

Budesonide/formoterol maintenance and reliever therapy in moderate-to-severe asthma: Effects on eosinophilic airway inflammation

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ABSTRACT

Although the budesonide and formoterol in a single inhaler for maintenance and reliever therapy has been evaluated in recent studies, the effects on eosinophilic airway inflammation remain uncertain. The purpose of this study was to compare the efficacy, including anti-inflammatory effects, of as-needed budesonide/formoterol with salbutamol in Japanese patients with moderate-to-severe asthma. Patients with asthma using an inhaled corticosteroid plus a long-acting β_2 -agonist as a controller and at least one asthma exacerbation in the previous 12 months were randomized to budesonide/formoterol maintenance therapy (160/4.5 micrograms, 2 inhalations twice daily) plus either as-needed budesonide/formoterol (160/4.5 micrograms; $n = 32$) or salbutamol (100 micrograms; $n = 31$) up to 4 inhalation daily for 48 weeks. The time to first asthma exacerbation was significantly prolonged with as-needed budesonide/formoterol compared with salbutamol (log-rank test; $p = 0.0342$). There was a 66% reduction in the hazard ratio for a first exacerbation with as-needed budesonide/formoterol ($p = 0.0334$). The frequencies of both mild and severe exacerbations and reliever use were consistently less with budesonide/formoterol than salbutamol. As-needed budesonide/formoterol significantly improved in lung function and symptom scores compared with salbutamol. In addition, the contents of eosinophil cationic protein and B12 tryptase, as well as number of eosinophils and mast cells in induced sputum, decreased to a greater extent with budesonide/formoterol compared with salbutamol. In conclusion, the budesonide and formoterol for maintenance and reliever therapy seems more effective in controlling persistent asthma with a significant reduction of airway inflammation.

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Bronchial asthma in adults is a chronic inflammatory disease of the airways that affects ~3% of the population, and its incidence is still increasing.¹ In the late 1990s in Japan, asthma death was observed at ~6000 people per year, but it has decreased to ~2000 per year by 2012.² The decrease of asthma death is parallel to the development of treatment guidelines for asthma in which the use of inhaled corticosteroids (ICSs) was recommended. Because the addition of long-acting β_2 -agonist (LABA) is recognized to be more effective than an additional increase of ICS dose if asthma was uncontrolled with low doses of ICS,^{3–5} combination therapy with ICS plus LABA is now widely used. In addition to the combination maintenance

therapy, a short-acting β_2 -agonist (SABA) is recommended for symptom relief in an as-needed fashion in all treatment steps.¹ ICS plus LABA with as-needed reliever therapy with SABA is the main stream of current treatment strategy in patients with moderate-to-severe asthma. However, questionnaire surveys have shown that the majority of patients using an ICS/LABA combination still report daytime symptoms, awakenings, hospitalization, and emergency room visits due to asthma exacerbations.^{6–8} Many patients also neglect their maintenance therapy and over-rely on their short-acting bronchodilator medication for symptom relief, which leaves the underlying inflammation undertreated and increases the risk of asthma exacerbations.⁹

There is increasing evidence that the budesonide and formoterol in a single inhaler for maintenance and reliever therapy (Symbicort SMART; AstraZeneca, Lund, Sweden) is useful for the treatment of uncontrolled asthma; double-blind comparative clinical trials have revealed a benefit of this strategy including reduction of asthma exacerbations, improvement of lung functions and symptom scores compared with higher doses of ICS alone, or similar or higher fixed dosage of ICS/LABA with SABA as a reliever.^{10–15} The concept

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of this treatment approach is that patients with persistent asthma can receive an anti-inflammatory medication immediately after they required an additional treatment, reducing airway inflammation that may trigger asthma exacerbation. However, it is still uncertain whether this single inhaler strategy could actually improve airway inflammation. Therefore, the purpose of this study was to compare the effect of two as-needed reliever strategies, budesonide/formoterol and salbutamol, on airway inflammation in Japanese patients with moderate-to-severe persistent asthma who have been treated with budesonide/formoterol maintenance therapy. We assessed both clinical outcomes and airway inflammation using induced sputum.

METHODS

Patients

Outpatients aged 16–80 years with a diagnosis of asthma (as defined by the American Thoracic Society) for at least 3 months treated with ICS (budesonide, 320–640 $\mu\text{g}/\text{day}$; fluticasone, 200–500 $\mu\text{g}/\text{day}$) plus LABA with a history of one or more asthma exacerbation in a previous year, asthma control test (ACT) score of ≤ 20 points, and reliever use five or more times per week at study entry were enrolled. All patients had been receiving a constant dose of ICS for ≥ 3 months. Patients had a forced expiratory volume in 1 second (FEV_1) 60–100% of predicted with 12% or more reversibility. Patients with any significant concomitant disorder, such as cardiovascular disease, current/previous smokers with a smoking history of >10 pack-years, pregnancy, and breast-feeding were excluded from the study. Anticholinergics, xanthines, and other antiasthma drugs were not permitted during the study except during hospitalizations or emergency department visits.

Study Design

This 1-year, randomized, parallel-group study was performed according to the Declaration of Helsinki and Good Clinical Practice guidelines. Independent ethics committees approved the study protocol. All patients gave written informed consent. Patients attended the clinic at the beginning and end of run-in and after 4, 8, 12, 24, and 48 weeks of treatment. Patients were randomized to the same maintenance regimen, budesonide/formoterol 160/4.5 μg , 2 inhalations twice a day, plus either as-needed budesonide/formoterol 160/4.5 μg or as-needed salbutamol at 100 μg . As-needed reliever use was permitted up to 4 inhalations/day. Patients recorded their intake of study medication (maintenance and as-needed) on diary cards, and adherence to therapy was assessed by reviewing the diary cards. At the start of the study, all patients were instructed on the correct use of devices.

Any patient who had a severe asthma exacerbation during the run-in period was excluded from the study.

Outcomes

The primary outcomes were the time to first asthma exacerbations and the cumulative number of both severe and mild exacerbations. Severe asthma exacerbations were defined as emergency department visits, systemic steroid use, or hospitalization. Mild exacerbations were defined as unscheduled outpatient visits or reliever use of more than four times a day. The secondary outcomes included mean use of as-needed medication, peak expiratory flow (PEF), FEV_1 , symptom scores (ACT), and airway inflammation.

Measurements

Following instructions, patients measured their own morning and evening PEF. The patient performed three consecutive measurements at each assessment before inhalation of the study medication, and the highest value was recorded. Spirometry measurements were determined at randomization (baseline) and at clinic visits after 4, 12, 24, and 48 weeks of treatment. ACT score, a simple 5-point questionnaire, which is self-completed by patients and each item is scored from 1 (poor control) to 5 (good control), were also recorded. These scores were summed to obtain the total daily ACT score (range, 5–25). Induced sputum samples were obtained at a run-in period and weeks 8, 24, and 48. Both eosinophil and mast cell counts were performed using standard methods.¹⁶ In addition, the contents of eosinophil cationic protein (ECP) and B12 tryptase were measured in the same samples using a B12 monoclonal antibody-based immunofluoroassay that detects both monomers and tetramers of α - and β -tryptases.^{16,17}

Statistical Analysis

All randomized patients with data were included in the intent-to-treat population for efficacy analysis. Approximately 30 patients per group were needed to detect an absolute difference of 20 percentage points in asthma exacerbations between the two groups, with 80% power (two-tailed α -level of 0.05). The time to first severe exacerbation was compared between the treatment groups, using a log-rank test, and further described using a Cox proportional hazards model. The total numbers of severe exacerbations per patient were compared between treatment groups using a Poisson regression model with treatment as factor and time in the study as an offset variable. The confidence limits and the p values were adjusted for overdispersion. Analyses were performed using analysis of variance, with treatment and country as fixed factors and the run-in period average as a covariate. The adjusted

Table 1 Characteristics of the study patients

	Budesonide/Formoterol (n = 32)	Salbutamol (n = 31)	p Value
Age (yr)	41	39	NS
Sex (M/F)	13/19	10/21	NS
ICS (BDP μ g/day)	574 $\pm$ 84	610 $\pm$ 92	NS
LABA: salmeterol	8	6	NS
tulobuterol	9	9	NS
Lung function			
FEV ₁ (L)	1.86 $\pm$ 0.33	1.89 $\pm$ 0.40	NS
FEV ₁ (%)	68.3 $\pm$ 8.7	70.4 $\pm$ 10.2	NS
PEF			
Morning PEF (L/min)	369 $\pm$ 41	380 $\pm$ 36	NS
Evening PEF (L/min)	420 $\pm$ 28	433 $\pm$ 35	NS
SABA usage (/wk)	11.2 $\pm$ 4.0	10.6 $\pm$ 3.2	NS
ACT score	15.3 $\pm$ 2.2	14.6 $\pm$ 3.0	NS

ICS = inhaled corticosteroid; LABA = long-acting β_2 -agonist; FEV₁ = forced expiratory volume in 1 s; PEF = peak expiratory flow; SABA = short-acting β_2 -agonist; ACT = asthma control test; NS = not significant; BDP = beclomethasone dipropionate.

mean change from run-in was obtained from the analysis model, and treatment differences and 95% confidence intervals were calculated. All hypothesis testing was two sided; values of $p > 5\%$ were considered statistically significant.

RESULTS

Patients

A total of 63 patients (from 315 screened) underwent randomization. Judging from serum IgE levels, $>80\%$ of patients were considered as atopic and the percentage was not significantly different between the two groups. After a run-in period, the patients were randomized to study treatment: 32 patients to as-needed budesonide/formoterol and 31 patients to as-needed salbutamol. Characteristics of the treatment groups were comparable at baseline (Table 1).

Asthma Exacerbations

The time to first asthma exacerbation was significantly prolonged with as-needed budesonide/formoterol compared with as-needed salbutamol (log-rank test, $p = 0.0342$; Fig. 1). There was a 34% reduction in the hazard ratio for a first asthma exacerbation with budesonide/formoterol compared with salbutamol (hazard ratio, 0.34; 95% confidence interval, 0.11–0.92; $p = 0.0334$). The total number of both severe and mild asthma exacerbations was significantly reduced with budesonide/formoterol compared with salbutamol (mild, 15.6% versus 29.0%, $p < 0.05$; severe, 0% versus 9.7%; $p < 0.05$; Fig. 2).

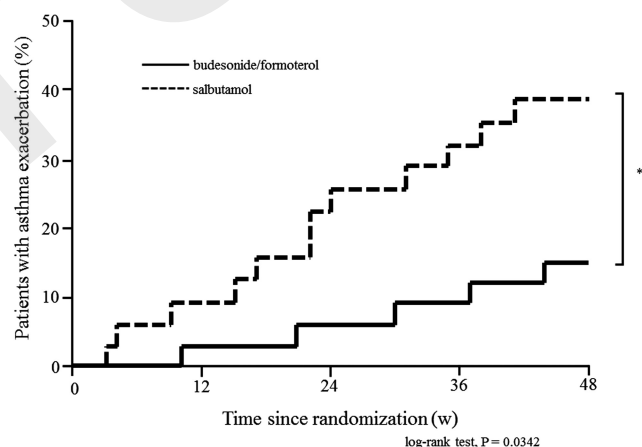


Figure 1. Kaplan-Meier plot of time to first asthma exacerbation. Time to first asthma exacerbations defined as a deterioration in asthma resulting in emergency department visits, systemic steroid use, hospitalization, unscheduled outpatient visits, or reliever use >4 times a day. A significant difference between the two groups was detected by a log-rank test ($*p = 0.0342$).

Reliever Use

The mean as-needed reliever use significantly decreased in both budesonide/formoterol (from 11.2 to 2.0 inhalations/wk) and salbutamol (from 10.6 to 3.6 inhalations/wk). The mean number of inhalations of reliever use during the study was significantly lower with budesonide/formoterol than salbutamol (budesonide/formoterol, 3.6 ± 0.9 inhalations/wk; salbutamol, 5.6 ± 0.8 inhalations/wk; $p < 0.05$; Fig. 3). The mean daily additional dose of budesonide used in the budesonide/formoterol group was 76.8 μ g. During the study, patients with as-needed budesonide/formoterol had never used systemic steroids.

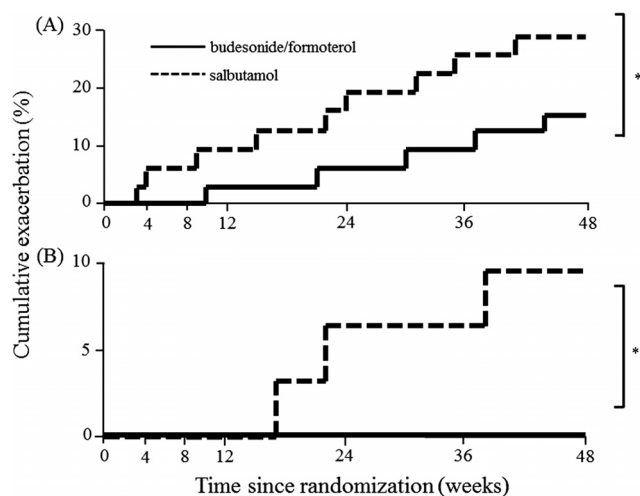


Figure 2. Cumulative rate of (A) mild asthma exacerbations (defined as unscheduled outpatient visits or reliever use more than four times a day) and (B) severe asthma exacerbations (defined as emergency department visits, systemic steroid use, or hospitalization). The total number of both severe and mild asthma exacerbations was significantly reduced with as-needed use of budesonide/formoterol compared with salbutamol ($p < 0.05$).

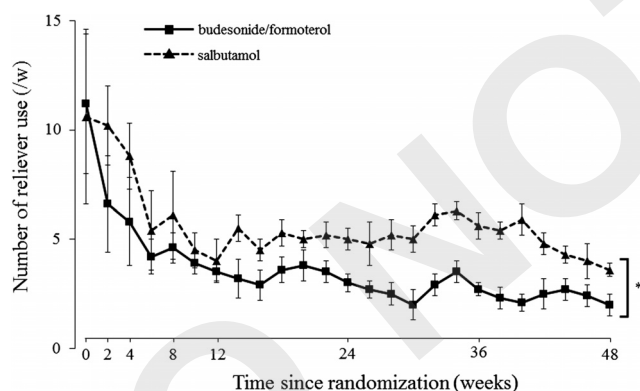


Figure 3. Changes in frequency of reliever use during the study. The mean number of reliever use during the study was significantly lower with budesonide/formoterol than salbutamol ($p < 0.05$).

Lung Function

The improvement in both morning and evening PEF from baseline were seen at week 24 in both treatment groups and were maintained throughout the 48-week treatment period. As-needed use of budesonide/formoterol caused significant greater increases in morning and evening PEF than did salbutamol at weeks 24 and 48 ($p < 0.05$; Fig. 4). Mean FEV₁ increased in both groups, but the improvements were significantly greater with budesonide/formoterol than salbutamol at weeks 24 and 48 ($p < 0.05$; Fig. 5).

Symptom Scores

The ACT scores were significantly improved from run-in (15.3 ± 2.2) to week 48 (22.2 ± 0.8) with as-

needed use of budesonide/formoterol ($p < 0.05$), and were significantly higher than that of salbutamol at week 48 ($p < 0.05$; Fig. 6). Achievement rate of the total control (25 in ACT score) was similar in both groups. No significant difference in the adherence to therapy was noted between two groups.

Airway Inflammation

Of the 63 subjects randomized into the study, 31 subjects (as-needed budesonide/formoterol, $n = 15$; as-needed salbutamol, $n = 16$) could produce sufficient sputum for analysis at weeks 0, 8, 24, and 48. Mean eosinophil and mast cell counts, as well as mean volume of ECP and B12 tryptase were similar between the two groups (budesonide/formoterol, eosinophil, $13 \pm 6\%$ and mast cell, $0.7 \pm 0.2\%$; salbutamol, eosinophil, $11 \pm 5\%$ and mast cell, $0.6 \pm 0.6\%$). Mean eosinophil counts and ECP contents significantly decreased with budesonide/formoterol compared with salbutamol at weeks 8, 24, and 48 ($p < 0.05$ at week 8 and $p < 0.01$ at weeks 24 and 48). In addition, mast cell count and B12 tryptase contents decreased only with budesonide/formoterol at week 48 ($p < 0.05$; Table 2).

DISCUSSION

This study examined whether as-needed reliever therapy with budesonide/formoterol would further reduce asthma exacerbations compared with as-needed therapy with SABA in uncontrolled Japanese patients with moderate-to-severe asthma who had been treated with budesonide/formoterol maintenance therapy. We found that the reliever use of budesonide/formoterol significantly prolonged time to first exacerbations and reduced the rate of asthma exacerbations, effects that were accompanied with the reduction of eosinophilic airway inflammation.

The use of the budesonide and formoterol in a single inhaler for maintenance and reliever therapy has been reported as an effective treatment strategy for preventing asthma exacerbations in several clinical trials.^{10–15} This treatment strategy prolonged time to first exacerbations compared with fluticasone/salmeterol plus as-needed reliever therapy with SABA.^{11,12,18} These trials assessed the efficacy of budesonide/formoterol for maintenance and reliever therapy compared with the different combination maintenance therapy with SABA. In the present study, we showed the efficacy of as-needed budesonide/formoterol compared with salbutamol in patients who received the same maintenance therapy. Rabe *et al.* reported that as-needed budesonide/formoterol ($160/4.5 \mu\text{g}$) provides increased protection from severe exacerbations compared with as-needed reliever therapy with either terbutaline or formoterol alone in patients with mild asthma receiving a lower dosage of budesonide/formoterol maintenance therapy.¹⁴ Kawai

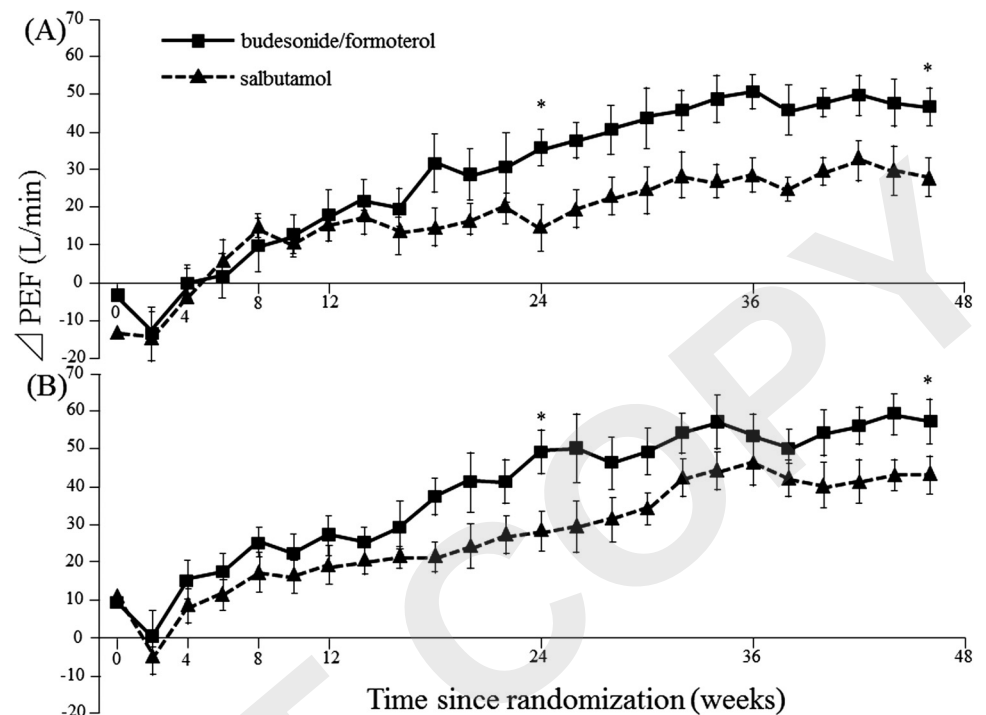


Figure 4. Changes in peak expiratory flow (PEF) during the study. As-needed use of budesonide/formoterol caused significant greater increases in morning and evening PEF than did salbutamol at weeks 24 and 48 (* $p < 0.05$).

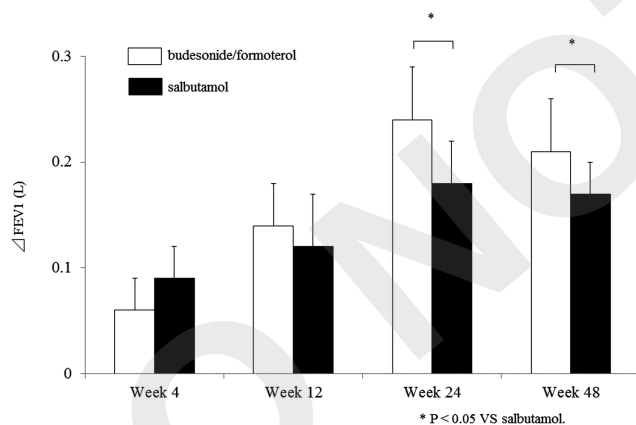


Figure 5. Forced expiratory volume in 1 second (FEV_1) during the study. Mean FEV_1 increased in both groups, but the improvements were significantly greater with as-needed use of budesonide/formoterol compared with salbutamol at weeks 24 and 48 (* $p < 0.05$).

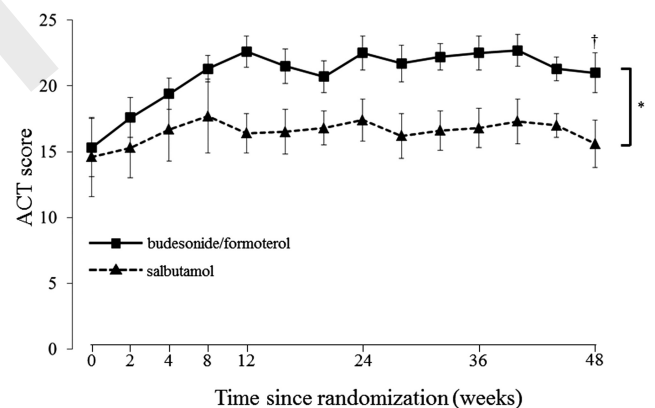


Figure 6. Changes in asthma control test (ACT) score during the study. The ACT scores were significantly improved from run-in to week 48 with as-needed budesonide/formoterol ($tp < 0.05$) and were significantly higher than that of salbutamol at week 48 (* $p < 0.05$).

et al. reported a similar benefit in Japanese patients with mild asthma receiving a lower dosage of budesonide/formoterol maintenance therapy.¹⁹ Our findings extend the benefit of as-needed reliever therapy with budesonide/formoterol in patients with moderate-to-severe asthma who had been receiving a higher dosage of budesonide/formoterol maintenance therapy. In addition, we also confirmed better exacerbation control in the as-needed reliever therapy with budesonide/formoterol compared with salbutamol, the drug that is commonly used in Japan.

An increase in the dose and dosing frequency of ICS when asthma worsens may be the key to prevent

the progression of asthma exacerbations. At the timing of asthma exacerbations, airway epithelial cells induce several cytokines, such as IL-8, RANTES, and $TNF-\alpha$, and budesonide was able to reduce these productions.²⁰ In addition, budesonide/formoterol is known to curtail excessive inflammation induced by rhinovirus infections by which asthma exacerbations are frequently triggered.²¹ Harrison *et al.* showed that doubling the dose of ICS when PEF or symptoms deteriorated had little effect on control and did not reduce the need for oral steroid treatment.²² In *in vitro* studies using peripheral blood mononuclear cells revealed that the productions of

Table 2 Analysis of inflammatory markers in induced sputum

	Budesonide/Formoterol (<i>n</i> = 15)				Salbutamol (<i>n</i> = 16)			
	Week 0	Week 8	Week 24	Week 48	Week 0	Week 8	Week 24	Week 48
Eosinophil (%)	13 ± 6	6 ± 4*	4 ± 2**	4 ± 3**	11 ± 5	9 ± 4	10 ± 4	7 ± 5
Mast cell (%)	0.7 ± 0.2	0.5 ± 0.3	0.5 ± 0.3	0.3 ± 0.2*	0.6 ± 0.6	0.7 ± 0.5	0.8 ± 0.3	0.7 ± 0.4
ECP (ng/ml)	23 ± 6	14 ± 4**	10 ± 5**	7 ± 6**	26 ± 8	25 ± 5	27 ± 6	30 ± 5
B12 tryptase (ng/mL)	41 ± 10	44 ± 8	35 ± 7	29 ± 6*	52 ± 10	57 ± 8	49 ± 9	53 ± 10

p* < 0.05; *p* < 0.01 compared with salbutamol.

ECP = eosinophil cationic protein.

IL-5 and RANTES were significantly inhibited by budesonide or budesonide/formoterol combination when the drugs were added 15 minutes, but not 4 hours, after cell stimulation.²³ The reason for the fewer efficacies of ICS in established inflammation may be related to the reduced glucocorticoid receptor binding affinity.²⁴ Our present study showed a significant reduction in exacerbations with a modest average increase in the ICS dose (the mean additional dose of budesonide, ~80 µg/day), suggesting an important role of the timing to increase anti-inflammatory medications.

Because corticosteroids can potentially suppress eosinophilic inflammation, it would be speculated that the additional use of budesonide might further reduce eosinophilic inflammation in airways. In this study we found that induced sputum taken from symptomatic patients showed eosinophilic inflammation and that the symptom-driven approach of an extra dosage with budesonide/formoterol significantly decreased mean eosinophil counts and ECP contents at weeks 8, 24, and 48. Sears *et al.* reported that the budesonide/formoterol for maintenance and reliever therapy did not significantly improve airway eosinophilic inflammation compared with guideline-based conventional best practice.²⁵ They showed that both approaches had similar effects on reducing eosinophilic airway inflammation. The reason for the difference of anti-inflammatory effect of the additional dosage of ICS between the studies may be because of the characteristics of the patients. In our study, baseline percentage of eosinophils was high (above 10%) compared with their study (below 2%). McGrath *et al.* reported that combined anti-inflammatory therapy caused significant improvements in airflow obstruction in eosinophilic asthma, but not in persistently noneosinophilic asthma, suggesting a relationship between the effect of ICS and the number of eosinophils in induced sputum.²⁶ Our results confirmed an efficacy of the budesonide/formoterol for maintenance and reliever therapy, especially in patients with eosinophilic asthma. Furthermore, mean mast cell count and B12 tryptase, a

specific marker of mast cell activation, decreased with as-needed use of budesonide/formoterol at week 48, suggesting a long-term effect of as-needed use of corticosteroids. The limitation of this study is that the induced sputum samples were not collected from all patients. Several biomarkers have been developed and evaluated to assess the airway inflammation associated with asthma, such as fraction of nitric oxide and various metabolites in exhaled breath^{27–29} and serum periostin.^{30,31} These markers might be measured to assess the changes of airway inflammation in patients treated with budesonide/formoterol for maintenance and reliever therapy.

The improvements in the mean number of inhalations of reliever use, lung function, and symptom scores were consistently greater in patients treated with as-needed budesonide/formoterol compared with as-needed salbutamol. These efficacies were maintained throughout the 48-week treatment period. However, the ACT scores did not reach the guideline-defined total control of asthma in a majority of patients at week 48. Rabe *et al.* have shown that the increase in asthma control days was seen with similar extent between two as-needed reliever strategies, ICS plus LABA and SABA.¹⁴ Despite the stable clinical control, the budesonide/formoterol for maintenance and reliever therapy was associated with higher eosinophil counts compared with fixed-dose combination treatment containing a fourfold higher maintenance dose of budesonide.³² The total control should be the aim of asthma management for all patients with persistent asthma. Thus, *e.g.*, increase in maintenance dose of corticosteroids might be considered in patients who required frequent reliever therapy with budesonide/formoterol.

In conclusion, we found that budesonide/formoterol for maintenance and reliever therapy provided not only protection from asthma exacerbations but also improvements of lung functions and symptom scores compared with as-needed reliever therapy with SABA in patients with moderate-to-severe asthma. We also found a corresponding reduction of eosinophilic airway inflammation. These results suggest an important

role of increase in ICS at the timing of the first sign of worsening of symptoms.

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