

# Transdermal Tulobuterol Patch, a Long-Acting $\beta_2$ -Agonist

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## ABSTRACT

Tulobuterol patch (Hokunalin™ Tape), which contains a  $\beta_2$ -adrenergic agonist, is the first bronchodilator to be available as a transdermal patch. This drug delivery system ensures that the time at which the peak drug concentration in the blood is reached coincides with the morning dip in respiratory function. The use of the patch also prevents excessive increase in blood drug concentrations, thereby reducing the incidence of systemic adverse reactions. Since 1998, when it was first approved in Japan and worldwide, the tulobuterol patch has been used widely in the treatment of bronchial asthma and chronic obstructive pulmonary disease (COPD), and evidence collected since it was approved has confirmed its clinical efficacy and safety. Because the patch is easy to use and requires only once-daily application, treatment adherence of patients using the patch is good. In this article, we discuss the rationale behind the development of the tulobuterol patch, evaluate data on its clinical efficacy and safety in the treatment of asthma and COPD, and examine the treatment adherence in individuals using the patch.

## KEY WORDS

adherence, asthma, COPD, transdermal patch, tulobuterol

## INTRODUCTION

The branded tulobuterol patch (Hokunalin™ Tape) is the first transdermal delivery system developed for a  $\beta_2$ -adrenergic agonist. It has been used extensively in the long-term management of asthma and chronic obstructive pulmonary disease (COPD) in Japan, Korea, and China. Its clinical efficacy and safety have been established in clinical practice over the 13 years since its launch in Japan in 1998. In addition, the patch has attracted attention in recent years after patients using it were reported to exhibit significant improvement in their quality of life (QOL) and excellent treatment adherence, which is important in the treatment of chronic diseases. The present review describes the properties of the tulobuterol patch formulation and outlines the clinical results obtained with its use in the treatment of asthma and COPD.

To prepare this review, we conducted a literature search using PubMed. The database was searched using the terms “tulobuterol patch” and “tulobuterol”

for articles published since 1998, these searches yielded 24 articles and 106 articles, respectively. Among them, English-language articles describing clinical trials of the patch and those supporting its clinical efficacy were selected and reviewed.

## FORMULATION PROPERTIES

### BRANDED PREPARATION

The branded tulobuterol patch is the first successfully introduced transdermal delivery system for a bronchodilator. The physiological functions and activities of living beings follow circadian rhythms. Respiratory functions are known to be most severely suppressed from late night until early in the morning.<sup>1</sup> This, so-called “morning dip,” is known to be associated with the development of asthma attacks in the early morning. Dethlefsen *et al.*<sup>2</sup> investigated approximately 3000 untreated asthma patients to determine the time of the day which asthma attacks are most frequent, and reported that the attacks occurred in clusters at around 4:00 am. Therefore, suppression of

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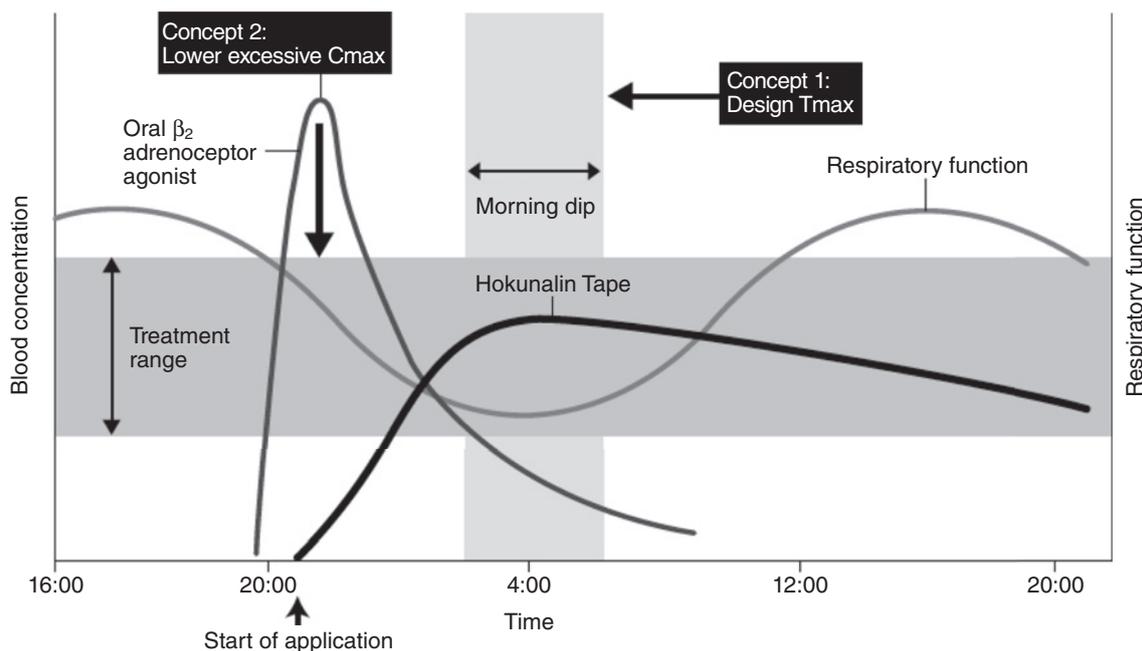


Fig. 1 Development concept of the tulobuterol patch.

this morning dip can be expected to bring about an improvement in the patient's QOL and also reduce the burden on the caregiver in cases of childhood asthma. The branded formulation was designed in accordance with the concept of chronotherapy: the blood drug concentration is controlled in such a manner that it is the highest during early morning, when the respiratory functions are most severely suppressed. This controlled release helps to reduce the systemic adverse reactions associated with excessive drug concentrations in the blood (Fig. 1). Long-acting  $\beta_2$ -agonists (LABA), such as salmeterol and formoterol, provide sustained action for 12 h by virtue of their molecular structures. Similarly, for sustained-release theophylline, which is administered orally, the release of the active substance is controlled to prolong the duration of its action. On the other hand, the tulobuterol patch employs a technology that prolongs the duration of the drug's action to 24 h. This technology is the crystal reservoir system, which has been patented for the patch.

**THE CRYSTAL RESERVOIR SYSTEM**

The crystal reservoir system, which is described below, was developed with a view to reduce the size of the formulation and prolonging the release of the drug from a simple structure (Fig. 2). The plaster body contains dissolved tulobuterol molecules and tulobuterol crystals, which are dispersed homogeneously in the plaster body and transferred directly to the skin when the tape is applied. The drug dissolves and is dispersed from the crystals to compensate for the reduction in the number of tulobuterol molecules

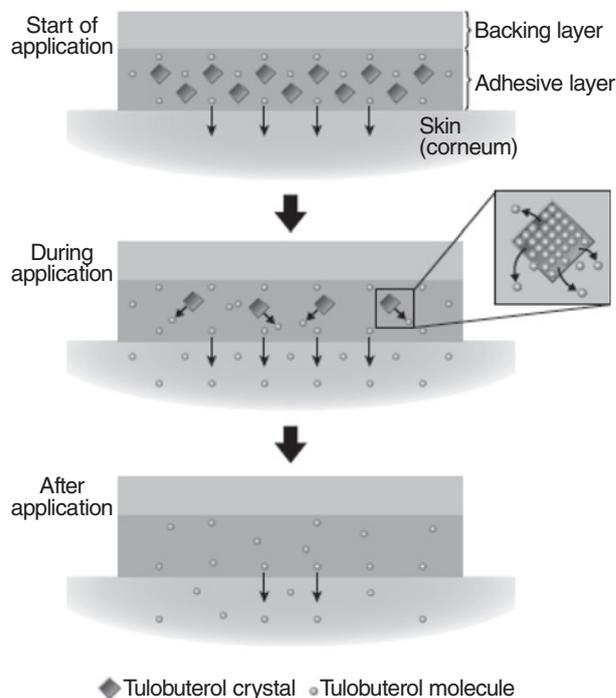
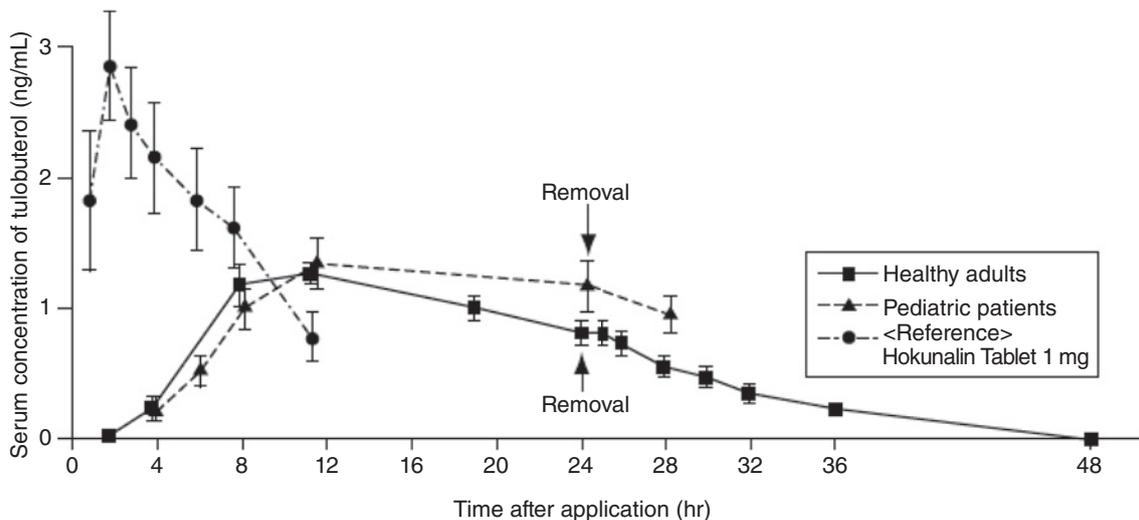


Fig. 2 The crystal reservoir system.

in the plaster body, thereby maintaining the concentration of the drug substance dissolved in the plaster body at a constant level and ensuring sustained release of the drug. This method of achieving sustained release of the active substance via a transdermal chrono-delivery system is based on the concept of



**Fig. 3** Blood concentration curves after the application of the tulobuterol patch (2 mg in healthy adults and 1 mg or 2 mg in pediatric patients) and administration of the tulobuterol tablet (1 mg) .

chronotherapy.

#### DIFFERENCES BETWEEN BRANDED AND GENERIC PREPARATIONS OF TULOBU TEROL

A generic preparation of the tulobuterol patch not using the crystal reservoir system employed for the preparation of the branded formulation was recently launched in the market. Yoshihara *et al.*<sup>3</sup> compared the skin permeation profiles between branded and generic tulobuterol patches using normal skin and corneum-removed skin of the rat. Their study showed that skin permeability of the branded preparation was not significantly different between normal skin and corneum-removed skin; however, the skin permeability of the generic preparation was significantly higher with corneum-removed skin than with normal skin. Tojo *et al.*<sup>4</sup> also conducted an *in vitro* study using nude mouse skin and found that the skin permeability of corneum-removed skin was significantly higher than that of normal skin with the generic preparation of the drug, whereas, for the branded preparation of the drug, the skin permeability was similar for both skin samples. Thus, there are differences in the formulation properties of the branded and generic preparations. In patients who have both childhood asthma and atopic dermatitis the generic preparation should be used with caution, with special attention being paid to the potential differences in the skin permeability of the drug between normal and atopic skin.

#### CLINICAL EXPERIENCE

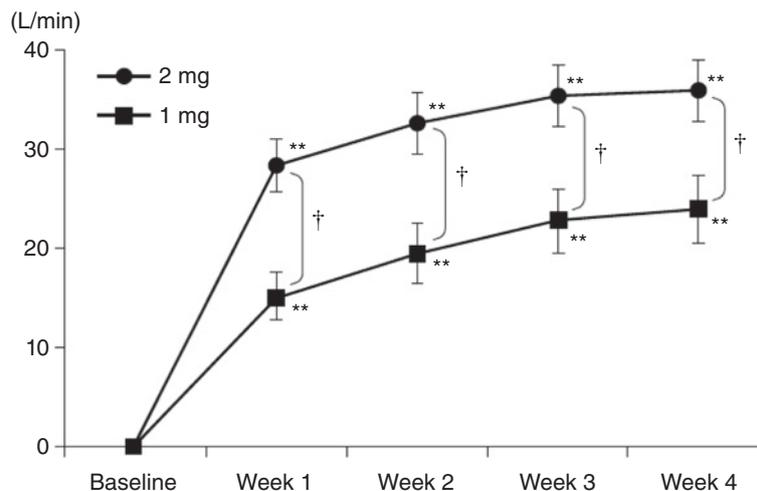
##### PHARMACOKINETICS

Blood concentration curves obtained after the application of the tulobuterol patch (2 mg) and administration of the tulobuterol tablet (1 mg) in healthy adults

are shown in Figure 3. There was no excessive increase in the blood drug concentration with the tulobuterol patch, and the effective blood concentration was maintained over a longer period with the tulobuterol patch than with the tablet. As evident from the figure, an ideal time-course for the increase in the blood drug concentrations was observed after application of the patch. The time to attainment of the maximum blood concentration was 9-12 h, and the effective blood concentration was maintained for 24 h after once-daily application of the patch. Therefore, when the patch is applied at bedtime, the maximum blood concentration is achieved during early morning, thereby suppressing asthmatic attacks occurring at that time of the morning dip in respiratory function. As shown in Figure 3, a similar blood concentration curve was obtained when a 1 or 2 mg patch was applied to children.<sup>5</sup> The branded tulobuterol patch, which produces clinically significant improvement in the peak expiratory flow (PEF) with minimal adverse reactions, is therefore very useful in patients with childhood asthma.

#### CLINICAL EFFECTS OF THE BRANDED TULOBU TEROL PATCH IN ADULTS WITH BRONCHIAL ASTHMA

According to the Japanese Guideline for Prevention and Management of Asthma, inhaled corticosteroids (ICS) are the first choice of drugs for the long-term management of bronchial asthma.  $\beta_2$ -agonists are the strongest bronchodilators among the standard drugs used to treat bronchial asthma. The combination of ICS and a long-acting  $\beta_2$ -agonist (LABA) is therefore recommended for the management of asthma from Step 2 onward. In our multicenter, double-blind, parallel-group study,<sup>6</sup> 239 adult patients with bron-



**Fig. 4** Increase in the morning PEF values after treatment with 1 mg or 2 mg tulobuterol patch. \*\* $p < 0.01$ , † $p < 0.05$ .

chial asthma under treatment with ICS were randomized to receive tulobuterol patch at either 1 mg/day or 2 mg/day, and the efficacy and safety of the patch were investigated. In both groups, significant increments of the mean PEF values from baseline values were observed, with the increase in the 2 mg/day group being significantly higher than that in the 1 mg/day group (Fig. 4). There was no significant difference in the incidence of adverse reactions between the two groups. Thus, the patch is included as a LABA in the above-mentioned Japanese Guidelines for the treatment of asthma, because its therapeutic effect persists for over 24 hours after once-daily application, and it has an additive effect when combined with an ICS in patients with bronchial asthma.<sup>5-10</sup> When ICS alone appears to be inadequate for the long-term management of asthma, the addition of a LABA, slow-release theophylline (SRT), or leukotriene receptor antagonist (LTRA) is considered more beneficial than doubling of the dose of the ICS. Hozawa *et al.*<sup>9</sup> investigated which of these drugs is the most desirable for combining with the ICS in the long-term management of bronchial asthma. Sixty-five asthma patients being treated with ICS alone were randomized to receive the tulobuterol patch, SRT, pranlukast (LTRA), or ICS alone (control), and the changes in the respiratory parameters in each group were compared. The improvement in the PEF tended to be the highest for the patch. That is, the results suggested that the addition of the tulobuterol patch to an ICS was the most effective strategy for the long-term management of asthma. A long-standing issue of concern in the treatment of bronchial asthma has been the emergence of tolerance, that is, a reduction in the bronchodilatory effect of a short-acting  $\beta_2$ -agonist after frequent and repeated use. Kume *et al.*<sup>7</sup> reported that long-term use of the

tulobuterol patch was not associated with any decrease in the drug susceptibility of adrenergic  $\beta_2$ -receptors in the airway smooth muscle; this indicates that the use of the tulobuterol patch did not lead to tolerance. In addition, Horiguchi *et al.*<sup>8</sup> reported that no signs of tachyphylaxis were found even after year-long use of the tulobuterol patch. A number of studies<sup>11-13</sup> have compared the tulobuterol patch with salmeterol. Fujimoto *et al.*<sup>11</sup> treated 54 asthma patients with PEF variations or symptoms despite ICS treatment with increasing dose, addition of salmeterol, or addition of tulobuterol, and assessed respiratory functions and QOL (the Asthma Quality of Life Questionnaire). Although the assessment of airway reversibility was not included in the patient background data, a significant improvement was noted at the 8th week only in patients treated with ICS and salmeterol. Kobayashi *et al.*<sup>12</sup> added tulobuterol tape and then replaced it with salmeterol in 64 patients receiving a dose of 200 to 800  $\mu\text{g}/\text{day}$  of ICS for at least 3 months. These authors observed greater improvement of PEF when salmeterol was administered. However, the possibility of an order effect cannot be ruled out. A study with the drugs administered in the reverse order is required to clarify this. Nishiyama *et al.*<sup>13</sup> assigned 54 patients with moderate to severe asthma not responding well to a low dose of ICS to two groups—one receiving salmeterol and the other, tulobuterol—and assessed respiratory functions and QOL (the St. George's Hospital Respiratory Questionnaire, SGRQ). They found that both groups showed improvement in respiratory functions and QOL, indicating that the tulobuterol patch is a useful bronchodilator for combining with ICS. Thus, clinical studies where the use of adequate inhalation techniques is guaranteed, the tulobuterol patch may be less effective than salmeterol with respect to improve-

ments in respiratory functions. However, the patch is a useful LABA for combining with ICS in actual clinical practice, and its efficacy and safety are equivalent to those of salmeterol.

#### **CLINICAL EFFECTS OF THE BRANDED TULOBU-TEROL PATCH IN CHILDREN WITH BRONCHIAL ASTHMA**

The combined use of the tulobuterol patch and an ICS has also been reported to be effective in the treatment of bronchial asthma in children. In addition, the tulobuterol patch has the advantage of being highly convenient to use in children of all ages. Yoshihara *et al.*<sup>14</sup> conducted a randomized, parallel-group, comparative study in 10 pediatric patients with severe asthma who were under ICS treatment. They demonstrated that the tulobuterol patch (once-daily application) showed an add-on effect equivalent to that of inhaled salmeterol (twice-daily inhalation). In addition, they compared the effect of increasing the dose of the ICS to that of adding the tulobuterol patch to the ICS in 18 pediatric patients with severe asthma and found that the latter strategy resulted in a significantly greater improvement in the PEF values and a significantly higher percentage of respiratory symptom-free days than the former. These results showed that the tulobuterol patch is also useful for the long-term management of asthma in the pediatric population. Thus, the tulobuterol patch appears to be suitable for the treatment of asthma in almost all age groups, from infants aged  $\geq 6$  months to the elderly, and the combined application of this patch with an ICS plays an important role in the long-term management of asthma.

#### **CLINICAL EFFECTS OF THE BRANDED TULOBU-TEROL PATCH IN PATIENTS WITH STABLE COPD**

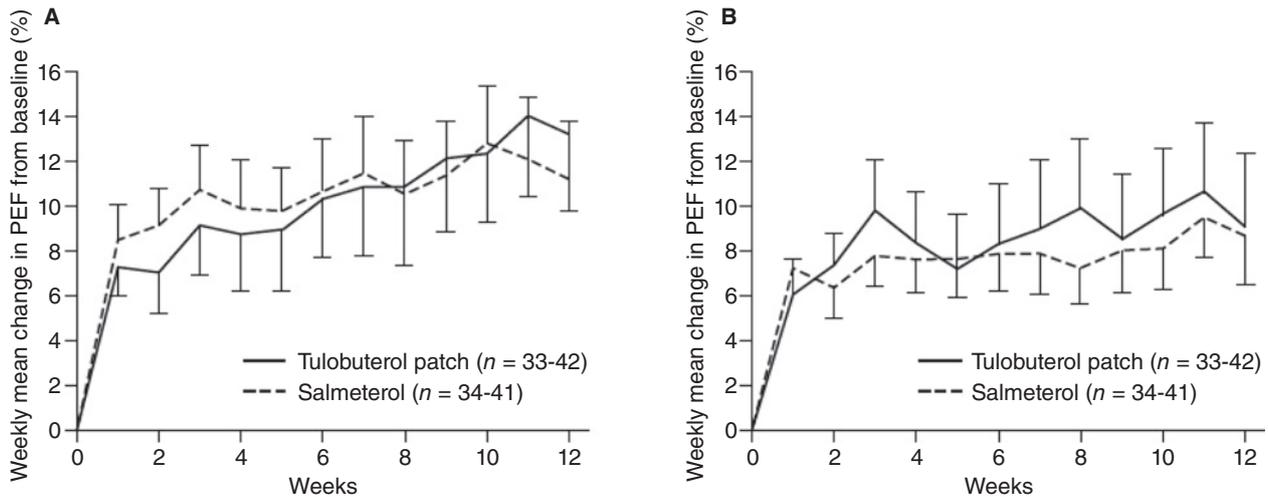
According to the current Japanese Guidelines for the diagnosis and treatment of COPD, the drug of first choice for the pharmacotherapy of stable COPD is a long-acting anticholinergic agent or LABA. However, because COPD treatment has to be continued for a prolonged period, drugs having not only high efficacy and safety but also a good compliance rate are desirable in the treatment of COPD. An inhaled bronchodilator is directly administered into the airways and is regarded as a desirable dosage form, in view of its efficacy and safety. However, inhalation of a sufficient dosage may be difficult in some COPD patients because of compromised respiratory functions. Even in patients who have difficulty in learning the inhalation technique, the tulobuterol patch is easy to use. In addition, the patch has the advantage that it can be removed at any time, for example, in the event of adverse reactions.

#### **COMPARISON OF THE BRANDED TULOBU-TEROL PATCH AND SLOW-RELEASE THEOPHYLLINE**

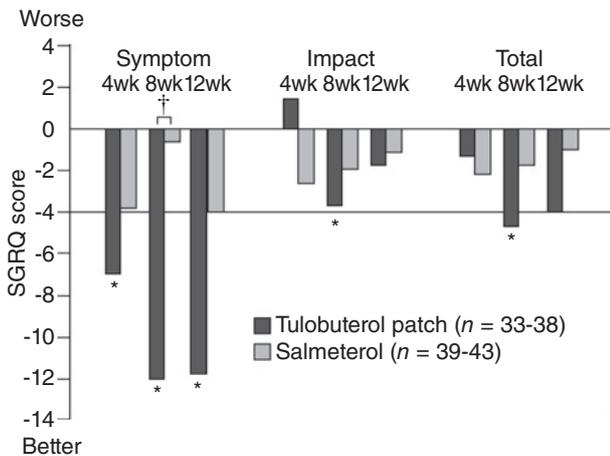
Minami *et al.*<sup>15</sup> conducted a randomized controlled study of the tulobuterol patch and SRT in 16 patients with moderate to severe COPD. They reported a significantly greater improvement in subjective symptoms and the QOL in the tulobuterol patch group than in the SRT group. Evaluation of the number of expectorations, ability to expectorate, wheezing score, cough score, and the "Total," "Impact," and "Symptoms" scores in the SGRQ revealed a significantly greater improvement in the tulobuterol patch group than in the SRT group. The only adverse reaction noted was increased volume of sputum in one case in the tulobuterol patch group. Kanehara *et al.*<sup>16</sup> compared theophylline and tulobuterol in 26 patients with mild to moderate COPD, by using a crossover design. These authors reported that, while only patients treated with theophylline showed improvement in respiratory functions, an anti-inflammatory effect on neutrophil inflammation was not observed with either drug. However, six patients treated with theophylline—five of whom developed adverse reactions and one who cited personal reasons—dropped out of the study, while all patients treated with tulobuterol completed the study. Thus, clinical evaluation of this study may be difficult.

#### **THE BAREC STUDY: COMPARISON BETWEEN THE BRANDED TULOBU-TEROL PATCH AND INHALED SALMETEROL**

Fukuchi *et al.*<sup>17</sup> conducted a multicenter, parallel-group, comparative study (the BAREC study) of the tulobuterol patch and inhaled salmeterol in 92 patients with stable COPD (GOLD stage II and III phases). They reported improvements in the morning and evening PEF values in both groups, with no significant intergroup difference (Fig. 5). However, a significantly greater improvement of the SGRQ at 8 weeks after the start of treatment was observed in the tulobuterol patch group compared with the salmeterol group (Fig. 6). In addition, treatment compliance was also significantly better in the tulobuterol patch group than in the salmeterol group. No serious adverse reactions occurred in either group. These findings show that, in terms of clinical efficacy, the tulobuterol patch is equivalent or superior to inhaled salmeterol and that it is useful in the long-term management of patients with stable COPD. Yamagata *et al.*<sup>18</sup> conducted a crossover comparative study of salmeterol and tulobuterol in 11 COPD patients. Their study revealed that the forced expiratory volume in 1 second (FEV<sub>1</sub>) and forced vital capacity (FVC) were significantly higher in the salmeterol group than in the tulobuterol group. However, because the sustained-release technology in tulobuterol is designed such that the drug is effective for 24 h, a



**Fig. 5** Improvement in the morning (A: left panel) and evening (B: right panel) PEF values over a 12-week treatment period with tulobuterol patch and inhaled salmeterol in patients with stable COPD.



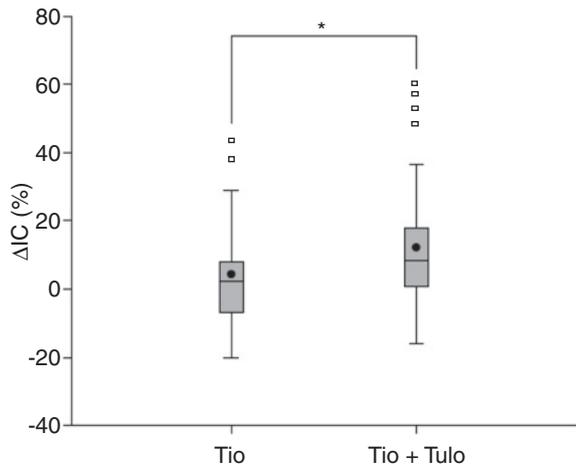
**Fig. 6** Changes in the St George's Respiratory Questionnaire score during 12 weeks of treatment with tulobuterol patch and inhaled salmeterol in patients with stable COPD. \* $p < 0.05$ , † $p < 0.05$  (Intergroup).

steady concentration of the drug is achieved after the patch has been applied two or more times,<sup>19</sup> therefore, the effect of a single dose may not have been 100%. On the other hand, we speculate that a sufficient effect of salmeterol might have been obtained 24 h later because the second dose had been administered within this period.

### THE BAREC II STUDY: ADD-ON EFFECTS OF THE TULOBU TEROL PATCH IN PATIENTS WHO WERE TREATED WITH INHALED TIOTROPIUM

The Global Initiative for Chronic Obstructive Lung Disease (GOLD)<sup>20</sup> and the Japanese Guidelines recommend combining 2 or more drugs rather than increasing the dose of a single drug when a single drug fails to sufficiently alleviate the symptoms. This is be-

cause the use of multiple drugs with differing mechanisms of action has shown better treatment outcomes in COPD, without an increase in the frequency of adverse reactions. Ichinose *et al.*<sup>21</sup> conducted a multicenter, parallel-group comparative study (the BAREC II study) to evaluate the clinical effects and safety of a combination of the tulobuterol patch and inhaled tiotropium<sup>22</sup> in patients with COPD. After a 2-week run-in period, 103 patients with stable COPD were randomized to receive either inhaled tiotropium alone (Tio group) or both tulobuterol patch and inhaled tiotropium (Tio + Tulo group). In both groups, the FVC and FEV<sub>1</sub> as well as the dyspnea improved significantly after 8 weeks of treatment. A comparison of both groups showed that the percent changes in the inspiratory capacity (Fig. 7) and morning and evening PEF values were significantly greater in the Tio + Tulo group than in the Tio group (Fig. 8). In addition, a significant improvement in the total SGRQ score and improvements in the "Activity" and "Impact" scores were observed only in the Tio + Tulo group (Fig. 9). Adverse reactions suspected to be causally related to the treatment included mild urticaria and decreased mastication in one case in each group; moderate dysuria associated with elevated blood pressure in one case in the Tio group; and mild headache in one case of the Tio + Tulo group. In COPD patients, addition of the tulobuterol patch to inhaled tiotropium produced significant improvements in dyspnea and SGRQ score, as well as in the pulmonary function parameters. These benefits may be attributable to a reduction in pulmonary hyperinflation resulting from an improvement in the patency of the peripheral airways effected by tulobuterol entering the systemic circulation. Akamatsu *et al.*<sup>23</sup> divided 60 COPD patients into two groups—one treated with tulobuterol alone or the other treated with a combina-

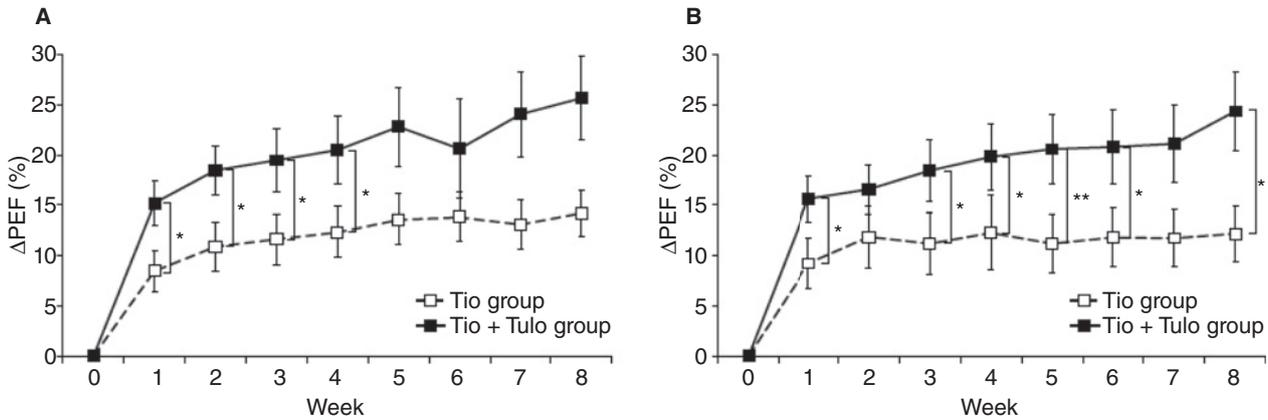


**Fig. 7** Effect of the tulobuterol patch used in combination therapy on the percent change in inspiratory capacity. Each group was assessed for the percent change from baseline at week 8. \* $p < 0.05$ .

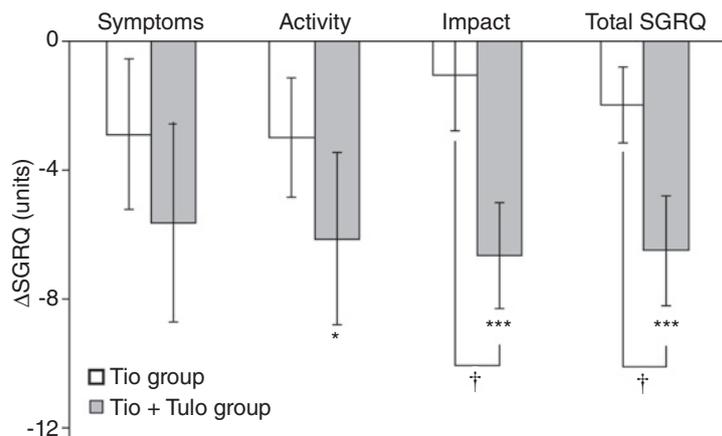
tion of tulobuterol and tiotropium—and assess their respiratory functions. The findings of this study supported those of the BAREC II study, confirming the add-on effects of tulobuterol when combined with tiotropium.

**TREATMENT ADHERENCE**

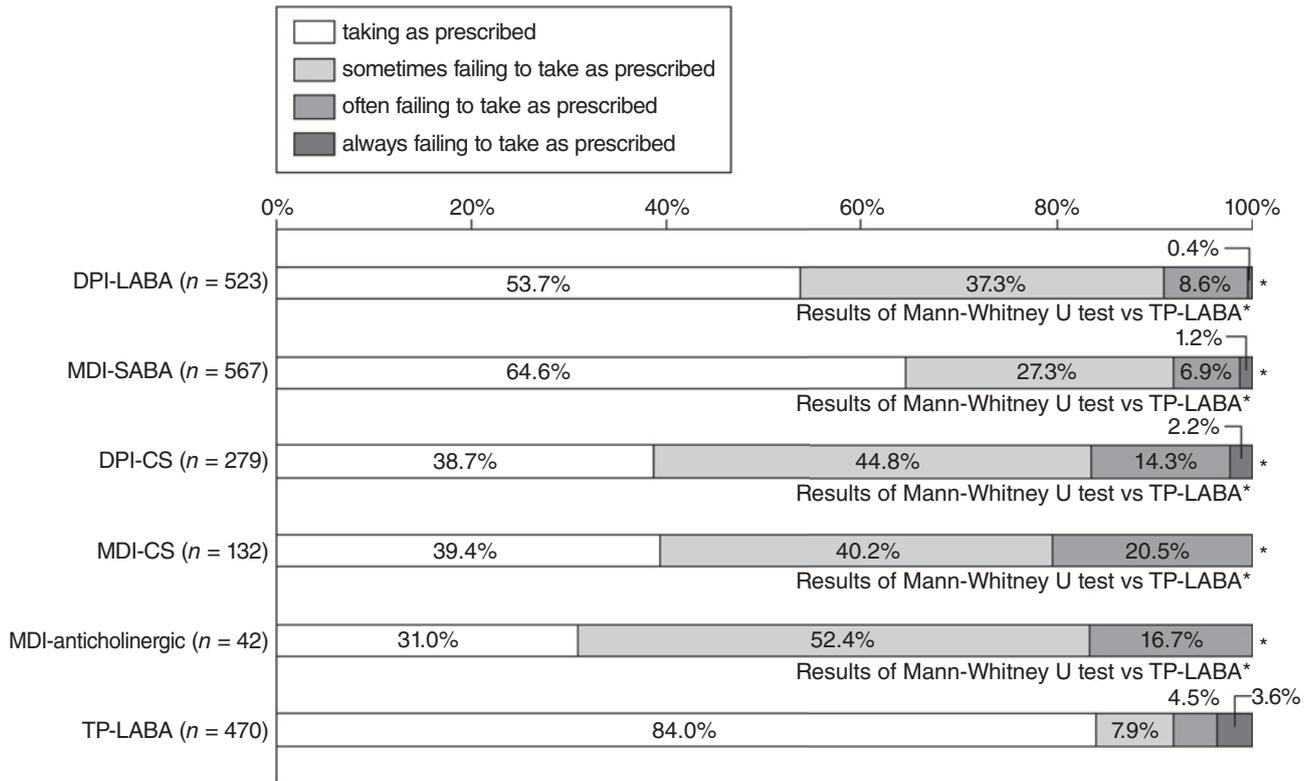
Treatment adherence is a very important factor in the management of chronic diseases. Tamura and Ohta<sup>24</sup> conducted a web-based survey on the treatment adherence to drugs used in asthma and COPD patients and collected the responses of 1470 individuals, including patients with asthma or COPD and their parents. The percentage of patients who took the prescribed drug as instructed was 31.0-64.6% for inhaled drugs and 84.0% for the tulobuterol patch; in other words, treatment adherence to the tulobuterol patch was significantly higher than that for any inhaled drug (Fig. 10). In addition to the complexity of the inhalation technique, the need for frequent administra-



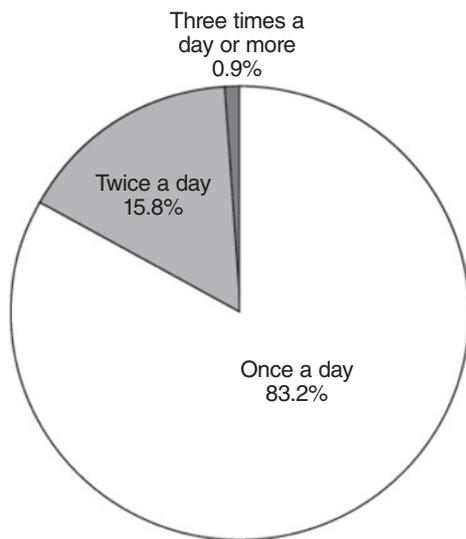
**Fig. 8** Effect of using the tulobuterol patch in combination therapy on morning (A: left panel) and evening (B: right panel) PEF values. \* $p < 0.05$ , \*\* $p < 0.01$ .



**Fig. 9** Effect of tulobuterol patch used in combination therapy on St George's Respiratory Questionnaire. \* $p < 0.05$ , \*\*\* $p < 0.001$ , † $p < 0.05$  (Intergroup).



**Fig. 10** Adherence with regimens by indication. Q: Are you taking drugs currently prescribed for treatment of asthma/COPD as directed by your physicians? Please provide an answer for each drug. \* $p < 0.01$ .



**Fig. 11** Preferred frequency of administration. Q: Please indicate the most preferable frequency of administration for your asthma/COPD drugs.

tion of an inhaled drug is another reason for the lower treatment adherence to an inhaled drug. Further, the percentage of individuals who preferred once-daily administration was 83.2% (Fig. 11). Patient

adherence to the use of the tulobuterol patch is high because of the ease of its application and the need for only once-daily administration. The patch satisfies the prerequisites of a drug for long-term management of chronic respiratory diseases, such as asthma and COPD. Sugawara *et al.*<sup>25</sup> compared the treatment adherence of salmeterol to that of tulobuterol in 26 patients with moderate to severe COPD using a cross-over design. Among patients aged <80 y, adherence to tulobuterol was found to be better than that to salmeterol, and a similar but more significant difference was noted among those aged  $\geq 80$  y. The findings of this study support the results reported by Tamura and Ohta.

### PERSPECTIVE AND CLINICAL INTERPRETATION

#### CLASSIFICATION AS A LABA

Tulobuterol patch is a unique  $\beta_2$  adrenergic agonist drug preparation that allows transdermal delivery of tulobuterol through the crystal reservoir system, thereby avoiding the decrease in respiratory functions seen in asthma patients receiving other formulations during the early morning hours (morning dip). This is because the patch prevents excessive increase in blood drug concentrations, while also reducing the incidence of systemic adverse reactions. The effect of

the drug after once-daily application persists for over 24 h, and the formulation is designed such that, once the patch is applied at bedtime, the blood drug concentration reaches its peak in the early morning and the therapeutic effect is sustained for a prolonged period. The tulobuterol patch was found to exert an additive effect when combined with ICS in bronchial asthma patients,<sup>6</sup> therefore, the patch is positioned as a LABA in the Japanese Guidelines for Prevention and Management of Asthma and in the Guidelines for Diagnosis and Treatment of COPD. The synergistic effects of ICS and LABAs are explained by the fact that inhaled steroids increase the expression of  $\beta_2$  adrenergic receptors, while  $\beta_2$  adrenergic agonists causes the down regulation of these receptors.<sup>26</sup> On the other hand, the  $\beta_2$  agonists activate the steroid receptors to potentiate the effect of the steroids.<sup>27</sup> In addition, the tulobuterol patch may exert both local effects on the lungs and systemic effects. Yamaguchi *et al.*<sup>28</sup> investigated the effect of tulobuterol on the adhesive forces between blood eosinophils and human umbilical vein endothelial cells (HUVEC) in an *in vitro* study. They reported that tulobuterol significantly inhibited the adhesion between eosinophils and HUVECs activated by IL-4 + TNF $\alpha$ , IL-5, or formyl-methionyl-leucyl-phenylalanine. Thus, tulobuterol can decrease the adhesion of blood eosinophils to endothelial cells. These findings imply that the tulobuterol patch may possibly exert an anti-inflammatory effect.<sup>9</sup>

#### ROLE AS A THERAPEUTIC AGENT FOR COPD

Although COPD is recognized as an intractable disease, its treatment has advanced in recent times. It is now accepted that early aggressive treatment, including the use of long-acting bronchodilators, can improve the prognosis of the disease. Treatment of COPD has been focused not only on improving respiratory functions but also on the patients' QOL. In particular, because many COPD patients are elderly and have problems such as difficulty mastering the technique of using inhalers and insufficient inhalation rates, a different, more convenient route of administration may be useful for these patients. In the BAREC study, the tulobuterol patch improved the subjective symptoms and QOL, probably by relieving the peripheral airway obstruction. Use of the tulobuterol patch causes the drug to reach the peripheral airways through the systemic circulation after transdermal absorption, thereby maintaining the patency of the peripheral airways and resulting in more effective expiration and reduction of the residual volume. This prevents pulmonary hyperinflation and improves the exercise tolerance, which in turn improves the patients' QOL. Many studies have shown that, pathologically, COPD involves mainly the peripheral airways. Thus, the improvement in peripheral airway function may well be the reason for the improvement in QOL brought about by the use of the

tulobuterol patch. In the BAREC II study, an add-on effect of the tulobuterol patch was noted in patients treated with inhaled tiotropium, and the difference sites of action of these two drugs was speculated to underlie this effect: tiotropium exerts its effects via muscarinic M3 receptors, while tulobuterol acts via the  $\beta_2$  adrenergic receptors. Because activated muscarinic M3 receptors are found mainly in the central airways,<sup>29</sup> tiotropium, an anticholinergic agent, may mainly improve the functions of the central airways rather than those of the peripheral airways. On the other hand, tulobuterol may activate the  $\beta_2$  adrenergic receptors in the peripheral airways via the systemic circulation; thus, the combination of the two agents would be expected to have complementary effects and improve the functions of both the peripheral and central airways.

#### PHARMACOLOGICAL STUDIES SUPPORTING THE CLINICAL RESULTS

The results of pharmacological studies of the tulobuterol patch support its clinical effects. One such study demonstrated that tulobuterol promotes airway ciliary movement, thereby enhancing airway clearance.<sup>30</sup> This effect may underlie the improvement of expectoration and cough, which are the subjective symptoms of COPD. COPD patients have low flat diaphragms, and the consequent decrease in the contractility of the respiratory muscles may be associated with decreased respiratory functions and subjective symptoms in patients with COPD. Shindoh *et al.*<sup>31,32</sup> reported the significance of the systemic effects of the tulobuterol patch. They also found that the increased contractility of the mouse diaphragmatic muscle was maintained for 24 h after the application of the tulobuterol patch and that the patch suppressed the decrease in the contractility of the diaphragmatic muscle for 24 h observed in a mouse model of endotoxin-induced sepsis. These findings suggest that the tulobuterol patch may increase the contractility of the weakened diaphragmatic muscle in both asthma and COPD patients. Burioka *et al.*<sup>33</sup> assessed the effects of tulobuterol on the expression of the human clock gene *Per1* mRNA and confirmed that the drug does not affect its expression. This finding implies that the administration of tulobuterol at bedtime does not affect night sleep.

#### IMPORTANT PREREQUISITES OF THERAPEUTIC AGENTS FOR THE TREATMENT OF CHRONIC RESPIRATORY DISEASES

Treatment adherence is very important in the management of patients with chronic respiratory diseases. Although it has been established beyond doubt that inhaled drugs play central roles in the treatment of chronic respiratory diseases, such as asthma and COPD, they are often associated with low treatment adherence. Other problems contributing to

low patient adherence to inhaler therapy include difficulty in mastering the technique for using inhalers and insufficient inhalation rate. Because of the ease of its application and the need for only once-daily administration, the use of the tulobuterol patch is associated with good treatment adherence. Consequently, the preparation satisfies the prerequisites of a drug for the long-term management of asthma and COPD. In addition, in the treatment of chronic respiratory diseases, it is important that long-term use of a drug is not associated with reduced efficacy; that is, that no tolerance is induced by its long-term use. Neither a decrease in efficacy nor the development of tolerance was observed with the use of the tulobuterol patch, even after year-long use. Thus, the drug preparation is considered suitable for use in the long-term management of chronic respiratory diseases, such as asthma and COPD. Generic preparations of the tulobuterol patch have recently been launched in the market, but they lack the crystal reservoir technology incorporated in the branded preparation. Some reports<sup>3,4,34</sup> indicate that tulobuterol is released within a shorter time from the generic preparation than from the branded preparation. Therefore, differences in the properties of the two types of preparations should be taken into consideration when using the tulobuterol patch.

## CONCLUSION

The tulobuterol patch is a unique transdermal delivery system prepared using crystal reservoir technology. It has been shown to significantly contribute to the pharmacotherapy of asthma by countering the morning dip in respiratory function. Evidence indicates that the drug reaches the peripheral airways via the systemic circulation, is useful for the long-term management of COPD, and improves the patients' QOL. In addition, the tulobuterol patch is excellent in terms of treatment adherence and convenience of use because it requires only once-daily application. These properties make this transdermal delivery patch suitable for the long-term management of chronic respiratory diseases.

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