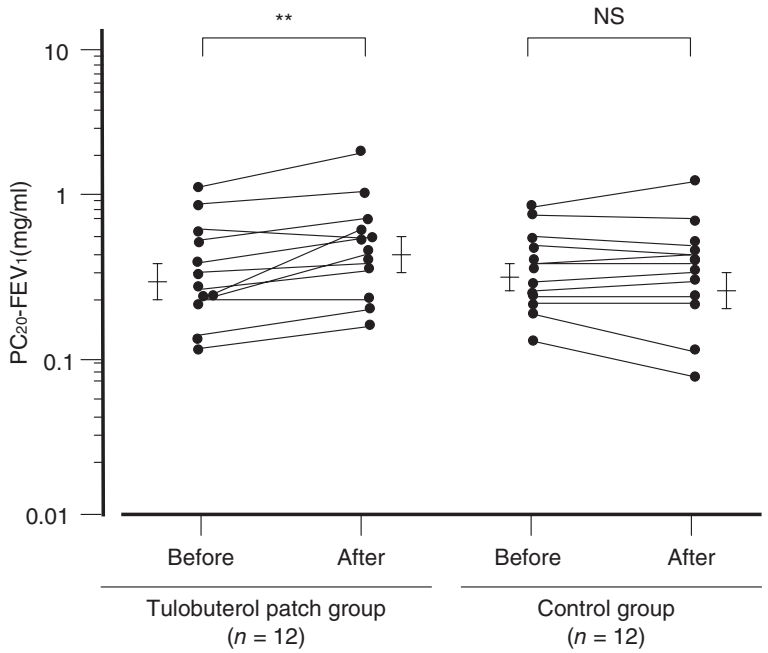

Fig. 2 Bronchial responsiveness to methacholine before and after four-week treatment in the tulobuterol patch and control groups. Group values are presented as geometric means and geometric standard errors of the mean (SEM). PC_{20}-FEV_1 indicates provocative concentration of methacholine producing a 20% fall in FEV_1. NS indicates not significant. $^{**}p < 0.01$.

Table 3 FVC and FEV_1 at methacholine challenge testing before and after treatment for 4 weeks in the tulobuterol patch and control groups†

	Tulobuterol patch group (n = 12)		Control group (n = 12)	
	Before	After	Before	After
FVC (L)	2.96 ± 0.14	2.87 ± 0.18	2.80 ± 0.21	2.72 ± 0.19
FVC (% pred)	100 ± 2.7	97 ± 4.8	95 ± 4.4	93 ± 4.7
FEV_1 (L)	2.19 ± 0.12	2.17 ± 0.16	2.12 ± 0.19	2.05 ± 0.19
FEV (% pred)	85 ± 2.5	85 ± 3.3	84 ± 4.4	81 ± 5.0
FEV_1/FVC (%)	73 ± 0.7	76 ± 2.0	75 ± 1.7	74 ± 2.0

† Values are the mean ± SEM.

Spirometry were performed before the treatment period and after a two-day washout period following the treatment period.

significantly from week 1 to week 4 of treatment ($p < 0.01$) (Fig. 1).

Bronchial responsiveness, as measured by methacholine PC20-FEV_1, was 0.35 (GSEM, 1.24) mg/mL before treatment and 0.51 (GSEM, 1.22) mg/mL after treatment with the tulobuterol patch, with a significant improvement observed after treatment ($p < 0.01$) (Fig. 2). FEV_1 and FVC at the time of methacholine challenge testing exhibited no changes from baseline values (Table 3). Percentage of sputum eosinophils decreased significantly from 12.7 ± 1.8% before treatment to 8.7 ± 0.9% after treatment ($p < 0.05$) (Fig. 3). The patients in the control group exhibited no changes over time in %PEF, PC20-FEV_1, or percentage of eosinophils (Fig. 1–3). None of the 12 patients in the tulobuterol patch group experienced systemic adverse drug reactions such as tremor or palpitations.

STUDY 2

Table 2 shows the clinical characteristics and conditions during the observation period for the 65 patients. There were no significant biases in the distribution of patients among groups for any background factor.

Spirometry findings improved after treatment with the tulobuterol patch compared with the baseline: in the tulobuterol patch group, FEV_1 increased from 2.08 ± 0.15 L to 2.25 ± 0.17 L ($p < 0.05$) and peak expiratory flow rate (PEFR) from 6.05 ± 0.45 L/s to 6.52 ±

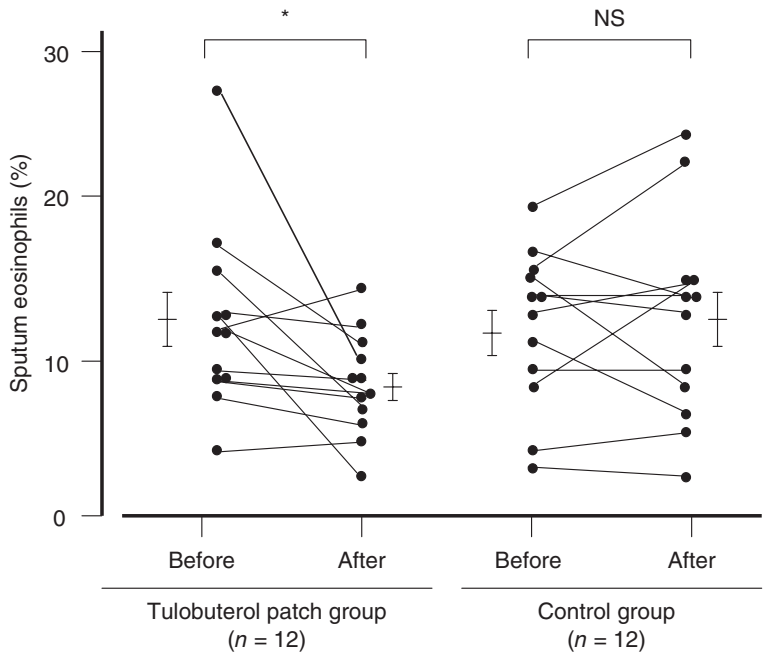

Fig. 3 Percentages of sputum eosinophils before and after treatment for 4 weeks in the tulobuterol patch and control groups. Group values are means and standard errors of the mean. NS indicates not significant. *$p < 0.05$.

0.45 L/s ($p < 0.05$). No significant improvement in spirometry findings was observed in the pranlukast, slow-release theophylline, or control group (Table 4).

Baseline morning PEF values were 404.5 ± 26.7, 356.1 ± 20.8, 360.1 ± 25.9, and 372.5 ± 27.1 L/minute in the control, pranlukast, slow-release theophylline, and tulobuterol groups, respectively. Morning PEFs in the corresponding groups were 404. 2 ± 27.1, 377.5 ± 28.5, 386.2 ± 28.4, and 406.5 ± 29.2 L/minute in week 1 of treatment; 400.7 ± 27.9, 379.6 ± 28.0, 385.8 ± 28.4, and 405.5 ± 30.5 L/minute in week 2 of treatment; 405.0 ± 25.7, 378.5 ± 27.4, 378.4 ± 27.6, and 406.4 ± 31.3 L/minute in week 3 of treatment; and 394.1 ± 25.5, 378.7 ± 27.8, 383.1 ± 28.0, and 411.2 ± 31.1 L/minute in week 4. Change in morning PEF from that during the 2-week observation period was significant in all 3 add-on groups from weeks 1 to 4 of treatment (Fig. 4). There were no significant differences in morning PEF values among the 3 add-on groups. On the other hand, the difference in %PEF from baseline to week 4 of treatment (Δ%PEF) was ≥ +5% in 1 of the 15 patients in the control group, 8 of the 17 patients in the pranlukast group, 7 of the 16 patients in the slow-release theophylline group, and 13 of the 17 patients in the tulobuterol patch group (Fig. 5). A significant difference in %PEF was observed between the tulobuterol patch and control groups ($p < 0.05$). There were no significant differences in this parameter between the other add-on groups and the control group. None of the 65 patients included in the present study experienced adverse drug reactions during the observation or treatment period.

DISCUSSION

We set out to determine whether the tulobuterol patch, the world's first transdermal beta2-agonist preparation, which is considered a useful controller of bronchial asthma in Japan,[14,15] is usefuls as an add-on controller for patients receiving inhaled corticosteroid for long-term management of asthma cases, who had experienced decrease in morning PEF to <80% of the predicted value at least twice a week. The primary endpoint for Study 1 was bronchial hyperresponsiveness (methacholine PC20-FEV_1), while that for Study 2 was PEF.

In Study 1, patients for whom the tulobuterol patch was added to a regimen of inhaled corticosteroid exhibited an increase in morning PEF, an improvement in bronchial hyperresponsiveness, and a decrease in percentage of sputum eosinophils. These findings suggest that the addition of the tulobuterol patch may have beneficial effects in the treatment of asthma, such as improvement/disappearance of the morning dip as well as improvement of bronchial hyperresponsiveness and allergic airway inflammation.

Since bronchial responsiveness was evaluated before the treatment period and after a 2-day wash-out period following the treatment period, and FEV_1 and FVC values obtained on the day of methacholine challenge testing did not differ from baseline values, it ap-

Table 4 Effects on spirometry findings of addition of pranlukast, slow-release theophylline or tulobuterol patch to a regimen of inhaled corticosteroids

Group C (*n* = 15)	before addition	after addition	*P*
FVC (L)	2.84 ± 0.17	2.78 ± 0.15	NS
FVC (%Pred)	95.6 ± 3.77	94.0 ± 4.24	NS
FEV_1 (L)	2.15 ± 0.15	2.10 ± 0.15	NS
FEV_1/FVC (%)	84.6 ± 4.23	83.0 ± 4.88	NS
FEV_1 (%Pred)	75.2 ± 1.6	74.8 ± 1.81	NS
PEFR (L/sec)	6.31 ± 0.50	5.83 ± 0.50	NS
Group U (*n*=16)	before addition	after addition	*P*
FVC (L)	3.10 ± 0.19	3.18 ± 0.20	NS
FVC (%Pred)	95.7 ± 3.91	97.7 ± 3.34	NS
FEV_1 (L)	2.19 ± 0.17	2.23 ± 0.17	NS
FEV_1/FVC (%)	78.1 ± 4.50	79.0 ± 3.54	NS
FEV_1 (%Pred)	70.1 ± 2.20	69.9 ± 2.39	NS
PEFR (L/sec)	5.81 ± 0.52	6.09 ± 0.50	NS
Group P (*n*=17)	before addition	after addition	*P*
FVC (L)	2.76 ± 0.16	2.77 ± 0.16	NS
FVC (%Pred)	95.2 ± 2.12	95.6 ± 2.19	NS
FEV_1 (L)	2.32 ± 0.33	2.11 ± 0.14	NS
FEV_1/FVC (%)	83.1 ± 2.78	85.2 ± 2.93	NS
FEV_1 (%Pred)	74.5 ± 2.27	75.9 ± 2.22	NS
PEFR (L/sec)	5.48 ± 0.46	5.77 ± 0.44	NS
Group T (*n*=17)	before addition	after addition	*P*
FVC (L)	2.83 ± 0.16	2.92 ± 0.17	NS
FVC (%Pred)	96.4 ± 3.67	99.0 ± 3.61	NS
FEV_1 (L)	2.08 ± 0.15	2.25 ± 0.17	$P<0.05$
FEV_1/FVC (%)	81.4 ± 3.33	85.3 ± 3.08	NS
FEV_1 (%Pred)	72.5 ± 1.88	74.1 ± 2.01	NS
PEFR (L/sec)	6.05 ± 0.43	6.52 ± 0.45	$P<0.05$

Abbreviations: Group C, control group; Group P, pranlukast group; Group U, slow-release theophylline group; Group T, tulobuterol patch group; FVC, forced vital capacity; FVC%, ratio of measured to expected FVC; FEV_1, forced expiratory volume in 1 second; $\%FEV_1$, ratio of measured to expected FEV_1; PEFR, peak expiratory flow rate.

peared that the measured values of bronchial responsiveness in the patients in the tulobuterol patch group were not influenced by the direct bronchodilatory effects of tulobuterol. The improvement of bronchial hyperresponsiveness observed in the patients in the tulobuterol patch group thus appeared to be due largely to improvement of airway inflammation, although no significant correlation was found between PC20 and sputum eosinophil percentage.

Reasons for this may include the fact that bronchial hyperresponsiveness is associated with other factors in addition to eosinophilic inflammation, and that only a small number of cases were included in this study. This conclusion is based on the following possible mechanisms of interaction between inhaled corticosteroid and the tulobuterol patch.

First, distribution of inhaled corticosteroid into the airway may be enhanced by the stable and prolonged bronchodilation induced by tulobuterol patch. In a recent study using impulse oscillometry (IOS), use of the tulobuterol patch as an add-on controller improved IOS indices of peripheral airway function such as R5-R20 (small airway component) and X5 (distal capacity reactance) in patients with asthma receiving ICS.[19] This finding indicates that tulobuterol patch exhibits a bronchodilator effect that covers the peripheral airways to ensure sufficient distribution of ICS not only to the central but also the peripheral airways, enabling exertion of the full effects of ICS.

Secondly, interactions between corticosteroids and beta2-agonists may play a role in improving bronchial responsiveness.[20-22] Corticosteroids diffuse from the surface of the cell membrane into cytoplasm, where they bind to corticosteroid receptors (CRs). CRs activated by this binding translocate into the nucleus where they bind corticosteroid-responsive elements and activate the transcription of genes regulated by these elements, and inhibit the activity of transcription factors involved in the expression of genes for proinflammatory cytokines such as activating protein-

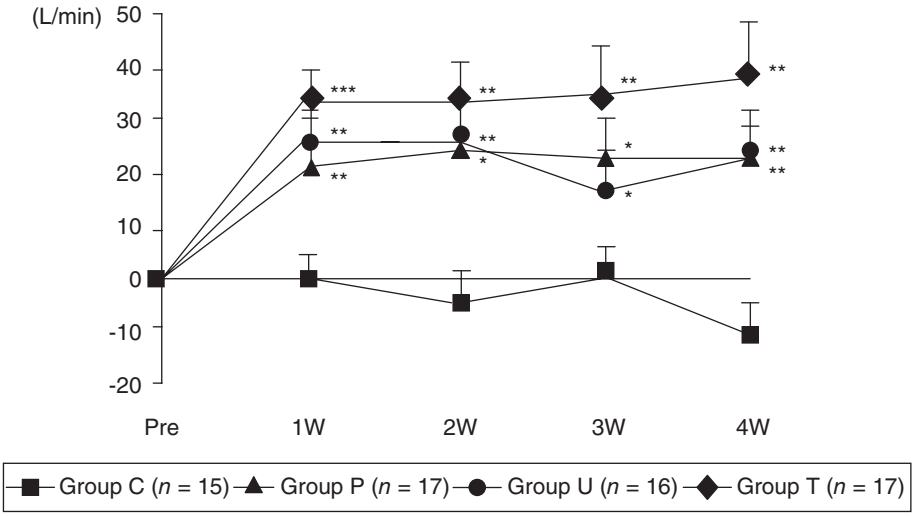

Fig. 4 Effects of addition of pranlukast, slow-release theophylline, and tulobuterol patch to a regimen of inhaled corticosteroid on difference in morning PEF before to after treatment (PEF). Abbreviations: Group C, control group; Group P, pranlukast group; Group U, slow-release theophylline group; Group T, tulobuterol patch group. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ vs Group C.

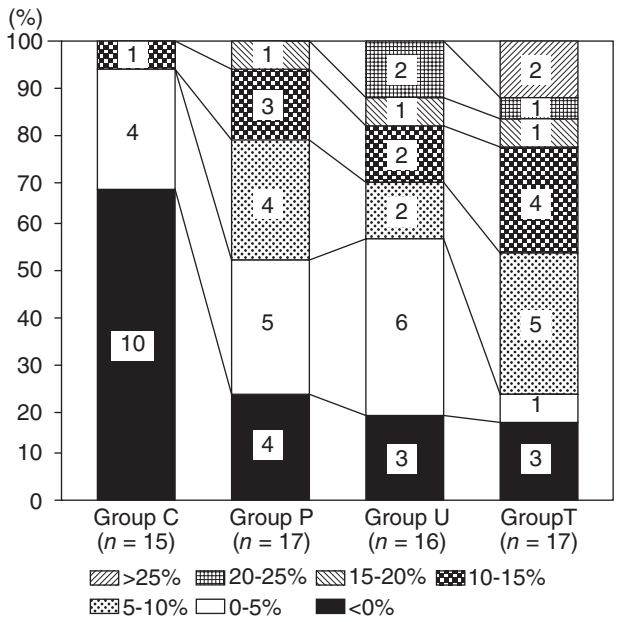

Fig. 5 Effects of addition of pranlukast, slow-release theophylline, or tulobuterol patch to a regimen of inhaled corticosteroid on difference in morning %PEF before to after treatment (Δ%PEF). Abbreviations: Group C, control group; Group P, pranlukast group; Group U, slow-release theophylline group; Group T, tulobuterol patch group.

1 (AP-1) and nuclear factor κB (NF-κB). In addition, CS-CR complexes bind transcription factors directly and inhibit the transcription of proinflammatory cytokine genes. Corticosteroids increase the number of beta2-receptors and inhibit down-regulation of beta2-receptors. On the other hand, beta2-agonists produce bronchodilation and prime and activate CRs, thus enhancing the anti-asthmatic effects of corticosteroids. Maintenance of effective blood tulobuterol concentration for 24 hours through once-daily application of tulobuterol patches is important for ensuring clinically significant add-on effects of tulobuterol for inhaled corticosteroids, given the types of interactions that occur between these two drugs.

Thirdly, tulobuterol has been found to significantly inhibit the adhesion of eosinophils to endothelial cells at clinically relevant blood concentrations *in vitro*.[23] Since the transdermal preparation delivers tulobuterol into the systemic circulation, the effects of tulobuterol on endothelial cells appeared to contribute to the significant decrease in the percentage of sputum eosinophils observed in patients of the tulobuterol patch group.

Of the 3 possible mechanisms described above, the first 2 appear to be related to the effects of adding inhaled beta2-agonists to inhaled corticosteroid, while the third appears unrelated to topical administration of beta2-agonists. Moreover, it has been reported that allergic airway inflammation may be masked by combined treatment with inhaled corticosteroid and salmeterol.[24,25] It has also been suggested that inhaled beta2-agonists may accumulate in airway tissues with allergic inflammation, and may shift the Th1/Th2 balance toward a Th2-dominant pattern that results in exacerbation of allergic airway inflammation.[26] This risk associated with inhaled beta2-agonists can be prevented with transdermal administration of beta2-agonists. These considerations strongly suggest the effectiveness of adding tulobuterol patch to inhaled

corticosteroid regimens. Study 2 demonstrated that tulobuterol patches have benefits equivalent or superior to those of slow-release theophylline and leukotriene receptor antagonist as an add-on controller for patients undergoing long-term management of asthma using ICS. Thus our findings support the positioning of the tulobuterol patch in the guidelines for management and treatment of asthma in Japan.[14]

Kume *et al.* reported that the effects of tulobuterol patches were not attenuated at clinically relevant doses, and that patients treated with tulobuterol patches and ICS did not develop resistance to treatment.[27] Their findings support the appropriateness of adding tulobuterol patches as a long-term add-on controller to an ICS. However, whether tulobuterol patches can be positioned similarly to long-acting inhaled beta2-agonists is still unclear, as are the differences in efficacy and safety between inhaled and transdermal beta2-agonists. Animal and human clinical studies comparing transdermal and inhaled preparations of beta2-agonists in terms of clinical benefits and effects on beta2-receptors, including developing resistance, are needed before definitive conclusions can be drawn regarding the positioning of tulobuterol patch in the treatment of asthma.

Our findings suggest that the addition of tulobuterol patches to ICS has beneficial effects in the treatment of asthma, including disappearance of morning dip as well as improvement of bronchial hyperresponsiveness and allergic airway inflammation, and that tulobuterol patches can be used as a long-term add-on controller for patients with asthma receiving ICS.

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