CHEST

Original Research

ASTHMA

Budesonide/Formoterol in a Single Inhaler for Maintenance and Relief in Mild-to-Moderate Asthma*

A Randomized, Double-Blind Trial

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Study objective: **To compare a novel asthma management strategy—budesonide/formoterol in a single inhaler for both maintenance therapy and symptom relief—with a higher dose of budesonide plus as-needed terbutaline.**

Methods: **This was a 6-month, randomized, double-blind, parallel-group study in patients with mild-to-moderate asthma (n = 697; mean age, 38 years [range, 11 to 79 years]; mean baseline FEV_1, 75% of predicted; mean inhaled corticosteroid [ICS] dosage, 348 μg/d). Following a 2-week run-in period, all patients received two blinded, dry powder inhalers, one containing maintenance medication and one containing medication to be used as needed for the relief of symptoms. Patients were randomized to receive either budesonide/formoterol (80 μg/4.5 μg, two inhalations qd) for maintenance plus additional inhalations as needed for symptom relief, or budesonide (160 μg, two inhalations qd) for maintenance medication plus terbutaline (0.4 mg) as needed. The primary efficacy variable was morning peak expiratory flow (PEF).**

Results: **Patients receiving budesonide/formoterol showed greater improvements in morning PEF than patients receiving budesonide (increases of 34.5 L/min vs 9.5 L/min, respectively; $p < 0.001$). The risk of having a severe exacerbation (hospitalization/emergency department [ED] treatment, oral steroids for asthma, or a ≥ 30% decrease from baseline in morning PEF on 2 consecutive days) was 54% lower with budesonide/formoterol vs budesonide ($p = 0.0011$). Budesonide/formoterol patients experienced 90% fewer hospitalizations/ED treatments due to asthma than budesonide patients (1 vs 10, respectively; $p = 0.026$). The increased efficacy with budesonide/formoterol was achieved with less ICS than was used in the budesonide group (mean dose, 240 μg/d vs 320 μg/d, respectively) and with 77% fewer oral steroid treatment days vs budesonide (114 days vs 498 days, respectively). Both treatments were well tolerated.**

Conclusions: **Budesonide/formoterol for both maintenance and relief improves asthma control with a lower steroid load compared with a higher dose of budesonide plus terbutaline.**

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Key words: asthma; budesonide/formoterol; inhaled corticosteroids

Abbreviations: ED = emergency department; ICS = inhaled corticosteroid/corticosteroids; PEF = peak expiratory flow

Asthma is characterized by chronic inflammation of the airways with variable airflow limitation resulting in recurrent wheezing, chest tightness, and cough.[1] The presence or absence of airway triggers, such as allergens, infectious agents, and exercise, causes anti-inflammatory requirements to change, and this impacts on both the day-to-day and long-term management of asthma.

According to international guidelines,[1] the aims of asthma treatment are to control underlying airway inflammation, to avoid exacerbations, and to reduce symptoms using the minimum effective drug load, therefore minimizing the impact of asthma on quality of life. However, despite the availability of effective asthma medication, many patients continue to receive suboptimal asthma control.[2,3]

Maintenance therapy with long-acting β_2-agonists such as formoterol and salmeterol in combination with inhaled corticosteroids (ICS) is an effective alternative to higher doses of ICS in patients whose symptoms persist despite treatment with low-dose ICS.[4,5] The introduction of single inhalers that co-administer ICS and long-acting β_2-agonists has simplified asthma therapy, providing a mechanism that ensures that patients receive a fixed proportion of both components with each inhalation. Providing both products in a single inhaler simplifies the treatment regimen and should improve adherence. Many patients, however, neglect their controller medication and overrely on their short-acting bronchodilator medication for symptom relief, which leaves the underlying inflammation undertreated and increases the risk of asthma exacerbations.

This study examined the effectiveness of a new asthma management strategy, a single inhaler containing budesonide and formoterol for both maintenance therapy and symptom relief. This concept mirrors the overall approach advocated in asthma treatment guidelines,[1] as it is based on ensuring that patients with persistent asthma receive anti-inflammatory medication every day, that they increase the dose rapidly during periods of symptoms to regain control quickly, and that they reduce the dose automatically during periods of good control when asthma is nonsymptomatic. This treatment concept is possible because formoterol has an onset of action similar to that of salbutamol.[6] Accordingly, budesonide/formoterol for both maintenance and relief should provide additional asthma control while avoiding the need for a separate reliever inhaler.

In the present study, the efficacy and safety of budesonide/formoterol for both maintenance and symptom relief were compared with that of double the maintenance dose of budesonide (160 μg, two inhalations qd) and terbutaline (0.4 mg as needed) over 6 months. All patients had mild-to-moderate persistent asthma.

Materials and Methods

This double-blind, randomized, parallel-group, active-controlled study (study No. 0667) was conducted at 77 centers in Argentina, Brazil, China, Denmark, Indonesia, Norway, the Philippines, Spain, and Sweden. The study was performed in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines, and local regulations (each study center received ethical approval of the protocol prior to study commencement). Adult patients and parents/guardians of underage children were required to give written informed consent prior to entering the study.

Male and female patients aged 12 to 80 years with a diagnosis of asthma for at least 6 months (FEV_1, 60 to 100% of predicted normal; ≥ 12% reversibility of basal FEV_1 15 min after inhalation of terbutaline [1 mg] at either enrollment or randomization) were eligible for inclusion in the study. For adults (≥ 18 years old), an increase in basal FEV_1 ≥ 200 mL 15 min after terbutaline inhalation was also required either at study entry or at randomization. If the reversibility criterion was not met at enrollment or randomization, the patient could be included if their peak expiratory flow (PEF) variability was ≥ 12% on at least 3 of the last 10 days of the run-in period. All patients had received ICS (any brand, 200 to 500 μg/d) for at least 3 months and at a constant dose for ≥ 30 days prior to study entry. Exclusion criteria included use of systemic corticosteroids or inhaled cromones within 30 days of study commencement, any respiratory infection affecting asthma control within the previous 30 days, and known hypersensitivity to the study medications or inhaled lactose. Patients with any significant concomitant disorder, such as cardiovascular disease (judged by the investigator to make the patient unsuitable for inclusion), and current/previous smokers with a smoking history of > 10 pack-years, were excluded from the study. Anticholinergics, xanthines, and other antiasthma products were not permitted during the study except during hospitalizations or emergency department (ED) visits. In addition, β-blocker therapy was not allowed during the study.

Study Design

During an open run-in period of 14 to 18 days, patients received budesonide, 100 μg bid (metered dose), and inhaled terbutaline, 0.5 mg as needed (metered dose). Both drugs were administered via a dry powder inhaler. In order to secure a symptomatic population that could respond differently to different treatments, patients were required to have had ≥ 7 inhalations of as-needed medication during the last 10 days of the

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run-in period but < 10 inhalations on any single day. Any patient who had a severe asthma exacerbation during the run-in period was excluded from the study.

Patients were randomized to a 6-month regimen of either budesonide/formoterol (80 μg/4.5 μg, two inhalations qd in the evening) plus budesonide/formoterol as needed (budesonide/formoterol for both maintenance and relief), or double the dose of budesonide (160 μg, two inhalations qd in the evening) plus terbutaline (0.4 mg as needed). During the treatment period, all drugs were administered via a dry powder inhaler that dispensed the drugs as delivered doses rather than metered doses. A delivered dose of 80 μg of budesonide corresponds to a metered dose of 100 μg, and a delivered dose of 0.4 mg of terbutaline corresponds to a metered dose of 0.5 mg. Patients were allowed to receive a maximum of 10 as-needed inhalations of either budesonide/formoterol or terbutaline each day. If > 10 inhalations were required in a single day, treatment was left to the discretion of the investigator based on individual reassessment. Therefore, patients receiving budesonide/formoterol for both maintenance and relief could have a total daily dose of budesonide/formoterol up to 960 μg/54 μg. This dose is well within the tolerability ranges of the monocomponents, as budesonide/formoterol in a single inhaler has been shown to be well tolerated at occasional high doses of 1,920 μg/54 μg.[7] 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.

Blinding and Randomization

All patients received two identical inhalers (labeled as inhaler 1 and inhaler 2). Patients were instructed to take two inhalations from inhaler 1 (containing either budesonide/formoterol or budesonide) every evening before going to bed, and to take one inhalation from inhaler 2 (containing treatment-specific reliever medication [budesonide/formoterol for patients randomized to budesonide/formoterol or terbutaline for those randomized to treatment with budesonide]) as needed whenever they experienced asthma symptoms.

Efficacy Evaluations

Following instruction, patients measured their own morning and evening PEF using a peak flow meter (Mini-Wright; Clement Clark; Harlow, UK). Measurements were to be performed before inhalation of the study medication and were recorded on the diary cards. The patient performed three consecutive measurements at each assessment, and the highest value was recorded. Spirometry measurements were determined at enrollment, randomization (baseline), and at clinic visits following 1 month, 3 months, and 6 months of treatment. Assessments of lung function were performed as recommended by the European Respiratory Society,[8] and the best of three satisfactory FEV_1 tests was recorded as a percentage of the predicted normal value.[8,9]

The number of nighttime awakenings was recorded in patient diaries. Daytime and nighttime asthma symptom scores, measured on a scale of 0 to 3 (0 = no symptoms; 1 = mild symptoms; 2 = moderate symptoms; 3 = severe symptoms), were also recorded. These scores were summed to obtain the total daily asthma symptom score (range, 0 to 6).

The percentage of symptom-free days (a night and a day without asthma symptoms and no nighttime awakenings due to asthma) and the percentage of as-needed medication-free days were calculated from diary card data. These end points were combined to determine the percentage of asthma-control days (a night and a day with no asthma symptoms, no intake of reliever medication, and a night with no awakenings due to asthma symptoms).

A severe exacerbation was defined as hospitalization/ED treatment due to asthma worsening, the need for oral steroids because of asthma (as judged by the investigator), or a ≥ 30% decrease from baseline in morning PEF on 2 consecutive days. Patients with severe exacerbations were treated with prednisone, 30 mg/d, for 10 days. If a patient needed > 10 days of treatment with oral steroids, the eleventh day was regarded as a second exacerbation. The decision whether to use additional oral steroids for a further 10 days was left to the discretion of the investigator. Patients were withdrawn from the study if they required three or more courses of oral steroids.

Clinical Safety Assessments

The incidence of any adverse events, reported either spontaneously or in response to a standard question asked by the investigator, was recorded at clinic visits. A serious adverse event was one that resulted in death, was life threatening, required new or prolongation of existing hospitalization, resulted in persistent or significant disability, or resulted in a birth defect. ECG measurements, laboratory assessments of hematology, clinical chemistry, morning plasma cortisol, and urinalysis were conducted during the run-in period and at the end of the treatment period in a subpopulation of 200 patients (100 patients from each treatment group).

Statistical Analysis

Efficacy analysis was carried out on all randomized patients (intention-to-treat population). The primary efficacy variable, morning PEF, together with all other patient diary variables were analyzed as change from baseline (average value over the last 10 days of the run-in period). The treatment mean was the average value calculated for the entire treatment period. 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 mean change from run-in was obtained from the analysis model, and treatment differences and 95% confidence intervals (CI) were calculated. For FEV_1, baseline values (measurements recorded at randomization) together with the average value from measurements after 1, 3, and 6 months of treatment were analyzed in the same way.

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. To assess the severity of severe exacerbations, individual averages for total asthma symptom scores and reliever medication use were calculated for the period from 7 days before to 7 days after the start of an exacerbation. Similarly, the recovery from a severe exacerbation was quantified by calculating average daily symptom scores and reliever medication use from days 8 to 14 after the start of an exacerbation.

Results

From a total of 919 patients enrolled in the study, 697 patients (270 males) aged 11 to 79 years (mean age, 38 years) were randomized to treatment with either budesonide/formoterol in a single inhaler for both maintenance and relief (n = 355) or double-

dose budesonide plus as-needed terbutaline (n = 342). A total of 58 patients discontinued the study: 27 patients in the budesonide/formoterol group (19 because eligibility criteria were not fulfilled, 3 because of adverse events [cramps, tachycardia plus atrial fibrillation, aggravated asthma]; 5 for other reasons) and 31 patients in the budesonide group (13 because eligibility criteria were not fulfilled; 8 because of adverse events [5 cases of aggravated asthma, 1 case of rosacea, 1 case of pharyngitis, 1 case of palpitations plus headache plus pruritus]; 1 was not available for follow-up; 9 for other reasons) [Fig 1].

Overall, the two treatment groups were comparable in terms of baseline demographics and clinical characteristics (Table 1). Patients in both groups showed high levels of adherence to their maintenance medication (mean > 97% in both groups), and both groups were comparable in terms of mean reliever medication usage (1.6 inhalations/d vs 1.8 inhalations/d for budesonide/formoterol and double-dose budesonide, respectively). During the last 10 days of the run-in period, patient diary data demonstrated that 95% of patients had asthma symptoms, with 43% of patients experiencing at least one nighttime awakening due to asthma.

Lung Function

Patients receiving budesonide/formoterol for both maintenance and relief showed greater improvements from baseline in morning PEF than those receiving budesonide (34.5 L/min vs 9.5 L/min, $p < 0.001$; Table 2). Similar improvements were observed for evening PEF (Table 2). The improvements in morning PEF (Fig 2) and evening PEF were apparent in the budesonide/formoterol group from the start of treatment and were maintained throughout the 6-month treatment period. Mean FEV_1 increased in both treatment groups, but the improvements were significantly greater for patients in the budesonide/formoterol group compared with the budesonide group (0.210 L vs 0.062 L, respectively; $p < 0.001$).

Severe Exacerbations

When case report forms and patient diary data were examined to determine the total number of

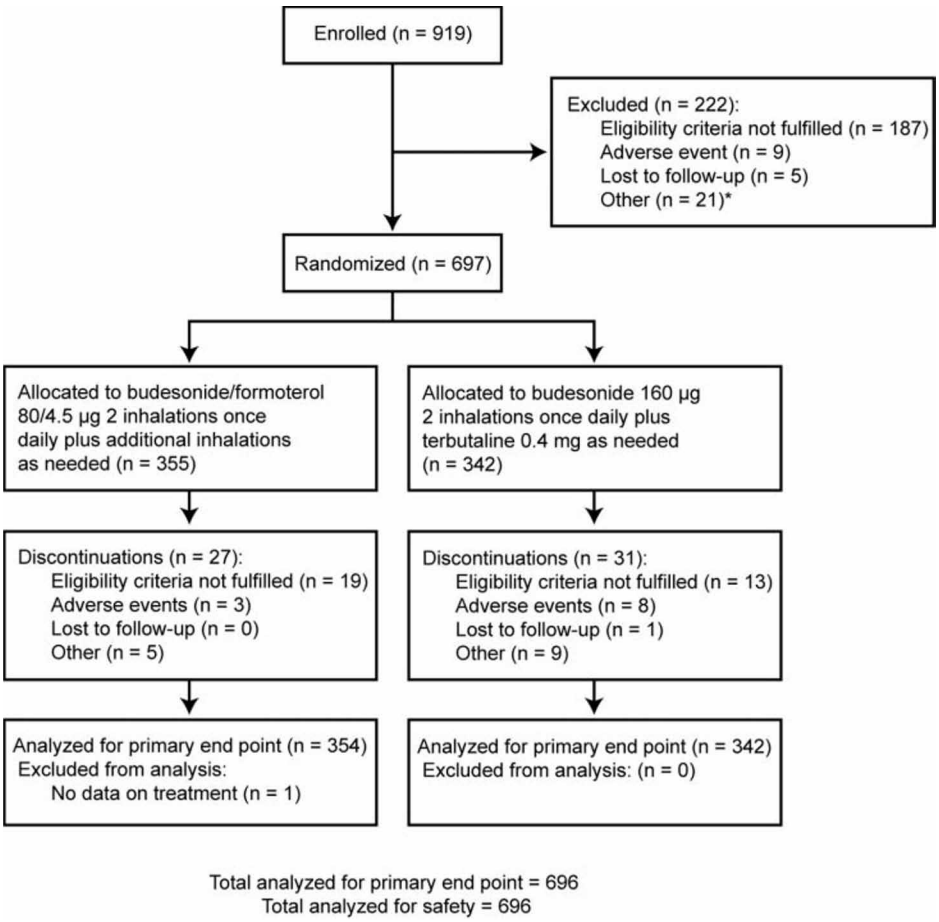

FIGURE 1. Trial profile. *Fourteen patients withdrew consent, 5 patients were incorrectly enrolled, 1 patient was noncompliant, and 1 patient was withdrawn in error.

Table 1—*Patient Characteristics at Baseline

Characteristics	Treatment Groups: Budesonide/Formoterol, 80 μg/4.5 μg, Two Inhalations qd	Treatment Groups: Budesonide, 160 μg, Two Inhalations qd
Patients, No.	355	342
Male gender	147 (41)	123 (36)
Mean age, yr	38 (12 to 79)	38 (11 to 78)
Median duration of asthma, yr	10 (1 to 70)	10 (1 to 61)
Mean dose of inhaled steroid, μg/d	353 (200 to 500)	343 (200 to 500)
Asthma medication at study entry		
Inhaled long-acting β_2-agonists	45 (13)	35 (10)
Combination of inhaled long-acting β_2-agonists and ICS	36 (10)	26 (8)
Mean FEV_1, % predicted	75 (51 to 123)†	75 (52 to 109)†
Mean reversibility, %	17 (− 22 to 101)	17 (− 3 to 55)
Smoking history		
Nonsmoker‡	330 (93)	314 (92)
Occasional	12 (3)	14 (4)
Habitual	13 (4)	14 (4)

*Data are presented as No. (%) or mean or median (range) unless otherwise indicated.
†FEV_1 % predicted deviated from inclusion criteria in both groups (18 patients in the budesonide/formoterol group and 11 patients in the budesonide group). No deviation was considered significant to justify exclusion of data from the analysis.
‡Includes previous smokers.

exacerbations, it was found that 57 of 66 exacerbations (86%) defined retrospectively by the fall in morning PEF criterion in patient diaries had not been recorded by the investigator during the study. It was assumed that this was because patients did not believe that their condition was severe enough to seek medical treatment on many of these occasions. In view of this, data for severe exacerbations are presented first including and then excluding those based on the fall in morning PEF criterion.

The total number of severe exacerbations (including those based on the fall in morning PEF criterion) was approximately 50% lower among patients receiving budesonide/formoterol for maintenance and re-

Table 2—*Mean Patient Diary Card Efficacy Variables Before and During 6 Months of Inhaled Treatment With Either Budesonide/Formoterol for Both Maintenance and Symptom Relief or Budesonide for Maintenance with Terbutaline as Reliever Medication*

Efficacy Variables	Budesonide/Formoterol, 80 μg/4.5 μg, Two Inhalations qd: Baseline*, Mean (Range)	Budesonide/Formoterol, 80 μg/4.5 μg, Two Inhalations qd: Treatment†, Mean (Range)	Budesonide, 160 μg, Two Inhalations qd: Baseline*, Mean (Range)	Budesonide, 160 μg, Two Inhalations qd: Treatment†, Mean (Range)	Adjusted Between-Group Difference (95% Confidence Interval)	p Value
Morning PEF, L/min	345 (137 to 707)	379 (163 to 828)	335 (127 to 734)	345 (140 to 704)	25.0 (19.4 to 30.6)	< 0.001
Evening PEF, L/min	353 (155 to 744)	378 (167 to 817)	342 (113 to 696)	349 (139 to 701)	18.8 (13.3 to 24.3)	< 0.001
As needed inhalations per day	1.64 (0.0 to 6.9)	1.04 (0.0 to 9.2)	1.77 (0.2 to 8.2)	1.48 (0.0 to 8.6)	− 0.34 (− 0.51 to − 0.17)	< 0.001
As needed medication-free days,‡ %	24.3 (0 to 100)	55.3 (0 to 100)	21.9 (0 to 90)	45.4 (0 to 100)	8.1 (3.5 to 12.7)	< 0.001
Total asthma symptom score (0 to 6)§	1.25 (0.0 to 4.1)	0.73 (0.0 to 4.7)	1.33 (0.0 to 4.7)	0.94 (0.0 to 4.0)	− 0.17 (− 0.26 to − 0.07)	< 0.001
Nighttime awakenings,‖ %	13.3 (0 to 100)	6.5 (0 to 100)	18.6 (0 to 100)	10.7 (0 to 100)	− 2.2 (− 4.5 to 0.1)	0.065
Symptom-free days,¶ %	29.6 (0 to 100)	55.1 (0 to 100)	25.9 (0 to 100)	46.4 (0 to 100)	6.5 (2.0 to 11.0)	0.0043
Asthma-control days,# %	18.1 (0 to 100)	47.4 (0 to 100)	16.9 (0 to 90)	38.8 (0 to 100)	7.6 (3.0 to 12.3)	0.0012

*Mean values over the last 10 days of the run-in period.
†Mean values over the 6-month treatment period, excluding day of randomization.
‡A night and day with no use of as-needed medication.
§Sum of the mean daytime and nighttime scores.
‖Nighttime awakenings due to asthma.
¶A night and day with no symptoms (symptom score = 0) and no asthma-related nighttime awakenings.
#A night and day with no symptoms (symptom score = 0), no use of reliever medication, and no asthma-related nighttime awakenings.

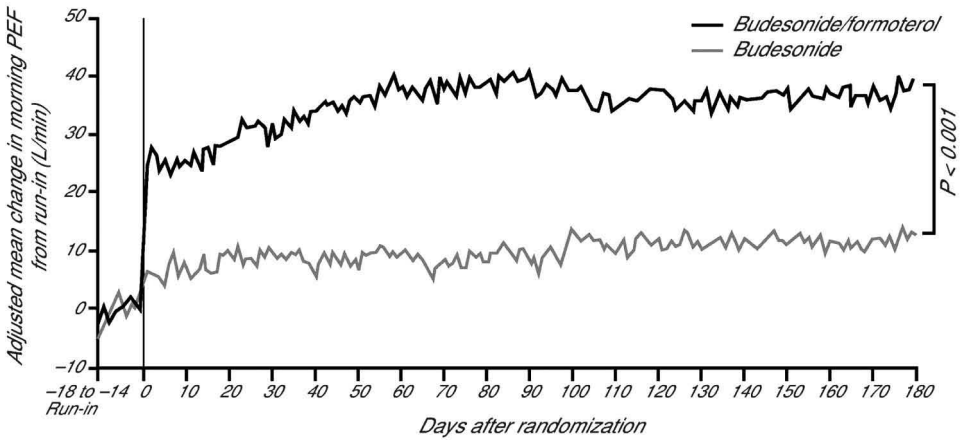

FIGURE 2. Change in morning PEF during 6 months of treatment (0 to 180 days) with either budesonide/formoterol (80 μg/4.5 μg, two inhalations qd) with additional inhalations as needed, or budesonide (160 μg, two inhalations qd) with terbutaline (0.4 mg as needed).

lief compared with those receiving double the maintenance dose of budesonide (43 exacerbations vs 94 exacerbations, respectively), and only half as many patients in this group had a severe exacerbation compared with the budesonide group (8% vs 16%, respectively). The risk of having a severe exacerbation was estimated to be 54% lower for patients receiving budesonide/formoterol than for those treated with budesonide ($p < 0.01$).

Overall, 14 severe exacerbations and 57 severe exacerbations requiring medical intervention (hospitalization/ED treatment or oral steroids) occurred in

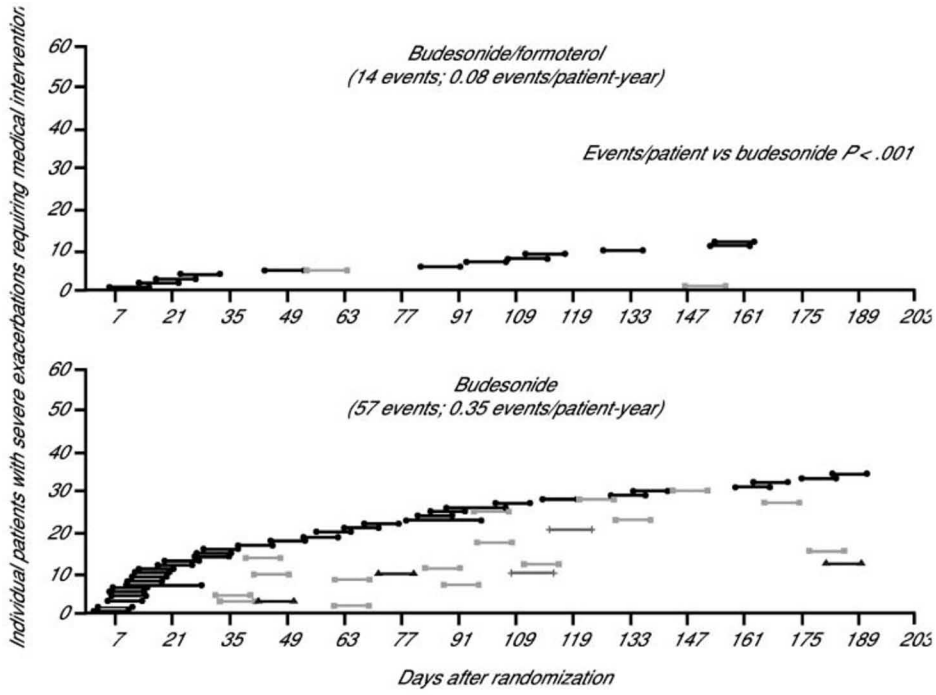

FIGURE 3. Number and time course of severe exacerbations requiring medical intervention in individual patients, and incidence of repeated exacerbations during 6 months of treatment with either budesonide/formoterol (80 μg/4.5 μg, two inhalations qd) with additional inhalations as needed, or budesonide (160 μg, two inhalations qd) plus terbutaline (0.4 mg as needed). The x-axis represents time, each integer on the y-axis represents one patient, and each exacerbation is indicated by a solid line. Bars with circles indicate first exacerbation; bars with squares indicate second exacerbation; bars with triangles indicate third exacerbation; and bars and crosses indicate fourth exacerbation.

the budesonide/formoterol and budesonide groups, respectively. The total number of severe exacerbations requiring medical intervention per patient was reduced by 76% in the budesonide/formoterol group compared with the budesonide group ($p < 0.001$). The risk of a patient having at least one such severe exacerbation was 70% lower for patients receiving budesonide/formoterol than for double-dose budesonide patients ($p < 0.001$). Rates of severe exacerbations requiring medical intervention per patient-year were 0.08 in the budesonide/formoterol group vs 0.35 in the budesonide group.

Importantly, treatment with budesonide/formoterol for both maintenance and relief reduced the rate of hospitalizations/ED treatments during the study compared with budesonide (1 event vs 10 events, respectively; $p = 0.026$). Figure 3 shows the number and time course of severe exacerbations requiring medical intervention, and the incidence of repeated exacerbations in individual patients. Extrapolated over a 1-year period, it is estimated that for every 100 patients treated with budesonide/formoterol for both maintenance and relief, there would be 27 fewer severe exacerbations requiring medical intervention compared with budesonide (the number needed to treat to prevent one patient having a severe exacerbation requiring medical intervention per year with budesonide/formoterol vs budesonide was 3.7).

Duration and Severity of Exacerbations

Figure 4 shows the total asthma symptom scores and as-needed medication use during the period around severe exacerbations (including those based on the fall in morning PEF criterion). During the period from 7 days before until 7 days after the start of an exacerbation, patients receiving budesonide/formoterol had a lower mean total asthma symptom score than those in the budesonide group (1.1 vs 1.8, respectively), and the budesonide/formoterol patients also used less as-needed medication (mean 2.0 inhalations/d vs 3.4 inhalations/d, respectively). Thus, there was no evidence that the reduced number of exacerbations that occurred in the budesonide/formoterol group were more severe than the larger number experienced by patients receiving budesonide alone. Patients in both treatment groups appeared to have a similar rate of recovery from exacerbations, achieving pre-exacerbation levels in symptoms scores and reliever medication use within 14 days of the start of an exacerbation (Fig 4).

Overall Steroid Load

Patients in the budesonide/formoterol group had 77% fewer treatment days with oral steroids than

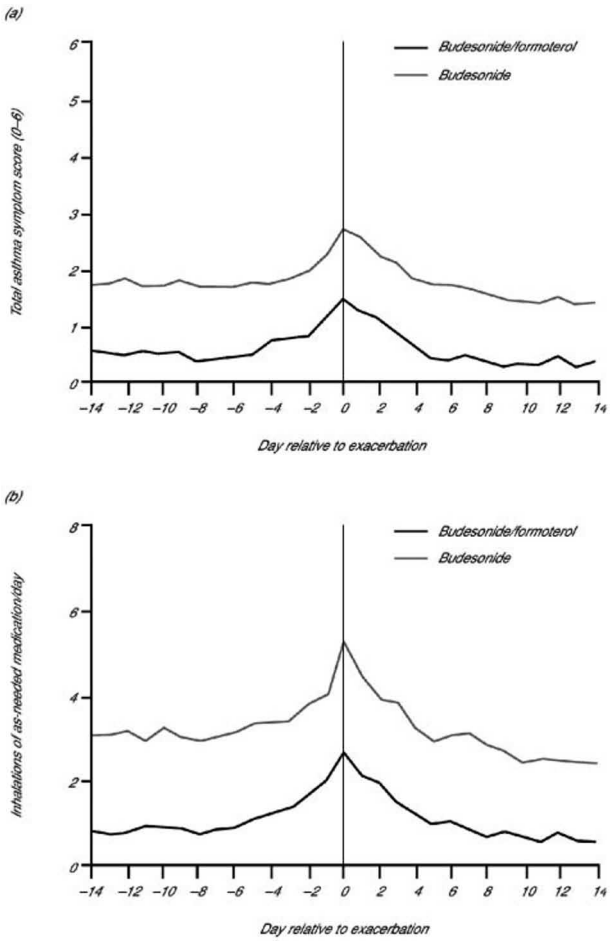

FIGURE 4. Total asthma symptom scores (*top*, *a*) and total as-needed medication use (*bottom*, *b*) during the period from 14 days before to 14 days after the start of a severe exacerbation (day 0) in patients receiving either budesonide/formoterol (80 μg/4.5 μg, two inhalations qd) with additional inhalations as needed, or budesonide (160 μg, two inhalations qd) with terbutaline (0.4 mg as needed).

patients in the budesonide group (114 days vs 498 days, respectively). Furthermore, despite taking additional doses of ICS with each inhalation of reliever medication, patients receiving budesonide/formoterol for both maintenance and relief had a lower mean daily dose of ICS compared with those receiving a fixed dose of budesonide and terbutaline as needed (240 μg vs 320 μg, respectively). In the budesonide/formoterol group, the majority of patients (85%) had a mean daily ICS dose of 160 to 320 μg, whereas all patients in the budesonide group received a fixed ICS dose of 320 μg/d (Fig 5). Only five patients (1.4%) receiving budesonide/formoterol for both maintenance and relief had a mean budesonide dose > 640 μg.

Diary Card Variables

As-Needed Medication Use: Patients receiving budesonide/formoterol for both maintenance and

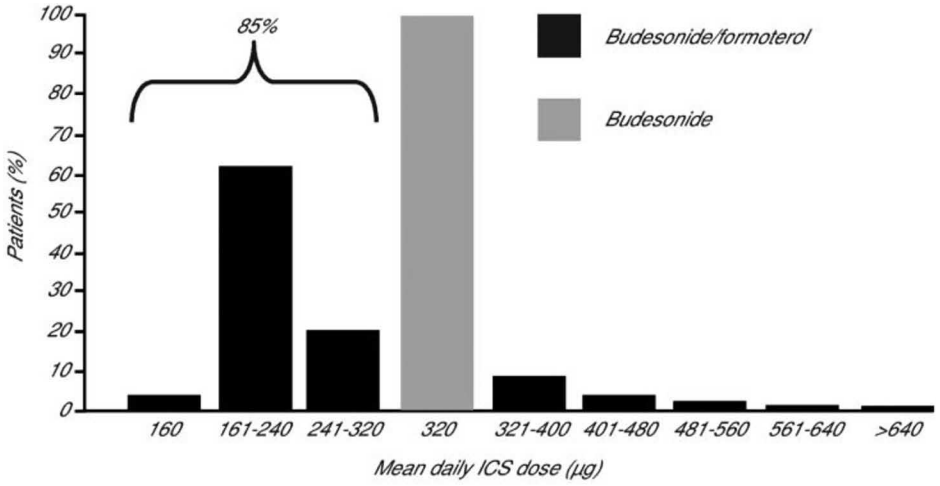

FIGURE 5. Percentage of patients with different daily doses of ICS during 6 months of treatment with either budesonide/formoterol (80 μg/4.5 μg, two inhalations qd) with additional inhalations as needed, or budesonide (160 μg, two inhalations qd) with terbutaline (0.4 mg as needed). Overall, 85% of budesonide/formoterol patients used ≤ 320 μg budesonide, while budesonide patients received a fixed daily dose of 320 μg.

relief used significantly less as-needed medication ($p < 0.001$; Table 2) and experienced 8% more as-needed medication-free days compared with those receiving traditional asthma therapy ($p < 0.001$; Table 2). There was no evidence of overuse of reliever medication in the budesonide/formoterol group. A total of 22 patients receiving budesonide/formoterol used more than eight inhalations on at least 1 day during the treatment period, compared with 53 patients receiving budesonide. Interestingly, however, in the subgroup of patients who used more than eight inhalations of as-needed medication on at least 1 day, those receiving budesonide/formoterol experienced only 4 severe exacerbations requiring medical intervention, while those receiving budesonide experienced 37 events. Patients in both groups took > 10 inhalations of as-needed medication—above the recommended limit—on 0.2% of days during the study. Overall, 11 patients (3%) in the budesonide/formoterol group used > 10 as-needed inhalations during any 1 day, compared with 24 patients (7%) in the double-dose budesonide group.

Symptom-Free Days and Asthma-Control Days: Patients receiving budesonide/formoterol for both maintenance and relief had significantly lower asthma symptom scores ($p < 0.001$) as well as significantly more symptom-free days ($p < 0.01$) and asthma-control days ($p < 0.01$) compared with those receiving traditional asthma therapy (Table 2). The mean difference in asthma-control days corresponded to an extra month (28 days) per year with total freedom from asthma symptoms and reliever use for patients using budesonide/formoterol for both maintenance and relief.

Safety

The incidence, frequency, and profile of adverse events were similar between treatment groups. Both treatments were well tolerated, and adverse events were mostly mild to moderate in intensity. Adverse events were reported by 135 of 354 patients (38%) in the budesonide/formoterol group, compared with 139 of 342 patients (41%) in the budesonide-only group. Respiratory infection was the most common adverse event reported in both treatment groups (reported by 53 patients and 54 patients in the budesonide/formoterol and budesonide groups, respectively). Five patients in the budesonide group experienced aggravated asthma, compared with one patient in the budesonide/formoterol group. There was no difference between the two groups in the incidence of pharmacologically predictable adverse events related to treatment with ICS or β_2-agonists (Table 3). Fourteen serious adverse events were recorded: 8 events in the budesonide-treated group and 6 events in the budesonide/formoterol group. No clinically important differences in ECG, laboratory assessments of hematology, clinical chemistry, or urinalysis were observed between treatment groups or over time.

DISCUSSION

This study is the first of its kind in the management of mild-to-moderate asthma demonstrating that asthma control can be improved using budesonide and formoterol in a single inhaler for both maintenance and as-needed relief, without the need

Table 3—*Incidence of Patients Reporting Class-Related Adverse Events During 6 Months of Inhaled Treatment With Either Budesonide/Formoterol for Both Maintenance and Symptom Relief or Budesonide for Maintenance With Terbutaline as Reliever Medication*

Adverse Events	Budesonide/Formoterol, 80 μg/4.5 μg, Two Inhalations qd (n = 354), No. (%)	Budesonide, 160 μg, Two Inhalations qd (n = 342), No.(%)
Palpitation*	0 (0)	3 (1)
Tremor*	0 (0)	3 (1)
Tachycardia*	3 (1)	0 (0)
Dysphonia†	3 (1)	1 (< 0.5)
Candidiasis†	0 (0)	2 (1)

*Adverse event frequently related to treatment with β_2-agonists.
†Adverse event frequently related to treatment with ICS.

for a separate inhaler containing reliever medication. Budesonide/formoterol for both maintenance and relief was more effective than traditional asthma therapy using a higher dose of budesonide alone, as demonstrated by improved lung function, reduction in severe exacerbations, and improvements in daily asthma-control measures.

Budesonide/formoterol for maintenance and relief of symptoms resulted in a marked improvement in morning PEF—the primary efficacy variable—compared with a higher dose of budesonide, which was sustained throughout the treatment period. This is in agreement with results from previous studies[10–13] that have shown that a fixed combination of budesonide and formoterol improves lung function compared with ICS alone. The prevention of severe exacerbations is an additional parameter of asthma control that has been used in studies[4,5,14] to assess the value of an ICS/long-acting β_2-agonist combination compared with a higher dose of ICS. In one study in patients with mild persistent asthma receiving ≤ 400 μg/d of budesonide, doubling the dose of budesonide or the addition of maintenance formoterol was shown to reduce the risk of a severe exacerbation by 19% and 43%, respectively.[5] Furthermore, a metaanalysis[14] of 10 studies has demonstrated that salmeterol plus either fluticasone or beclomethasone reduces the incidence of severe exacerbations by approximately 2 to 3% compared with a double dose of ICS. In the present study, the rate of patients experiencing a severe exacerbation requiring medical intervention was 76% lower among patients receiving budesonide/formoterol for both maintenance and relief than in the higher-dose budesonide group (0.08 events/patient-year vs 0.35 events/patient-year, respectively). Importantly, patients in the budesonide/formoterol group also had a significant reduction of 90% in hospitalizations/ED treatments (1 event vs 10 events in the higher-dose budesonide group). Overall, the number needed to treat to prevent one patient having a severe exacerbation requiring medical intervention per year with budesonide/formoterol vs a double dose of budesonide was 3.7.

Patients receiving budesonide/formoterol for both maintenance and relief used less as-needed medication than those receiving traditional therapy with budesonide plus separate as-needed reliever medication. Overall, 22 patients in the budesonide/formoterol group used more than eight inhalations of reliever medication on any 1 day during the treatment period, compared with 53 patients in the budesonide group. In this subgroup of patients using more than eight as-needed inhalations on 1 day, a total of 41 severe exacerbations requiring medical intervention were recorded, only 4 of which (1 in 10 exacerbations) occurred in the budesonide/formoterol group. These data strongly suggest that additional as-needed inhalations of budesonide/formoterol may prevent worsening asthma control from developing into an exacerbation compared with the use of traditional reliever medication, such as terbutaline or salbutamol as needed. Furthermore, as patients with high as-needed medication use are generally considered to be at increased risk for severe exacerbations, this finding shows that tolerance to the long-acting β_2-agonist formoterol did not occur in our study.

Current asthma management guidelines advise that ICS should be used at the minimum effective dose during periods of stable asthma, but during periods of poor control the dose should be stepped up until control is regained.[1] Evidence suggests that an increase in the dose and dosing frequency of anti-inflammatory medication when asthma worsens may be the key to prevent the progression of asthma exacerbations.[15] However, a recent 12-month study[16] in 390 patients with asthma found that doubling the dose of ICS once peak flow or symptoms deteriorated had little effect on control and did not reduce the need for oral steroid treatment. Similarly, FitzGerald and colleagues[17] showed that patients receiving a constant daily maintenance dose of ICS had a similar incidence of severe exacerbations to those who doubled the dose of ICS during an exacerbation. The present study demonstrated that low-dose ICS combined with a long-acting β_2-agonist in a single inhaler, used for both maintenance and relief of symptoms, reduced the incidence of severe exacerbations compared with a higher maintenance dose of budesonide plus short-acting β_2-agonists for relief. Using budesonide/formoterol in this way may help to overcome the problem of undertreatment with ICS during periods of poor

asthma control because the delivery of reliever medication is accompanied by a timely increase in anti-inflammatory medication.

There is growing evidence that increasing the frequency of ICS delivery may be as important as the dose of ICS. Toogood and colleagues[18] found that increasing the dosing frequency while maintaining the same total daily dose of budesonide markedly increased its antiasthmatic properties during periods of poor asthma control. Foresi and colleagues[15] showed that for patients receiving inhaled budesonide, 100 μg bid, early intervention with a temporary 7-day increase in dose and dosing frequency (200 μg qid) when asthma control worsened was as effective at reducing the number of exacerbations requiring oral corticosteroids as a fixed maintenance dose of budesonide (400 μg bid). The importance of rapid intervention with high doses of steroid treatment to reduce inflammatory responses has been demonstrated in both *in vitro* and *in vivo* animal studies.[19–21] In contrast, steroids have been shown to be less efficacious in established inflammation, possibly because of reduced glucocorticoid receptor binding affinity.[22]

Increasing the dose of formoterol during periods of asthma worsening has also been shown to be beneficial in asthma therapy. Patients using formoterol as needed in addition to routine maintenance therapy with ICS have fewer exacerbations compared with those using terbutaline[23] or salbutamol[24] as needed. In particular, the rate of exacerbations defined by PEF criteria may be reduced because long-acting β_2-agonists provide a longer duration of bronchodilation and bronchoprotection compared with short-acting β_2-agonists.[23] Furthermore, formoterol has an onset of action as rapid as that of salbutamol[6] and provides rapid and effective relief from acute bronchoconstriction.[25] This means that formoterol can be used as needed, removing the need for a separate reliever inhaler. Indeed, a recent study[26] has shown that budesonide/formoterol provides relief from methacholine-induced bronchoconstriction that patients can feel within 1 min of inhalation. Increasing the doses of both budesonide and formoterol has been shown to be more effective than increasing the dose of either component alone in providing protection from inflammatory challenges.[27]

The favorable safety profiles of budesonide and formoterol are an important consideration in using budesonide/formoterol for both maintenance and relief. The safety profile of budesonide/formoterol in a single inhaler is well established.[28] Several studies[29–31] have shown that, despite having a prolonged bronchodilator effect in the airways, formoterol has a short duration of systemic effects. Patients in this study were allowed to take a maximum of 10 as-needed inhalations per day, a total daily budesonide/formoterol dose of 960 μg/54 μg for patients receiving budesonide/formoterol for both maintenance and relief. This dose was well within the tolerability range for budesonide/formoterol, as evidence suggests that budesonide/formoterol is well tolerated at occasional high doses of 1,920 μg/54 μg[7] and at regular high doses of 1,280 μg/36 μg.[32] Despite taking additional doses of ICS with each inhalation of as-needed medication, the mean daily steroid dose taken by patients in the budesonide/formoterol group was lower than that taken by patients in the traditional therapy group (240 μg vs 320 μg, respectively). Furthermore, patients receiving budesonide/formoterol for both maintenance and reliever medication had a similar incidence of serious adverse events to those receiving budesonide alone.

The findings from this study are very encouraging in terms of simplifying therapy and achieving effective asthma control; however, it is important to consider the limitations of the study. Although effective asthma control was maintained throughout the 6-month study period, further studies are required in order to assess the long-term efficacy and safety of budesonide/formoterol for both maintenance and relief compared with the same or a higher fixed maintenance dose of budesonide/formoterol. Findings from a study[33] of this nature have recently been reported in patients with moderate-to-severe persistent asthma. It may also be desirable to obtain biopsy specimens or examine sputum in further studies to examine the long-term effects of budesonide/formoterol for both maintenance and relief on key biomarkers of airway inflammation and remodeling. This would help confirm findings by Kips and coworkers[34] that the improved asthma control achieved with long-acting β_2-agonists combined with ICS, when compared with a higher dose of budesonide alone, is not associated with masking of the underlying airway inflammation.

In conclusion, we have shown that an innovative treatment strategy—a low maintenance dose of budesonide/formoterol with additional doses as needed for relief of symptoms—provides improved asthma control compared with conventional treatment, and has the potential to simplify asthma therapy. This strategy reduced the incidence of severe exacerbations while also reducing hospitalizations and the need for rescue treatment with oral steroids. The improved efficacy provided by budesonide/formoterol for maintenance and relief was achieved with a lower overall drug load, resulting in a more favorable risk/benefit profile compared with traditional fixed-dosing regimens. These findings call into question the current treatment algorithm that relies on short-acting medication for relief of symp-

toms. Given the treatment benefits achieved with budesonide/formoterol in a single inhaler for both maintenance and relief, this novel asthma management strategy could potentially help reformulate future treatment guidelines.

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