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ORIGINAL ARTICLE

Asthma Control Can Be Maintained after Fixed-Dose, Budesonide/Formoterol Combination Inhaler Therapy is Stepped Down from Medium to Low Dose

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ABSTRACT

Background: In cases using a budesonide/formoterol combination inhaler, many patients are started on fixed-dose treatment at 640/18 μg (4 puffs) daily, but there are no guidelines yet regarding the step-down method when control has been maintained.

Methods: Patients with moderate asthma treated with either budesonide 400 μg and salmeterol 100 μg (GINA step3 group) or salmeterol/fluticasone 250 at 2 puffs (GINA step4 group) were enrolled and started on therapy of budesonide/formoterol 4 puffs. Thereafter, step-down to 2 puffs was performed if either of the following criteria was met at 8-week intervals: fractional exhaled nitric oxide (FeNO) ≤ 28 ppb plus asthma control test (ACT) score ≥ 22, or ACT score ≥ 24 at 3 consecutive visits regardless of FeNO level. Thereafter, changes in ACT score, the number of acute exacerbations and reliever use, and FeNO level were monitored through 48th week.

Results: Fifty-one patients, 27 in step3 group and 24 in step4 group, underwent step-down. ACT scores and the number of reliever use remained stable in both groups even after step-down. In contrast, FeNO levels increased gradually in step4 group, whereas in the step3 group they increased immediately after step-down. Step-down was considered to be safely performed because the numbers of reliever use and those of moderate or more severe exacerbations during the 48-week period has not changed significantly compared to before step-down.

Conclusions: If complete control of asthma, not only of clinical symptoms but also airway inflammation, is achieved by 3-6 months of fixed-dose budesonide/formoterol 4 puffs/day, it should be possible to safely perform step-down to 2 puffs/day.

KEY WORDS

asthma, Asthma Control Test, budesonide/formoterol combination inhaler, fractional exhaled nitric oxide (FeNO), step down

ABBREVIATIONS

ACT, asthma control test; BUD, Budesonide; 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. TM carried out statistical analysis. MI and SH helped collecting data of asthmatics. NK and HS contributed to study design and interpreted data. All authors approved the final version of the manuscript.

Conflict of interest: MH has received lecture fee from Astellas and AstraZeneca. Other authors have no conflict of interest.

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INTRODUCTION

GINA[1] and most other asthma treatment guidelines recommend the use of an inhaled corticosteroid (ICS)/long-acting β2-agonist (LABA) combination inhaler as the first-line choice of a controller for chronic asthmatic patients for whom control with ICS monotherapy is difficult. Thus, in Japan as in many other countries, two ICS/LABA combination inhaler preparations are widely used: fluticasone/salmeterol (SM) combination inhaler (SFC) and budesonide/formoterol combination inhaler.[2] The guidelines are clear in regard to step-up methods for treating poorly controlled asthma, recommending ICS dose-escalation[3] as well as combined therapy with an added controller. There is abundant evidence in support of those step-up methods, whereas there is only limited evidence in support of step-down methods when asthma has been controlled for a long time. Recommendations in this regard go no further than stating that step-down should be considered when stable control of at least 3 months' duration has been confirmed, etc..[1,2,4]

Similarly, there are still few reports regarding step-down methods for treatment of moderate asthma patients being controlled with an ICS/LABA combination inhaler, the most commonly used such treatment worldwide. The potent bronchodilating activity of LABA preparations shows efficacy even at the time of exacerbation of airway inflammation. This may lead to delay of add-on anti-inflammatory therapy, which is actually of greater importance. For this reason, the US FDA has issued an alert in regard to continuous use of LABA.[5] Accordingly, there is a critical need in clinical practice for establishment of guidelines for step-down methods for ICS/LABA combination inhalers. Although a few reports of step-down methods for SFC have been published,[6-10] there have been none in regard to budesonide/formoterol, which is mainly used in single inhaler maintenance and reliever therapy (SMART) in many countries, except the United States and Japan. Moreover, the few reports published to date have focused on respiratory function and clinical symptoms as indicators, while none have compared airway inflammation, which is of greatest concern.

We postulated that step-down of the drug dosage following achievement of complete control of asthma, in terms of not only the clinical symptoms but also airway inflammation, would subsequently lead to a safer long-term clinical course. On that basis, we carried out step-down to 2 puffs/day in adult patients with persistent moderate asthma that was being controlled with fixed-dose budesonide/formoterol 4 puffs/day therapy, and then compared the clinical course during the following 48 weeks with the status prior to the dosage step-down. The primary endpoint was the change in the asthma control test (ACT) score. At the same time, with the objective of confirming the long-term safety of the step-down therapy, the respiratory function tests and the fractional exhaled nitric oxide (FeNO) level was also measured and analyzed as an index of airway inflammation.

METHODS

The subjects of the study were adult outpatients of the National Center for Global Health and Medicine (Tokyo) or at Kohnodai Hospital (Chiba, Japan), 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 (an increase in FEV1 > 12% after inhalation of albuterol), or by demonstrating bronchial hyperreactivity using methacholine challenge (provocative concentration causing a 20% decrease in FEV 1 < 8 mg/dL). The asthmatics treated for at least 6 months with BUD 400 μg/day plus SM 100 μg/day combined therapy or SFC 250 Diskus 2 puffs/day (equivalent to BUD 1000 μg/day and SM 100 μg/day) therapy (GINA treatment steps 3-4), in whom the disease was "well-controlled" or "totally controlled", i.e., an 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. Combined use of an ICS and a controller other than an ICS/LABA combination inhaler was permitted, but changing the dosage of any drugs other than budesonide/formoterol during the study period was not permitted.

The study had an open-label, dose comparison design for before and after changing the dosage (i.e., step-down). Written, informed consent was obtained from each patient, followed by a 4-week observation period after which the treatment stage commenced. Before starting the observation period, the patient's adherence to the prior treatment was confirmed, and instruction regarding inhalation was repeated. Then, the study drug, dry powder inhaler of budesonide/formoterol at 640/18 μg (4 puffs)/day, was administered, and step-down to 320/9 μg (2 puffs)/day was performed when either of the following response criteria was satisfied at the time of outpatient visits to the hospital at 8-wk intervals: (1) FeNO showed a clear trend of improvement and decreased to ≤ 28 ppb, while the ACT score was ≥ 22 points, or if these conditions were not met, (2) regardless of the FeNO level, the ACT score was ≥ 24 points at 3 consecutive visits.

Table 1 Baseline characteristics of the study population

		GINA step3 group	GINA step4 group	*p* value
Patient number		27	24	-
Male : Female		12 : 15	11 : 13	0.92
Age (years old)		50.2 ± 8.8	48.9 ± 11.3	0.41
Asthma duration (years)		13.1 ± 11.7	13.9 ± 14.8	0.44
FEV1.0 (L)		2.28 ± 0.62	2.31 ± 0.69	0.42
% FEV1.0 (%)		74.4 ± 11.9	78.4 ± 11.6	0.18
BMI		23.7 ± 2.8	22.9 ± 1.9	0.48
Ex-smoker		8	5	0.26**
Allergic rhinitis	none	12	9	
	seasonal	11	10	0.89*
	perennial	4	5	
Add-on controller	none	17	10	
	LTRA	6	11	0.07*
	theophylline	4	6	
ACT score		23.1 ± 1.4	22.2 ± 1.6	0.07
FeNO (ppb)		44.5 ± 28.7	48.8 ± 31.1	0.35

Data are presented as mean ± SD. *P*-values of Student t-test (measured value), Fisher exact test* and chi-square test** are shown.

Step-down was followed by a 48-week study period. The ACT score, respiratory function tests, the number of reliever, short-acting β2-agonists (SABA) use one week, and the FeNO level were measured every 8 weeks, and other assessment parameters were the number of moderate or more severe acute exacerbations (i.e., events requiring treatment with a systemic steroid for at least 3 days) and the number of dropout cases due to the need for re-escalation of dosages. FeNO was measured using NIOX-MINO (Aerocrine Ltd., Solna, Sweden).[11] The step-down criterion for FeNO was decided with reference to the ATS guideline[12] and the normal range for Japanese (15-37 ppb) shown in the Japanese handbook for FeNO measurement.[13] In addition, we referred to the methods presented in earlier reports[14-17] that compared the guideline treatment and methods that decided the treatment strategy by also measuring FeNO. In particular, the above-described step-down criterion (2) for patients showing a continuously high FeNO level, the ACT score ≥ 24 points at 3 consecutive visits seemingly very conservative, was decided primarily on the basis of the Japanese guideline,[2] which aimed for more strict asthma control than any other guidelines.

Performance of this clinical study was approved by the Ethics Committee of the National Center for Global Health and Medicine (2009-795). All measurement values are presented as means ± SD. Differences between populations were analyzed for significance using Student's *t*-test, the chi-square test (without continuity correction), and Fisher's exact test, using a significance level of 0.1 (as used in comparison of general background factors). Comparisons between baseline and post-treatment measured values were analyzed using the paired Student's *t*-test, the Cochran-Cox test, and the log-rank test.

RESULTS

In total, 54 asthma patients were enrolled in the study. Analyses were performed for 51 patients, after exclusion of 3 patients for whom step-down could not be performed because of failure to satisfy the step-down criteria during the 48-week test period. The male to female ratio was 23 : 28, and the mean age was 49.8 ± 10.1 years (range: 23-81 years). The mean duration of asthma was 13.4 ± 12.6 years, while the mean FEV 1.0% was 76.2% ± 11.8%. The prior treatment was a combination of BUD 400 μg/day and SM 100 μg/day, corresponding to GINA treatment step 3 (step3 group), in 27 patients, and SFC 250 Diskus 2 puffs/day, corresponding to GINA treatment step 4 (step4 group), in 24 patients. Significant differences in the background factors between the two patient groups were found in regard to the concomitant controller drugs and baseline ACT scores, but no other factors were significant (Table 1).

The mean treatment time required until step-down was possible was 13.2 ± 5.6 weeks in step3 group and 23.4 ± 10.1 weeks in step4 group, with the latter being significantly longer ($p < 0.01$, Kaplan-Meier method, log-rank test). Because of a persistently high FeNO level, the possibility of step-down was based on meeting criterion (2) rather than criterion (1) for 4/27 patients in the step3 group and 5/24 patients in step4 group.

At the time of step-down, the mean ACT score had significantly improved from the baseline score as a result of the fixed-dose budesonide/formoterol 4 puffs/day therapy: from 23 ± 1.28 to 24.31 ± 1.01 in step3 group and from 22.15 ± 1.57 to 24.08 ± 1.32 in

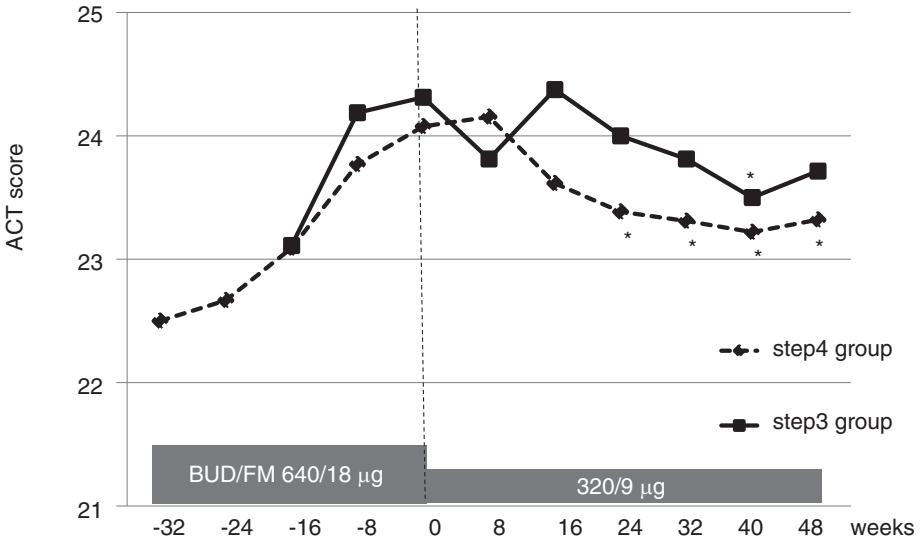

Fig. 1 The changes in mean Asthma Control Test (ACT) score before and after the step-down. *$p < 0.01$ using *t*-test from the time step-down was initiated (week 0).

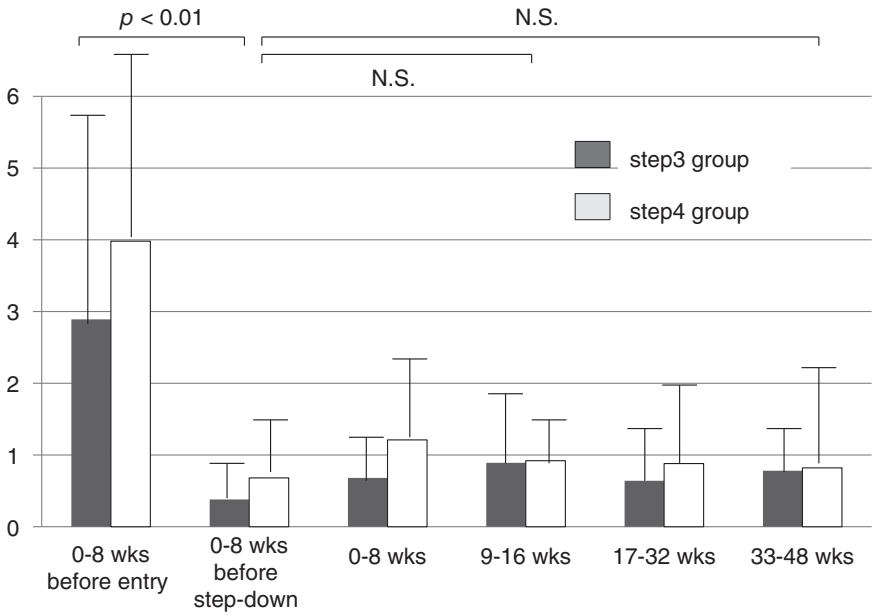

Fig. 2 The changes in mean number of weekly SABA use before and after the step-down. *P*-values of Student t-test (measured value) are shown. N.S., not significant.

step4 group ($p < 0.01$, *t*-test). In step3 group, the ACT score during the 48-week period following step-down remained nearly the same as prior to step-down. In step4 group, which can be considered to have had more serious asthma, the ACT score decreased gradually following step-down, and it had decreased significantly at the 24-week point (23.38 ± 1.33, $p < 0.01$). However, even after 48 weeks, it had not decreased to the score recorded before starting budesonide/formoterol (Fig. 1).

Similarly, the mean number of SABA use one week at the time of step-down had significantly improved from the baseline: from 2.89 ± 2.93 to 0.38 ± 0.52 in step3 group and from 3.98 ± 2.55 to 0.68 ± 0.76 in step 4 group ($p < 0.01$, *t*-test). In both groups, the number of weekly SABA use during the 48-week period following step-down remained almost same as prior to step-down (Fig. 2). In contrast, the respiratory function tests such as FVC, FEV1.0 and MMF revealed no remarkable change before and after step down (Table 2).

In terms of the FeNO level, step-down was per-

Table 2 The changes of Spirometry parameters before and after the step-down

	GINA step3 group (n = 27)			GINA step4 group (n = 24)		
	Before entry	0 wk	48 wks after step-down	Before entry	0 wk	48 wks after step-down
FVC	3.01 ± 0.88	3.18 ± 0.51	2.94 ± 1.11	2.81 ± 1.01	3.03 ± 1.33	2.77 ± 0.97
FEV1.0	2.28 ± 0.62	2.41 ± 0.55	2.25 ± 0.87	2.31 ± 0.69	2.35 ± 0.93	2.33 ± 0.72
% FEV1.0	74.4 ± 11.9	72.6 ± 9.7	76.4 ± 13.5	78.4 ± 11.6	76.5 ± 16.2	79.4 ± 12.4
MMF	1.82 ± 0.95	1.91 ± 1.35	1.95 ± 1.29	1.68 ± 0.98	1.61 ± 1.15	1.74 ± 1.31
V50	1.68 ± 1.21	1.84 ± 1.57	1.77 ± 1.23	1.59 ± 0.87	1.67 ± 0.74	1.60 ± 1.04
V25	0.79 ± 0.77	0.87 ± 0.96	0.84 ± 0.99	0.91 ± 0.96	1.11 ± 1.36	1.04 ± 0.91

Data are presented as mean ± SD. All the values revealed no significant change before and after step-down using ANOVA.

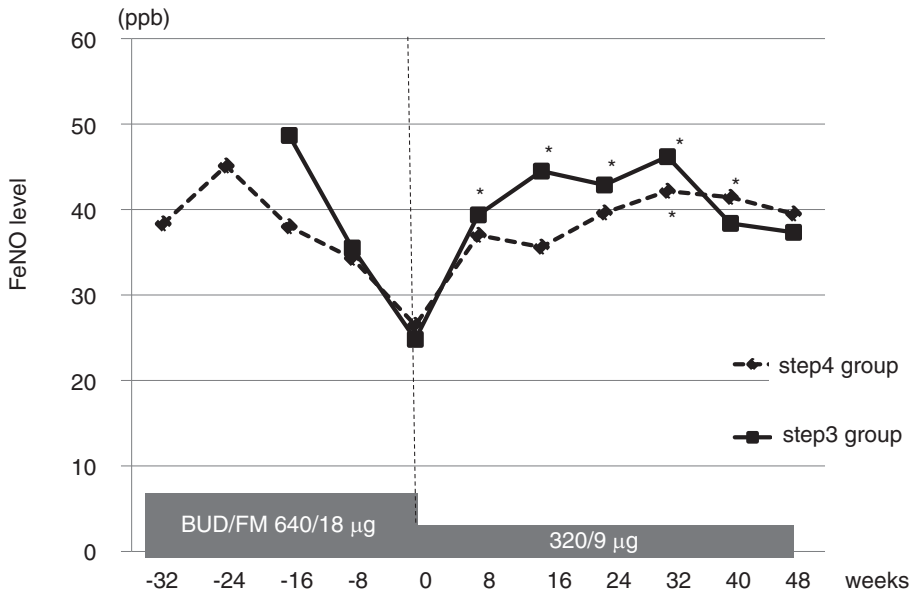

Fig. 3 The changes in mean fractional exhaled nitric oxide (FeNO) values before and after the step-down. *p < 0.01 using t-test from the time step-down was initiated (week 0).

formed in both patient groups following confirmation of significant improvement due to the fixed-dose budesonide/formoterol 4 puffs/day therapy (decreasing from 44.5 ± 28.7 ppb to 25.3 ± 9 ppb in step3 group and from 48.8 ± 31.1 ppb to 26.5 ± 7.4 ppb in t step4 group; p < 0.01). In step3 group, significant deterioration of the FeNO level was seen at 8 weeks following step-down (39.4 ± 25.5 ppb) (p < 0.01), but from 40 weeks onward, the significant difference disappeared, and there was a return to the trend of improvement. In step4 group, there was gradual deterioration of the FeNO level following step-down, showing significant worsening at 39.6 ± 23.6 ppb after 24 weeks. However, as seen for the ACT score, even after 48 weeks, the FeNO level never increased to the level recorded before starting budesonide/formoterol (Fig. 3).

Two patients in step4 group dropped out of the study (after 8 weeks) due to the need for re-escalation of the budesonide/formoterol dosages following step-down. Moderate or more severe exacerbations of asthma were experienced by 6 patients (22%) in the step3 group, but only 3 in step4 group. Thus, in step4 group patients, when the dropout above is added, it can be presumed that adverse events occurred in a total of 5 (21%) patients. Six patients in each patient group had experienced exacerbations during the 6 months of prior treatment. Therefore, it appears that there was no significant change in the frequency of exacerbations occurring between before and after dosage step-down.

DISCUSSION

We proposed and investigated the clinical validity of simple clinical criteria to enable safe step-down of the drug dosage from fixed-dose budesonide/formoterol 4 puffs/day therapy for asthma. The results of observations performed over a 48-week period following

step-down indicated that stable control of the asthma had been maintained in terms of the ACT score, the number of SABA use and those of exacerbations as clinical indicators. Although the ACT score, which has already been established as a standardized endpoint for clinical practice,[18] showed a significant difference before and after step-down in step4 group, taking a report that minimally important difference of ACT score was 3 points,[19] it might be deemed as no clinical significance. Moreover the number of SABA use, those of acute exacerbations and Spirometry parameters, which is more commonly used as a general assessment parameter, revealed no deterioration after step-down.

However, the FeNO level, which is an indicator of eosinophilic airway inflammation, did not necessarily demonstrate any changes that correlated with the aforementioned clinical indicators, such as an immediate re-increase after step-down. In addition, because the transiently elevated FeNO level also showed a subsequent trend of gradual improvement, the present findings suggest the possibility that use of the FeNO level as the sole marker for treatment may lead to the over-administration of controller therapy such as ICS.

The present findings do not contradict the results of earlier reports[14,15] and a meta-analysis[20] that found that, even if the therapeutic approach is decided on the basis of the addition of FeNO measurement to the guideline therapy formulated on the use of clinical symptoms and respiratory function as indicators, there may be no significant improvement in asthma control, and there may also be an increase in the use of an ICS compared with conventional therapy. It can be surmised that these results are in agreement with the current positioning of FeNO, which has not been evaluated to the same extent as sputum eosinophils as a biomarker of eosinophilic airway inflammation. However, at the 48-week point following step-down, FeNO also had not increased to the level seen prior to the budesonide/formoterol 4 puffs/day inhalation therapy, and it can be thought that control of airway inflammation had been maintained to some extent. Moreover, the mean treatment time until step-down was feasible on the basis of our proposed criteria was 13.2 weeks for step3 group, and 23.4 weeks for step 4 group, which might have been due to the effects of continuation of the 4-puff therapy for a longer period of time in this group. These time intervals are in agreement with most asthma guidelines' recommendation that step-down be considered after confirming disease stability for 3-6 months.

On the basis of the findings described above, we believe that our initial hypothesis, that step-down of the drug dosage after attaining a nearly normal state in terms of not only the clinical symptoms but also airway inflammation would lead to a safer subsequent long-term clinical course, is clinically significant.

As noted earlier, there are still few reports regarding step-down in treatment of asthma patients being controlled with an ICS/LABA combination inhaler. It has been reported that patients whose asthma had been controlled by 12-week therapy with SFC 250 showed no deterioration in terms of the frequency of acute exacerbations for 3 months even following a subsequent step-down to SFC 100 with results significantly superior to those in patients in an ICS monotherapy (FP 500 μg/day) group.[6] There have been a few similar reports regarding SFC.[7-10] However, in each study, it was shown that step-down from SFC 250 to SFC 100 tended to result in a slight deterioration of the endpoints, including the peak flow, symptom-free days, etc.. Nevertheless, each of those studies had a short observation period of only 3-6 months, and there have been no reports describing either the safety over a long period of approximately 1 year or the anti-inflammatory effects. In addition, reports regarding step-down of budesonide/formoterol therapy are limited to treatment based on AMD (adjustable maintenance dosing)[21] or SMART.[22] Each of these studies dealt with treatment that adjusted the inhaled drug dose according to the clinical symptoms, and there have been no reports regarding step-down of fixed-dose therapy.

There still remain unresolved issues in our understanding of FeNO. One of the major issues is that there are at least some asthma patients in whom a high FeNO level persists despite control of their asthma. In the present study, step-down was performed in a total of 9 patients in accordance with our postulated criterion (2) while a high FeNO level persisted, but each of those patients had allergic rhinitis. However, there were no asthma exacerbations following step-down in these patients. It is known that there is a high incidence of allergic rhinitis in patients with persistently high FeNO levels despite asthma control having been achieved,[12] and that extra caution is needed when performing step-down in patients with allergic rhinitis.

Our division of patients into two groups, namely a BUD400/SM100 (step3) group and an SFC250 (step 4) group, based on the prior treatment, was strongly influenced by the circumstances unique to Japan. There are currently only two ICS/LABA combination inhalers available for clinical use in Japan, and budesonide/formoterol was only introduced in the year the study was conducted. Therefore, most of our patients were switched to budesonide/formoterol from those 2 treatments. Even in our clinical study concerning the anti-inflammatory effects of fixed-dose budesonide/formoterol 4 puffs/day therapy,[23] these 2 prior treatments accounted for more than 90% of the patients, and a difference in the prognosis following step-down was seen between the 2 treatment groups. For that reason, we decided to divide the patients into 2 groups at the start of the present study. The step4

group showed a low ACT score despite not only the ICS dosage being high, but also the use of a greater number of concomitant controller drugs, indicating that the group included a greater number of more severe cases of asthma. Although there was a difference in the clinical course following step-down, good asthma control was achieved for approximately 1 year in both patient groups after step-down. Therefore this fact suggested that if complete control of asthma, not only of clinical symptoms but also airway inflammation, is achieved by 3-6 months of fixed-dose budesonide/formoterol 4 puffs/day, it should be possible to safely carry out step-down to 2 puffs/day for most patients with asthma of moderate severity.

The results of this study should be considered along with the limitations. First, the study was small, with only about 25 patients per group. The primary endpoint ACT score showed a significant difference before and after step-down in step4 group, but the number of SABA use and those of acute exacerbations, which is more commonly used as a general assessment parameter, did not. One possible reason for that could be that the 21-22% exacerbation rate was lower than the rate of approximately 27% reported for 2 other studies[14,15] that similarly used FeNO as an indicator, but we think that it can actually be attributed to the small number of patients. Second, this study had an open-label, non-placebo, non-crossover design, comparing the data recorded before and after changing the dosage. Therefore, the presence of bias in the assessment of the assayed parameters cannot be ruled out. The difficulty of using FeNO as an assessment parameter has already been described. Nevertheless, considering the paucity of reports regarding the step-down method, the present study can be thought to have great significance because it has generated new evidence. In terms of budesonide/formoterol in particular, the possibility has also been highlighted of exacerbation of not only clinical symptoms[22] but also airway inflammation,[24] even if SMART is added to continuous therapy at 2 puffs/day. Hence, we believe that the present study, in which changes in FeNO were monitored over the long-term, will serve as a reference point for carrying out similar, larger-scale, clinical trials in the future.

As a conclusion, simple clinical criteria were proposed for deciding to step-down from fixed-dose budesonide/formoterol 4 puffs/day therapy to 2 puffs/day for asthma patients. It was suggested that it should be possible to safely perform step-down to 2 puffs/day following the achievement of complete control of asthma for a period of 3-6 months, regardless of prior treatment. Additional studies are needed to expand on the current findings in a larger sample, and determine whether the effects in airway inflammation can be maintained for the long term and reduce exacerbations even after step down is performed.

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