

Effect of Switching from Salmeterol/Fluticasone to Formoterol/Budesonide Combinations in Patients with Uncontrolled Asthma

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ABSTRACT

Background: Combination therapy with an inhaled corticosteroid (ICS) and a long-acting β_2 -agonist (LABA) in a single inhaler is the mainstay of asthma management and salmeterol/fluticasone combination (SFC) and fixed-dose formoterol/budesonide combination (FBC) are currently available in Japan; however, there is nothing to choose between the two. The purpose of this study was to clarify the effect of switching from SFC to FBC in patients with asthma not adequately controlled under the former treatment regimen.

Methods: This was a prospective, multicenter, open-label, uncontrolled longitudinal study in 87 adult patients with an Asthma Control Questionnaire, 5-item version (ACQ5) score of greater than 0.75 under treatment with SFC 50/250 μg one inhalation twice daily (bid). SFC was switched to FBC 4.5/160 μg two inhalations bid. Study outcomes included ACQ5 score, peak expiratory flow (PEF), FEV₁, and fractional exhaled nitric oxide (FeNO) at the end of treatment period.

Results: Eighty-three patients completed the study. ACQ5 scores improved and exceeded the clinically meaningful difference after 12 weeks of treatment and well-controlled asthma (ACQ5 score ≤ 0.75) was attained in 37 (44.6%) patients. Minimum and maximum PEF and FEV₁ values improved significantly, but not FeNO values, after switching from SFC to FBC.

Conclusions: Switching ICS/LABA combination therapy is a useful option in the management of asthma that is not optimally controlled.

KEY WORDS

Asthma Control Questionnaire, combination therapy, formoterol/budesonide, salmeterol/fluticasone, switching

INTRODUCTION

The Japanese Guideline for Adult Asthma as well as the Global Initiative for Asthma (GINA) recommend the use of an inhaled corticosteroid (ICS) in combina-

tion with a long-acting β_2 -agonist (LABA) for patients with asthma not adequately controlled with low- to medium-dose ICS monotherapy.^{1,2} Combination products, containing both an ICS and a LABA in a single inhaler, have been available in Japan in recent years

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Conflict of interest: No potential conflict of interest was disclosed.

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Received 12 October 2011. Accepted for publication 8 December 2011.

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and may help to improve patient acceptability and adherence in terms of taking both medications at the same time: salmeterol/fluticasone combination (SFC; Adair®) and formoterol/budesonide combination (FBC; Symbicort®). These two combination products have different properties, including inhalation devices, onset of bronchodilatory action,³ and particle size^{4,5}; however, it is uncertain which of these medications to choose for each patient.

Previous studies have compared the efficacy of these combination products directly, a fixed-dose of SFC 100/500 µg per day versus a fixed-dose of FBC 18/640 µg per day, and shown controversial results. The EXCEL study showed that both regimens significantly improved asthma symptoms and lung function but SFC was found to be significantly superior to FBC in reducing the rate of moderate/severe exacerbations.⁶ In contrast, the COMPASS study demonstrated that, compared with SFC, FBC significantly reduced the risk of hospitalizations/emergency-room visits by 28%.⁷ Since only fixed-dose use of each combination therapy is currently approved in Japan, there is nothing to choose between the two. Also, switching treatment regimens is sometimes necessary in a real clinical setting; however, very few studies have examined this.

In this prospective, multicenter, open-label, uncontrolled longitudinal study we evaluated the effectiveness of switching between the medium dose of ICS/LABA combinations, from SFC delivered via Diskus 50/250 µg one inhalation twice daily (bid) to FBC delivered via Turbuhaler 4.5/160 µg two inhalations bid in improving symptoms, pulmonary functions and airway inflammation in terms of the fractional exhaled nitric oxide (FeNO) over a 12-week study period in patients with asthma not adequately controlled under the former treatment regimen.

METHODS

SUBJECTS

Patients with asthma who attended outpatient clinics at Hamamatsu University School of Medicine and 10 related hospitals in Shizuoka Prefecture for routine check-ups between February and December 2010 were enrolled in this study. All patients satisfied the definition of asthma of GINA.² Atopy was defined by positive specific IgE antibodies to at least one common inhalant allergen (CAP system; Pharmacia, Uppsala, Sweden). Inclusion criteria were as follows: (1) age over 18 years; (2) ability to perform an adequate forced expiratory maneuver; (3) asthma duration more than 6 months; and (4) receiving SFC 50/250 µg one inhalation bid with or without other medications for asthma, including leukotriene receptor antagonists, or sustained release theophylline for at least 8 weeks. Patients were excluded from the study if they (1) had had any acute viral infections within at least 1 month before the study; (2) had chronic ob-

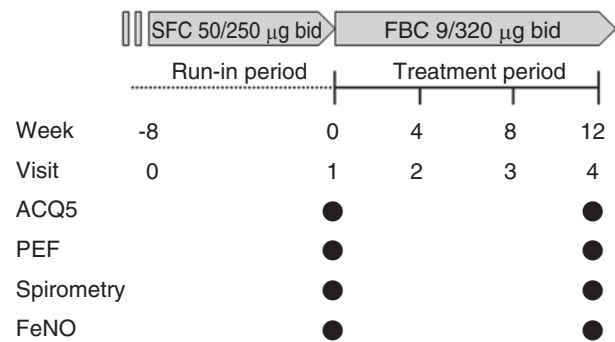


Fig. 1 Study design. ACQ5, Asthma Control Questionnaire, 5-item version; FeNO, fractional exhaled nitric oxide; FBC, formoterol/budesonide combination; PEF, peak expiratory flow; SFC, salmeterol/fluticasone combination.

structive pulmonary disease; (3) had cardiovascular diseases; or (4) were pregnant. Peak expiratory flow (PEF) monitoring was performed in 134 patients using a Miniwright peak flow meter (Clement Clarke Int. Ltd, Harlow, UK).

STUDY DESIGN

This was a prospective, multicenter, open-label, uncontrolled longitudinal study. At visit 1, after 8 weeks of a run-in period, patients completed the Asthma Control Questionnaire, 5-item version (ACQ5) and patients with a score of greater than 0.75 were eligible for this study. SFC was switched to FBC 4.5/160 µg two inhalations bid and they attended each hospital at weeks 4, 8 and 12 of the treatment period, as shown in Figure 1. The inhaler technique of each patient was checked appropriately by the involved doctors, nurses, or pharmacists not only during the run-in period but when switching the regimens and during the treatment period. This study was conducted in accordance with the principles of the Declaration of Helsinki, the protocols were approved by each local ethics committee and informed consent was obtained from all patients prior to the study.

MEASUREMENTS

ACQ5

The ACQ5 (Japanese version) consists of 5 items assessing nocturnal waking, morning symptoms, activity limitation, shortness of breath, and wheeze during the previous 7 days, excluding the frequency of short-acting β₂-agonist (SABA) use and FEV₁% predicted, each scored on a scale of 0-6, where 0 represents good control and 6 represents poor control.⁸ The overall score of the ACQ5 is the mean of the five responses. The cut-point for well-controlled asthma is less than or equal to 0.75, and a value of greater than or equal to 1.50 confirms not well-controlled asthma.⁹ A 0.5 change in each score was considered a clinically meaningful difference, that is, minimum impor-

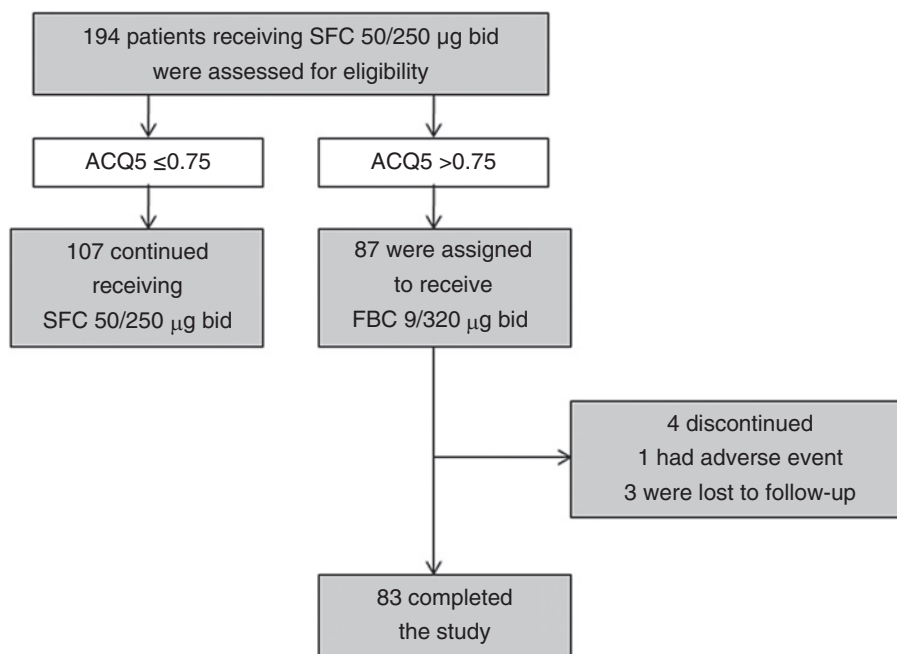


Fig. 2 Patient selection. ACQ5, Asthma Control Questionnaire, 5-item version; FBC, formoterol/budesonide combination; SFC, salmeterol/fluticasone combination.

tant difference (MID).⁸

Pulmonary Functions

Spirometry was performed at visits 1 and 4 using computerized equipment (model CHESTAC-8100; CHEST MI, Inc., Tokyo, Japan). FVC, FEV₁, forced expiratory flow at 50% of FVC (FEF_{50%}), and FEF_{75%} were expressed as a percentage of predicted values according to the formula of the Japanese Respiratory Society.¹⁰ In patients who recorded their PEF values at home, the lowest PEF expressed as a percentage of the highest PEF (Min%Max PEF) values¹¹ during the 1-week period prior to examination were calculated. Patients were requested not to use SABA for at least 6 h prior to the measurement.

Fractional Exhaled Nitric Oxide (FeNO)

FeNO levels were measured in 97 of 194 patients by the online method at a flow rate of 50 ml/sec using an NO analyzer (Sievers NOA 280i; GE Analytical Instruments, Boulder, CO, USA) according to the American Thoracic Society/European Respiratory Society recommendations.¹²

Statistical Analysis

All values are expressed as the means with ranges. Comparisons between the 2 groups were made using the unpaired *t* test and the chi-square or Fisher's exact test. Paired *t* test was used to compare changes between baseline and after switching therapies. There was no difference in quantitative data and categorical data between the 97 patients with FeNO data

and the remaining 97 patients without FeNO data by the *t* test and the chi-square or Fisher's exact test, respectively. Stat View Version 5.0 (SAS Institute, Cary, NC, USA) was used for statistical calculations. A *p* value of <0.05 was considered significant, and all tests were 2 sided.

RESULTS

The patient selection is presented in Figure 2. Of the 194 patients receiving SFC 50/250 µg bid and assessed for eligibility, 107 (55.2%) patients with an ACQ5 score ≤ 0.75 continued the same treatment regimen. The comparison between 107 patients with well-controlled asthma and the remaining 87 patients with asthma not adequately controlled is shown in Table 1. Eighty-seven patients with an ACQ5 score of >0.75 had nonatopic state predominance, lower PEF parameters and pulmonary functions, longer duration of treatment with SFC, and more systemic corticosteroid use, which were statistically significant.

Of the patients assigned to receive FBC 9/320 bid, 4 discontinued because of throat discomfort in 1 and inability to attend regular check-ups in 3; thus, 83 patients completed the study. The mean change from baseline in clinical parameters at the end of treatment is shown in Table 2 and Figure 3-5. Overall ACQ5 score and each item improved significantly and exceeded the MID after 12 weeks of treatment. Well-controlled asthma was attained in 37 (44.6%) patients, while not well-controlled asthma was reduced to 22 patients. Further, there was a significant improvement in Min and Max PEF and FEV₁ values after

Table 1 Characteristics of the study patients

Characteristics	ACQ5 ≤ 0.75 (n = 107)	ACQ5 > 0.75 (n = 87)	p-Value
Age, y	58.1 (20-88)	59.4 (18-85)	0.560
Male/female	52/55	34/53	0.184
Atopic/nonatopic	68/39	45/42	0.037
Non/ex/current smokers	68/35/5	46/35/9	0.150
Duration of asthma, y	14.9 (0.5-75)	12.3 (0.5-50)	0.141
Coexisting nasal diseases	32	20	0.277
Current pet owners	30	14	0.047
Body mass index, kg/m ²	22.8 (15.2-34.3)	23.5 (16.2-38.1)	0.297
Total IgE, IU/ml	461 (3-3220)	660 (2-15339)	0.358
ACQ5 overall score	0.19 (0-0.6)	1.63 (0.8-5.0)	< 0.0001
Min PEF, L/min	362 (126-640)	314 (40-540)	0.020
Max PEF, L/min	405 (130-780)	364 (50-650)	0.0523
Min%Max PEF, %	88.6 (44.4-100)	85.5 (51.7-97.7)	0.033
FVC, L	3.07 (1.57-6.63)	2.68 (0.65-5.48)	0.003
%FVC, %	103.0 (60.1-147.9)	94.7 (28.9-148.4)	0.002
FEV ₁ , L	2.17 (0.76-5.72)	1.86 (0.36-3.69)	0.007
%FEV ₁ , %	85.0 (44.1-167)	80.0 (20.8-140.7)	0.141
%FEF _{50%}	47.9 (7.8-127.2)	50.1 (4.4-175.4)	0.622
%FEF _{75%}	36.3 (8.6-125.0)	34.9 (2.5-146.5)	0.692
FeNO, ppb	39.9 (13.6-197.3)	38.1 (9.8-142.3)	0.865
Duration of treatment with SFC, m	9.6 (2-32)	12.7 (2-34)	0.020
Leukotriene receptor antagonists	41	45	0.061
Sustained-release theophylline	12	17	0.107
Prednisolone	0	4	0.011

Data are expressed as the means with ranges or No.

Abbreviations: ACQ5, Asthma Control Questionnaire, 5-item version; FEF50%, forced expiratory flow at 50% of FVC; FeNO, fractional exhaled nitric oxide; Max PEF, highest PEF over a week; Min PEF, lowest PEF over a week; Min%Max PEF, lowest PEF over a week expressed as a percentage of the highest PEF; PEF, peak expiratory flow; SFC, salmeterol/fluticasone combination.

switching from SFC to FBC. FeNO values were measured in 33 patients and there was no significant change after switching from SFC to FBC.

DISCUSSION

We assessed the effect of switching from SFC 50/250 μ g one inhalation bid to FBC 4.5/160 μ g two inhalations bid in 83 patients with asthma not adequately controlled under the former treatment regimen. We demonstrated that ACQ5 scores improved and exceeded the MID after 12 weeks of treatment and well-controlled asthma was attained in 37 (44.6%) patients. We also found that Min and Max PEF and FEV₁ values improved significantly after switching from SFC to FBC.

Several reports have compared the effect of FBC and SFC on asthma treatment outcomes; however, very few have concerned switching treatment regimens. Recently, Hozawa *et al.*¹³ reported a study on the comparison of FBC with SFC on small airway impairment and airway inflammation. After SFC 50/250 μ g one inhalation bid, patients were randomized into

FBC 4.5/160 μ g two inhalations bid or continued the same dose of SFC. They found that patients in the FBC group showed significant improvement in respiratory mechanics, small airway pulmonary functions, FeNO values, and ACQ scores compared with the SFC group. There are several differences in the study design between Hozawa *et al.* and the present study, including no other asthma medications, nonsmokers, %FEV₁ $> 80\%$, baseline FeNO levels > 35 ppb, and 4 weeks of treatment in their study; however, the effectiveness of switching from SFC to FBC in patients with asthma not adequately controlled was shown in the present study as well as in their study.

Possible explanations for the effectiveness of switching from SFC to FBC are as follows. First, FBC Turbuhaler particles are smaller than SFC Diskus particles. The Aerosol Consensus Statement reported that aerosols with mass median aerodynamic diameters (MMADs) of 2-5 μ m are optimal for delivery to the airways, whereas aerosols with MMADs of 0.8-3.0 μ m are suitable for drug delivery to the parenchyma.¹⁴ Tarsin *et al.*⁴ reported that the particle size

Table 2 Mean change from baseline in clinical parameters at the end of treatment

	Baseline value	Final value	p-Value
ACQ5, overall score	1.62 (0.8-5.0)	0.96 (0-3.2)	<0.0001
Q1: nocturnal waking	1.23 (0-6)	0.66 (0-4)	<0.0001
Q2: morning symptoms	1.53 (0-5)	1.00 (0-4)	<0.0001
Q3: activity limitation	1.59 (0-5)	0.87 (0-4)	<0.0001
Q4: shortness of breath	1.96 (0-5)	1.22 (0-4)	<0.0001
Q5: wheeze	1.80 (0-5)	1.24 (0-5)	<0.0001
ACQ5 ≤0.75	0	37	
ACQ5 >0.75-<1.50	43	24	<0.0001
ACQ5 ≥1.50	40	22	
Min PEF, L/min	319 (40-540)	340 (50-580)	0.0008
Max PEF, L/min	366 (50-650)	377 (50-600)	0.022
Min%Max PEF, %	85.7 (51.7-97.7)	88.6 (60.0-100)	0.065
FVC, L	2.71 (0.65-5.48)	2.77 (0.83-5.56)	0.080
%FVC, %	95.0 (28.9-148.4)	96.9 (37.3-135.6)	0.110
FEV ₁ , L	1.90 (0.36-3.69)	1.97 (0.45-3.75)	0.027
%FEV ₁ , %	79.8 (20.8-140.7)	82.6 (26.3-131.7)	0.040
%FEF _{50%}	51.3 (4.40-175.4)	52.2 (4.43-152.4)	0.633
%FEF _{75%}	35.8 (6.70-146.5)	39.6 (2.39-145.5)	0.128
FeNO, ppb	38.1 (9.8-142.3)	41.6 (11.5-154.2)	0.719

Data are expressed as the means with ranges or No.

Abbreviations: ACQ5, Asthma Control Questionnaire, 5-item version; FEF50%, forced expiratory flow at 50% of FVC; FeNO, fractional exhaled nitric oxide; Max PEF, highest PEF over a week; Min PEF, lowest PEF over a week; Min%Max PEF, lowest PEF over a week expressed as a percentage of the highest PEF; PEF, peak expiratory flow; SFC, salmeterol/fluticasone combination.

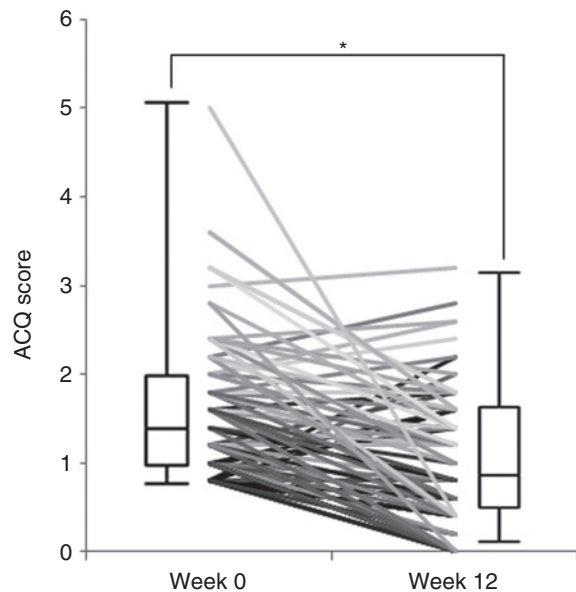


Fig. 3 Changes in ACQ5 score. The line across the box is the median, the top and bottom portions of the box represent the 25th and 75th percentiles, respectively, and the whiskers indicate the maximum and minimum values at week 0 and 12. * $p < 0.0001$. ACQ5, Asthma Control Questionnaire, 5-item version.

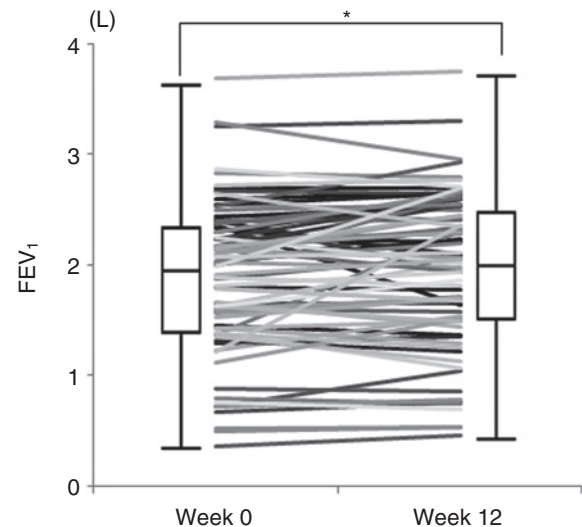


Fig. 4 Changes in FEV₁. The line across the box is the median, the top and bottom portions of the box represent the 25th and 75th percentiles, respectively, and the whiskers indicate the maximum and minimum values at week 0 and 12. * $p < 0.05$.

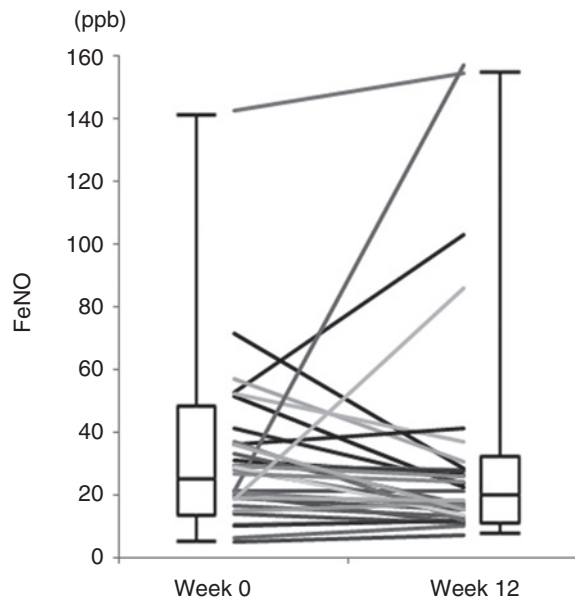


Fig. 5 Changes in FeNO. The line across the box is the median, the top and bottom portions of the box represent the 25th and 75th percentiles, respectively, and the whiskers indicate the maximum and minimum values at week 0 and 12. FeNO, fractional exhaled nitric oxide.

of FBC Turbuhaler inspired at a flow rate of 60 l/min was 2.4 μm for budesonide and 2.5 μm for formoterol, respectively, while Granlund *et al.*⁵ reported that the particle size of SFC Diskus inspired at a flow rate of 60 l/min was 4.4 μm for both salmeterol and fluticasone. These findings suggest that more FBC particles reached the peripheral airways/alveolar lesions than SFC particles, thereby enabling the improvement of ACQ5 scores and pulmonary functions in the present study. Secondly, there is a marked difference in intrinsic efficacy between formoterol and salmeterol. Intrinsic efficacy refers to the ability of a drug to activate its receptor without regard for drug concentration. Hanania *et al.* stated in their review that the intrinsic efficacy of formoterol is 20% of isoproterenol, while that of salmeterol is less than 2%.¹⁵ Kume¹⁶ reported that the values of intrinsic efficacy, expressed as the maximum percent inhibition for β_2 -agonists against 1 μM methacholine-induced contraction in guinea pig tracheal smooth muscle, were 100% for formoterol and 62.4% for salmeterol, respectively. Palmqvist *et al.*³ found that salmeterol was less efficacious for methacholine-induced bronchoconstriction than formoterol. Thus, the difference in intrinsic efficacy may explain the effectiveness of switching from SFC to FBC. Thirdly, there is a difference in the onset of bronchodilation between FBC and SFC. Studies have reported that FBC treatment elicited more rapid onset of bronchodilatory effects than SFC treatment.¹⁷ A rapid onset of effect may result in improved treatment adherence. In a comparison of a fixed-dose

FBC metered-dose inhaler versus a SFC dry powder inhaler, O'Connor *et al.*¹⁸ found that patients receiving FBC had more timely relief of symptoms and feeling the medication work right away compared with those receiving SFC; therefore, the more rapid onset of the bronchodilatory effects of FBC may lead to improvement after switching the treatment regimens.

Concerning the daily ICS doses, SFC 50/250 μg one inhalation bid delivers 500 μg fluticasone propionate, while FBC 4.5/160 μg two inhalations bid delivers 640 μg budesonide, which is equivalent to the labeled dose of 800 μg of the same drug. Since 500 μg fluticasone propionate is estimated to be equipotent to 800 μg budesonide as a medium daily dose in GINA 2010,² we consider that both ICS/LABA combinations are equipotent in the potency of ICS. In this regard, Japanese Guidelines recommend 400 μg fluticasone propionate and 800 μg budesonide as medium doses.¹ The potency of an ICS may change when combined with a LABA. Also, the efficacy of some products varies when administered via different inhaler devices. Future studies will confirm the clinical relevance of these differences.

There was no effect of switching regimens on FeNO levels in the present study (from 38.1 ppb to 41.6 ppb). Exhaled NO is the quickest marker to respond to glucocorticoids of asthma control measures, including symptoms, airflow obstruction, and airway hyperresponsiveness.¹⁹ Gelb *et al.*²⁰ reported mean FeNO values of 48 ppb in the 22 patients with clinically stable asthma (more than 8 weeks) on SFC 50/250 μg one inhalation bid more than 1 year. Thus, it might be possible that FeNO levels had reached a plateau before switching ICS/LABA combinations; however, there were patients with high levels of FeNO or not optimally controlled with FBC 4.5/160 μg two inhalations bid, suggesting the possibility that FeNO levels would be reduced by increasing the FBC doses.

In the present study, we found that 107 of 194 (55.2%) patients receiving SFC 50/250 μg one inhalation bid for more than 8 weeks had well-controlled asthma according to the ACQ5 score, while patients eligible for the study had nonatopic predominance and more impaired pulmonary functions. These findings suggest the effectiveness and limitations of a medium daily dose of fluticasone and salmeterol combination therapy in a real clinical setting. Indeed, it is thought that SFC 50/250 μg is the most useful and available regimen of the medication, but adequate assessment of asthma control should occasionally be performed and, if asthma is not optimally controlled, an increased dose (SFC 50/500 μg) or switching treatment regimens (FBC) are options, although we cannot recommend which is better at this time. The present study suggests, at least partly, that a nonatopic state and impaired pulmonary functions may be clues to detect patients with asthma not adequately

controlled, and switching from SFC to FBC is a reliable strategy for achieving asthma control.

This was a prospective, multicenter, open-label, uncontrolled longitudinal study. The evidence from an uncontrolled study is weaker than that from a controlled study, which is the major limitation of the present study. The reasons for selecting this type of study are as follows. First, it is difficult to perform double blind placebo-controlled trials in Japan with regard to asthma treatment, including ICS. Secondly, the protocols should be used for a cross-over study model to compare the effect of SFC and FBC accurately; however, this was associated with the conditions concerning the asthma medications when the present study was conducted. SFC had been introduced into Japan more than 2 years before the beginning of the present study and its usefulness in asthma treatment had been accepted throughout the country, while FBC had just been introduced. Under such conditions, since we could not collect sufficient patients receiving FBC, we selected the present study design to assess the effect of switching from SFC to FBC and to obtain a sufficient sample size from the multicenters. We preferred a large sample size rather than a higher evidence level. We also consider that this simple study design reflects the real clinical setting and that continuing the same dose of SFC as another arm was not a genuine control group. Our real intention lies not in discussing the merits between SFC and FBC, but in reporting as soon as possible that switching ICS/LABA combination therapy is an important option in the management of asthma.

In conclusion, switching from SFC 50/250 µg one inhalation bid to FBC 4.5/160 µg two inhalations bid improved the asthma control level and pulmonary functions in patients with asthma not adequately controlled under the former treatment regimen. Switching ICS/LABA combination therapy is an important option in the management of asthma.

ACKNOWLEDGEMENTS

There was no funding.

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