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ORIGINAL ARTICLE

A Comparison of Long-Term Anti-Inflammatory Effect of Two ICS/LABA Combination Inhalers; Fix-Dosed Maintenance Therapy with Budesonide/Formoterol and Salmeterol/Fluticasone

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ABSTRACT

Background: The clinical usefulness of fixed-dose maintenance therapy with salmeterol/fluticasone (SFC) and budesonide/formoterol combination inhaler (BUD/FM) has been established, though evidence of the long-term anti-inflammatory effects of these 2 inhalers are limited.

Methods: Patients with moderate persistent adult asthma who had received SFC 50/250 μg bid with well-control status were recruited. After switching to 8-week therapy with fixed-dose BUD/FM 4 puffs (640/18 μg) (phase-1), patients chose either SFC or BUD/FM. FeNO and ACT score were evaluated every 8 weeks until the end of the 52-week treatment period for both treatment groups (phase-2).

Results: In total, 103 patients were examined: BUD/FM was chosen by 34 patients (BUD/FM group), while SFC was chosen by 23 (SFC group). Thirty-six received SFC consistently from the beginning of the study (control). Patients in the BUD/FM and SFC groups showed significant improvements in ACT scores and FeNO levels in phase-1; these beneficial effects persisted for 52 weeks in the BUD/FM group. On the other hand, in the SFC group, although the FeNO level decreased from 54.3 ± 26.4 ppb to 41.9 ± 18.3 ppb in phase-1, it increased to 54.5 ± 26.2 ppb, a level similar to the baseline prior to the beginning of BUD/FM therapy, at 8 weeks in phase-2, and remained at 50-odd ppb thereafter.

Conclusions: These results suggest that maintenance therapy with fixed-dose BUD/FM is a useful treatment option exerting an airway anti-inflammatory effect for a period as long as 1 year, even for asthmatics who could not accomplish total control with SFC.

KEY WORDS

airway inflammation, bronchial asthma, budesonide/formoterol combination inhaler, fractional exhaled nitric oxide (FeNO), salmeterol/fluticasone combination inhaler

ABBREVIATIONS

ACT, asthma control test; BUD/FM, budesonide/formoterol combination inhaler; FeNO, fractional exhaled nitric oxide; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroids; LABA, long-acting β_2-agonists; SABA, short-acting β_2-agonists; SFC, Salmeterol/Fluticasone combination inhaler.

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Authors' contributions: MH performed the primary data analysis and wrote the manuscript. MI, JH and MS helped data collection of asthmatics. HS contributed to study design and interpreted data. All authors approved the final version of the manuscript.

Conflict of interest: MH received honoraria for lectures from AstraZeneca, GlaxoSmithKline, Astellas, and Merck Sharp & Dohme. The rest of the authors have no conflict of interest.

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INTRODUCTION

According to asthma treatment guidelines such as GINA[1] and Japanese guideline,[2] a long-acting β2 agonists (LABA) are deemed as most favorable add-on drugs to inhaled corticosteroid (ICS) in patients whose asthma is not adequately controlled on low or medium dose ICS which is the first choice medication for long-term asthma control. Combination products, containing both an ICS and LABA in one inhaler, have been used for more than 10 years and two ICS/LABA combination inhalers - budesonide/formoterol (BUD/FM) and salmeterol/fluticasone (SFC) - are currently available. They have contributed to improvement of patient acceptability and adherence in taking both therapies,[3,4] and highly effective at providing early and sustained amelioration in asthma control for patients symptomatic on ICS. Even with such treatments, however, asthma control could be suboptimal. Bateman and coworkers reported that the patients who could attain "total control" in which asthma symptoms are completely controlled, by long-term treatment with SFC remain to 50% or less.[5] The patient who could not accomplish "total control" remains symptomatic and it is thought that inflammation also exists on its airway. It has been pointed out that inflammation may be present not only in central but also in peripheral airways. The mean diameter of particles in a BUD/FM combination dry powder inhaler is reported to be 2.4 μm,[6] which is smaller than the corresponding particle diameter (4.4 μm) of SFC dry powder.[7] Therefore, the probability of BUD/FM particles reaching the peripheral airway is considered to be higher than for SFC particles.[8] In fact, a high anti-inflammatory effect of BUD/FM has occasionally been reported,[9-13] but none of these studies followed the effect of BUD/FM for more than a short period of approximately 8-16 weeks. Long-term, approximately 1 year, clinical effects of BUD/FM fixed-dose maintenance therapy and SFC therapy have been compared. However, all of these comparisons focused mainly on clinical symptoms as the evaluation items in view of preventing acute exacerbation,[14-19] and the reported results are not consistent. Thus, long-term comparative data on anti-inflammatory effects on the airway are limited.

We carried out a 52-week change-over before-and-after trial that evaluated changes in exhaled nitric oxide (FeNO) as an index of airway inflammation, aiming at comparison of the therapeutic effects on airway inflammation in long-term management with BUD/FM and SFC. Randomized controlled trials are definitely superior to studies of other designs when comparing the effects of different drugs. However, considering that inhalation treatment was to be continued for approximately 1 year in this study, it was likely that treatment preference would affect the study results even with repeated guidance on inhalation therapy. We thus considered 1-year treatment with a drug chosen by the patients themselves to likely lead to better adherence to the treatment protocol and be closer to real-world situations. Therefore, the effects of two types of inhalers were compared by allowing patients to choose the inhaler that they preferred.

METHODS

The subjects of the study were adult outpatients of the National Center for Global Health and Medicine (Tokyo) or at Kohnodai Hospital (Chiba), aged 20 years or older, with persistent moderate asthma. The diagnosis of asthma was defined as the presence of compatible clinical history and pulmonary function tests demonstrating variable airflow obstruction by means of bronchodilator responsiveness, or by demonstrating bronchial hyperreactivity using methacholine challenge. The asthmatics treated for at least 6 months with SFC 50/250 μg Diskus (dry powder inhaler) bid therapy (GINA treatment steps 3-4), in whom the disease was "well-controlled" or "totally controlled", i.e., an asthma control test (ACT) score of 20-25 points, were eligible. Current smokers, those who had a smoking history (smoking index >400) and patients with suspected COPD with either non reversible airflow obstruction or obvious low attenuation area on chest CT were excluded from the analysis. Moreover patients who had a respiratory tract infection within the last 4 weeks were also excluded. Patients with allergic rhinitis were eligible if their rhinitis symptoms had fully settled down.

This was a non-blind change-over before-and-after comparative study. Written, informed consent was obtained from each patient. Patients chose to continue SFC 50/250 μg bid therapy (control group) or change to BUD/FM (dry powder inhaler) 640/18 μg therapy (2 puffs twice daily) as the first step. Patients who chose BUD/FM therapy received 8-week fixed-dose treatment with BUD/FM (phase 1). As the second step after phase 1, patients chose to continue BUD/FM 4-puff fixed-dose therapy (BUD/FM group) or to return to SFC 50/250 μg bid therapy (SFC group), and then continued the treatment they chose for 52 weeks (phase 2). The maintenance dose of BUD/FM was left unchanged. Combined use of a controller other than an ICS/LABA combination inhaler was permitted, but changing the dosage of any drugs during the study period was not permitted. Patients who received an increased maintenance dose or 5-day or longer systemic steroid therapy because of acute exacerbation or for any other reason were regarded as study drop-outs.

Changes in the FeNO level were observed as the primary endpoint. The ACT score, the frequency of using short-acting β_2-agonists (SABA) for additional relief of symptoms, and medication side effects were also examined. The patients' conditions were evaluated in the outpatient clinic at intervals of 8-12 weeks.

Table 1 Baseline characteristics of the study population

	BUD/FM group	SFC 250 group	Control group	*P* value
Number	34	23	36	-
Male/Female	14/20	15/8	20/16	0.04*
Age (y.o)	59.4 ± 8.6	56.1 ± 12.5	54.4 ± 16.7	0.26
Ex/never-smoker	17/17	14/9	21/15	0.87*
Allergic rhinitis (-)/(+)	15/19	11/12	15/21	0.78*
Treatment LTRA	14	8	10	0.49*
Theophyline	5	4	7	0.87*
Asthma duration (yrs)	15.3 ± 10.5	14.9 ± 11.2	15.8 ± 10.4	0.85
$FEV_{1.0}$ (L)	1.78 ± 0.83	2.27 ± 0.83	2.45 ± 0.77	0.03
$FEV_{1.0}$%	68.9 ± 9.6	73.9 ± 13.2	76.1 ± 11.8	0.05
% $FEV_{1.0}$ (% predicted)	76.3 ± 8.4	84.1 ± 10.6	85.7 ± 9.9	0.04
ACT score	21.9 ± 1.6	23.2 ± 1.5	23.2 ± 1.4	0.01
FeNO (ppb)	49.6 ± 24.9	54.5 ± 26.9	42.4 ± 23.5	0.37

Data are presented as mean ± SD. *P*-values of chi-square test, and Fisher exact test* are shown.

At every visit to the outpatient clinic, patients were given guidance on inhalation therapy, and examined for the remaining quantity of inhaler to determine its consumption during the previous 8 weeks and to calculate the rate of adherence to inhalation therapy. Pulmonary function tests (FVC, $FEV_{1.0}$, MMF etc.) were also carried out using computerized equipment (model CHESTAC-8100; CHEST MI, Inc., Tokyo, Japan) before and after the study. FeNO was measured using NIOX-MINO (Aerocrine Ltd., Solna, Sweden)[20] before any forced expiratory maneuvers, two readings were obtained and the mean value was used for the analysis. All the medications for maintenance therapy were stopped 12 hours before FeNO and spirometry measurements, and these measurements were performed in the same order at similar times of the day before inhalation of the morning dose.

Performance of this clinical study was approved by the Ethics Committee of the National Center for Global Health and Medicine (2009-795). Clinical trial registration number was UMIN000010151. All measurement values are presented as means ± SD. Differences between populations were analyzed for significance using chi-square test (without continuity correction), and Fisher's exact test. Comparisons between baseline and each measured values were analyzed using repeated-measures ANOVA, paired Student t-test, and McNemar test.

RESULTS

PATIENT CHARACTERISTICS

Although a total of 103 patients participated in the study, 2 patient dropped out because of an adverse event, and 8 dropped out due to asthma exacerbation, data from 93 patients were thus analyzed. Among these 93 patients, the male to female ratio was 49 to 44, the mean age was 56.5 ± 12.5 years (24-78 years), and the mean disease duration was 15.3 ± 11.1 years. Ex-smokers were 52 patients (56%) with mean smoking index 225 ± 123. Concomitant medication was leukotriene receptor antagonist in 32 patients and a theophyline preparation in 16. These background factors showed no significant differences among the three groups (Table 1).

The BUD/FM group was comprised of 34 patients, and the SFC group of 23. The control group was comprised of 36 patients who chose at the beginning of the study to continue using SFC. Women significantly outnumbered men in the BUD/FM group. The reasons for choosing BUD/FM therapy included that they were aware of improved control that clearly surpassed the benefits of SFC and they also acknowledged the better portability of BUD/FM. In addition, in the BUD/FM group, $FEV_{1.0}$ was significantly lower, and the ACT score at baseline was low, indicating that patients who had not obtained adequate control with the conventional treatment were predominant in this group. In SFC group, the reason for returning to SFC therapy included mainly that they could not recognized better control with BUD/FM and wanted to continue their familiar medication and devices. Drop-out due to asthma exacerbation occurred in 2 patients in the BUD/FM group, 3 cases in the SFC group, and 3 cases in the control group, showing no significant differences among the three groups (Fig. 1).

FRACTIONAL EXHALED NITRIC OXIDE (FeNO)

The primary endpoint, the FeNO level, was significantly improved at the end of phase 1 in both groups, showing improvement from 49.5 ± 24.5 ppb to 34.4 ± 12.6 ppb in the BUD/FM group, and from 54.3 ± 26.7 ppb to 41.7 ± 18.8 ppb in the SFC group ($p < 0.01$, ANOVA). In the BUD/FM group, the beneficial effect persisted during the phase 2 period, with levels equal to or lower than 38 ppb, varying within the nor-

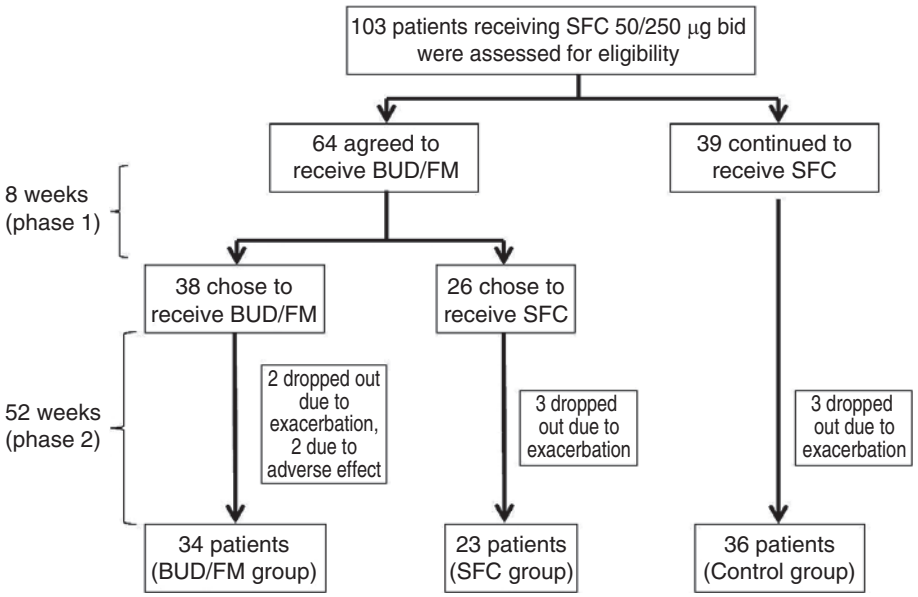

Fig. 1 Study design and patient selection.

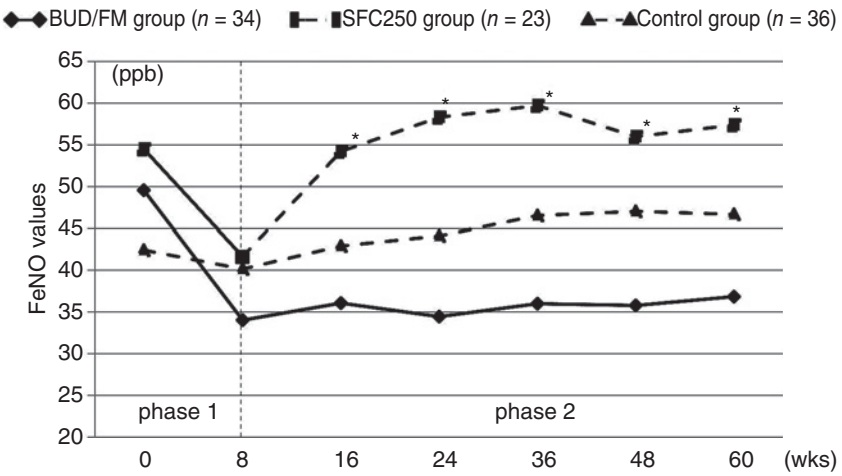

Fig. 2 The changes in mean fractional exhaled nitric oxide (FeNO) values. *p < 0.05 vs 8 weeks, ANOVA.

mal range for Japanese people.[21] The FeNO level at 1 year in this group was 36.8 ± 14.3 ppb. On the other hand, in the SFC group, the FeNO level was 41.9 ± 18.3 ppb at the beginning of phase 2, but was significantly increased to 54.5 ± 26.2 ppb 8 weeks later, showing worsening of the patients' conditions (p < 0.05, ANOVA), and then returned to the baseline level prior to BUD/FM therapy. The level remained over 50-odd ppb thereafter. In the control group, the FeNO level varied between 40.4 ± 19.5 ppb and 46.8 ± 29.3 ppb in both phase 1 and phase 2, showing no significant changes (Fig. 2).

Respiratory function tests included measurements of FVC, $FEV_{1.0}$, and MMF at three time points, i.e., before the study, at the end of phase 1, and at the end of phase 2. There were no significant changes in any measurement item at any of these three time points (Table 2).

ASTHMA CONTROL TEST

Asthma control test (ACT) scores also showed similar variations. In both the BUD/FM group and the SFC group, there was significant improvement at the end of phase 1. Although the beneficial effect persisted during the phase 2 period in the BUD/FM group, there was a significant increase in the SFC group at 16 weeks after phase 2 (Fig. 3). Total control represented by a full ACT score of 25 was found in only 13 (13%) patients at the time of entry. In the BUD/FM group, the achievement rate was 9% in-

Table 2 The changes of Spirometry parameters

	BUD/FM group (n = 34)			SFC 250 group (n = 23)			Control group (n = 36)		
	0 wk	8 wks	60 wks	0 wk	8 wks	60 wks	0 wk	8 wks	60 wks
FVC	2.62 ± 0.78	2.72 ± 0.59	2.75 ± 1.11	3.07 ± 1.01	3.03 ± 1.33	2.87 ± 1.27	2.81 ± 1.01	2.87 ± 1.22	2.77 ± 0.97
$FEV_{1.0}$	1.78 ± 0.83	1.84 ± 0.52	1.88 ± 0.87	2.27 ± 0.83	2.35 ± 0.93	2.33 ± 0.72	2.45 ± 0.77	2.35 ± 0.93	2.33 ± 0.72
$FEV_{1.0}$%	68.9 ± 9.6	67.7 ± 9.7	68.4 ± 13.5	73.9 ± 13.2	76.5 ± 16.2	77.4 ± 18.4	76.1 ± 11.8	76.5 ± 16.2	79.4 ± 11.7
MMF	1.62 ± 0.75	1.71 ± 1.39	1.65 ± 1.29	1.68 ± 0.98	1.61 ± 1.15	1.73 ± 1.31	1.58 ± 0.98	1.66 ± 1.14	1.71 ± 1.42
V_{50}	1.44 ± 1.08	1.64 ± 1.52	1.57 ± 1.21	1.59 ± 0.87	1.67 ± 0.74	1.62 ± 1.11	1.49 ± 0.87	1.54 ± 0.71	1.49 ± 0.96
V_{25}	0.69 ± 0.77	0.77 ± 0.96	0.74 ± 0.99	0.91 ± 0.96	1.11 ± 1.36	1.07 ± 0.98	0.81 ± 0.96	0.94 ± 1.29	0.89 ± 1.11

Data are presented as mean ± SD. All the values revealed no significant using ANOVA.

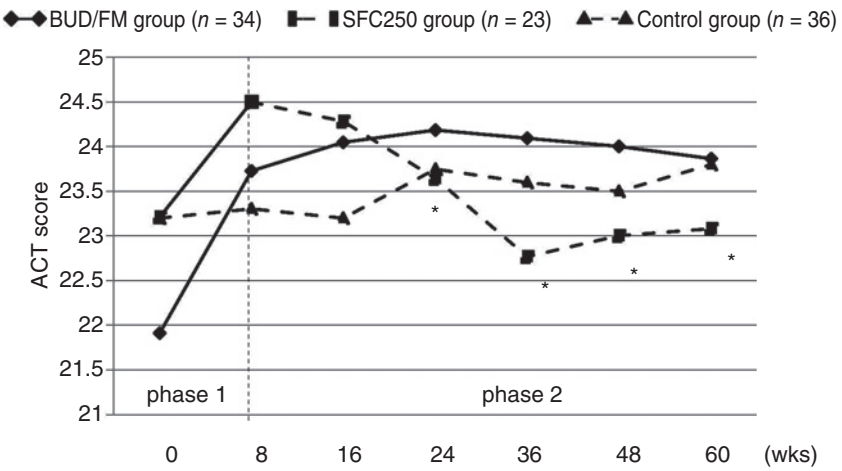

Fig. 3 The changes in mean Asthma Control Test (ACT) score. *p < 0.05 vs 8 weeks, ANOVA.

itially and then increased to 35% at the end of phase 1, showing a significant improvement (p < 0.01, McNemar test). Thereafter, the achievement rate increased gradually to reach 70% at 24 weeks. Although the achievement rate decreased gradually thereafter, it remained at 46% even at the end of phase 2. On the other hand, in the SFC group, the rate of achieving total control increased rapidly from 14% to 64% in phase 1, and also showed a gradual increase up to the 24th week (70%), although the achievement rate decreased after the 36th week and then returned to the baseline level. In the control group, the rate of total control was 20% before the study and was maintained between 40% and 50% throughout most of the phase 2 period.

FeNO value correlated with not only ACT Question 4 (p = 0.465, p < 0.03) but also total score of ACT (p = 0.315, p < 0.05) in total study period. There were good correlations between FeNO and ACT score changes in phase 1 both BUD/FM and SFC group (r = 0.715, 0.662, p < 0.03). FeNO also correlated with ACT score in phase 2 (when comparing baseline and end of phase 2) only in BUD-FM group (r = 0.447, p < 0.05), but correlation coefficient was lower than those in phase 1, while it was not found by SFC treatment (r = 0.169, p = 0.35).

RELIEVER USE AND ADHERENCE

Figure 4 shows the frequency of using the SABA for additional symptom relief (mean number of uses/week during the 2 weeks prior to each evaluation point). There was also a similar trend in the frequency of SABA use. In other words, in the BUD/FM group, the number of SABA uses was 3.11 ± 1.59/week at the time of entry but was significantly reduced to 0.39 ± 0.56/week at the end of phase 1 (p < 0.01, paired Student t-test), and maintained at less than 1/week thereafter. In contrast, there were no significant changes in the frequency of SABA use in either the SFC group or the control group. The frequency of SABA use correlated with not only ACT Question 4 (p = 0.785, p < 0.01) but also total score of ACT (p = 0.515, p < 0.05). Thereafter, the frequency of SABA use correlated with FeNO (p = 0.385, p < 0.05).

The adherence rates at the time of entry ranged from 77% to 81% in the three groups, showing no significant intergroup differences. The adherence rate

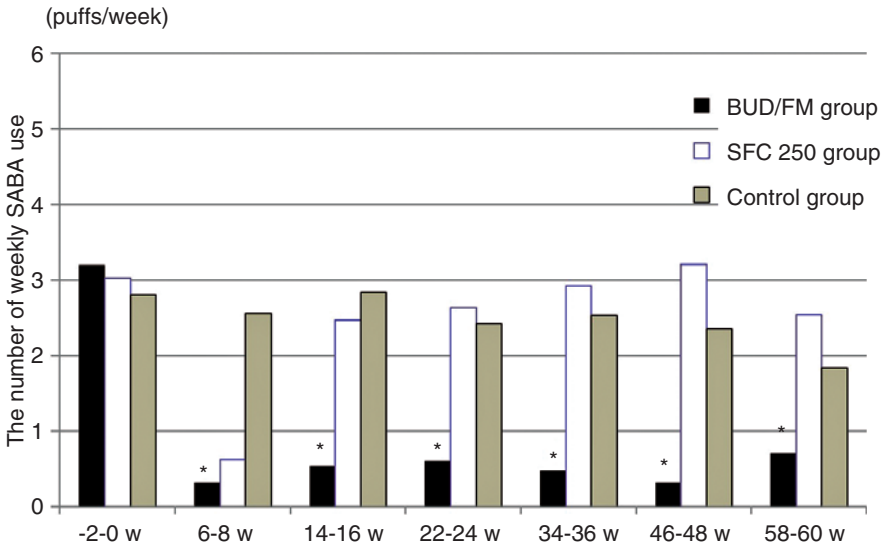

Fig. 4 The changes in mean weekly SABA use. *$p < 0.01$ vs -2-0 weeks, paired t-test.

increased significantly during phase 1 in all three groups ($p < 0.03$, ANOVA). In both BUD/FM group and SFC group, the adherence rate was increased to approximately 90% at the end of phase 1, but then gradually decreased, reaching 85% at the end of phase 2, with no significant differences between groups. In the control group, the adherence rate varied between 83% and 88% throughout the study.

SAFETY

In regard to safety, among the 103 patients enrolled in this study, 2 patient dropped out because of a cough associated with BUD/FM inhaler. The other adverse events were hoarseness in 2 patients, mild palpitation during body motion in 5, and unpleasant sensation (bitter taste) during inhalation in 4 in the BUD/FM group. All of these patients were able to continue the study without difficulty.

DISCUSSION

In order to verify the long-term inhibitory effect of BUD/FM on airway inflammation, we examined the effects of treatment with fixed dose BUD/FM (640/18 μg/day) during an approximately 1 year period in patients with moderate persistent asthma controlled by SFC 50/250 μg bid. The therapeutic effects were assessed in terms of the FeNO level and the ACT score. Fixed-dose BUD/FM therapy achieved significant improvements in both the FeNO level and the ACT score. The rate of achieving total control in terms of the ACT score was also significantly higher, showing that this therapy can bring about total control including inhibition of airway inflammation in many patients. This study adopted a design by which patients chose the inhaler they preferred. Among patients who chose BUD/FM after maintenance therapy with SFC, there were many individuals in whom control was inadequate, showing persistent obstructive respiratory disorder associated with significantly lower $FEV_{1.0}$ and ACT scores. In other words, the ACT score was significantly higher ($p < 0.03$, Student-*t* test) at 0 week in the control group, suggesting that persistent use of SFC was chosen because of the good control status achieved.

In this study, the fixed-dose BUD/FM therapy (640/18 μg/day) produced no significant improvement in $FEV_{1.0}$ or peripheral airway parameters such as $\dot{V}_{25}$ on respiratory function tests. A recent Japanese study that used a similar change-over before-and-after comparative design with the BUD/FM[11] reportedly achieved significant improvement in not only peripheral airway resistance determined by impulse oscillometry but also in $\dot{V}_{50}$ and $\dot{V}_{25}$, even though the study period was only 4 weeks. The subjects of their study were asthma patients with disease durations of 4-8 years, shorter than that in our present study, suggesting a high likelihood that there was remaining reversibility of peripheral airway remodeling in their cases. Because our study targeted patients with relatively advanced airway remodeling in whom the $FEV_{1.0}$% was 71.5% on average, it can be inferred that their responses would not have been adequate to produce improvement of these indices. It is of great significance that the fixed-dose BUD/FM therapy achieved good clinical effects and a persistent anti-inflammatory effect on the airways for a period as long as 1 year in such patients with advanced disease.

In recent years, it has been advocated that treatment of asthma focus on both aspects of current control such as stabilization of clinical symptoms and varying respiratory functions, and the reduction of future risk caused by constant respiratory impairment

due to recurrent exacerbations or persistent unstable control.[22-24] Although which indices should be used for evaluation of the future risk of asthma is controversial, peripheral airway lesions and remaining airway inflammation are considered to be important factors.[23] In general, it is said that the FeNO level correlates with eosinophilic inflammation of the airway if factors, such as airway neutrophilic infection and rhinitis, which may exert an influence are excluded.[25] However, there may be a dissociation between clinical control status and the FeNO level, and it has been reported that adding evaluation of the FeNO level as an index to guideline-based treatment failed to improve control status.[26,27]

In our present study, the FeNO level decreased in 49 of 57 patients at 8 weeks after switching from SFC to the fixed-dose BUD/FM 4-puff therapy, and there was significant overall improvement. There were 3 possible mechanisms to explain these improvements. First, as mentioned previously, this may be explained by the small and proper particle size of both ICS and LABA in the BUD/FM, which facilitates drug particles reaching the peripheral airway. Small particle size had another advantage for the patients in our study in whom not only $FEV_{1.0}$% but also inhalation flow rate were low. Second, the intrinsic efficacy of the different LABAs in two medications could be important factor. Intrinsic efficacy refers to the ability of a drug to activate its receptor, without regard for drug concentration.[28] It is reported that LABAs that have greater intrinsic efficacy (e.g. formoterol) could be more effective in causing beta2-adrenergic action than those agents that have less intrinsic efficacy (e.g. salmeterol).[29] Third, the property of the BUD/FM allowing rapid onset of the bronchodilator effect of LABA and thus promoting a positive perception of the inhalation effect contributed to the improved adherence.[30] It can thus be inferred that our study design, permitting patients to choose the inhaler that they preferred while continuing treatment, improved adherence, thereby achieving a better anti-inflammatory effect on the airway.

As shown in Figure 2 and 3, in phase 1, not only ACT score but also FeNO level improved at 8 weeks after switching from SFC to the fixed-dose BUD/FM 4-puff therapy in almost all the patients. The reason why the coefficient of correlation in SFC group was lower than BUD/FM group in phase 1 could be that the baseline ACT score in BUD/FM group was significantly lower than SFC group, so that changes of ACT score were larger in BUD/FM group in comparison with those in SFC group. In contrast, comparing ACT score and FeNO value between baseline and end of phase 2, both parameters improved in BUD/FM group, while in SFC group, there were no significant changes. That is a reason why there was a correlation between FeNO and ACT by BUD/FM treatment continuation, and that it was not found by SFC treatment. The continuation treatment for more than 1 year by BUD/FM could preserve lower level of FeNO that was an index of the airway inflammation in asthma and was able to inhibit the frequency of SABA use that could be an index of the current asthma control. In addition, it was reported that there was an association between the frequency of SABA use and FeNO level, and the improvement of the frequency of SABA use linked FeNO level in the time course for treatment by BUD/FM more than 1 year in this study, while these tendency were not found in the SFC treatment continuation. In other words, it was shown that the likelihood which the long-term management of asthma by BUD/FM could be an appropriate treatment preference for the achievement of current control and the reduction of future risk.

In recent years, potent anti-inflammatory effects of the fixed-dose BUD/FM 4-puff (640/18 μg) therapy on the airway, as examined during short periods of 4-12 weeks, have occasionally been reported.[11-13,31] In general, on a global scale, BUD/FM is mainly used for long-term management with single-inhaler maintenance and reliever therapy (SMART) in which the inhalation dose is adjusted according to the patient's symptoms. Therefore, although there have been a number of reports on preventive effects against acute exacerbation, reports on the anti-inflammatory effect on the airway have been limited. Conversely, some reports have suggested airway inflammation to be exacerbated by prolonged SMART.[32,33] In Japan, although insurance coverage of SMART was not approved until 2012, it is assumed that BUD/FM described herein will become the mainstay of long-term maintenance therapy in the near future. The results of our present study suggest the potent long-term therapeutic effect of fixed-dose BUD/FM medium-dose inhalation therapy on airway inflammation. Even when employing SMART, it may be necessary to provide treatment that takes airway inflammation into account, e.g., by implementing the fixed-dose (640/18 μg) inhalation therapy for 8 weeks or more, in patients in whom the frequency of BUD/FM use for symptom relief is increased, suggesting worsening of airway inflammation.

The results of this study should be considered along with the limitations. First, the study is small, with about 30 patients per group. Second, this study is not designed as randomized study and each study group is obviously biased. During the study period, the patients have chosen their favorite ICS/LABA two times at their decision. This could be a major weakness of this study. The adherence rates of inhalation therapy are not different in each groups throughout the study, still there are substantial bias inherent in this study and it may be difficult to quantitate exactly the primary outcome of this study. However, a pragmatic trial[34] and a real-world observational study[35] have shown that prolonged use of inhalation therapy

results in a decrease in the ICS adherence rate to less than 50%. Therefore, in patients in whom adherence to inhalation therapy remains poor despite various measures being taken, patient-oriented therapy in which they could choose their favorite inhaler by themself may be more useful in real-world clinical setting.

It is of major clinical significance that the present results suggest that the anti-inflammatory effect of the BUD/FM 4-puff (640/18 μg) therapy on the airway persists for at least 1 year. More specifically, from the aspects of current control and future risk reduction, the two major concepts in recent asthma care, this therapy is not only extremely useful for current control in view of the high total control achievement rate but also contributes to the reduction of future risk in terms of its anti-inflammatory effect on the airway. Although the position of SMART therapy with BUD/FM may be established in the near future in Japan, 4-puff fixed-dose inhalation therapy should be evaluated from the viewpoint of more prolonged inhibition of airway inflammation. It is important to further investigate the efficacy and safety of prolonged use of BUD/FM on airway inflammation, through clinical experience with patients suffering from different severities of asthma.

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