

PHARMACOTHERAPY

Real-world effects of two inhaled corticosteroid/long-acting β_2 -agonist combinations in the treatment of asthma

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Abstract

Objective: There are several inhaled corticosteroid/long-acting β_2 -agonist (ICS/LABA) combinations currently used to treat asthmatic patients, but the differences in the clinical effects of these ICS/LABAs are currently unknown. We herein evaluated the effects of two currently available ICS/LABA combinations in a real-world setting. **Methods:** A fluticasone propionate/salmeterol combined Discus inhaler (FP/SM; 250/50 μ g bid) was switched to a budesonide/formoterol Turbuhaler inhaler (BUD/FM; 160/4.5 μ g two inhalations bid) and FP/SM (500/50 μ g bid) was also switched to BUD/FM (160/4.5 μ g four inhalations bid) in symptomatic asthmatic patients treated with FP/SM over 20 years of age. **Results:** Sixty patients were enrolled in this study, and the scores of the asthma control test (ACT) and asthma control questionnaire-5 item version (ACQ5) were significantly improved 4 and 8 weeks after the switch to ICS/LABA treatments, and well-controlled asthma (ACQ5 score <0.75) and good control (ACT score >20) was achieved in 54 (90%) and 40 (66.7%) patients, respectively, at 8 weeks. The spirometric analysis revealed significant improvements of the values of the peak expiratory flow (PEF) and forced expiratory volume in one second (FEV₁) after switching from FP/SM to BUD/FM, and significantly improved small airway impairments ($\dot{V}_{50}$ and $\dot{V}_{25}$) were observed in patients treated with high-dose ICS/LABA. These subjective and objective improvements were also seen in patients aged over 65 years old. **Conclusion:** These data demonstrated that changing the combined ICS/LABA inhaler from FP/SM to BUD/FM can lead to more effective management of symptomatic patients with asthma, especially in patients treated with high-dose ICS/LABA.

Keywords

Asthma, asthma control test, asthma control questionnaire, budesonide/formoterol, elderly patients, fluticasone propionate/salmeterol, inhaled corticosteroid, long-acting β_2 -agonist, spirometry

History

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Introduction

Recent advances in inhalation treatments, including inhaled corticosteroids (ICS) and long-acting β_2 -agonists (LABA) in a single inhaler, have led to better control in asthmatic patients. Currently, there are several combined dry-powder ICS/LABA delivery devices available, including the fluticasone propionate/salmeterol delivered by the Discus (FP/SM) and the fixed-dose budesonide/formoterol delivered by the Turbuhaler (BUD/FM), which are used worldwide. The increasing use of ICS/LABA may have contributed to a decrease in asthma-related deaths. The Global Initiative for Asthma (GINA) guidelines describe the combined use of ICS and LABA for asthma patients, and these ICS/LABA combined delivery devices may also be helpful for ensuring better treatment adherence [1].

These two ICS/LABA combined delivery devices show different characteristics, are used with different delivery devices (Turbuhaler and Discus), particle size [2,3], mechanisms of

action and onset of bronchodilation [4]. Recent studies have demonstrated more flexible application and better asthma control for BUD/FM, such as for single maintenance and reliever therapy (SMART) [5].

Controversial results of previous reports comparing these two ICS/LABA for controlling asthmatic patients have been demonstrated, with FP/SM (500/100 μ g/day; medium dose) being superior to BUD/FM (640/18 μ g/day; medium dose) in reducing moderate-to-severe exacerbations [6]. Conversely, a significant reduction of hospitalizations and/or emergency room visits due to BUD/FM (640/18 μ g/day) compared to FP/SM (500/100 μ g/day) was reported [7]. Akamatsu et al. [8,9] and Hozawa et al. [10] recently showed the favorable effect of switching from medium-dose FP/SM to BUD/FM in patients with symptomatic asthma in a real clinical setting. However, the clinical differences between these two ICS/LABA combinations, especially high-dose ICS/LABA, have not been fully investigated.

The mortality rate of asthma has been decreasing, but the large part of the patients dying are elderly patients over 65 years old [11], and controlling the asthma in elderly patients is important for reducing the mortality rate of asthma. FP/SM has been used as an accepted and effective treatment

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for asthma throughout Japan, while BUD/FM was recently introduced in 2011. We performed the present study to assess the effects of switching ICS/LABA combination therapy (from FP/SM to BUD/FM) as an important option in the management of asthma, including that observed in elderly patients over 65 years of age in the real-world clinical setting in Japan.

Patients and methods

Patients

This study was performed at the University of Occupational and Environmental Health, Japan and related hospitals in Japan between February 2010 and December 2012. All patients satisfied the definition of asthma based on the GINA [1]. The inclusion criteria were (i) age over 20 years, (ii) ability to perform an adequate spirometric maneuver, (iii) receiving FP/SM 250/50 µg or 500/50 µg in one inhalation twice per day (bid) with or without other medications for asthma, including theophylline, leukotriene receptor antagonists and oral corticosteroids for at least 8 weeks and (iv) non-smoking during the study. The exclusion criteria were (i) having a history of any respiratory tract infections within at least 1 month before this study, (ii) having uncontrollable chronic respiratory infections, (iii) having chronic obstructive pulmonary disease and (iv) being pregnant.

Study design

This study was a prospective, open-label, multi-center, uncontrolled longitudinal study. After a 4-week run-in period, patients completed the asthma control test (ACT) and Asthma Control Questionnaire, the five-item version (ACQ5), and patients with an ACT score <25 and/or ACQ5 score >0 were enrolled. FP/SM 250/50 µg and FP/SM 500/50 µg given by one inhalation bid were switched to BUD/FM 160/4.5 µg given by two inhalations bid and four inhalations bid, respectively, and all other asthma treatments were sustained. The dose of dry-powder BUD/FM delivered by the Turbuhaler in Japan is equal to that of the spray device (pressured metered-dose inhaler) used in USA in terms of the clinical efficacy and safety [12,13]. Each patient completed the ACT, ACQ5 and spirometry examination 4 and 8 weeks after switching the ICS/LABA. We assessed the inhaler training of each patient during the run-in period and when switching the ICS/LABA regimen, as well as at 4 and 8 weeks after the switch.

This study was approved by the Ethics Committee of the University of Occupational and Environmental Health, Japan, and was conducted in accordance with the principles of the Declaration of Helsinki. Each local ethics committee approved this study, and informed consent from all patients was obtained prior to the study.

Subjective symptom measurements

ACT

The ACT consists of five questions assessing the interference with activity, shortness of breath, nocturnal symptoms, rescue medication use and self-rating of asthma control, and is a

validated assessment of asthma control [14,15]. A score of 20 or higher was identified for well-controlled asthma, and a difference of three points was considered to be the minimally important difference (MID) of the ACT [16]. The Japanese version of the ACT was adequately validated in Japanese asthmatic patients [17], and was obtained and used with permission from GlaxoSmithKline.

ACQ5

The ACQ5 (Japanese version) consists of five items assessing nocturnal waking, morning symptoms, activity limitations, shortness of breath and wheezing during the previous seven days, with each item scored on a scale of 0 to 6 (0 and 6 represent good and poor control for each question, respectively), and the overall ACQ5 score is expressed as the mean of the five scores [18]. A value of ≤0.75 and ≥1.50 is considered to indicate well-controlled and not well-controlled asthma, respectively [19]. A difference of 0.5 points or more was considered to be the MID [18].

Pulmonary function test

Spirometry was performed at the start of the study and 4 and 8 weeks after switching the ICS/LABA, between 9:30 and 11:00 AM after the patients inhaled the ICS/LABA treatment at around 7:00 AM. Short-acting β₂-agonist use was prohibited for at least 6 h prior to the spirometry evaluation. The forced vital capacity (FVC), forced expiratory volume in one second (FEV₁), peak expiratory flow (PEF), V₅₀ and V₂₅ were measured according to the formula of the Japanese Respiratory Society [20].

Statistical analysis

All values are expressed as the means with ranges. The data on the time course of the effects were analyzed with the Friedman repeated-measures analysis of variance on ranks with a *post hoc* Dunn's multiple comparison *post hoc* test using the StatFlex version 6 software program (Artech Co. Ltd, Osaka, Japan). A value of *p* < 0.05 was considered to be statistically significant.

Results

The patient characteristics are shown in Table 1. Seventy-four patients were assigned to the study, and 14 patients could not complete all the study protocols. Therefore, 60 patients (including 22 patients aged ≥65 years old) eventually completed the study protocols and were enrolled in this study. Among these, 35 (13) and 25 (9) patients had received medium- and high-dose ICS/LABA (aged ≥65 years), respectively. There were no patients received other new medications including corticosteroids for treating bronchial asthma. Adherence to the medication regimen during the run-in and study periods was confirmed by the doctors, nurses and pharmacists, and no major problems were identified among the subjects included in this study.

ACT

The changes in the ACT scores over time after switching the ICS/LABA are shown in Figure 1(a) and 2(a). The ACT

Table 1. Clinical characteristics of the patients.

Characteristics	N (F/M)	Age (years)	Disease duration (years)	LTRA n (%)	OCS n (%)
All patients					
Total	60 (33/27)	58.0 ± 15.4	12.2 ± 13.4	32 (53.3)	6 (10.0)
<65	38 (21/17)	49.2 ± 12.0	13.0 ± 14.5	19 (50.0)	4 (10.5)
>65	22 (12/10)	72.6 ± 7.3	10.9 ± 11.7	13 (59.1)	2 (9.1)
Moderate dose					
Total	35 (20/15)	59.2 ± 16.5	9.8 ± 13.5	15 (42.9)	2 (5.7)
<65	22 (12/10)	46.6 ± 12.9	11.6 ± 15.9	10 (45.5)	2 (9.1)
>65	13 (8/5)	74.3 ± 8.0	6.8 ± 8.0	5 (38.5)	0 (0)
High dose					
Total	25 (13/12)	56.3 ± 14.0	15.9 ± 12.7	17 (68.0)	4 (16.0)
<65	16 (9/7)	48.7 ± 14.0	15.3 ± 12.2	9 (56.3)	2 (12.5)
>65	9 (4/5)	69.9 ± 5.3	16.9 ± 14.0	8 (88.9)	2 (22.2)

F, female; M, male; LTRA, leukotriene receptor antagonist.

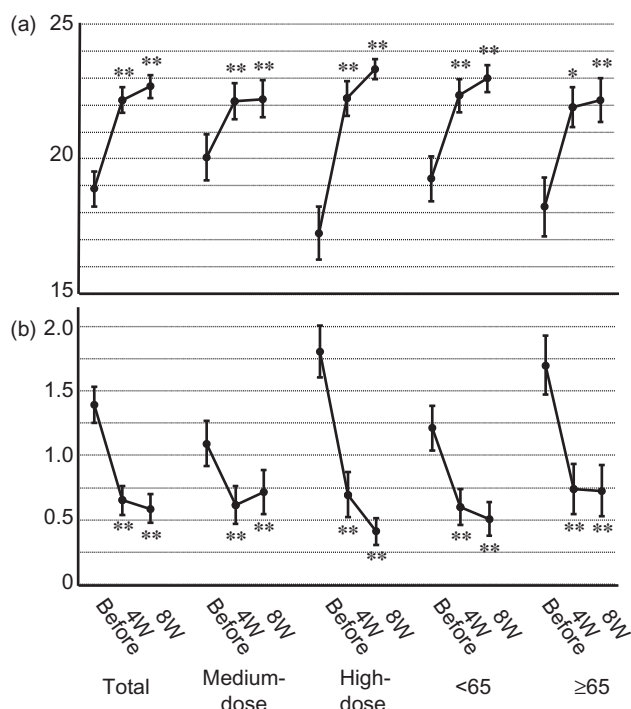


Figure 1. The changes in the ACT (a) and ACQ5 (b) scores over time after switching from the fluticasone propionate/salmeterol combined Discus inhaler (FP/SM) to the budesonide/formoterol Turbuhaler inhaler (BUD/FM). The average and standard error plots show the changes in the ACT scores from baseline to 4 and 8 weeks after switching from FP/SM to BUD/FM. The symbols reported in graphs refer to the results of Dunn's multiple comparison *post hoc* tests (* $p < 0.05$ and ** $p < 0.01$ versus baseline) applied among the aforementioned parameters.

was significantly improved after switching the ICS/LABA in the analysis of all patients, including patients treated with medium- and high-dose ICS/LABA. The average ACT scores improved from 18.9 to 22.2 and to 22.7 from before to 4 and 8 weeks after switching the ICS/LABA, respectively (Figure 1a). The numbers of patients who showed improvements of more than three scores on the ACT at 4 and 8 weeks after switching the ICS/LABA compared to the baseline values are shown in Table 2. ACT scores ≥ 20 (good control) were noted in 30/60 of all patients, 23/35 and 7/25 in patients treated with medium- and high-dose ICS/LABA before switching the ICS/LABA, respectively, and these numbers

were increased to 54/60 in all patients and 30/35 and 24/25 in patients treated with medium- and high-dose ICS/LABA after switching the ICS/LABA, respectively (Figure 2a). Additionally, 30.0% of patients (31.4% in the medium- and 28.0% in high-dose ICS/LABA group, respectively) achieved ACT (total control) scores of 25 8 weeks after switching the ICS/LABA (Figure 2a). Moreover, even patients over 65 years old showed significant improvement of the ACT after switching the ICS/LABA (Figure 1a).

ACQ5

The changes in the ACQ5 scores over time are shown in Figures 1(b) and 2(b). The scores for the overall ACQ5 and for each item (data not shown) were also significantly improved after switching the ICS/LABA in the analysis of all patients, and the average scores of the ACQ5 improved from 1.39 to 0.65 and 0.59 from before to 4 and 8 weeks after switching the ICS/LABA, respectively (Figure 1b). The numbers of patients who showed an improvement of >0.5 points on the ACQ5 at 4 and 8 weeks after switching the ICS/LABA compared to the baseline values are shown in Table 2. ACQ5 scores of ≤ 0.75 (well-controlled) were noted in 19/60 of all patients; 15/35 and 4/25 in patients treated with the medium- and high-dose ICS/LABA, respectively, and these numbers increased to 40/60 in all patients and 22/35 and 18/25 in patients treated with medium- and high-dose ICS/LABA 8 weeks after switching the ICS/LABA, respectively (Figure 2b).

Additionally, 45.0% of patients (48.6% in the medium- and 40.0% in the high-dose ICS/LABA group, respectively) achieved a score of 0 for the ACQ5 8 weeks after switching the ICS/LABA (Figure 2b). The patients over 65 years old also showed significant improvement of the ACQ5 after switching the ICS/LABA (Figure 1b).

Spirometry

The changes of the PEF and FEV₁ over time are shown in Figure 3. The PEF demonstrated significant improvement for all patients, patients treated with medium- and high-dose ICS/LABA and patients <65 and ≥ 65 years old (Figure 3a). The VC, FVC (data not shown) and FEV₁ (Figure 3b) showed significant improvements in all patients, patients treated with high-dose ICS/LABA (but not those treated with medium-dose ICS/LABA) and those <65 years old after switching the ICS/LABA. Significant improvement of the small airway impairments ($\dot{V}_{25}$, $\dot{V}_{50}$) were observed 8 weeks after switching the high-dose ICS/LABA, even in patients over 65 years old (data not shown).

Discussion

We herein evaluated the effects of switching the medium- and high-dose ICS/LABA in symptomatic asthmatic patients initially treated with FP/SM in a real-world clinical setting. The ACT and ACQ5 assessments demonstrated relatively fast and significant subjective symptomatic improvement after switching the ICS/LABA to BUD/FM. Objectively, significant improvement of the PEF was also observed after switching the ICS/LABA, even in elderly patients over 65 years old. Moreover, the patients treated with high-dose ICS/LABA showed an improvement of the small

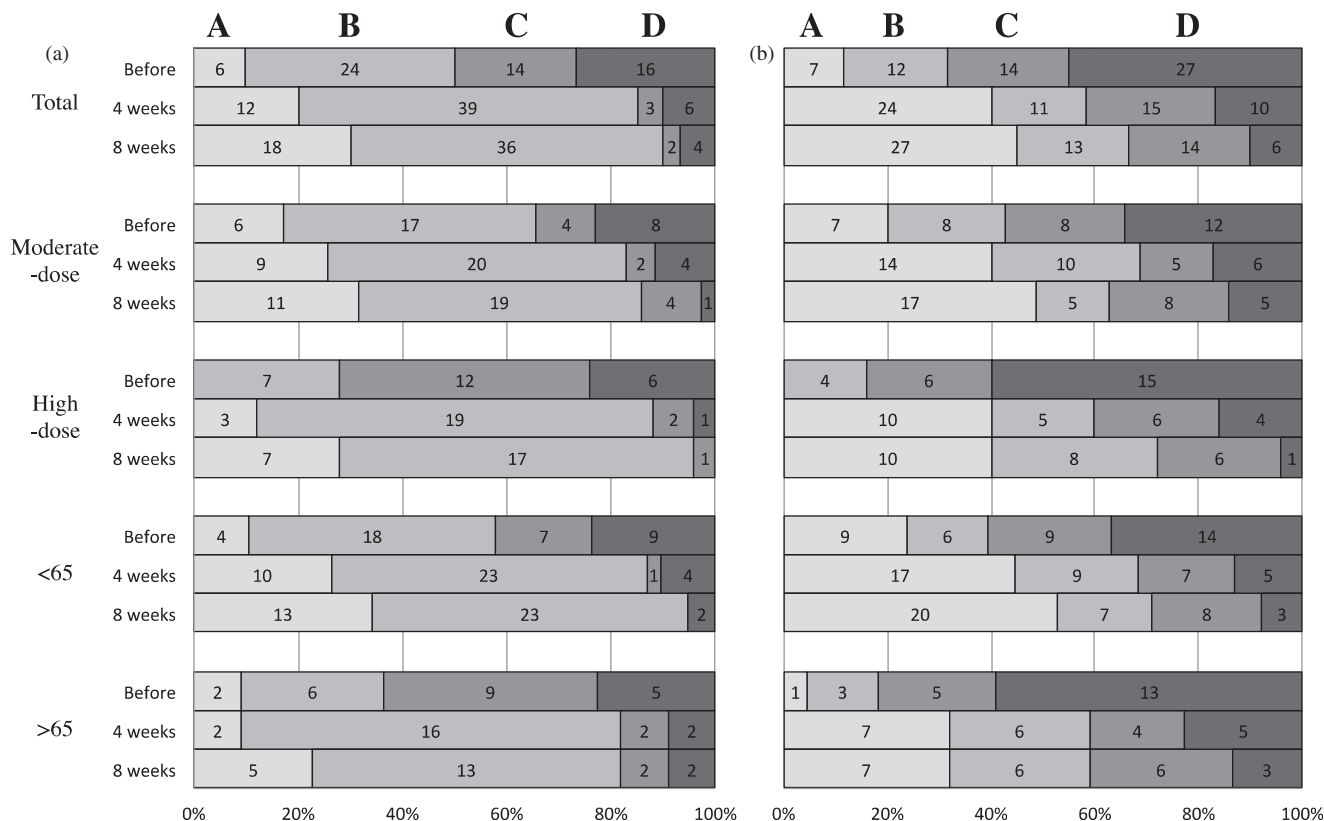


Figure 2. The changes in each of the ACT and ACQ5 scores over time. The changes of the ratio of each control category in the ACT (a) and ACQ5 (b) from baseline to 4 and 8 weeks after switching from the fluticasone propionate/salmeterol combined Discus inhaler (FP/SM) to the budesonide/formoterol Turbuhaler inhaler (BUD/FM). (a) The categories indicate A; 25 (total control) B; 20–24 (good control), C; 16–19 (not well controlled), D; 1–15 (very poorly controlled) for the ACT scores. (b) The categories were A: 0 scores (perfect control) B: <0.75 (well controlled), C: 0.75–1.5 (moderately controlled) and D: >1.5 (poorly controlled) of the ACQ5.

Table 2. The number of patients with MID of ACT and ACQ5 score compared to the baseline value.

		4 weeks				8 weeks			
		Number of patients (n) with increased/decreased MID (%)							
		ACT		ACQ5		ACT		ACQ5	
		n/n	%/%	n/n	%/%	n/n	%/%	n/n	%/%
Number of patients (n)									
Total	60	32/2	53.3/3.3	30/1	50.0/1.67	33/4	55.0/6.7	33/4	55.0/6.7
Medium dose									
Total	35	17/2	48.6/5.7	15/1	42.9/2.9	15/4	42.9/11.4	14/4	40.0/11.4
<65	22	8/2	36.4/9.1	6/1	27.3/4.5	7/2	31.8/9.1	7/3	31.8/13.6
>65	13	9/0	69.2/0	9/0	69.2/0	8/2	61.5/15.4	7/1	53.8/7.7
High dose									
Total	25	15/0	60.0/0	15/0	60.0/0	18/0	72.0/0	19/0	76.0/0
<65	16	10/0	62.5/0	8/0	50.0/0	13/0	81.3/0	12/0	75.0/0
>65	9	5/0	55.6/0	7/0	77.8/0	5/0	55.6/0	7/0	77.8/0

n: number of patients, ACT: Asthma Control Test, ACQ5 Asthma Control Questionnaire, 5-item version, MID: minimally important difference. The numbers of patients with significant change of ACT and ACQ5 scores in patients treated with medium- or high-dose of ICS/LABA. A change (increase or decrease) of more than and equal to three scores of ACT and 0.5 points of ACQ5 compared to the baseline value was considered significant (MID). In the column, n/n and %/% represent the total number and %, respectively, of patients with an increased/decreased MID.

airway impairments, even in the elderly patients aged over 65 years old.

With regard to the different effects of FP/SM and BUD/FM, several reports, including those by Hozawa et al. [10] and Akamatsu et al. [8,9] have recently demonstrated comparable effects of medium-dose FP/SM and medium-dose BUD/FM on subjective symptoms, small airway function and airway inflammation, and when subjects switched from FP/SM to BUD/FM, they showed significant improvement in small

airway impairments, the exhaled nitric oxide fractions and ACQ5 scores compared to those continuing FP/SM. These results are similar to our present findings.

The differences between the former reports [8–10] and this study are that our results were from relatively longer consecutive periods of evaluation after switching the ICS/LABA, and the present study is also the first report of the effect on switching high-dose ICS/LABA combined inhalers. In addition, simultaneous evaluation of the scores of the ACT

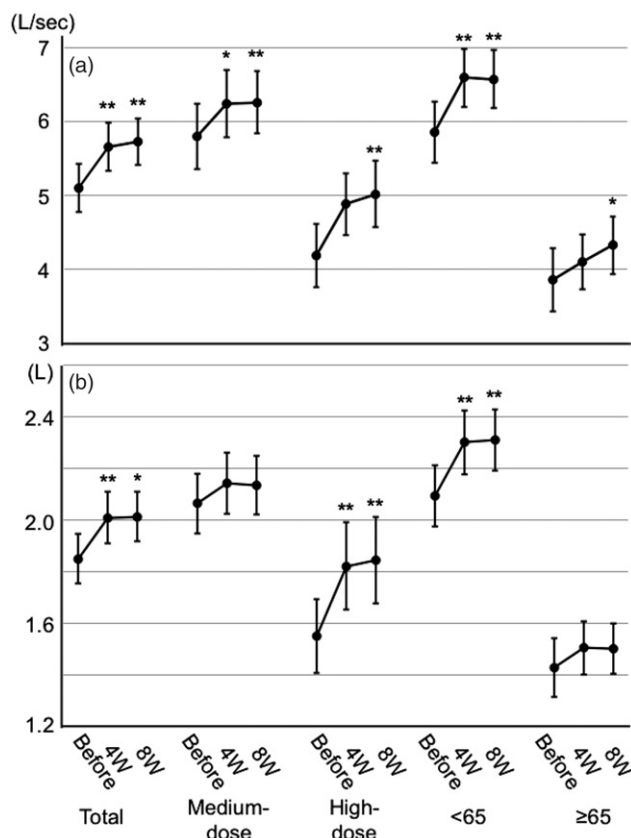


Figure 3. (a) The changes of the PEF and (b) FEV₁ over time after switching from the fluticasone propionate/salmeterol combined Discus inhaler (FP/SM) to the budesonide/formoterol Turbuhaler inhaler (BUD/FM). The average and standard error plots show the changes of the ACT scores from baseline to 4 and 8 weeks after switching from FP/SM to BUD/FM. The symbols reported in graphs refer to Dunn's multiple comparison *post hoc* tests (**p* < 0.05 and ***p* < 0.01 versus baseline) applied among the aforementioned parameters.

and ACQ5 reflected the changes in the subjective symptoms of asthma, in addition to the observed changes in the spirometric evaluation in the present study. The ratios of poorly controlled asthmatic patients evaluated by the ACT (<20) and ACQ5 (>1.5) were similar, but the ratios of well-controlled patients evaluated by these two different modalities (ACT >20 and ACQ5 <0.75) were relatively different, with the ACT identifying more patients with well-controlled asthma over time (Figure 2). In addition, patients treated with high-dose ICS/LABA showed more drastic improvements as evaluated by the ACT and ACQ5 than did patients treated with medium-dose ICS/LABA. The ratios of patients with totally controlled asthmatic symptoms evaluated by the scores of the ACT (25) and ACQ5 (0) quickly and significantly changed from 0 to 40% within 4 weeks after switching the high-dose ICS/LABA (Figure 2).

The possible mechanisms underlying the favorable effects of switching from FP/SM to BUD/FM may be at least partly based on the differences in the devices, bronchodilators and corticosteroids used, as well as their particle sizes. First, the inhaled dry-powder particle size of BUD/FM is smaller than that of FP/SM. Aerosol particles with mass median aerodynamic diameters (MMADs) of 2–5 and 0.8–3.0 μ m are suitable for drug delivery to the airway and lung parenchyma, respectively [21], and the particle size (flow rate of 60 l/min)

of BUD/FM was 2.4 μ m for budesonide and 2.5 μ m for formoterol, respectively [2], and the particle size of FP/SM was 4.4 μ m for both salmeterol and fluticasone [3]. Recently, small airway impairment in stable symptomatic asthmatic patients has been reported [22–24], and controlling this small airway impairment may be one of the key factors required for the successful treatment of patients with asthma. The inhalation of more particles by using BUD/FM might lead to more effective dispersal to the peripheral airways than is achieved using the particles inhaled with FP/SM. Therefore, improvements of the subjective symptoms (ACT and ACQ5 scores) and pulmonary functions were achieved in this study. The smaller size of the MMAD for distributing the aerosols to the peripheral airways, which led the BUD/FM particles to more effectively reach the small airways compared to FP/SM, may have been important for improving the airway inflammation and exerting its bronchodilator effect, thereby decreasing peripheral airway resistance.

Interestingly, significant improvement of the small airway impairments was only observed after switching the high-dose ICS/LABA, not the medium dose, in this study. Second, there are marked differences in intrinsic efficacy between salmeterol and formoterol in these two ICS/LABA. Formoterol directly affects β_2 -adrenergic receptors, being simultaneously stored and released from the cell membrane, and also has rapid and consistent bronchodilatory effects [4]. Several reports have described that the intrinsic efficacy of formoterol is greater than that of salmeterol [4,25,26], especially when symptoms are accompanied by increased inflammation [27], and BUD/FM showed a more rapid onset of bronchodilatory effects than FP/SM [28,29]. Therefore, the intrinsic differences in the efficacy of the drugs may explain the effectiveness of switching the ICS/LABA observed in this study and other reports. In addition, the different bronchodilatory effects of salmeterol and formoterol under inflammatory circumstances have been discussed, and the bronchodilation induced by the combination of budesonide and formoterol was more significant than that observed following treatment with the combination of budesonide and salmeterol using a constricted murine trachea induced by carbacol exposure, especially in the presence of inflammatory cytokines [30].

A possible explanation for the inhibitory effects of salmeterol on the bronchodilation under conditions of inflammation is that formoterol does not have stimulation of inhibitory G protein (Gi) by salmeterol and subsequent Gi-induced inhibition of adenylate cyclase, which leads to an inhibition of bronchodilation [30], and this mechanism may partly explain the enhanced efficacy of BUD/FM in this study, especially in patients treated with high-dose ICS/LABA, who are considered to have consistent airway inflammation.

Reversible esterification of budesonide with long-chain fatty acids [31] results in an intracellular pool of esterified budesonide, and the free steroid is slowly released to bind to the glucocorticosteroid receptor, allowing it to be retained in the airway tissue for a longer time than other ICS [32]. This esterification of budesonide is associated with a significant prolongation of the anti-inflammatory effects of budesonide compared with fluticasone propionate [33]. The ICS doses were similar before and after switching the

ICS/LABA in the GINA guidelines [1], but the clinical efficacy of ICS/LABA may be affected by the LABA, and the clinical differences and *in vivo* effects of both FP/SM and BUD/FM are not fully understood, and further studies are necessary.

There are several options to control uncontrolled patients treated with medium-dose FP/SM, and the results of the present study demonstrate that switching from medium-dose FP/SM to medium-dose BUD/FM may be a good option to achieve better control in such patients, and represents an alternative to increasing the dose of fluticasone. Moreover, this trial of switching high-dose ICS/LABA inhalers indicates that such a switch may be a useful and effective treatment option in the real-life clinical setting. Further clinical studies will be necessary to confirm these findings.

There are several limitations associated with this study. First, this study was an uncontrolled, open-label, non-cross-over study with a relatively small number of patients and a relatively short duration. However, the purpose of this study was to evaluate the effects of switching the ICS/LABA treatment with similar doses in a real clinical situation, so continuing the same dosage of FP/SM as another arm did not seem to be useful as a genuine control group. There are currently only two ICS/LABA combination products available for clinical use in Japan, so that one of the other arms in switching ICS/LABA medications would have to be randomized to continue to their prior treatment with FP/SM. Second, we only enrolled patients who were already being treated with FP/SM with asthma symptoms. In addition, all of the enrolled patients were on FP/SM at baseline and changed to BUD/FM. None were continued on their current regimen, and no patients on medium-dose FP/SM were stepped up to high-dose FP/SM (a real-world choice) to compare with BUD/FM.

In conclusion, we demonstrated that changing both medium- and high-dose ICS/LABA improved the asthmatic symptoms and pulmonary functions in symptomatic asthmatic patients treated with FP/SM in a real-world clinical setting, even in elderly patients. Changing the ICS/LABA combination inhaler may be an option to achieve better control of symptomatic asthma in patients treated with FP/SM.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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