

BUDESONIDE/FORMOTEROL ADJUSTABLE MAINTENANCE DOSING REDUCES ASTHMA EXACERBATIONS VERSUS FIXED DOSING

B STÄLLBERG¹ MD, P OLSSON² MD, LA JÖRGENSEN³ MSc, N LINDARCK³ MSc, T EKSTRÖM³ MD, PhD,

¹Primary Health Care Centre, Trosa, and Department of Public Health and Caring Sciences, University of Uppsala, Sweden;

²Primary Health Care Centre, Sjöbo, Sweden; ³AstraZeneca, Lund, Sweden

SUMMARY A guided, adjustable-dosing regimen with budesonide/formoterol was investigated in asthma patients. In a randomised, open, multicentre study, 1034 patients received budesonide/formoterol (Symbicort®, Turbuhaler®) 80/4.5 µg or 160/4.5 µg (depending on pre-study inhaled corticosteroid dose) two inhalations twice daily for four weeks, followed by adjustable or fixed maintenance dosing for six months. Patients receiving adjustable dosing stepped down to one inhalation twice daily if symptoms were controlled and could, if symptoms worsened, step up to four inhalations twice daily for one or two weeks according to a self-guided management plan. The primary efficacy variable was occurrence of exacerbations. Compared with fixed dosing, adjustable dosing was associated with fewer patients experiencing exacerbations (6.2% vs 9.5%, NNT 30, $p < 0.05$), fewer daily inhalations of budesonide/formoterol (2.35 vs 3.95, $p < 0.001$), lower costs (six-month saving €98, $p < 0.001$) and was similarly well tolerated. Adjustable maintenance dosing with budesonide/formoterol provides more effective asthma control than fixed dosing, and reduces costs. (*Int J Clin Pract* 2003; **57**(8): 656-661)

The primary aim of asthma treatments is to maintain control of the disease and allow patients to live as normally as possible with the lowest adequate dose of medication.¹ Patients with asthma, receiving any level of fixed maintenance medication, experience worsenings and exacerbations periodically, which can range in severity from mild to life threatening and require additional therapy.

Inhaled corticosteroids (ICS) have long-term, anti-inflammatory effects and are the most effective controller medications. Budesonide is an ICS with significant acute effects in improving lung function.²⁻⁴ Furthermore, Foresi *et al*⁵ have shown that by temporarily increasing the dose of budesonide at the onset of an exacerbation from 200 µg to 1000 µg daily for seven days, the severity and duration of exacerbations could be significantly reduced. Thus, stepping up the budesonide dose promptly at the onset of worsening may limit short-term increases in symptom severity and prevent exacerbations.

Over the long term, if patients are not satisfactorily controlled with standard doses of ICS alone, addition of formoterol, a rapid and long-acting β_2 -agonist (LABA), is a more effective alternative than increasing the dose of ICS for achieving control and has been shown to reduce the frequency of severe exacerbations requiring a course of oral corticosteroids in mild to moderate asthma.^{6,7} The bronchoprotective effects of formoterol in asthma patients are dose dependent across a wide range (12-120 µg, metered dose).⁸ Similarly,

budesonide demonstrates a dose-response relationship between 200 and 800 µg daily in patients with asthma.⁹ Budesonide and formoterol are well tolerated when used together in a single inhaler, at high cumulative doses¹⁰ and during long-term treatment.¹¹

Fixed-dosing regimens with controller medications make it difficult to provide asthma control while adhering to the principle of minimal medication, as they do not take into account the variability of asthma. Inevitably there are times when patients are receiving either more medication than required during periods of control, or less than is necessary to control symptoms during periods of worsening. A treatment strategy that allows the controller dosage to be adjusted upwards, to prevent worsenings developing into exacerbations, and then reduced to a minimal level again when control is re-established, may offer advantages over fixed dosing in asthma control, while at the same time meeting guideline goals of maintaining control with the minimal amount of medication necessary. Budesonide and formoterol, because of their dose-response relationship, might be particularly suitable for use together within a single inhaler; effective adjustment of doses with both drugs can be achieved simply by increasing or decreasing the number of inhalations.

The value of patient self-management programmes, which couple a written action plan with regular medical review, is well established in asthma.¹² The aim of the present study

ADDRESS CORRESPONDENCE TO: Dr Björn Stållberg, Trosa Primary Health Care Centre, SE-619 33, Trosa, SWEDEN

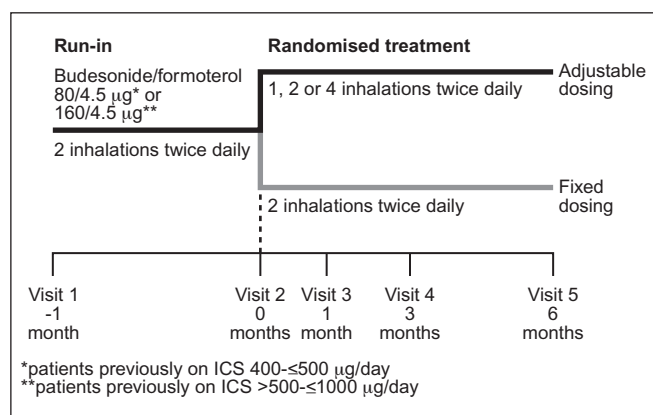


Figure 1. Overview of study design

was to examine the potential clinical benefits of a guided adjustable-dosing regimen with budesonide/formoterol in a single inhaler over a six-month period based on patient assessment of their asthma, compared with a fixed-dosing regimen; this was the first study to examine adjustable maintenance dosing with an ICS plus LABA in one inhaler over six months. The study was conducted in a real-life clinical setting, where patients and doctors were aware of the different regimens they were using.

METHODS

Study design

This was a randomised, open, parallel-group study conducted in 94 primary healthcare and hospital centres in Sweden. After enrolment (visit 1), patients were treated with fixed doses of budesonide/formoterol (Symbicort® Turbuhaler®) 80/4.5 µg or 160/4.5 µg, two inhalations twice daily, during a one-month run-in; thereafter, patients were randomised (visit 2) to receive either budesonide/formoterol adjustable or fixed dosing for six months (Figure 1). The adjustable-dosing group received one, two or four inhalations twice daily according to defined criteria assessed by each patient (Table 1). The fixed-dosing group remained on two inhalations twice daily; during periods of worsening, actions such as the use of permitted concomitant medications were taken at the discretion of the investigator. Any patients who experienced more than two episodes of worsening symptoms requiring treatment with oral corticosteroid were withdrawn from the study. Patients used the same strength of inhaler throughout the study.

Terbutaline or salbutamol inhalations were used as reliever medication throughout the study. Patients measured their peak expiratory flow (PEF) before intake of study and reliever medication every day in the morning during the run-in period and during the rest of the study on days when they experienced asthma symptoms.

Patients recorded the following in a diary: details of their study and reliever medication usage; nocturnal awakenings due to asthma; unscheduled contacts with healthcare professionals due to asthma; and days off work or school due to asthma. Patients attended the clinic for assessment after one,

Table 1. Adjustable dosing: criteria for step up and step down

Initial step down to one inhalation twice daily^a

Patient felt well in his/her asthma and in the previous seven days and met both of the following:

- reliever medication ≤2 times in previous seven days
- no nocturnal awakening due to asthma

Step up to four inhalations twice daily

If on two consecutive days/nights met any of the following:

- reliever medication for symptom relief on three occasions during the day
- nocturnal awakening due to asthma
- morning PEF <85% of the mean baseline value

Step down to one inhalation twice daily after a period of worsening asthma (i.e. after a step-up period)^b

During the previous two days/nights met all of the following:

- no more asthma symptoms than before the worsening of asthma, as judged by the patient
- no reliever medication used for symptom relief
- no nocturnal awakenings due to asthma
- morning PEF ≥85% of the mean baseline value

^aInitial step-down criteria were assessed by the physician at visit 2 and were reassessed at visits 3 and 4. If patients did not meet the initial step-down criteria, the maintenance dose during run-in (two inhalations twice daily) was continued until patients fulfilled the initial step-down criteria

^bPatients were able to step down after seven or 14 days of increased dosing (step-up period) if the criteria were met. If patients did not meet the step-down criteria after 14 days, they were instructed to contact the investigator for a decision on further treatment PEF, peak expiratory flow

three and six months of randomised treatment (visits 3, 4 and 5), when their diary cards were reviewed by an investigator. During clinic visits the investigators discussed the diary records with the patients and established if they had suffered an exacerbation. Investigators also recorded any serious adverse events (SAEs) and non-serious adverse events (AEs) causing discontinuation. Approval for conducting the study was obtained from ethics committees and patients gave written informed consent.

Study subjects

Patients with asthma (according to ATS criteria¹³) aged ≥12 years were included in the study if they had received ICS for at least six months with a constant dose of between 400 and 1000 µg/day for 30 days before enrolment; had a forced expiratory volume in one second ≥70% of predicted normal after bronchodilation; and were either well controlled on treatment with ICS and regular daily LABA, or were uncontrolled on ICS plus short-acting β₂-agonist (SABA). Control was defined as having all of the following: symptoms on ≤2 days during the last seven days, using reliever medication no more than twice during the last seven days, and having ≤2 nights of disturbed sleep due to asthma during the last 30 days.

Patients were excluded from the study if they had received corticosteroids (other than ICS), leukotriene antagonists, inhaled sodium cromoglycate, oral β₂-agonists, xanthines or inhaled anticholinergics within 30 days of enrolment; used nebulised bronchodilators; had upper respiratory tract infection in the previous 30 days; were pregnant or planning a pregnancy; were breast feeding; had a smoking history of more than 10 pack years; or had a severe disease which might have interfered with the study. No other asthma

Table 2. Direct^a and indirect^b asthma-related treatment costs (2001 prices) per patient over six months (€)

Type of cost	Adjustable dosing	Fixed dosing	Cost difference (adjustable-fixed) ^a	p-value
Study medication	221	363	-142	<0.001
Short-acting bronchodilator	4	4	0	0.600
Additional asthma medication, taken by patient during treatment	1	1	0	0.350
Total asthma medication costs	226	369	-142	<0.001
Outpatient care	30	29	1	0.997
Hospitalisation	9	5	4	0.684
Total healthcare costs	265	403	-137	<0.001
Informal care	0	1	-1	-
Total direct costs	265	404	-138	<0.001
Indirect costs ^b	90	50	40	0.407
Total costs	355	454	-98	<0.001

^athe differences between adjustable and fixed dosing are rounded to the nearest euro after calculation of absolute values in Swedish kroner (1 SEK = €0.11)

^bestimated from the number of days patients were absent from work, taking into account their employment status

^cdirect costs (SEK/unit): dose of study medication (5.20); dose of reliever medication (0.72); telephone contact with physician (114); telephone contact with nurse (35); unscheduled physician visit (805); unscheduled nurse visit (351); emergency room visit (2846); night in hospital (3724)^{14,15}

^dindirect costs (SEK/unit): day of absence from work, full-time worker (1560), part-time worker (936), based on 195/hr for industrial worker and assuming full time is eight hr/day, part time is 60% of full time

medications, except study medications or those used for the treatment of exacerbations, were permitted during the study. In order to be randomised, patients were not allowed to have any sign of suboptimal asthma control during run-in (exacerbation, reliever medication for symptom relief ≥ 3 times/day, or night-time awakening, on two consecutive days/nights in last week of run-in), and have demonstrated the ability to use the Turbuhaler and PEF meter correctly.

Efficacy and safety assessments

The primary efficacy variable was the proportion of patients having one or more exacerbations of asthma during the study. Exacerbations were defined as one or more of the following (as judged by the investigator): use of oral corticosteroids for treatment due to worsening of asthma; treatment at a medical care unit due to worsening of asthma; an asthma-related SAE; withdrawal due to a need to use non-study asthma medication.

Secondary efficacy variables were: intake of study medication; use of reliever medication (SABA); nocturnal awakenings; and health economics. Health economic calculations in Swedish krona (1 SEK = €0.11) were based on direct and indirect resource-use variables collected from the diary cards and available pre-established unit costs for the different resource categories. Unit costs (Table 2), based on 2001 prices, were taken from public Swedish sources or calculations in Swedish health economic studies published in peer-reviewed international journals. Costs for all unscheduled physician contacts in each group were included in the analysis. For patients who discontinued participation, resource use and costs during the data collection period were extrapolated to the nominal study length of six months (patient-year approach¹⁶). The safety variables were the number of patients with SAEs, and the number of patients who discontinued study treatment due to adverse events (DAEs).

Statistical analysis

Analysis of efficacy variables was based on all patients who were randomised and who took at least one dose of study

medication after randomisation. All patients who received at least one dose of study medication were included in the safety analysis.

Differences between treatment groups for the primary efficacy variable (exacerbations) were analysed with a Cochran-Mantel-Haenszel test, from which a common relative odds ratio was calculated. Number of step-up periods and duration of these periods, and safety variables were analysed by descriptive statistics. The secondary efficacy variables (intake of study medication, reliever use for symptom relief and prevention of asthma, nocturnal awakenings, health economic variables) were investigated by analysis of variance. The size of the study population (478 per group) was estimated in order to detect an increase in the proportion of exacerbations from 20% to 29%, with 90% probability and 5% significance, assuming an exacerbation frequency of 20% in the fixed-treatment group (data on file, AstraZeneca, Sweden).

RESULTS

Of the 1153 patients enrolled, 1112 entered the run-in. Of these, 78 patients discontinued during the run-in (23 AEs, 49 entry criteria not met, six other) and 517 patients in each treatment group were randomised to receive treatment. There were 57 subsequent discontinuations during the study (31 adjustable dosing, 26 fixed dosing) and 977 patients (486 adjustable dosing, 491 fixed dosing) completed the study. The reasons for discontinuation were: AEs, 28 (14 in each group); lost to follow-up, 4; entry criteria not met, 8; other, 17. Demographic and baseline characteristics of the patients were similar between treatment groups (Table 3). Seventy-three per cent of patients were well controlled on ICS plus LABA on entry to the run-in, and the other patients were not adequately controlled on ICS alone.

Exacerbations

A lower proportion of patients experienced one or more exacerbations in the adjustable-dosing group compared with the fixed-dosing group (6.2% vs 9.5%, odds ratio 0.63 [95%

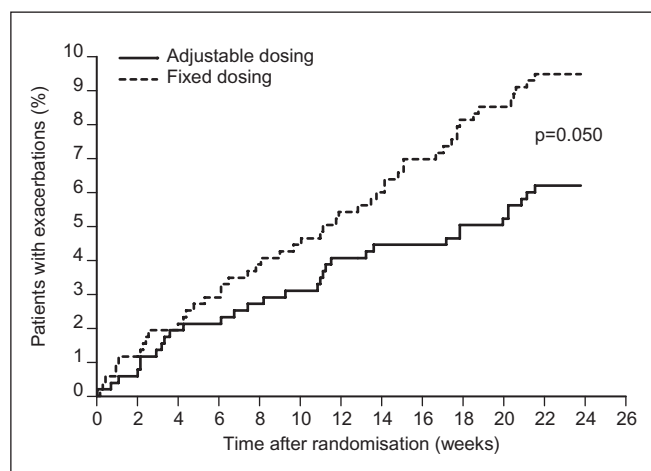
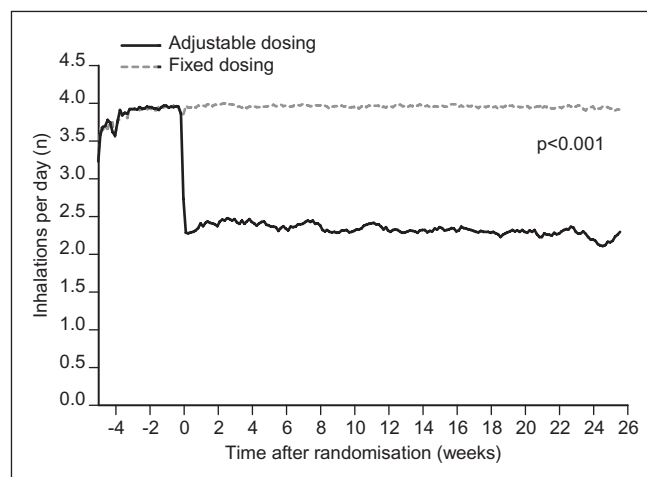
Table 3. Patient demographic and baseline characteristics (efficacy population)

	Adjustable dosing (n=517)	Fixed dosing (n=517)
Gender, n (%)		
male	202 (39)	214 (41)
Age, yr		
mean (SD)	44 (17)	44 (16)
range	12-83	12-83
Smoking status, n (%)		
non-smoker	353 (68)	356 (69)
ex-smoker	109 (21)	123 (24)
current smoker	55 (11)	38 (7)
Employment status, n (%)		
full-time employed	268 (52)	255 (49)
part-time employed	71 (14)	77 (15)
student/not working	178 (34)	185 (36)
Mean FEV ₁ post bronchodilation, l/min (SD)	3.1 (0.8)	3.1 (0.8)
Mean FEV ₁ post bronchodilation, % of predicted normal value (SD)	95.8 (15.2)	95.4 (14.5)
Mean total pre-study daily ICS, µg (SD)		
patients on 80/4.5 µg during study	424 (45)	420 (40)
patients on 160/4.5 µg during study	810 (66)	815 (80)
Previous treatment, n (%)		
well controlled on ICS + LABA	366 (71)	388 (75)
uncontrolled on ICS + SABA	151 (29)	129 (25)

ICS, inhaled corticosteroid; LABA, long-acting β_2 -agonist; SABA, short-acting β_2 -agonist; FEV₁, forced expiratory volume in one second

CI 0.40-1.00]); this difference was statistically significant ($p=0.049$). The number of patients who would need to be treated (NNT) with adjustable dosing for six months to avoid one additional exacerbation is 30. The time to first exacerbation was longer with adjustable dosing than fixed dosing ($p=0.050$). The difference between the treatment groups was particularly apparent over the last three months of the study (Figure 2).

In total, 81 patients experienced 115 exacerbations (49 adjustable dosing, 66 fixed dosing), with 27 patients having more than one exacerbation (12 adjustable dosing, 15 fixed dosing). Most of the exacerbations were identified by the use of oral corticosteroids (45 adjustable dosing, 58 fixed

**Figure 2. Kaplan-Meier curve of the time to first exacerbation****Figure 3. Mean number of inhalations of budesonide/formoterol during the study**

dosing) or treatment at a medical care unit (12 adjustable dosing, 25 fixed dosing). In four patients (three adjustable dosing, one fixed dosing), the sole reason for having an exacerbation was withdrawal due to a need to use non-study asthma medication. There was no significant difference in the proportion of patients experiencing an exacerbation between the 80/4.5 µg and 160/4.5 µg strengths of budesonide/formoterol ($p=0.46$).

Use of study medication

Patients on adjustable dosing used on average fewer inhalations per day of budesonide/formoterol than patients on fixed dosing (2.35 vs 3.95, 40% reduction, $p<0.001$) (Figure 3). The reduction in overall dose was similar for both strengths of budesonide/formoterol. Most of the patients (88%) on adjustable dosing met criteria for stepping down to one inhalation twice daily at visit 2. Only 2% of the patients on adjustable dosing were not able to step down to one inhalation twice daily during the study. Forty-nine per cent of patients in the adjustable-dosing group stepped up their dose during the treatment period at least once; 26% stepped up once, 12% twice, 5% three times, 3% four times, and 2% five or more times. A temporary increase in dose for seven days was sufficient to regain asthma control in 71% of patients who stepped up (90% with 14 days).

Other secondary efficacy variables

Patients on adjustable and fixed dosing had 90% and 91% asthma-free days (no nocturnal awakenings and no use of reliever medication), respectively. The use of reliever medication was low both for prevention of symptoms and symptom relief (approximately once per week in both groups). A slightly greater use of reliever medication for relief of symptoms (10.5% vs 9.5% of days, $p=0.0011$) was recorded in the adjustable-dosing group compared with the fixed-dosing group. Nocturnal awakenings were rare in both treatment groups, but more frequent in the adjustable-dosing group (1.7% vs 1.3% of nights, respectively, $p=0.011$).

Health economics

Estimated total asthma medication costs, sum of healthcare costs, sum of direct costs and total costs were all significantly lower for adjustable dosing than fixed dosing over the six-month treatment period (all, $p < 0.001$). Apart from study medication costs (€221 vs €363, $p < 0.001$), there were no significant differences between treatment groups for individual cost components (Table 2). Extrapolated to one year, it was estimated that use of adjustable dosing with budesonide/formoterol would result in a cost saving per patient of €275 in healthcare costs and €196 in total (direct and indirect) costs, compared with fixed dosing.

Safety evaluations

There were 33 SAEs reported in the study (3% of patients on adjustable dosing and 2% on fixed dosing), which were variable in nature; none was considered related to study treatment. There were 51 DAEs (3% of patients in each group); during the randomised treatment period, eight patients on fixed dosing and six patients on adjustable dosing discontinued due to asthma aggravation. There were no deaths during the study.

DISCUSSION

Use of budesonide/formoterol in a single inhaler provides patients with a simple and effective method of maintaining control of their asthma using the lowest appropriate dose. In this large, multicentre study, budesonide/formoterol adjustable maintenance dosing significantly reduced the proportion of patients experiencing exacerbations, compared with fixed dosing, while requiring a lower overall dose of medication, and at a lower total cost.

The primary efficacy variable used in this study (exacerbations of asthma) is an important measure of asthma control because of the disabling impact of exacerbations on patients' daily lives and the burden placed on healthcare resources, in terms of hospitalisation and emergency treatment.¹ In the present study, significantly fewer patients on adjustable dosing had exacerbations compared with fixed dosing. The time to first exacerbation was also prolonged with adjustable dosing, although the difference did not quite reach statistical significance ($p = 0.050$). Interestingly, the difference between the rates at which exacerbations occurred in the two groups appeared to widen with time (Figure 2). This difference was most apparent during the last three months of the study. This finding shows that the reduction of the overall ICS dose in the adjustable-dosing group does not lead to a deleterious effect on asthma control in the long term. It could be argued that 'withdrawal due to a need to use non-study asthma medication' does not represent a true exacerbation. However, if the four patients with a need for additional asthma medication were excluded from the statistical analysis of exacerbations, the difference between the treatment groups further increases with respect to this primary efficacy variable ($p = 0.0245$).

Subsequent analysis of data from the present study

revealed there were similar numbers of patients in the adjustable- and fixed-dosing groups who met the criteria for step up based on increased reliever medication use or nocturnal awakenings during the study (136 vs 127, respectively). As there was a smaller proportion of patients experiencing exacerbations in the adjustable-dosing group, this suggests that by promptly stepping up their dose for seven or 14 days at onset of worsening symptoms, patients may have prevented the development of an exacerbation. This finding is consistent with the results of the study by Foresi *et al.*⁵ in which early intervention with a short-term increase in budesonide dose, given two days after the start of an exacerbation, significantly reduced the number of days with exacerbations and the number of days during which patients received oral steroids over a six-month period.

In the present study, temporarily increasing the dose of formoterol may also have had a role in reducing exacerbations, beyond that obtained by simply increasing the dose of ICS. This is supported by a study by Pauwels *et al.*¹⁷ in asthma patients treated with maintenance formoterol, where the risk of exacerbation was significantly reduced in patients taking additional formoterol as needed compared with patients taking salbutamol as needed for symptom relief.

In the present study, both groups demonstrated a good level of asthma control, with approximately 90% asthma-free days. This was achieved in the adjustable-dosing group at a significantly lower overall medication dose.

The differences between the groups with regard to usage of reliever medication for symptom relief and the incidence of nocturnal awakenings were small and corresponded to an average of less than two additional days of reliever use and less than one additional nocturnal awakening per patient during the six-month treatment period. These are unlikely to represent clinically important differences (particularly when balanced against the reduction in exacerbations).

There were no safety concerns identified for the use of budesonide/formoterol in the present study. Other studies in children and adults with budesonide and formoterol administered with a single inhaler confirm this good tolerability.^{18,19}

Patients on budesonide/formoterol adjustable dosing required considerably less medication overall during the study period than patients on fixed dosing, which was directly responsible for a decrease in direct and overall treatment costs, shown in the health economic analysis. This analysis indicates that switching patients from fixed to adjustable dosing could save €196 per patient per year in total ($p < 0.001$).

It is possible that some patients, 73% of whom were controlled on ICS and LABA before the study, were overtreated with corticosteroids on entering the run-in, and this may have contributed to the reduction in the mean number of inhalations in the adjustable-dosing group immediately after randomisation. Nevertheless, the doses of medication used before and during the run-in reflected normal clinical practice. The study demonstrates how the adjustable dosing concept provides a practical, safe and

effective way of reducing the dose of medication to a lower dose if appropriate, while enabling a prompt increase in dose during periods of asthma worsening.

This was a pragmatically designed, open-label study conducted in a 'real-life' setting in patients considered to have mild to moderate asthma according to lung function and previous treatment. The design was selected to investigate two treatment approaches with the same budesonide/formoterol single inhaler. The open design can be considered a weakness, since it may influence the perception of the treatment approaches. Bias in the treatment of patients with oral steroids during periods of asthma worsening may have been introduced; however, this bias could be in either direction. Patients on fixed dosing may have been treated too early because they were unable to increase their dose of ICS, while patients on adjustable dosing may have been treated with oral steroids because the investigator was concerned that the ICS dose was too low to protect against an exacerbation. However, this design was selected to maintain the single inhaler simplicity in preference to a complex, double-dummy design using three different inhalers for maintenance treatment in both of the treatment groups. The double-dummy design was considered to introduce unnecessary complexity with the potential of compromising patient outcomes and compliance.

The results of this study have a number of clinical implications. For patients who require ICS and LABA, adjustable dosing with budesonide/formoterol in a single inhaler is a more effective means of controlling asthma than use of a fixed-dosing regimen. A key benefit of using an adjustable-dosing regimen is that it allows an appropriate dose of medication to be used at the right time for optimal effect. Patients can promptly increase the number of inhalations when experiencing an onset of worsening symptoms to prevent development of an exacerbation, remain at a higher level of medication until control is regained, and then decrease the dose again for maintenance. Furthermore, because of the lower overall medication dose, treatment with adjustable maintenance dosing is cheaper than fixed dosing.

CONCLUSION

Adjustable maintenance treatment with budesonide/formoterol reduced the incidence of exacerbations and maintained overall asthma control, despite lower use of asthma medication and associated lower total costs, compared with a fixed-dosing regimen. Both treatments were well tolerated, and no safety concerns were identified.

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