

PHARMACOTHERAPY

Step-down of budesonide/formoterol in early stages of asthma treatment leads to insufficient anti-inflammatory effect

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Abstract

Objective: Administration of the combination of an inhaled corticosteroid (ICS) and a long-acting beta agonist (LABA) is the main treatment strategy for bronchial asthma. The ICS/LABA dosage can be reduced (stepped down) when the patient's symptoms and lung functions are well-controlled. In this study, we obtained fractional exhaled nitric oxide (FeNO) measurements to clarify whether the anti-inflammatory effect of budesonide/formoterol is shortened by step-down. **Methods:** Fifty-four patients who visited the Kawasaki Medical School Hospital with newly diagnosed asthma from November 2008 to July 2010 received budesonide/formoterol for 8 weeks or more. In 29 patients, the forced expiratory volume in 1 s% predicted increased to 80% or more, and the Asthma Control Questionnaire (ACQ) score decreased to 0.5 or less within 12 weeks. These 29 patients were randomly divided into two groups: the dosage-continued group ($n = 14$) and the step-down group ($n = 15$). Then, the impact of budesonide/formoterol step-down on ACQ score, pulmonary function and FeNO level was compared between the groups. **Results:** In the step-down group, the dosage was stepped down from 538 mcg/day to 331 mcg/day. In both groups, pulmonary function indicators and symptoms did not change. However, the mean FeNO level decreased significantly in the dosage-continued group (from 50.9 ppb to 45.0 ppb), and increased significantly in the step-down group (from 51.0 ppb to 65.7 ppb). **Conclusions:** Clinicians should be more careful when stepping down budesonide/formoterol based solely on patients' symptoms and/or pulmonary function.

Keywords

Asthma control test, asthma control questionnaire, asthma quality of life questionnaire, budesonide/formoterol, fractional exhaled nitric oxide, step-down, symbicort

History

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Introduction

Airway inflammation and bronchoconstriction are the initial pathogenetic mechanisms in bronchial asthma. The main treatment strategy for the disease consists of administration of the combination of an inhaled corticosteroid (ICS) and a long-acting beta agonist (LABA) [1,2]. This combination therapy (ICS/LABA) is superior to ICS monotherapy in terms of the time required for improvement of symptoms and pulmonary function [3–5]. The proportion of ICS monotherapy-treated patients showing complete control of symptoms is lower than that of ICS/LABA-treated patients by 26% [5]. It also has been reported that ICS/LABA combination therapy improves bronchial hyperresponsiveness better than ICS monotherapy [6]. Therefore, ICS/LABA combination therapy is predominantly presented as a treatment approach for asthma; however, an adequate ICS dose is essential [7]. According to the major guidelines used worldwide, the dosage of ICS or ICS/LABA inhalation can be reduced (stepped down) when the patient's symptoms and lung function (determined by peak expiratory

flow rate [PEFR] and/or forced expiratory volume in 1 s [FEV1]) are confirmed as well-controlled. In the typical course of ICS/LABA treatment, symptoms and expiratory functions improve rapidly, regardless of sufficient suppression of airway inflammation. It is possible that this strong and speedy airway dilatation effect can lead to premature step-down of ICS/LABA treatment [8].

In this study, we performed fractional exhaled nitric oxide (FeNO) measurements [9] with a unique protocol to clarify whether the anti-inflammatory effect of budesonide/formoterol (Symbicort; AstraZeneca Japan, Tokyo, Japan) is shortened by step-down.

Methods**Subjects**

A total of 54 patients who visited the Kawasaki Medical School Hospital with newly diagnosed asthma from November 2008 to July 2010 participated in this study, which was approved by the Human Ethics Review Committee of the hospital. Written informed consent was obtained from each patient.

The inclusion criteria were as follows: (1) age >18 years, (2) no respiratory infection in the preceding 4 weeks, (3) moderate severity, (4) reversible airflow limitation

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($\geq 15\%$ improvement in FEV1 following inhalation of a bronchodilator [0.3 mL of salbutamol solution; Venetlin 5 mg/mL, Sankyo Co., Tokyo, Japan]), and/or positive methacholine bronchial challenge (provocative concentration causing 20% reduction in FEV1 < 8.0 mg/mL), (5) absence of any systemic or cardiopulmonary disease other than asthma and (6) oral or inhaled corticosteroid-naïve newly diagnosed asthma. The patients received budesonide/formoterol for 8 weeks or more (first entry; Figure 1). When the prebronchodilator FEV1% predicted value increased to 80% or more and the Asthma Control Questionnaire (ACQ) score [10] decreased to 0.5 or less within 12 weeks, the patient was asked if he/she agreed to be randomized into either an ICS/LABA dosage-continued group or an ICS/LABA dosage-stepped-down group (second entry, $n = 37$; Figure 1). Twenty-nine patients accepted and were randomly divided into the two groups (dosage-continued group, $n = 14$; step-down group, $n = 15$). The impact of step-down on the Asthma Control Test (ACT) score [11], ACQ score [10], Asthma Quality of Life Questionnaire (AQLQ) score [12], pulmonary function and FeNO level (Figure 1). Four patients of the dosage-continued group and five patients of the step-down group had rhinitis, but no patient used any antiallergic medication, including leukotriene antagonists. None of the patients were current smokers, and two patients of the dosage-continued group and one patient of the step-down group were ex-smokers.

Protocol

In the step-down group, the dosage was stepped down from 640/18 mcg/day to 480/13.5 mcg/day, or from 480/13.5 mcg/day to 320/9 mcg/day, after second entry, whereas, in the dosage-continued group, the dosage used in the first entry was continued. All the patients underwent a pulmonary function test, FeNO measurement, and ACT, ACQ and AQLQ assessments at every visit.

PEFR measurement and pulmonary function test

PEFR was measured using a peak flow meter (MiniWright; Clement Clarke International Ltd., Harlow, UK) by maximal

expiratory flow from maximal inhalation. The best data of three time trials were adopted [13].

The pulmonary function test was performed using a dry spirometer (CHESTAC-33; CHEST MI, Tokyo, Japan), which meets the 1994 American Thoracic Society (ATS) recommendations for diagnostic spirometry. Three trials were performed, and the two higher inspiratory capacity values were required to agree within 5% or 60 mL [14].

ACT, ACQ and AQLQ

The ACT is an index for asthma control and is copyrighted by Quality Metric Incorporated, Boston, MA, who permitted us to use the ACT in this study [11].

The ACQ can indicate the adequacy of asthma control in individual patients [10]. In general, patients with a score below 0.75 have adequately controlled asthma; those with a score above 1.0 do not have well-controlled asthma. On the seven-point scale of the ACQ, a change of 0.5 in the score is the smallest that can be considered clinically important. In this study, we set a score of 0.5 or less as confirmation of adequate asthma control by ICS/LABA at second entry and 8 weeks after randomization.

The AQLQ measures health-related quality of life in adults with asthma [12]. It has excellent test-retest reliability and can discriminate between patients with different levels of impairment. It is also very responsive to within-patient changes over time. The questionnaire consists of 32 questions within four domains: symptoms, activity limitation, emotional function and environmental stimuli.

FeNO measurement

The FeNO level was measured by employing the online method with a nitric oxide analyzer (NOA 280i; Sievers Instruments, Inc., Boulder, CO). In accordance with the guidelines presented by ATS/European Respiratory Society (ERS) [9], measurements were performed three times or more from the maximal expiratory state in a seated position at rest, so that the expiratory resistance, expiratory flow rate and duration reached 5–20 H₂O, 0.05 L/s $\pm$ 10% and 6 s or more, respectively. The mean of three measurements with an error of 10% or less was employed as the measurement result.

Statistical analysis

For statistical analysis, we employed StatView 5.0 statistical software (SAS Institute, Inc., Cary, NC). All data were expressed as mean values (95% confidence interval [CI]). Budesonide/formoterol-induced improvement from the first entry to the second entry was analyzed using the Wilcoxon signed-rank test (Table 1). To compare the factors between the step-down and dosage-continued groups at second entry (randomization), the Mann-Whitney *U*-test was used, and, to analyze the changes after randomization, the Wilcoxon signed-rank test was used (Table 2). For intergroup comparisons of the ratio of the changes in FeNO level after second entry, the Mann-Whitney *U*-test was used (Figure 2). A *p* value of < 0.05 was regarded as significant.

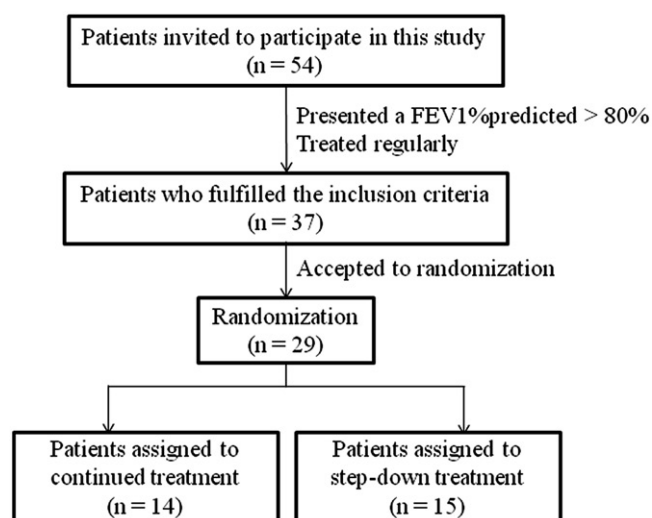


Figure 1. Patient selection. FEV1, forced expiratory volume in 1 second.

Results

Of the 54 patients who participated at first entry, 29 achieved the second-entry criteria (FEV1% predicted >80% and ACQ score <0.5). Changes in the factors between first and second entry are presented in Table 1. FeNO level, mean ACQ score, mean AQLQ score and mean score in the four domains of the AQLQ improved significantly (symptoms, $p=0.004$; activity limitation, $p=0.007$; emotional function, $p=0.005$; and environmental stimuli, $p<0.0001$). The reasons for excluding the other 25 patients from the second entry included the following: did not maintain the designated inhalation dosage ($n=11$), did not achieve the criteria ($n=6$), declared his/her own wish with regard to budesonide/formoterol continuation or stepping down before randomization ($n=5$) and did not revisit ($n=3$).

There was no difference in atopic status or sensitized antigens between the dosage-continued and the step-down groups (all patients were atopic, and one patient in each group had positive sensitization to cat dander and all the others had positive sensitization to house dust mite). Entry season distribution was also the same across groups: four patients in each group were entered during Japan's

cedar pollen season (from January to March). The initial treatment period was similar as well (dosage-continued, 10.0 weeks [95% CI, 9.1–11.0] and step-down, 9.8 weeks [95% CI, 8.9–10.7]; $p=0.80$). In the step-down group, the dosage was stepped down from 538 mcg/day to 331 mcg/day ($p=0.002$; dose reduction rate, 35.3% [95% CI, 25.6–44.9]). In both the dosage-continued and step-down groups, the pulmonary function factors and symptoms did not change (Table 2). However, the mean FeNO level decreased significantly in the dosage-continued group (from 50.9 ppb [95% CI, 33.9–67.9] to 45.0 ppb [95% CI, 25.9–64.1]; reduction rate, 15% [95% CI, –14.0 to 31.3]; $p=0.041$), and increased significantly in the step-down group (from 51.0 ppb [95% CI, 38.5–63.4] to 65.7 ppb [95% CI, 36.0–95.4]; appreciation rate, 24.7% [95% CI, –8.0 to 50.1]; $p=0.043$; Table 2; Figure 2). There was no significant relationship between the reduction and appreciation rates of FeNO (data not shown). None of the patients showed respiratory infection after the second entry.

Table 1. The symptom score and pulmonary function factors at first and second entry ($n=29$).

	First entry, mean (95% CI)	Second entry, mean (95% CI)	<i>p</i> Value
ACT score	22.8 (21.5–24.2)	24.1 (23.5–24.6)	0.09
PEFR% predicted	83.2 (75.2–91.3)	87.5 (82.4–92.7)	0.25
FEV1% predicted	96.3 (87.2–105.3)	99.0 (91.2–106.9)	0.43
V50/V25	2.95 (2.59–3.32)	2.98 (2.66–3.29)	0.94
FeNO, ppb	80.3 (59.9–100.6)	50.9 (41.3–60.5)	0.0001
ACQ score	0.368 (0.119–0.617)	0.080 (0.027–0.133)	0.021
AQLQ score	6.24 (5.89–6.58)	6.70 (6.56–6.97)	0.0029

ACQ, Asthma Control Questionnaire; ACT, Asthma Control Test; AQLQ, Asthma Quality of Life Questionnaire; CI, confidence interval; FeNO, fractional exhaled nitric oxide; FEV1, forced expiratory volume in 1 second; PEFR, peak expiratory flow rate.

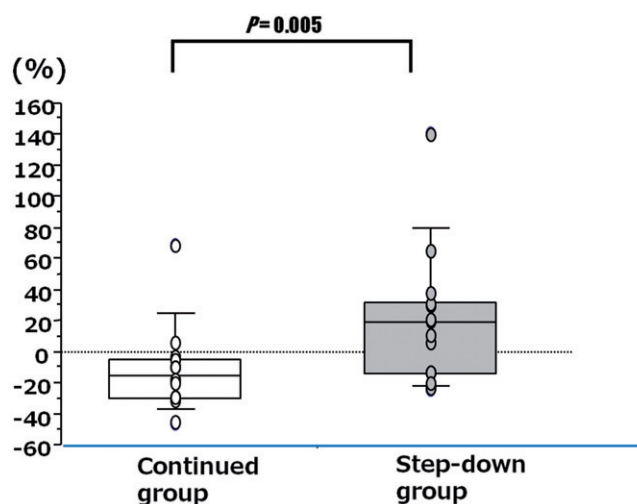


Figure 2. Change rate of fractional exhaled nitric oxide (FeNO) 8 weeks after randomization. The change ratio was compared using the Mann-Whitney *U*-test. The FeNO level decreased by 15% in the dosage-continued group but increased by 25% in the step-down group.

Table 2. The comparisons of the factors of “step-down and continued groups” between second entry and 8 weeks after randomization.

	Step-down group ($n=15$), mean (95% CI)			Continued group ($n=14$), mean (95% CI)			
	At second entry	8 Weeks after randomization	<i>p</i> Value ^a	At second entry	<i>p</i> Value ^b (versus Step-down group)	8 Weeks after randomization	<i>p</i> Value
Age (years)	46.5 (37.1–56.0)	–	–	45.3 (34.7–55.8)	0.944	–	–
Budesonide/formoterol dosage, mcg/day	538 (424–653)	331 (285–376)	0.002	500 (385–615)	0.548	500 (385–615)	–
ACT score	24.3 (23.6–25.0)	22.9 (20.2–25.6)	0.610	23.8 (22.8–24.8)	0.589	24.0 (22.4–25.6)	0.609
PEFR% predicted	90.9 (84.8–97.0)	90.4 (84.1–96.7)	0.889	83.8 (74.7–92.9)	0.196	87.5 (76.3–98.6)	0.712
FEV1% predicted	98.8 (84.2–113.3)	105.2 (94.9–115.5)	0.475	94.0 (80.6–107.3)	>0.999	92.0 (76.8–107.3)	>0.999
V50/V25	3.11 (2.56–3.67)	3.03 (2.40–3.66)	0.169	2.84 (2.44–3.23)	0.393	2.72 (2.39–3.06)	0.859
ACQ score	0.04 (–0.02–0.10)	0.31 (–0.07–0.68)	0.140	0.13 (0.03–0.22)	0.075	0.25 (–0.05–0.55)	0.726
AQLQ score	6.66 (6.43–6.88)	6.34 (5.84–6.85)	0.837	6.76 (6.56–6.96)	0.869	6.57 (6.16–6.99)	0.529
FeNO, ppb	51.0 (38.5–63.4)	65.7 (36.0–95.4)	0.043	50.9 (33.9–67.9)	0.957	45.0 (25.9–64.1)	0.041

ACQ, Asthma Control Questionnaire; ACT, Asthma Control Test; AQLQ, Asthma Quality of Life Questionnaire; CI, confidence interval; FeNO, fractional exhaled nitric oxide; FEV1, forced expiratory volume in 1 second; PEFR, peak expiratory flow rate.

^aMann–Whitney *U*-test was used for the comparison between groups at second entry.

^bWilcoxon signed-rank test was used for analysis of the changes from second entry to 8 weeks after randomization.

Discussion

This study suggests that clinicians should not allow stepping down of budesonide/formoterol dosage, at least for some months after new administration to asthma patients, based solely on the guideline recommendations of stability or improvement in asthma symptoms and/or lung function, because airway inflammation might not be suppressed sufficiently due to shortage of budesonide.

In this study, after two-month administration of budesonide/formoterol to patients with asthma, symptoms and pulmonary function improved and the FeNO level decreased dramatically, but sufficient inhibition of inflammation was not achieved. After the ACT, AQLQ and ACQ symptom scores were confirmed as almost diminished, and the FEV1 and PEFR airflow limitation had normalized, however, a reduction of 35% in budesonide/formoterol dosage resulted in an increase of 25% in FeNO level, which may indicate that step-down should be performed more carefully. One of the marketing points of budesonide/formoterol is the rapid bronchodilating effect by the included formoterol [4], which is beneficial for relief of dyspnea, cough, etc. [4,8]; however, the anti-inflammatory effect cannot be confirmed by assessment of symptoms and/or pulmonary function tests. It may need to be assessed over a long period or investigated using a good index for checking airway eosinophilic inflammation, such as the FeNO level or sputum eosinophil number [15]. With regard to the FeNO level after stepping down, there is insufficient justification to advocate the routine use of either sputum analysis (due to the technical expertise required) or FeNO level assessments in everyday clinical practice [16].

A unique aspect of this study is that we set second-entry criteria after confirming an adequate effect of budesonide/formoterol after 8 weeks or more. We monitored compliance by maintaining an asthma diary, and the LABA could have decreased symptoms and increased pulmonary function. Many patients ($n=11$) were omitted at the second entry due to insufficient adherence; this is thought to be an effect of the study design. It was possible to select whether the patient enters the second entry in practice. The patients who wanted to continue the budesonide/formoterol treatment and wished to avoid randomization to the step-down group could declare insufficiency of adherence to ensure that they were categorized in the dropout group. After second entry, we confirmed adherence by maintaining an asthma diary.

None of the symptoms or pulmonary function factors, except FeNO level, changed after second entry. The important fact is that airway inflammation remained even though the patients used budesonide/formoterol until symptoms diminished and lung function normalized almost completely (FeNO level was still as high as 50.9 or 51.0 ppb). Although FeNO significantly increased to 65.7 ppb in the step-down group, the level was still lower than that at first entry (80.3 ppb); the decrease in the step-down group was less than that in the dosage-continued group but could be sufficient for some patients since their symptoms and pulmonary functions were well-controlled. FeNO assessments may have limitations for determining airway inflammation. Longer initial treatment (e.g., 12 weeks) might cause stronger reduction in inflammation, which could lead to a different outcome.

Conclusion

In conclusion, clinicians should be more careful when stepping down budesonide/formoterol based solely on symptoms and/or pulmonary function. Further studies are required to clarify the effects of timing as well as the use of FeNO assessments in the stepping down of treatment.

Declaration of interest

None of the authors has any financial, consulting, and personal relationships with other people or organizations that could influence (bias) this work.

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