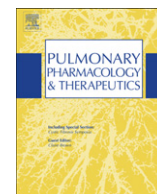


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Switching from salmeterol/fluticasone to formoterol/budesonide combinations improves peripheral airway/alveolar inflammation in asthma

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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. We previously showed that switching from salmeterol/fluticasone combination (SFC) 50/250 μg bid to a fixed-dose formoterol/budesonide combination (FBC) 9/320 μg bid improved asthma control and pulmonary functions, but not fractional exhaled nitric oxide (FeNO), in patients with asthma not adequately controlled under the former treatment regimen.

Objective: To assess whether switching from SFC to FBC improves peripheral airway/alveolar inflammation in asthma (UMIN000009619).

Methods: Subjects included 66 patients with mild to moderate asthma receiving SFC 50/250 μg bid for more than 8 weeks. Patients were randomized into FBC 9/320 μg bid or continued the same dose of SFC for 12 weeks. Asthma Control Questionnaire, 5-item version (ACQ5) score, peak expiratory flow, spirometry, FeNO, alveolar NO concentration (CANO), and maximal NO flux in the conductive airways (J'awNO) were measured.

Results: Sixty-one patients completed the study. The proportion of patients with an improvement in ACQ5 was significantly higher in the FBC group than in the SFC group (51.6% vs 16.7%, respectively, $p = 0.003$). A significant decrease in CANO was observed in the FBC group (from 8.8 ± 9.2 ppb to 4.0 ± 2.6 ppb; $p = 0.007$) compared to the SFC group (from 7.4 ± 7.8 ppb to 6.4 ± 5.0 ppb; $p = 0.266$) although there was no significant difference in the changes in pulmonary functions between the 2 groups. Similar significant differences were found in the CANO corrected for the axial back diffusion of NO (FBC, from 6.5 ± 8.2 ppb to 2.3 ± 2.5 ppb; and SFC, from 4.3 ± 5.3 ppb to 3.9 ± 4.3 ppb). There was no difference in the changes in FeNO or J'awNO between the 2 groups.

Conclusions: Switching therapy from SFC to FBC improves asthma control and peripheral airway/alveolar inflammation even though there is no improvement in pulmonary functions, and FeNO in asthmatic patients.

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1. Introduction

The Global Initiative for Asthma (GINA) recommends the use of an inhaled corticosteroid (ICS) in combination with a long-acting

β_2 -agonist (LABA) for patients with asthma not adequately controlled with low- to medium-dose ICS monotherapy [1]. Salmeterol/fluticasone combination (SFC) and formoterol/budesonide combination (FBC) are available in Japan as combination products,

Abbreviations: ACQ5, Asthma Control Questionnaire 5-item version; ANOVA, analysis of variance; CANO, alveolar NO concentration; FBC, formoterol/budesonide combination; FEF50%, forced expiratory flow at 50% of FVC; FeNO, fractional exhaled nitric oxide; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroid; J'awNO, maximal NO flux in the conductive airways; LABA, long-acting β_2 -agonist; Min%Max PEF, lowest PEF expressed as a percentage of the highest PEF; MMADs, mass median aerodynamic diameters; PEF, peak expiratory flow; SABA, short-acting β_2 -agonist; SFC, salmeterol/fluticasone combination.

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containing both an ICS and a LABA in a single inhaler, which may help to improve patient acceptability and adherence in terms of taking both medications at the same time. SFC was introduced into Japan in 2007 more than 2 years before the appearance of FBC and its usefulness in asthma treatment has been accepted throughout the country. 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 [2,3]. In addition to which to choose as an initial treatment regimen, switching regimens is sometimes necessary in a real clinical setting; however, very few studies have examined this.

We previously showed that switching from SFC 50/250 µg twice daily (bid) to fixed-dose FBC 9/320 µg bid improved asthma control and pulmonary functions, but not fractional exhaled nitric oxide (FeNO), in patients with asthma not adequately controlled under the former treatment regimen [4]. A possible explanation for the effectiveness of switching regimens included a smaller particle size of FBC than that of SFC [5,6], suggesting that more FBC particles reached the peripheral airways/alveolar lesions than SFC particles, leading to the improvement.

On the basis of the physiologic and pathologic evidence, small or peripheral airways and lung parenchyma are clearly implicated in the pathogenesis of asthma, and this aspect seems to be an important feature of patients with asthma and has important implications for drug delivery [7]. Thus, we hypothesized that switching from SFC to FBC would improve peripheral airway/alveolar inflammation. In this prospective, multicenter, randomized, open-label study we assessed the effect of switching treatment regimens, from SFC delivered via Diskus 50/250 µg one inhalation bid to FBC delivered via Turbuhaler 4.5/160 µg two inhalations bid, on peripheral airway/alveolar inflammation as assessed by alveolar NO concentration (CANO) according to the two-compartment model of Tsoukias and George [8].

2. Methods

2.1. Subjects

Patients with asthma who attended outpatient clinics at Hamamatsu University School of Medicine and Shizuoka General Hospital for routine check-ups between January and August 2011 were enrolled in this study. All patients satisfied the definition of asthma of GINA [1]. 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 obstructive pulmonary disease [3]; had cardiovascular diseases; or [4] were pregnant. Peak expiratory flow (PEF) monitoring was performed using a Miniwright peak flow meter (Clement Clarke Int. Ltd, Harlow, UK).

2.2. Study design

At visit 1, after 8 weeks of a run-in period, eligible subjects were randomized into the following two groups and treated for 12 weeks, as shown in Fig. 1. SFC was switched to FBC 4.5/160 µg two inhalations bid in the FBC group, while SFC was continued in the SFC group. They attended the hospital at weeks 4, 8 and 12 of the

treatment period. The inhaler technique of each patient was checked by the involved doctors, nurses, or pharmacists not only during the run-in period but when switching the regimens and during the treatment period. We used the training whistles for Diskus and Turbuhaler supplied by each pharmaceutical company to assess adequate peak inspiratory flow [9]. This study was conducted in accordance with the principles of the Declaration of Helsinki, this protocol was approved by each local ethics committee (UMIN000009619) and informed consent was obtained from all patients prior to the study.

2.3. Measurements

The ACQ5, pulmonary function tests, and exhaled NO parameters were measured at weeks 0 and 12.

2.3.1. 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 β_2 -agonist (SABA) use and FEV₁% predicted, each scored on a scale of 0–6, where 0 represents good control and 6 represents poor control [10]. The overall score of the ACQ5 is the mean of the five responses.

2.3.2. Pulmonary functions

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 [11] using computerized equipment (model CHESTAC-8100; CHEST MI, Inc., Tokyo, Japan). In patients who recorded their PEF values at home, the lowest PEF expressed as a percentage of the highest PEF (Min%Max PEF) values [12] 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.

2.3.3. Exhaled NO parameters

FeNO was measured by an online method at a flow rate of 50 mL/s using an NO analyzer (Sievers NOA 280i; GE Analytical Instruments, Boulder, CO, USA) in triplicate according to the American Thoracic Society/European Respiratory Society recommendations [13]. To avoid nasal NO contamination, mouth pressure greater than 5 cmH₂O was used and the NO analyzer was calibrated daily with a known NO concentration and NO-free air. The mean of three values (that were required to be within 10% of each other to

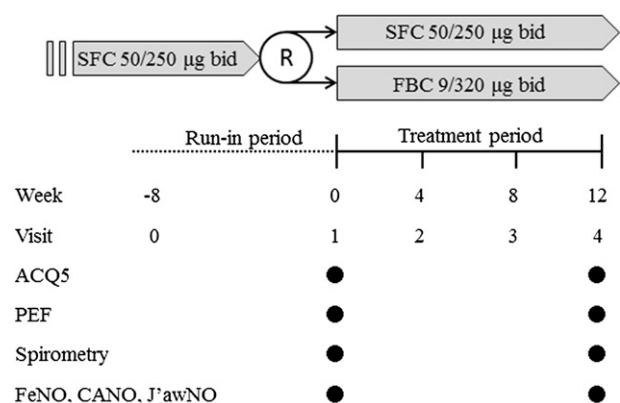


Fig. 1. Study design. ACQ5, Asthma Control Questionnaire, 5-item version; CANO, alveolar NO concentration; FBC, formoterol/budesonide combination; FeNO, fractional exhaled nitric oxide; J'awNO, NO flux in the conductive airways; PEF, peak expiratory flow; SFC, salmeterol/fluticasone combination.

be acceptable) was reported. Four exhalation flow rates (100, 150, 200, and 250 mL/s) in addition to 50 mL/s were used and CANO and maximal NO flux in the conductive airways (J'_{awNO}) were calculated according to the two-compartment model of Tsoukias and George [8]. Correction was made for potential underestimation of J'_{awNO} due to axial back diffusion of NO using the method of Condorelli et al. [14] by multiplying J'_{awNO} by a factor of 1.7. Furthermore, to adjust for possible spurious overestimation of values for CANO, initial uncorrected J'_{awNO} was divided by a correction factor of 0.74 and subtracted from initial uncorrected CANO (CANO_{corr}).

2.4. Statistical analysis

All data are expressed as the means with standard deviation. Comparisons between groups were made with the unpaired *t* test. The chi-square or Fisher's exact test was used to test for significance in group differences. Comparisons between groups and between pre- and post-switching therapies were performed by 2-way analysis of variance (ANOVA). StatView Version 5.0 (SAS Institute, Cary, NC) was used for statistical calculations. A *p* value of <0.05 was considered significant, and all tests were 2-sided.

3. Results

Sixty-six patients receiving SFC 50/250 µg bid were randomized to receive either FBC or SFC treatment. Thirty-four patients were switched to FBC 9/320 µg bid while 32 patients continued receiving SFC 50/250 µg bid. After switching therapy 5 patients (3 FBC, 2 SFC) were withdrawn before completing the treatment (Fig. 2). There was no difference in the baseline characteristics between the 2 groups, as shown in Tables 1–3.

The changes in ACQ5 and pulmonary functions after 12 weeks of treatment are shown in Table 2. Min PEF and Max PEF in the FBC group improved significantly but not in the SFC group; however, there was no significance between the 2 groups by 2-way ANOVA. There was no change in ACQ5 and pulmonary functions in each group or any difference between the 2 groups by 2-way ANOVA; however, the proportion of patients with an improvement in ACQ5 was significantly higher in the FBC group than in the SFC group (51.6% vs 16.7%, respectively, *p* = 0.003; Fig. 3). The analysis of patients with an ACQ5 score >0.75 revealed that the score improved significantly in 11 patients in the FBC group (from 1.22 ± 0.34 to 0.78 ± 0.47 , *p* = 0.023) but not in 12 patients in the SFC group (from 1.37 ± 0.37 to 1.12 ± 0.90 , *p* = 0.553), although there was no significance between the 2 groups by 2-way ANOVA.

The changes in exhaled NO parameters after 12 weeks of treatment are shown in Table 3. CANO and CANO_{corr} in the FBC group improved significantly but not in the SFC group; the difference was significant by 2-way ANOVA. Fig. 4 shows individual changes in CANO in each group. There was no significant change in other parameters or any difference between the 2 groups by 2-way ANOVA.

4. Discussion

We assessed whether switching from SFC 50/250 µg one inhalation bid to FBC 4.5/160 µg two inhalations bid improves peripheral airway/alveolar inflammation in asthma. We demonstrated that the proportion of patients with an improvement in ACQ5 was significantly higher in the FBC group than in the SFC group and that CANO, with or without correction for axial back diffusion of NO, improved significantly after switching therapy but not FeNO, J'_{awNO} , or pulmonary functions.

Several reports have compared the effect of FBC and SFC on asthma treatment outcomes; however, very few have concerned

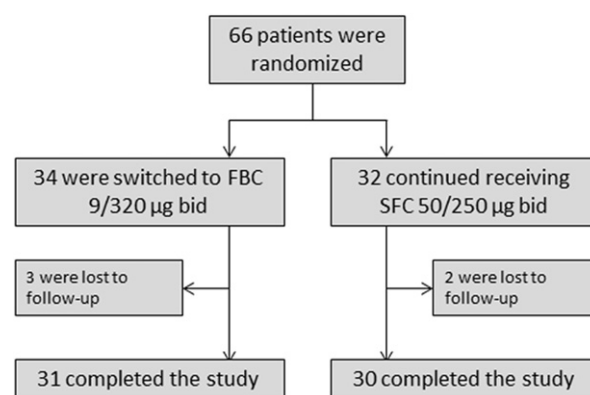


Fig. 2. Patient selection. FBC, formoterol/budesonide combination; SFC, salmeterol/fluticasone combination.

switching treatment regimens. Recently, Hozawa et al. [15] reported a study on the comparison of FBC with SFC on small airway impairment. After SFC 50/250 µg one inhalation bid, patients with baseline FeNO levels >35 ppb were randomized into FBC 4.5/160 µg two inhalations bid or continued the same dose of SFC. They found that patients in the FBC group showed significant improvement in small airway pulmonary functions, including impulse oscillometric parameters, and FEF_{25–75%} and FEF_{75%}, FeNO values, and ACQ5 scores compared with the SFC group. In the present study, we found that switching therapy from SFC to FBC improved ACQ5 scores in more patients in the FBC group than in the SFC group and CANO even though there was no improvement in pulmonary functions and FeNO. 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, these two studies show that switching from SFC to FBC improves not only small airway functions but also peripheral airway/alveolar inflammation. A possible explanation for the effect of switching from SFC to FBC on peripheral airway/alveolar inflammation may be a difference in the particle size. 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 µm are optimal for delivery to the airways, whereas aerosols with MMADs of 0.8–3.0 µm are suitable for drug delivery to the parenchyma [16]. Tarsin et al. [5] reported that the particle size of the FBC Turbuhaler inspired at a flow rate of 60 L/min was 2.4 µm for budesonide and 2.5 µm for formoterol,

Table 1
Characteristics of the study patients.

	FBC (n = 31)	SFC (n = 30)	<i>p</i> -Value
Age, years	61.6 ± 12.1	57.1 ± 14.6	0.320
Gender, male/female	14/17	17/13	0.368
Body mass index, kg/m ²	23.8 ± 3.6	24.2 ± 6.0	0.670
Atopic/nonatopic	18/13	19/11	0.674
Non/ex smokers	19/12	11/19	0.053
Pack-years	3.9 ± 4.8	4.7 ± 4.3	0.857
Duration of asthma, years	13.4 ± 8.3	14.2 ± 13.2	0.581
Coexisting nasal disease	13	17	0.249
Current pet owners	8	5	0.382
Total IgE, IU/mL	972 ± 2680	1159 ± 3155	0.122
Duration of treatment with SFC, months	10.3 ± 7.9	12.9 ± 8.4	0.223
Leukotriene receptor antagonists	17	11	0.153
Sustained release theophylline	2	6	0.121

Data are expressed as the means ± SD.

Abbreviations: FBC, formoterol/budenonide combination; SFC, salmeterol/fluticasone combination.

Table 2

Changes in ACQ5 and pulmonary functions after 12 weeks of treatment.

	FBC (n = 31)			SFC (n = 30)			ANOVA
	0 W	12 W	p-Value	0 W	12 W	p-Value	p-Value
ACQ5, overall score	0.58 ± 0.55	0.55 ± 0.68	0.794	0.59 ± 0.70	0.51 ± 0.78	0.535	0.809
Min PEF, L/min	389 ± 50	405 ± 54	0.021	406 ± 65	417 ± 69	0.226	0.573
Max PEF, L/min	420 ± 46	434 ± 51	0.0054	460 ± 81	460 ± 86	0.926	0.092
Min%Max PEF, %	92.3 ± 4.5	93.3 ± 3.2	0.403	88.8 ± 5.5	90.9 ± 4.9	0.139	0.506
FVC, L	2.95 ± 0.82	2.94 ± 0.81	0.786	3.15 ± 0.74	3.20 ± 0.74	0.248	0.353
%FVC, %	101.1 ± 19.3	100.5 ± 15.7	0.635	96.1 ± 15.6	97.3 ± 15.0	0.178	0.237
FEV ₁ , L	1.97 ± 0.60	1.99 ± 0.61	0.498	2.25 ± 0.72	2.26 ± 0.75	0.539	0.367
%FEV ₁ , %	83.0 ± 20.6	83.7 ± 18.6	0.625	82.5 ± 19.5	82.7 ± 19.9	0.619	0.497
%FEF _{50%} , %	51.8 ± 28.0	53.1 ± 27.7	0.374	58.2 ± 33.7	57.7 ± 34.7	0.492	0.290
%FEF _{75%} , %	35.9 ± 21.5	39.6 ± 23.5	0.213	43.8 ± 29.2	42.6 ± 34.2	0.715	0.348

Data are expressed as the means ± SD.

Abbreviations: ACQ5, Asthma Control Questionnaire, 5-item version; ANOVA, analysis of variance; FBC, formoterol/budesonide combination; FEF_{50%}, forced expiratory flow at 50% of FVC; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; Max PEF, the highest PEF over a week; Min PEF, the lowest PEF over a week; Min%Max PEF, the lowest PEF over a week expressed as the percentage of the highest PEF; PEF, peak expiratory flow; SFC, salmeterol/fluticasone combination.

respectively, while Granlund et al. [6] 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 peripheral airways/alveolar lesions than SFC particles, thereby enabling the improvement of ACQ5 scores and CANO in the present study.

In a previous study, we found an improvement in asthma control (mean ACQ5 scores) following the switch in patients not adequately controlled on SFC [4]. In the present study, however, no such effect was found, although the proportion of patients with an improvement in ACQ5 was higher in the FBC group than in the SFC group, which could relate to the inclusion of some patients who were adequately controlled at entry. The analysis of patients with an ACQ5 score >0.75 revealed that the score improved significantly in the FBC group but not in the SFC group (the between-group difference was not significant).

A previous study reported that mean values of CANO changed from 6.3 ppb to 3.6 ppb with significant improvement in ACQ5 (from 2.3 to 0.5) in 38 previously untreated patients after 3 weeks of treatment with budesonide (medium daily dose) or FBC two inhalations bid [17]. In the present study, the magnitude of changes in CANO was from 8.8 ppb to 4.0 ppb with less ACQ5 improvement at 12 weeks after switching SFC to FBC, suggesting an association between the levels of changes in CANO and clinical improvement, that is, switching treatment regimens produces comparable improvement in CANO with less clinical improvement but requires a longer period than the initial treatment in untreated patients.

There was no effect of switching regimens on FeNO and J'awNO levels in the present study. Gelb et al. 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 [18]. Thus, it might be possible that FeNO levels had already reached a

plateau before switching ICS/LABA combinations because SFC particles might have already reached the central airways sufficiently. FeNO and J'awNO values in the FBC group increased slightly after switching therapy despite no significance. In general, when airway inflammation improves after treatment, airways become enlarged and FeNO levels decrease; however, when bronchoconstriction occurs in the peripheral airway with ventilation inhomogeneity, FeNO levels can decrease, and then increase after treatment [19]. These paradoxical changes can be explained by the NO outflow from peripheral airway/alveolar lesions to central airways. This may explain the slight increase in FeNO and J'awNO values.

Recent studies have demonstrated, both experimentally and theoretically, axial back diffusion of NO from proximal to peripheral airway/alveoli sites against the direction of exhalation [14,20]. Furthermore, this may contaminate peripheral airway/alveolar levels, leading to an underestimation of J'awNO and an overestimation of CANO levels. The present study demonstrated that switching therapy from SFC to FBC significantly decreased both CANO and corrected CANO levels considered for the axial back diffusion of NO. These findings suggest that switching therapy improved not only actual alveolar inflammation but also axial back diffusion of NO from proximal to peripheral airway/alveoli in the present study.

The study design is a limitation of the present study. The protocols should be used for a cross-over study model to compare the effect of SFC and FBC accurately. The reasons for selecting this type of study are as follows. SFC was introduced into Japan more than several years before the beginning of the present study and its usefulness in asthma treatment had been accepted throughout the country, while FBC was introduced recently. 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. If patients treated with FBC have been increasing,

Table 3

Changes in exhaled NO parameters after 12 weeks of treatment.

	FBC (n = 31)			SFC (n = 30)			ANOVA
	0 W	12 W	p-Value	0 W	12 W	p-Value	p-Value
FeNO, ppb	32.5 ± 23.9	38.2 ± 36.8	0.273	41.8 ± 38.1	37.5 ± 24.2	0.324	0.141
CANO, ppb	8.8 ± 9.2	4.0 ± 2.6	0.007	7.4 ± 7.8	6.4 ± 5.0	0.266	0.047
CANO _{corr} , ppb	6.5 ± 8.2	2.3 ± 2.5	0.008	4.3 ± 5.3	3.9 ± 4.3	0.374	0.037
J'awNO, nL/s	1.2 ± 1.0	1.4 ± 1.4	0.188	1.7 ± 1.9	1.5 ± 1.1	0.235	0.145
J'awNO _{corr} , nL/s	2.1 ± 1.7	2.5 ± 2.4	0.188	2.8 ± 3.2	2.6 ± 1.9	0.236	0.147

Data are expressed as the means ± SD.

Abbreviations: ANOVA, analysis of variance; FBC, formoterol/budesonide combination; FeNO, fractional exhaled nitric oxide; CANO, alveolar NO concentration; CANO_{corr}, CANO corrected for back diffusion; J'awNO, maximal NO flux in the conductive airways; J'awNO_{corr}, J'awNO corrected for back diffusion; SFC, salmeterol/fluticasone combination.

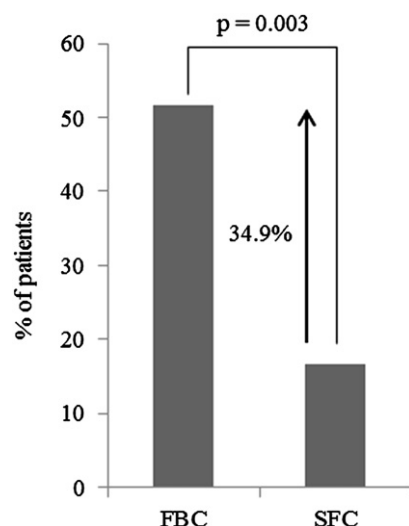


Fig. 3. Comparison of the proportion of patients with an improvement in ACQ5. The FBC group showed a higher proportion of patients with an improvement in ACQ5 than the SFC group (51.6% vs 16.7%, respectively, $p = 0.003$).

crossover study design is appropriate to validate the ICS/LABA switching therapy.

The inhalation technique is an important issue in the present study, since the two devices, including Diskus and Turbuhaler, show different degrees of flow-dependency. A previous study found a different delivered dose (% of the label claim) between Diskus and Turbuhaler at a flow rate of 30 L/min: 83.4% and 56.5%, respectively [21]. Thus, we used each training whistle to assess adequate peak inspiratory flow. A recent study reported that the training whistles as well as In-Check had suitable mouthpiece

pressure and flow relationships, and that the flows at which sounds were generated from the whistles reached adequate peak inspiratory flow levels [9].

There was an almost significant trend towards a higher proportion of ex-smokers in the SFC group; however, the ex-smokers were overall light smokers and there was no difference in pack-years between the 2 groups, so we believe that this could have not influenced the results.

In conclusion, switching from SFC 50/250 µg bid to fixed-dose FBC 9/320 µg bid improved peripheral airway/alveolar inflammation even though there was no improvement in symptoms, pulmonary functions, and FeNO in asthmatic patients. Switching ICS/LABA combination therapy is an option which should be considered occasionally in the management of asthma.

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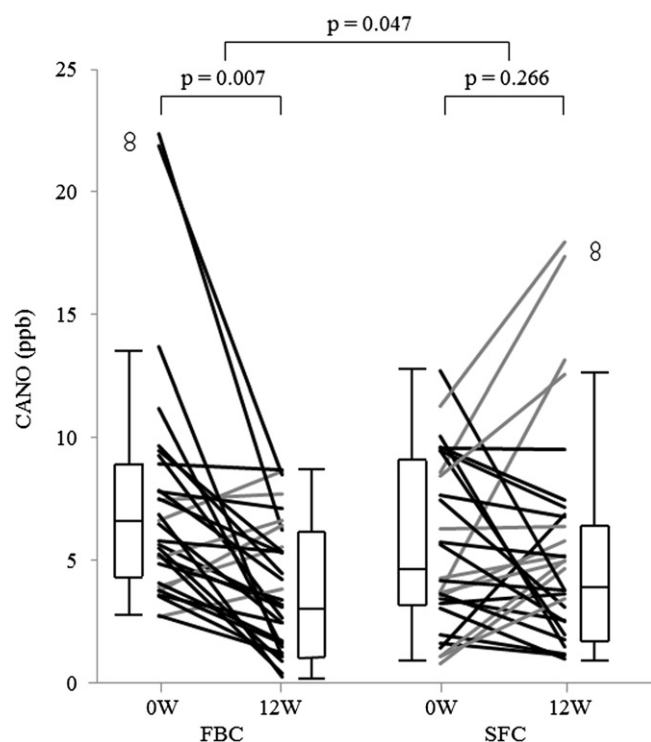


Fig. 4. Changes in CANO. The line across the box is the median; the top and bottom portions of the box represent the 25th and 75th percentiles, respectively; and the whiskers indicate the maximum and minimum values at week 0 and 12. CANO, alveolar NO concentration. Black lines, improved; grey lines, not improved.