



Adjustable maintenance dosing with budesonide/formoterol or budesonide: Double-blind study [☆]

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Summary Adjustable maintenance dosing with either budesonide/formoterol or budesonide was compared in asthma patients.

This double-blind trial randomized 133 patients (mean forced expiratory volume in 1 s 66% predicted) to receive 2 inhalations twice daily of budesonide/formoterol 160/4.5 µg (640/18 µg/day) or budesonide 320 µg (1280 µg/day) for 4 weeks. The study drug was adjusted in both groups according to symptoms to 2–4 inhalations daily during Weeks 5–8 and 1–4 inhalations daily during Weeks 9–20.

Asthma was well controlled in both groups, with minimal levels of treatment failure (5 budesonide/formoterol vs. 2 budesonide patients; $P = \text{NS}$) and minimal use of reliever therapy. Clinically important improvements in health-related quality of life (HRQL) occurred in the physical functioning and emotional role functioning domains (both $P < 0.05$) for the budesonide/formoterol group compared with budesonide. Physician and patient treatment satisfaction favored budesonide/formoterol (both $P < 0.05$). Budesonide/formoterol patients used fewer daily inhalations of study drug ($P = 0.024$). The median average daily inhaled corticosteroid dose during the study was 448 µg with budesonide/formoterol and 1152 µg with budesonide.

Adjustable maintenance dosing with budesonide/formoterol and budesonide resulted in high levels of asthma control. Adjustable budesonide/formoterol treatment achieved greater HRQL benefits and patient satisfaction, with lower overall drug use.

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Introduction

The goal of asthma therapy is to achieve early and optimal control of symptoms and then to maintain control using the lowest adequate dose of medication.¹ Current international and national asthma guidelines advocate a stepwise approach to asthma therapy^{1–4} and recommend that patients with persistent asthma receive inhaled corticosteroids (ICS).

Studies of patients who are not well controlled on low to moderate doses of ICS have shown that addition of a long-acting β_2 -agonist (LABA) to ICS therapy provides greater clinical benefit, in terms of improvements in symptoms and lung function, than increasing the dose of ICS.^{5–12} It has also been shown that adding a LABA is at least as effective as doubling the dose of ICS in preventing severe exacerbations.^{8,10,11,13} Indeed, addition of a LABA to ICS therapy is a recommended strategy for maintaining control of asthma using a lower overall steroid load. This concept has become well established, with patients who use LABA therapy together with an action plan being able to lower their overall ICS dose to a greater extent than patients using ICS therapy alone.^{1,14} The addition of a LABA to ICS therapy allows asthma control to be maintained at a lower overall ICS dose, but optimal regimens for stepping down have yet to be determined and stepping down ICS treatment too far with LABA therapy can induce greater airway inflammation during a period of exacerbation.¹⁵

Tailoring ICS treatment to achieve optimal asthma control can be achieved by starting with high doses and then stepping down the dose according to symptom-based criteria.^{16,17} Alternatively, patients can be started on low doses of ICS or ICS/LABA with the ICS dose being stepped up periodically until asthma is well controlled or a maximum dose is reached.¹⁸ Although this latter approach may achieve effective control in many patients, adjustments in the ICS dose can be made too late to optimize exacerbation control. In addition, if the ICS dose is not subsequently reduced from the higher doses when patients' asthma is stabilized, it is possible that patients may be overtreated for long periods.

As asthma is characterized by periods of worsening symptoms and exacerbations, treatment regimens need to be sufficiently versatile to enable stepping up at the earliest signs of asthma worsening and stepping down to the lowest effective dose once control has been achieved.^{1,2} Patients adopting adjustable dosing regimens are able to change their ICS and LABA doses in line with their

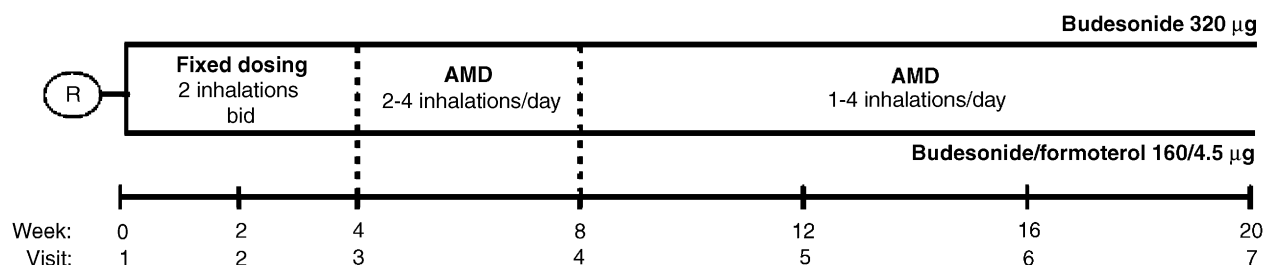
symptoms to maintain optimal control. Asthma treatment guidelines recognize the advantages of versatile treatment regimens and stress the need for self-management action plans, whereby patients are given written guidance on how to adjust their reliever medication according to their level of asthma control.^{1,2} When used appropriately, self-management strategies combined with a written action plan and effective treatment can improve asthma outcomes.¹⁹ Open-label studies using the ICS/LABA combination budesonide/formoterol (Symbicort[®], AstraZeneca, Lund, Sweden) have shown that adjustable dosing of both ICS and LABA components improves asthma control compared with a higher fixed dose of ICS/LABA.^{20–23} Adjustable dosing with budesonide vs. a higher fixed dose has also been examined and was shown to be similarly effective in a double-blind setting.²⁴ Although all of these studies demonstrate the benefits of adjustable dosing, a comparison of adjustable dosing with budesonide/formoterol vs. adjustable dosing with budesonide alone in a double-blind setting has yet to be performed.

This double-blind study examined the effects of adjustable maintenance dosing with budesonide/formoterol (160/4.5 μg) or higher-dose budesonide (320 μg); the ICS dose per inhalation was 2-fold higher in patients treated with budesonide than in those treated with budesonide/formoterol. The ICS doses were initiated at, and could be adjusted back up to, a maximum of 640 $\mu\text{g}/\text{day}$ in budesonide/formoterol-treated patients or 1280 $\mu\text{g}/\text{day}$ in those receiving budesonide. Treatment failure, health-related quality of life (HRQL) and daily asthma control were assessed over a period of 5 months to determine the relative clinical benefits of both regimens.

Patients and methods

Patients

Patients were recruited into this study (BA-039-0001) from 16 primary healthcare and hospital sites across Austria. Men and women (aged ≥ 19 years) with asthma (indicated by a record of reversibility of forced expiratory volume in 1 s [FEV₁] to a short-acting bronchodilator of $\geq 15\%$ or 200 ml within 1 month prior to enrollment) and an FEV₁ of 40–85% of predicted normal were included in the study. All patients had a requirement for ICS or ICS/LABA combination therapy within the given starting dose range, as judged by the investigator.



AMD - adjustable maintenance dosing; bid - twice daily; R - randomization
Terbutaline was available as reliever medication throughout the study

Figure 1 Design of a 20-week study comparing adjustable maintenance dosing with either budesonide/formoterol 160/4.5 µg or budesonide 320 µg in patients with asthma.

Patients were excluded from the study if they: had experienced an asthma exacerbation requiring oral steroids in the 4 weeks before study entry or an upper respiratory tract infection in the 6 weeks before study entry; were current smokers; had severe cardiovascular disease or other significant concomitant disease; were receiving another investigational drug; or if they were pregnant or planning a pregnancy. Patients receiving treatment with anti-asthma therapy (other than oral steroids) were allowed to participate providing that this treatment was discontinued at study entry. Other medication that was considered necessary for patients' safety and wellbeing was given during the study at the discretion of the investigator.

Study design

This was a 20-week, randomized, double-blind, parallel-group study. The study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee at each centre. Written informed consent was obtained from each patient. Patients could be withdrawn if they were nonadherent with study medication or if they experienced two asthma exacerbations requiring oral steroids. Eligible patients were initially randomized to treatment with fixed dosing of either budesonide/formoterol (Symbicort[®] Turbuhaler[®]) (160/4.5 µg, 2 inhalations twice daily) or budesonide (Pulmicort[®] Turbuhaler[®]) (320 µg^a, 2 inhalations twice daily) according to a computer-generated randomization schedule. Patients were randomized to the treatment on Day 0 (baseline) and returned for further examinations at Weeks 2, 4, 8, 12, 16, and 20 (end of study).

Patients were transferred to an adjustable dosing regimen from Week 4. At the Week 4 visit—and at

each monthly visit thereafter—study investigators assessed patients' peak expiratory flow (PEF) and their respiratory symptoms during the past month and adjusted patients' doses for the next month accordingly. Dose adjustments were performed according to local asthma guidelines and in line with the recommendations provided by the Austrian Society for Lung Diseases and Tuberculosis.²⁵ At Week 4, patients were transferred to an adjustable dosing regimen of 2–4 inhalations per day; from Week 8, the allowed dose range was 1–4 inhalations per day (Fig. 1). Doses were only stepped down—from 2 inhalations twice daily to 1 inhalation twice daily, or from 1 inhalation twice daily to 1 inhalation daily—at the investigator's discretion. Between the monthly visits, patients were allowed to step up their dosage themselves if, on two consecutive days, a short-acting bronchodilator was required for symptom relief on two occasions during the day or a night-time awakening due to asthma was experienced. Patients stepped up their medication from 1 inhalation daily to 1 inhalation twice daily or from 1 inhalation twice daily to 2 inhalations twice daily.

Terbutaline (Bricanyl[®] Turbuhaler[®]) (0.4 mg^b) was used as needed for symptom relief throughout the study.

Efficacy assessments

The primary efficacy endpoint was the number of patients per treatment group who experienced ≥ 1 treatment failure (defined as a severe exacerbation requiring one or more of: hospitalization; nebulized β_2 -agonists; oral steroids; or withdrawal owing to lack of efficacy or a life-threatening/fatal condition). Secondary efficacy endpoints included: HRQL; treatment satisfaction; dose of study med-

^aAverage delivered dose, corresponding to a metered dose of 400 µg.

^bAverage delivered dose, corresponding to a metered dose of 0.5 mg.

ication; the percentage of days on which patients required their reliever medication to relieve or prevent symptoms: FEV₁ and PEF.

Patients' demographics and medical histories were recorded at the baseline visit. HRQL was assessed using the Medical Outcomes Study Short-Form (36-item) Health Survey (SF-36).^{26,27} Differences between baseline scores and the values at Week 20 were calculated. Patient and physician assessments of satisfaction with treatment was measured at the end of the study using a visual analog scale (scale 0–100 mm, where 0 mm = not satisfying and 100 mm = very satisfying). Patients used daily diaries—which were assessed by the investigator at each visit—to record morning and evening PEF, use of terbutaline for symptom relief or prevention, night-time awakenings due to asthma, respiratory symptoms, and use of other medications to treat deterioration of their asthma. FEV₁ was recorded by the investigator at each visit.

Safety assessments

Safety assessments included evaluation of adverse events, which were recorded throughout the study. Safety data are reported for all patients who received at least one dose of study medication and had at least one post-baseline safety evaluation.

Statistical methods

Assuming that the incidence of treatment failure (primary endpoint) with budesonide is 25%, a sample size of 80 patients per group was required to give 80% power to demonstrate superiority of budesonide/formoterol vs. budesonide, given a true incidence of failure with budesonide/formoterol of 8.5% (5% significance level, two-sided alternative hypothesis). Intent to treat was the primary approach for the analyses. The intent to treat population included all patients who had received at least one dose of study medication and had a baseline assessment together with at least one post-baseline evaluation.

Baseline and demographic characteristics and all efficacy and safety endpoints were analyzed using standard descriptive statistical methods. No replacement of missing data was performed. The proportions of patients with treatment failure were compared using the Cochran–Mantel–Haenszel test, stratified by center. Exploratory comparisons of changes from baseline in SF-36 questionnaire scores, patient/physician satisfaction ratings,

study/reliever medication use, FEV₁, and PEF were compared using the Mann-Whitney *U*-test.

Results

Patients

Patients were enrolled and treated between June 2001 and October 2002. A total of 133 patients were randomized to receive adjustable dosing with budesonide/formoterol ($n = 65$) or budesonide ($n = 68$). Seven patients (2 budesonide/formoterol and 5 budesonide patients) had no efficacy measurement on treatment and were eliminated from the intent to treat population. The intent to treat population thus comprised 126 patients, with 63 patients in each treatment group. Twenty-four patients (9 in the budesonide/formoterol group and 15 in the budesonide group) withdrew after Week 2. Of these, 11 were lost to follow-up, 4 withdrew owing to an adverse event (one of which was a serious adverse event), and 9 patients withdrew for other reasons. The safety population comprised all randomized patients.

Owing to difficulties in recruitment, fewer patients were enrolled than originally planned. The study was therefore not powered to test the hypotheses for the primary efficacy endpoint. An exploratory approach to the statistical analysis was thus considered for all endpoints.

Demographic and baseline characteristics were generally well balanced across the treatment groups, the exception being that patients in the budesonide/formoterol group had a median asthma duration of 10 years compared with 4.5 years for patients receiving budesonide alone (Table 1).

Efficacy

Primary efficacy variable

Treatment failures were documented for 5 of 63 (8%) patients who received budesonide/formoterol (all of whom used nebulized β_2 -agonists) and 2 of 63 (3%) patients in the budesonide group (both of whom were treated with oral steroids). Treatment failure rates were similarly low in both treatment groups. The rate of treatment failure in the budesonide group was less than the value of 25% that had been assumed for calculation of the sample size. Treatment failures were recorded in 3 patients during the fixed dosing period (2 in the budesonide/formoterol group and 1 in the budesonide group) and in 4 patients during the period of

Table 1 Demographic and baseline characteristics of patients receiving adjustable maintenance dosing with either budesonide/formoterol 160/4.5 µg or budesonide 320 µg (intent to treat population).

Characteristic	Budesonide 320 µg (<i>n</i> = 63)	Budesonide/formoterol 160/4.5 µg (<i>n</i> = 63)
Male/female, <i>n</i>	37/26	30/33
Age, yrs (range)	45 (20–82)	45 (20–80)
Asthma duration, yrs (range)	4.5 (0–30)	10 (0–35)
Documented smoking habit, <i>n</i> (%)	21 (33)	24 (38)
Previous ICS treatment, <i>n</i> (%)	40 (63)	40 (63)
FEV ₁ , % predicted (range)	65 (39–85)	67 (35–88)

FEV₁: forced expiratory volume in 1 s; ICS: inhaled corticosteroid.

All values are presented as absolute numbers and percentages (*n* (%)) or as mean (range), except asthma duration, which is shown as median (range).

Table 2 Baseline (Week 0) and treatment (Week 20) values by domain for the Short-Form Health Survey (SF-36) questionnaire, and patient and physician satisfaction ratings of treatment for patients receiving adjustable maintenance dosing with either budesonide/formoterol 160/4.5 µg or budesonide 320 µg.

	Budesonide 320 µg		Budesonide/formoterol 160/4.5 µg	
	Week 0	Week 20	Week 0	Week 20
<i>SF-36 domain</i>				
Physical functioning	80.7	87.2	77.6	85.9
Physical role functioning	75.0	81.3	73.8	88.5
Bodily pain	82.0	88.4	78.8	89.6
General health	64.8	69.3	61.7	68.7
Vitality	56.9	66.4	55.4	63.4
Social functioning	86.2	92.7	87.6	93.7
Emotional role functioning	85.2	83.4	86.0	90.5
Mental health	70.0	78.0	71.3	73.5
<i>Satisfaction with treatment (VAS score)</i>				
Patient assessment		75.6		85.4*
Physician assessment		71.1		83.6 [†]

**P* = 0.013 for budesonide/formoterol vs. budesonide.

[†]*P* = 0.001 for budesonide/formoterol vs. budesonide. VAS: visual analog scale (0–100 [0 = not satisfying; 100 = very satisfying]). All values are shown as means.

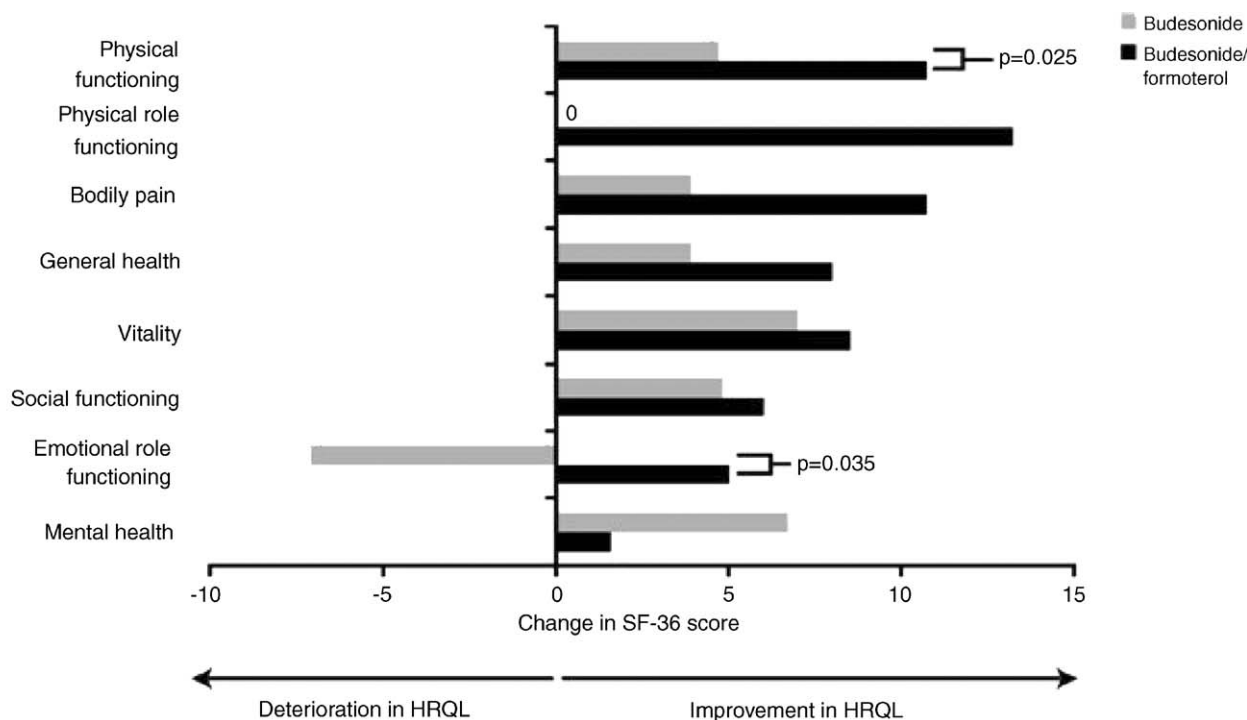
adjustable maintenance dosing (3 in the budesonide/formoterol group and 1 in the budesonide group). Only 3 exacerbations (2 in the budesonide/formoterol group and 1 in the budesonide group) were documented over the last 12 weeks of the study.

HRQL and treatment satisfaction

Greater HRQL benefits were evident with budesonide/formoterol compared with budesonide alone, as shown by improvements in SF-36 questionnaire domain scores between Weeks 0 and 20 (Table 2). Significant and clinically relevant differences between the two treatment groups were apparent in physical functioning (6.0 units; *P* = 0.025) and

emotional role functioning (12.1 units; *P* = 0.035) (Fig. 2). Patients treated with budesonide/formoterol showed a trend towards greater improvements for the domains of physical role functioning, bodily pain, general health, vitality, and social functioning. Although patients in the budesonide group showed a greater improvement in mental health domain scores than those receiving budesonide/formoterol, this difference was not statistically significant.

Treatment satisfaction with budesonide/formoterol was ranked as significantly superior to budesonide treatment by both patients (*P* = 0.013) and physicians (*P* = 0.001) at the end of the study (Table 2).



HRQL: health-related quality of life.

Figure 2 Change in Short-Form Health Survey (SF-36) scores (difference between scores at the Week 20 [end of study] visit and baseline) in patients receiving adjustable maintenance dosing with either budesonide/formoterol 160/4.5 μg or budesonide 320 μg .

Lung function

Mean improvements in FEV_1 between baseline and Week 20 were comparable between the treatment groups (0.36 and 0.37 l for patients treated with budesonide/formoterol and budesonide, respectively), as were average morning and evening PEF values recorded during the study. The mean morning PEF for patients in the budesonide/formoterol and budesonide treatment groups was 407 and 398 l/min, respectively; the corresponding values for mean evening PEF were 411 and 404 l/min, respectively.

Use of study drug

Patients in the budesonide/formoterol group used significantly fewer inhalations of study medication compared with those in the budesonide group (Fig. 3a). The mean number of inhalations per day for patients receiving budesonide/formoterol vs. budesonide was 3.1 vs. 3.4, respectively ($P = 0.024$), corresponding to mean daily ICS doses of 494 and 1072 μg , respectively. Expressed in terms of median inhalations per day, patients who received budesonide/formoterol used 2.8 inhalations daily (ICS dose of 448 μg) compared with 3.6 inhalations daily

(ICS dose of 1152 μg) for those in the budesonide group (Fig. 3b), giving a difference of approximately 700 μg (61%) in the ICS dose.

For patients with diary assessments on at least 5 clinic visits, a total of 36/47 (77%) patients receiving budesonide/formoterol and 25/42 (60%) patients receiving budesonide stepped down their medication during the study. Of the patients who stepped down, 21/36 (58%) patients in the budesonide/formoterol group and 15/25 (60%) patients in the budesonide group did not step up their medication again.

Most patients in both groups reported minimal requirement for reliever therapy. Seventy-five per cent of patients in the budesonide/formoterol group used reliever for symptom relief on less than 1 day per week. Fifty per cent of patients in the budesonide/formoterol group were reliever-free on 99% of the days in the study compared with 96% of study days being reliever-free for 50% of the patients receiving budesonide (Fig. 3c). There was no difference between the two treatment groups in the percentage of days on which patients used reliever medication for symptom relief, although patients in the budesonide/formoterol group used

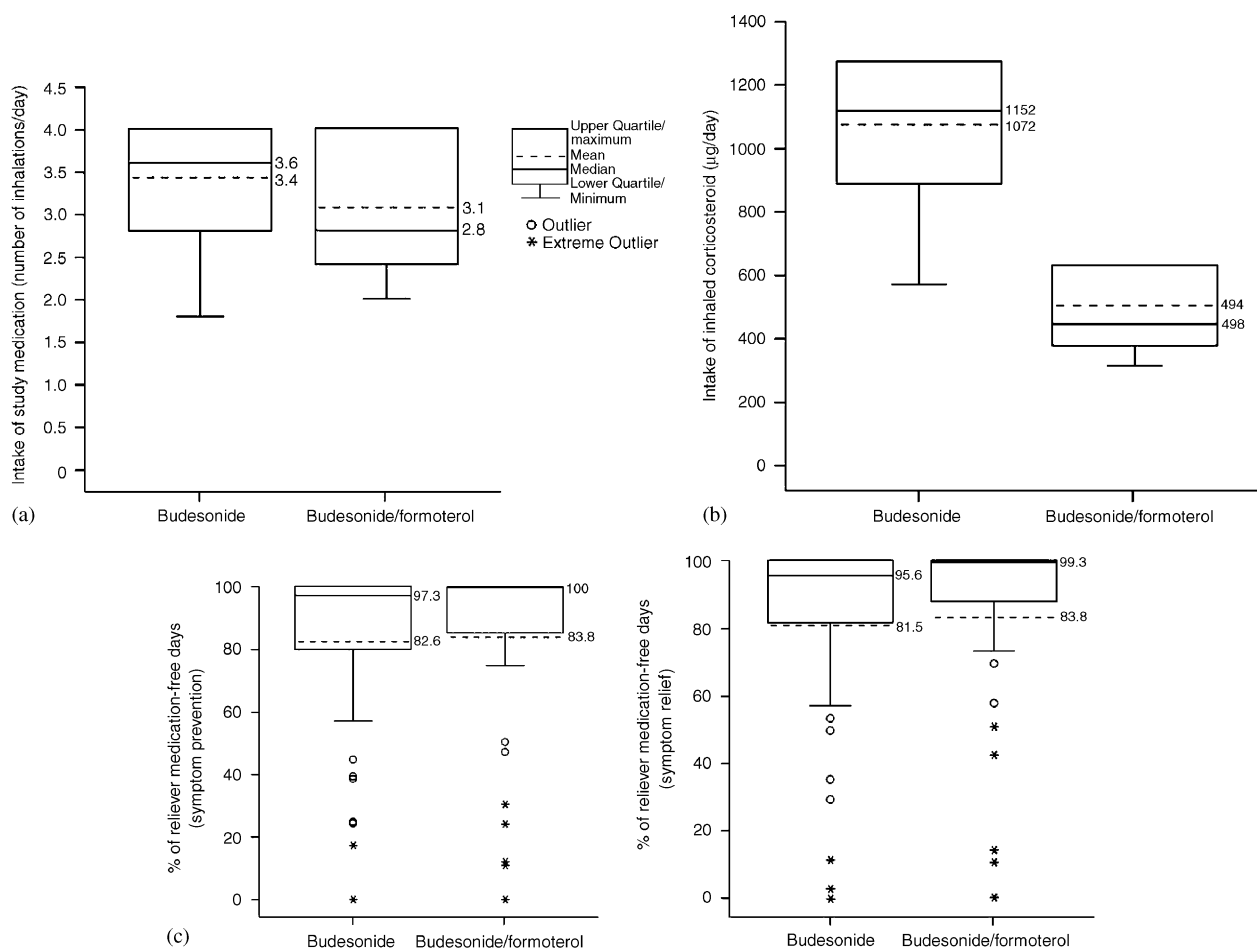


Figure 3 Box and whisker plots for drug use during the treatment period: (a) intake of study medication (number of inhalations/day); (b) intake of inhaled corticosteroid ($\mu\text{g}/\text{day}$); (c) reliever-free days (percentage of days that no reliever medication was used for symptom relief or symptom prevention) in patients receiving adjustable maintenance dosing with either budesonide/formoterol 160/4.5 μg or budesonide 320 μg . Median and mean values are shown. Outliers lie at least 1.5 box lengths from the end of the box and extreme outliers lie at least 3 box lengths from the end of the box.²⁸

reliever medication for the prevention of symptoms on a significantly lower percentage of days (mean 16.2%) than those in the budesonide group (mean 17.4%; $P = 0.040$).

Safety

A total of 155 adverse events were documented (74 in the budesonide/formoterol group and 81 in the budesonide group). The most frequently reported adverse events were related to the immune and respiratory systems. Twenty adverse events were regarded as being treatment-related: 3 cases each of myalgia and nervousness, and 1 instance each of heart disorder, dyspnea, rhinitis, pruritis, and taste alteration in budesonide/formoterol patients; in the budesonide group, there were 3 reports of candidiasis and 2 reports of dysphonia, with

cheilitis, stomatitis, asthma, and laryngitis each being recorded once. There were no reports of candidiasis or dysphonia in patients treated with budesonide/formoterol.

There were no treatment-related serious adverse events. Three patients reported serious adverse events in connection with hospitalization: an accident and a planned cardiac examination in the budesonide/formoterol group and an evaluation of hypertension in the budesonide group.

Discussion

In this study—the first double-blind trial to compare adjustable maintenance dosing with an ICS/LABA with adjustable maintenance dosing using an ICS alone—we have shown that adjustable main-

tenance dosing with both budesonide/formoterol and higher-dose budesonide maintains effective asthma control. There were few treatment failures in either group and the majority of patients required reliever medication on very few days of the study. Current asthma guidelines advocate gaining control of asthma, and subsequently maintaining this, using a stepwise approach to therapy.¹⁻⁴ Treatment should be tailored to the severity of the condition and to the individual patient by using the lowest adequate dose of medication.¹ Adjustable maintenance dosing enables patients with asthma to be treated according to these guidelines, taking into account the variable nature of the condition and thereby avoiding patients being temporarily undertreated at the onset of an exacerbation or overtreated during periods when asthma is quiescent.

In this study, patients receiving adjustable maintenance dosing with budesonide/formoterol used reliever medication for symptom relief on a median of 0.72% of the study days (i.e. 50% of patients used reliever medication on only 1 day during the 5-month study). This result compares favorably with the data obtained for patients in the budesonide treatment group, where median use of reliever medication for symptom relief was around 6 days. In this study, the low levels of reliever medication use and exacerbations illustrate the high degree of asthma control that was achieved in most patients with the adjustable maintenance dosing regimens. The very low levels of as-needed medication used in most patients throughout the study allowed us to confidently conclude that most patients had well-controlled asthma during this 5-month assessment period. Failure to achieve guideline-defined levels of control—i.e. freedom from exacerbations, no nocturnal awakenings, minimal daily symptoms and reliever medication use—can often be explained by a single outcome measure, and this measure can be the requirement for excess reliever medication.²⁹ Indeed, this study suggests that stepping down treatment using an adjustable maintenance dosing regimen with ICS/LABA or ICS alone can achieve and maintain well-controlled asthma in many patients, including guideline-defined control as reported in a recent study by Bateman and co-workers.¹⁸

Several studies have shown that patients with asthma treated with ICS alone can have their ICS dose reduced without compromising asthma control.^{16,17} Rapid and optimal asthma control is achievable in most patients with poorly controlled asthma treated initially with high doses of budesonide (1600 or 3200 µg per day).¹⁶ In patients stabilized on high-dose ICS therapy, doses can be

reduced according to symptom-based criteria without compromising disease control.^{16,17} Asthma control, as reflected in bronchial hyperreactivity and composite symptom control, can still continue to improve on a weekly basis while ICS therapy is being reduced.^{16,30} Foresi and colleagues²⁴ reported that in patients with moderate asthma who achieved a stable clinical condition with budesonide 1600 µg per day, budesonide 200 µg per day subsequently maintained control as effectively as a 4-fold higher dose (budesonide 800 µg per day) when patients were able to adjust their treatment in response to signs of deteriorating asthma control, such as a fall in PEF. We have shown that, in addition to maintaining asthma control at a lower overall ICS dose, adjustable maintenance dosing with ICS/LABA results in better HRQL benefits and improved patient satisfaction compared with an adjustable dosing regimen with ICS alone.

Downward dose adjustments have been shown to be facilitated with ICS plus LABA treatment compared with treatment involving ICS alone. In a 6-month, placebo-controlled study, Wilding and associates¹⁴ assessed the effect of adding salmeterol to the treatment regimen of patients who adjusted their ICS dose in accordance with guidelines. Addition of salmeterol reduced the ICS dose by 17%, with no change in exacerbations or use of oral steroids. In the present study, the starting dose of ICS was 50% lower in the budesonide/formoterol group than in the budesonide group. Over the whole trial period, the median ICS dose was 61% lower with budesonide/formoterol and effective control of asthma was maintained. Use of an adjustable maintenance regimen may therefore avoid the need for excessive doses of ICS, which may be associated with the risk of systemic adverse events.³¹

It is now firmly established that the combination of an ICS and a LABA delivers better daily symptom control than double the dose of ICS, with comparable exacerbation control.¹³ However, if the difference in ICS dose between the treatment groups in a study is too great, more exacerbations are encountered in patients treated with the lower ICS dose, irrespective of whether LABA is coadministered⁷ or not.²⁴ Similarly, if the steroid dose is reduced too far under the cover of as-needed salmeterol treatment, more inflammation is encountered when patients have exacerbations.¹⁵ This potential problem was not apparent in the current study, as the ICS dose was never allowed to drop too low in the adjustable dosing group nor to remain low if a loss in control was encountered.

Patients in the budesonide/formoterol group had greater HRQL benefits compared with those treated with budesonide alone. Clinically relevant differences between the two groups were apparent for the SF-36 domains of physical functioning and emotional role functioning. A previous study comparing treatment with budesonide and formoterol with therapy with budesonide alone or with nonsteroidal anti-asthma therapy found that both budesonide and budesonide plus formoterol improved HRQL compared with nonsteroidal anti-asthma therapy (assessed using the SF-36 questionnaire and the Asthma Quality of Life Questionnaire).³² However, no differences in HRQL were detected between fixed-dose budesonide and budesonide plus formoterol. This is, therefore, to our knowledge the first study to demonstrate a clinically relevant improvement in HRQL domains using the SF-36 for patients when treated with ICS/LABA compared with ICS alone. While the SF-36 is a widely used generic health status questionnaire, and is often used in conjunction with a disease-specific questionnaire in clinical studies, its use in asthma research has also been validated.³³ Generic questionnaires are more likely to detect the effects of comorbidities, but since the present study was randomized, the differences we observed in SF-36 scores are likely to have been a result of asthma or its treatment.

Although similar exacerbation control was seen in the budesonide/formoterol and budesonide groups in the current study, it should be noted that the exacerbation rate in this 5-month study was far lower than expected. Consequently, studies of a longer duration are warranted to determine whether adjustable maintenance dosing with budesonide/formoterol or a higher dose of budesonide alone maintains exacerbation control in patients with more severe asthma. A larger sample size would enable this hypothesis to be tested with a reduced possibility of a type I error for the primary efficacy endpoint. Nevertheless, this trial confirmed the good levels of control seen with adjustable-dose budesonide/formoterol in several other recent studies.^{20–23,33–36} All of these studies showed that budesonide/formoterol could maintain or improve asthma control at a reduced drug load compared with fixed-dose budesonide/formoterol. The present study extends the knowledge of budesonide/formoterol adjustable dosing by comparing its effect vs. a 2-fold higher dose of budesonide.

In conclusion, this double-blind study suggests that adjustable maintenance dosing with budesonide/formoterol maintains asthma control as effectively as adjustable maintenance dosing with

budesonide alone, whilst providing better HRQL benefits and greater treatment satisfaction. The benefits observed in the budesonide/formoterol group were achieved with a 61% lower median daily ICS dose and minimal use of reliever medication, demonstrating that adjustable maintenance dosing with budesonide/formoterol is in line with asthma treatment guidelines, providing asthma control at the lowest effective dose.

Acknowledgements

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