Budesonide/formoterol maintenance and reliever therapy: impact on airway inflammation in asthma

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ABSTRACT: The aim of the present study was to compare the effectiveness, safety and health economics of budesonide/formoterol maintenance and a novel reliever therapy with conventional best practice in patients with persistent asthma in Canada.

After 2 weeks of usual therapy, 1,538 patients were randomised for 6 months to open-label budesonide/formoterol maintenance and reliever therapy 160/4.5 µg twice daily and as needed, or to guideline-based conventional best practice. Severe asthma exacerbations, reliever medication use and total inhaled corticosteroid dose were analysed in all patients and airway inflammation was assessed in a sub-study of 115 patients.

No differences were seen in time to first severe exacerbation and severe asthma exacerbation rate. There were numerically fewer emergency room visits or hospitalisations with budesonide/formoterol maintenance and reliever therapy (4.4 *versus* 7.5 events per 100 patients·yr⁻¹, 41% reduction); however, this did not reach statistical significance. Mean total inhaled corticosteroid dose, reliever use, asthma medication costs and total annual costs per patient were all significantly lower with budesonide/formoterol maintenance and reliever therapy. Mean sputum eosinophil cell counts remained in the range for controlled inflammation in both groups.

In conclusion, budesonide/formoterol maintenance and reliever therapy achieved similar or improved clinical control compared with conventional best practice, with significantly lower total inhaled corticosteroid dose and lower cost, while maintaining similar control of eosinophilic inflammation.

KEYWORDS: Asthma, budesonide/formoterol, control, exacerbations, health economics, inflammation

Treatment guidelines for asthma recommend early introduction of inhaled corticosteroids (ICS) and addition of a long-acting β₂-agonist (LABA) if asthma is not well controlled on low-to-moderate doses of ICS [1, 2]. Numerous studies have shown the benefit of combination therapy over further increases in ICS dose [3, 4].

Formoterol, a rapid- and long-acting bronchodilator, can be used as a reliever as well as for maintenance therapy [5]. Budesonide/formoterol has also been assessed as reliever therapy in patients using this combination as maintenance therapy. This approach utilises a lower regular maintenance dose of budesonide/formoterol supplemented, when symptoms do occur, with as-needed treatment with the same combination,

providing a timely increase in both bronchodilator and corticosteroid treatment, leading to a significant reduction in exacerbations and in the need for oral corticosteroid therapy [6–11].

The adequacy of this management approach in controlling airway inflammation has been questioned. The potential for a subclinical increase in eosinophilic airway inflammation has previously been demonstrated when maintenance ICS dosage was progressively reduced during LABA treatment, despite clinical stability [12]. Therefore, it is important to determine whether this new management approach adequately controls inflammation.

The present report describes a 6-month study comparing the clinical effectiveness and health

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Received:

August 10 2007

Accepted after revision:

January 04 2008

CLINICAL TRIAL

This study is a registered clinical trial at www.ClinicalTrials.gov (identifier: NCT00238784). The airway sub-study was an initiative of the authors.

STATEMENT OF INTEREST

Statements of interest for all of the authors and the study itself can be found at www.erj.ersjournals.com/misc/statements.shtml

economics of budesonide/formoterol as maintenance and reliever therapy (Symbicort SMART®; AstraZeneca, Lund, Sweden) with conventional best practice (CBP) according to Canadian Asthma Consensus Guidelines [2]. In addition, control of airway inflammation was assessed using sputum eosinophil counts in a subgroup of subjects within the present study.

MATERIAL AND METHODS

Study subjects

Patients with asthma aged ≥ 12 yrs were recruited from multiple clinical practices across Canada. Inclusion criteria comprised: asthma diagnosis for ≥ 3 months (using the American Thoracic Society definition [13]); use of ≥ 400 μ g ICS daily; and either daily treatment with ICS alone and a history of suboptimal asthma control in the month before enrolment with ≥ 3 inhalations of as-needed rescue for symptom relief during the 7 days prior to enrolment, or daily maintenance treatment with both ICS and LABA.

Exclusion criteria included: previous treatment with budesonide/formoterol as both maintenance and reliever therapy; use of any β -blocking agent; use of oral corticosteroids as maintenance treatment; asthma exacerbations requiring change in asthma treatment during the previous 14 days; planned hospitalisation during the study; a smoking history >10 pack-yrs; pregnancy; breastfeeding or planned pregnancy; and any other significant disease that, in the opinion of the investigator, may put the patient at risk due to their participation in the study. The study was approved by research ethics committees in the multiple institutions involved and performed in accordance with the Declaration of Helsinki, International Conference on Harmonization/Good Clinical Practice and the AstraZeneca policy on bioethics. Written informed consent was obtained from each patient.

Study design

This randomised, open-label, parallel-group, multicentre study (study code D5890L00004) aimed to reflect ordinary clinical practice (fig. 1). An open design was necessary, first, to allow multiple treatment options in the comparator arm and, secondly, to implement the essential part of the new strategy, namely the use of budesonide/formoterol for both maintenance and as-needed use. Following a 2-week run-in period maintaining their usual asthma therapies, patients were randomised to budesonide/formoterol maintenance and reliever therapy or

to CBP. The budesonide/formoterol dosage was 160/4.5 μ g delivered dose, one inhalation twice daily (*b.i.d.*) plus additional doses as needed, up to a total of 12 inhalations daily. Patients allocated to this arm were instructed in the correct use of the Turbuhaler® (Symbicort Turbuhaler®; AstraZeneca) at randomisation. CBP was determined according to the investigators' judgement following the Canadian Asthma Consensus Guidelines [2] and could involve any therapy including either ICS/LABA combination product but not use of budesonide/formoterol as both maintenance and reliever therapy. Patients were evaluated at 4, 13 and 26 weeks after randomisation. This study is a registered clinical trial at the ClinicalTrials.gov website (identifier: NCT00238784).

Outcomes

The primary outcome was time to first severe asthma exacerbation, defined as hospitalisation or emergency room (ER) visit and/or use of oral corticosteroid for ≥ 3 days due to asthma. Secondary outcomes included the number of severe exacerbations, mean use of as-needed medication (recorded for 2 weeks before each visit), prescribed asthma medications, peak expiratory flow (PEF), Asthma Control Questionnaire (five-item version; ACQ-5) score [14], health economics and safety. In a subgroup of the present study, the primary outcome was the change in induced sputum eosinophil count.

Methods

A notebook was used to record exacerbations, changes in prescribed asthma medications and adverse events at any time, and use of reliever medication on each of the 14 days preceding the study visit. The notebook was reviewed by the investigator at visits 2–5.

Start and end dates for exacerbations were defined as the first and last day of hospitalisation/ER treatment, or the first and last day of prescribed oral corticosteroid treatment, respectively. If an exacerbation included both hospitalisation/ER treatment and oral corticosteroid treatment, the start and end dates were the first and last day that either criterion was fulfilled.

PEF measurements were performed by each patient at visits 1 and 5, using the same PEF meter at both visits.

The ACQ-5 [14] was self-administered during visits 2–5. All questions were assessed on a seven-point scale from 0 (good control) to 6 (poor control). The overall score was the mean of the five responses. Answers to four of the five questions were required to provide a value. Change in ACQ-5 score from visit 2 to the average during treatment (visits 3–5) was calculated.

Assessment of safety included reporting of common adverse events, serious adverse events (asthma and nonasthma related) and discontinuation of study treatment due to adverse events (asthma and nonasthma related).

In patients from five academic centres, sputum inductions were undertaken at visits 2 and 5, and sputum eosinophil counts were measured using standardised methods [15]. Treating physicians were blinded to results of sputum analyses so that treatment was not influenced by these measurements.

The health economic evaluation was conducted from the societal perspective, including direct and indirect costs. Direct

FIGURE 1. Study design.

costs included: study or prescribed medications; rescue medications; additional asthma medications taken during exacerbations; visits to family physicians, specialists or healthcare professionals; expenses, such as parking and public transportation for such visits; diagnostic tests; home visits; ambulance use; ER visits; and hospitalisations. Indirect costs included: number of days the patient missed work or school; number of days that caregivers were absent from work due to patient’s asthma; and total out-of-pocket expenses. The asthma medication cost per patient for the budesonide/formoterol maintenance and reliever therapy arm was calculated as follows:

Maintenance dose cost (2 × unit price × days in study) + as-needed dose cost (average daily inhalation × unit price × days in study) + cost of exacerbation treatments (if applicable) + dispensing fee

In the CBP arm, cost was calculated as follows:

(unit price of all maintenance therapy × days used) + as-needed dose cost (average daily inhalation × unit price × days in the study) + cost of exacerbation treatments (if applicable) + dispensing fee

Costs were adjusted to an annual rate.

Analysis

All analyses were undertaken using the intention-to-treat approach. Time to first severe exacerbation was determined using Kaplan–Meier curves and compared between treatments with a log-rank test. The treatment difference was estimated by the Cox proportional hazards model with treatment as a factor. The number of severe asthma exacerbations per patient was compared between treatment groups using a Poisson regression model with treatment as a factor and time in study as an offset variable. The use of as-needed medication, changes in PEF from baseline to visit 5 and changes in ACQ-5 score (visits 3–5) from baseline were compared between treatments using ANOVA with treatment as a factor and baseline mean as a covariate. The mean use of ICS was compared between

treatments using ANOVA. The annual asthma medication costs and annual total costs were compared between treatments using the bootstrapping method. A p-value <0.05 was considered statistically significant. Adverse events were analysed using descriptive statistics.

For the airway inflammation sub-study, a multiplicative ANOVA (*i.e.* log transformation) was used to compare the percentage change in eosinophil count in induced sputum from baseline to the end of treatment. To facilitate the log transformation, sputum eosinophil counts of 0% were assigned a value of 0.125% (half of the lowest nonzero value).

Using assumptions, based on previous studies, that 13% of patients would experience a severe exacerbation in one group and 8.2% in the other group, this difference would be detected with 80% probability at a 5% level of significance if the study included 650 patients per group. In order to compensate for an estimated dropout rate of 15% through run-in, a sample size of 1,530 patients was determined. The sample size for the airway inflammation subgroup analysis was calculated based on the log scale of the data. A sample size of 45 per group (90 subjects in total) would be able to detect a 40% difference (approximately equivalent to a treatment difference of -0.518 in log scale) between the two treatments with a power of 80% and a significance level of 5%. To compensate for dropouts, 110 enrolled subjects (or 105 randomised subjects) were recruited.

RESULTS

Study subjects

The number of patients enrolled, randomised and completing the study, including the airway inflammation sub-study, is shown in table 1. The treatment groups were comparable with respect to demographic and baseline data (table 2). The characteristics of the 115 patients enrolled who participated in the airway inflammation sub-study, and of the 88 patients completing the sub-study with sputum measurements at both time-points, did not differ from the full study population (please refer to supplementary table E1 and fig. E1).

TABLE 1 Number of patients enrolled, randomised and completing the study				
Enrolled [#]				
Main study randomised [†]		Sub-study randomised [‡]		
	BUD/FORM maintenance and reliever therapy	CBP	BUD/FORM maintenance and reliever therapy	CBP
Randomised	772	766	59	56
Completed	681	719	57	55
Withdrawals total	91	47	2	1
Eligibility criteria not fulfilled	6	8	0	1
Adverse event	27	7	0	0
Unwilling to continue study	17	8	1	0
Lost to follow-up	15	13	1	0
Other	26	11	0	0

Data are presented as n. BUD/FORM: budesonide/formoterol; CBP: conventional best practice. [#]: n=1,636; [†]: n=1,538; [‡]: n=115.

TABLE 2 Demographic and baseline characteristics

	Main study			Airway inflammation sub-study		
	BUD/FORM maintenance and reliever therapy	CBP	Total	BUD/FORM maintenance and reliever therapy	CBP	Total
Subjects n	772	766	1538	59	56	115
Male	326 (42.2)	287 (37.5)	613 (39.8)	21 (35.6)	23 (41.1)	44 (38.3)
Age yrs	42.1 ± 16.4 (12–92)	43.1 ± 16.0 (12–94)	42.6 ± 16.2 (12–94)	38.8 ± 13.9 (21–73)	39.9 ± 14.7 (18–71)	39.3 ± 14.2 (18–73)
Race						
Caucasian	728 (94.3)	726 (94.8)	1454 (94.5)	57 (96.6)	56 (100)	113 (98.3)
Black	18 (2.3)	25 (3.3)	43 (2.8)			
Oriental	17 (2.2)	13 (1.7)	30 (1.9)	2 (3.4)		
Use of LABA	564 (73)	573 (75)	1137 (74)	36 (61)	38 (68)	74 (64)
ICS dose during run-in µg·day⁻¹	566 ± 207 (250–1600)	572 ± 229 (160–2400)	569 ± 218 (160–2400)	617 ± 282 (320–1600)	573 ± 223 (250–1125)	596 ± 254 (250–1600)
As-needed inhala- tions during run-in inhalations·day⁻¹	1.25 ± 1.67 (0–13.2)	1.22 ± 1.69 (0–12.2)	1.24 ± 1.68 (0–13.2)	0.85 ± 0.99 (0–4.25)	1.11 ± 1.48 (0–6.33)	0.98 ± 1.26 (0–6.33)
As-needed-free days during run-in %	53.7 ± 38.2 (0–100)	55.7 ± 38.2 (0–100)	54.7 ± 38.2 (0–100)	59.4 ± 34.8 (0–100)	59.5 ± 34.8 (0–100)	59.4 ± 34.6 (0–100)
Smoking history pack·yrs	4.8 ± 2.9 (0–10)	4.8 ± 2.8 (0–10)	4.8 ± 2.8 (0–10)	3.9 ± 2.8 (0–9)	3.2 ± 1.8 (1–6)	3.6 ± 2.4 (0–9)
PEF % pred	94.8 (22–197)	94.1 (26–186)	94.5 (22–197)	97.3 (51–138)	92.2 (62–132)	94.8 (51–138)

Data are presented as n (%), mean ± SD (range) or mean (range), unless otherwise stated. BUD/FORM: budesonide/formoterol; CBP: conventional best practice; LABA: long-acting β_2 -agonist; ICS: inhaled corticosteroid; PEF: peak expiratory flow; % pred: % predicted.

Asthma severity at baseline (assessed by ICS dose, asthma symptoms and lung function) was classified as mild-persistent in 18%, moderate-persistent in 43% and severe-persistent in 39% of patients, based on a modification of the Global Initiative for Asthma guidelines [1]. Prior to randomisation, ~66% of patients were prescribed an ICS/LABA combination, with similar use of fluticasone/salmeterol and budesonide/formoterol between groups, and ~10% in each arm were prescribed leukotriene receptor antagonists (LTRA).

Time to first severe exacerbation

The primary efficacy variable, time to first severe exacerbation, is shown in figure 2. There was no significant difference between the two treatments (Cox hazard ratio 0.99, 95% confidence interval (CI) 0.70–1.41; $p=0.95$, log-rank test).

Number of severe exacerbations

The incidence of severe exacerbations, in total and by subtype, is shown in table 3. In total, 61 (7.9%) subjects on budesonide/formoterol maintenance and reliever therapy reported 69 severe exacerbations, while 63 (8.2%) subjects on CBP reported 77 severe exacerbations. Using Poisson regression, the mean number of severe exacerbations per patient per year was 0.19 *versus* 0.21 (ratio 0.92, 95% CI 0.67–1.28; $p=0.63$) for budesonide/formoterol maintenance and reliever therapy compared with CBP (table 3).

Of those reporting severe asthma exacerbations based on oral corticosteroid use, no difference was seen in the number of patients with at least one event or the total number of events.

Total days of oral corticosteroid use were, however, 17% lower with budesonide/formoterol maintenance and reliever therapy (590 days) compared with CBP (709 days; table 3).

Of those reporting severe asthma exacerbations based on hospitalisation and/or ER visits, Poisson regression demonstrated a trend towards fewer such exacerbations per patient per year with budesonide/formoterol maintenance and reliever therapy: 0.04 *versus* 0.08 with CBP (ratio 0.59, 95% CI 0.32–1.09; $p=0.09$; table 3). The incidence of severe asthma exacerbations leading to hospitalisation and/or ER visit is shown in figure 3.

As-needed reliever use

Mean as-needed reliever use decreased slightly, from 1.25 to 0.94 inhalations·day⁻¹ with budesonide/formoterol maintenance and reliever therapy and from 1.22 to 1.09 inhalations·day⁻¹ with CBP (table 4), a 14% lower use with budesonide/formoterol maintenance and reliever therapy ($p=0.0036$). A total of 15 (2%) subjects in the budesonide/formoterol maintenance and reliever therapy arm required more than eight as-needed inhalations on ≥ 1 day *versus* 30 (4%) subjects in the CBP arm ($p=0.028$).

Prescribed asthma medications

Maintenance medication in the budesonide/formoterol maintenance and reliever therapy arm was fixed by protocol. In the CBP arm, ICS without LABA were prescribed in 18% and ICS with LABA in 82% of subjects: 44% used budesonide/formoterol, 32% fluticasone/salmeterol and 8% separate

FIGURE 2. Kaplan-Meier plot of time to first severe asthma exacerbation. —: budesonide/formoterol maintenance and reliever therapy; ----: conventional best practice. $p=0.95$.

inhalers of ICS and LABA, with some overlap in these groups. LTRAs were prescribed in 11% of subjects, while more than three separate classes of controllers were used in 9% of CBP patients.

Inhaled corticosteroid doses

The mean (range) ICS dose (expressed as beclomethasone dipropionate equivalents [2]) was $1,015$ (30 – $4,000$) $\mu\text{g}\cdot\text{day}^{-1}$ in the CBP group and 748 $\mu\text{g}\cdot\text{day}^{-1}$ (500 $\mu\text{g}\cdot\text{day}^{-1}$ maintenance + 248 (range 0 – $2,710$) $\mu\text{g}\cdot\text{day}^{-1}$ as needed) in the budesonide/formoterol maintenance and reliever therapy group, a total reduction of 26% (267 $\mu\text{g}\cdot\text{day}^{-1}$, 95% CI 226 – 307 ; $p<0.0001$).

Peak flow

PEF increased from 94.8 to 98.0% predicted with budesonide/formoterol maintenance and reliever therapy, and from 94.1 to 96.3% with CBP. No significant difference was found between treatment groups ($p=0.32$).

Asthma Control Questionnaire

The ACQ-5 score decreased from 1.27 to 1.08 with budesonide/formoterol maintenance and reliever therapy and from 1.24 to 1.09 with CBP, representing an improvement in asthma control in both groups. No significant difference was found between the treatment groups ($p=0.46$).

Sputum eosinophil counts

Of the 115 subjects randomised into the airway inflammation sub-study, 88 subjects produced sufficient sputum for analysis at visits 2 and 5. Mean eosinophil cell counts were within the range for controlled inflammation in both groups at baseline and at the end of the study. The geometric mean (range) sputum eosinophil count decreased in the budesonide/formoterol maintenance and reliever therapy group (from 0.99 (0.125–26.0) to 0.73 (0.125–19.75); $p=0.0502$) and in the CBP group (from 1.22 (0.125–51.5) to 1.16 (0.125–57.5); $p=0.97$; fig. 4). No significant difference was found between the treatment groups for reduction in mean sputum eosinophil count ($p=0.193$). The number of patients with eosinophil counts $>2\%$ at the beginning (14 out of 40 and 11 out of 48) and

FIGURE 3. Incidence of severe asthma exacerbations leading to hospitalisation and/or emergency room visit by subject. ○: budesonide/formoterol maintenance and reliever therapy; ●: conventional best practice (CBP) first exacerbation; ■: CBP second exacerbation; □: CBP third exacerbation; ▲: CBP fourth exacerbation; ◇: CBP first exacerbation subject was hospitalised for 5 days.

end (12 out of 40 and 13 out of 48) of study in CBP *versus* budesonide/formoterol maintenance and reliever therapy, respectively, were not significantly different.

Health economics

The asthma medication cost and the total cost per patient per year were 28 and 23% lower, respectively, with budesonide/formoterol maintenance and reliever therapy *versus* CBP. The between-group difference (95% CI) in asthma medication costs (Can\$ -353.60 (-419.72 – -293.27); € -240.83 (-285.87 – -199.75)) and total cost (Can\$ -315.55 (-420.50 – -200.52); € -214.92 (-286.40 – -136.57); Can\$1=€0.6811, exchange rate of November 26, 2007) were statistically significant (both $p<0.0001$).

Safety

All treatments were well tolerated and no new safety concerns were identified. There were no clinically important differences between the treatment groups in the patterns of adverse events and serious adverse events (table 5). Deterioration of asthma was only recorded as an adverse event if it was a serious adverse event or resulted in discontinuation of treatment. In total, 34 patients discontinued treatment due to adverse events (27 on budesonide/formoterol maintenance and reliever therapy and seven on CBP). Discontinuation due to asthma worsening or exacerbation was reported in 12 patients (nine on budesonide/formoterol maintenance and reliever therapy and three on CBP). The majority (85%) of those who discontinued therapy in the budesonide/formoterol maintenance and reliever arm had changed from metered-dose inhalers as their usual therapy to Turbuhaler® (AstraZeneca) delivery at randomisation. There were only four discontinuations on budesonide/formoterol maintenance and reliever therapy due to a severe exacerbation and three on CBP. Discontinuation due to serious adverse events occurred in six patients, three in each treatment group.

There were three deaths, one in the budesonide/formoterol maintenance and reliever therapy arm (due to injury) and two

TABLE 3 Incidence of severe exacerbations, in total and by subtype

Incidence	BUD/FORM maintenance and reliever therapy	Conventional best practice	Treatment comparison [#]	p-value [†]
Subjects	772	766		
Severe asthma exacerbations				
At least one event	61 (7.9)	63 (8.2)		
Total events	69	77		
Total days with event	609	725		
Events per patient per year	0.19 (0.15–0.24)	0.21 (0.17–0.26)	0.92 (0.67–1.28)	0.63
Oral glucocorticosteroid				
At least one event	57 (7.4)	55 (7.2)		
Total events	65	65		
Total days with event	590	709		
Events per patient per year	0.18 (0.14–0.23)	0.17 (0.14–0.22)	1.03 (0.73–1.45)	0.86
Emergency room treatment				
At least one event	16 (2.1)	23 (3.0)		
Total events	16	28		
Total days with event	16	28		
Hospitalisation				
At least one event	0 (0.0)	1 (0.1)		
Total events	0	1		
Total days with event	0	5		
Hospitalisation and/or emergency room treatment				
Events per patient per year	0.04 (0.03–0.07)	0.08 (0.05–0.11)	0.59 (0.32–1.09)	0.09

Data are presented as n, n (%) or n (95% confidence interval), unless otherwise stated. BUD/FORM: budesonide/formoterol. [#]: ratio of BUD/FORM maintenance and reliever therapy to conventional best practice; [†]: derived using Poisson regression analysis.

in the CBP arm (due to myocardial infarction and myopericarditis). Deaths were not considered by the investigators to be causally related to study treatment.

DISCUSSION

The primary objective of the present study was to compare the effectiveness of budesonide/formoterol maintenance and reliever therapy with asthma treatment according to CBP. The primary outcome variable, time to first severe exacerbation, showed no statistically significant difference between treatment groups. However, events were treated for ~2 days

fewer per event in the budesonide/formoterol maintenance and reliever therapy group, and a trend for improvement was seen in the number of ER treatments and hospitalisations (0.04 events per patient per year for budesonide/formoterol maintenance and reliever therapy *versus* 0.08 for CBP; $p=0.09$). The rate of 0.04 events per patient per year is consistent both with results in other double-blind studies of this strategy [11] and of escalating fluticasone/salmeterol treatment in the Gaining Optimal Asthma Control study [16].

The second major finding from the present study was that both approaches had similar effects on control of eosinophilic

TABLE 4 As-needed reliever use

	BUD/FORM maintenance and reliever therapy	CBP	Mean treatment difference or odds ratio (95% CI)	p-value
Subjects n	748	756		
As-needed inhalations during treatment period inhalations·day⁻¹	0.94	1.09	-0.158 [#] (-0.265– -0.052)	0.0036
As-needed free days during treatment period %	60.1	61.1	0.024 [#] (-3.162–3.210)	0.9881
Patients with >2 inhalations·day⁻¹ on ≥1 day	294 (39)	369 (49)	0.679 [†] (0.553–0.833)	0.0002
Patients with >8 inhalations·day⁻¹ on ≥1 day	15 (2)	30 (4)	0.495 [†] (0.264–0.928)	0.0283

Data are presented as mean or n (%), unless otherwise stated. BUD/FORM: budesonide/formoterol; CBP: conventional best practice; CI: confidence interval. Missing data were excluded from the analysis. [#]: mean treatment difference; [†]: odds ratio.

FIGURE 4. Change in sputum eosinophil count in subjects who completed both visits. Data are displayed as geometric mean. The mean ratio between baseline and treatment was 0.710 ($p=0.050$) and 0.993 ($p=0.972$) for budesonide/formoterol maintenance and reliever therapy and conventional best practice, respectively. The mean ratio between treatment groups of budesonide/formoterol maintenance and reliever therapy and conventional best practice was 0.715 ($p=0.1930$).

airway inflammation. It is not known whether all participants in the sub-study had eosinophilic inflammation without treatment, as that was not an entry requirement and it would have been unethical to withdraw ICS treatment to ascertain that. However, the numbers of patients with eosinophil counts above and below 2% on treatment were well balanced at baseline, and there was no indication that the budesonide/formoterol maintenance and reliever therapy management approach allowed eosinophil counts to increase. Rather, there were small reductions in mean counts in both groups, which approached statistical significance ($p=0.0502$) in the budesonide/formoterol maintenance and reliever therapy group. Hence, the suggestion that the symptom-driven approach of using extra ICS/LABA doses as reliever therapy on top of the

maintenance dose could permit persistent airway inflammation, is not supported. While the sub-study was conducted in only a small proportion of the study subjects (constrained by the availability of the methodology), those subjects were similar to the full study population in all respects.

The study had a different design to the five large double-blind studies comparing budesonide/formoterol maintenance and reliever therapy with fixed-dose combination treatments or higher doses of ICS with a rapid-acting β_2 -agonist as reliever therapy [6, 8–11], where both risk and rate of exacerbations have been consistently and significantly reduced by this strategy *versus* all comparators. In the present study, physicians and patients had full freedom to change maintenance treatment in the CBP arm and to use an action plan for worsening symptoms, whereas change in maintenance treatment in the budesonide/formoterol maintenance and reliever therapy arm was not allowed. This design, and the fact that patients could enter into the study with stable control while already receiving combination therapy, may have reduced the potential for showing continuing advantage of the budesonide/formoterol maintenance and reliever therapy approach over CBP in the present study. However, the maintained or improved levels of asthma control in the budesonide/formoterol maintenance and reliever therapy group were achieved with 26% lower overall ICS load (748 *versus* 1,015 $\mu\text{g}\cdot\text{day}^{-1}$; $p<0.0001$) and less use of oral corticosteroids (590 *versus* 709 days for CBP).

Healthcare resource use favoured budesonide/formoterol maintenance and reliever therapy, with 41% fewer hospitalisations and/or ER treatments. Other healthcare visits were similar between treatment groups. Asthma medication costs and societal cost were lower for budesonide/formoterol maintenance and reliever therapy, making it a more cost-effective treatment option.

There were some limitations to the study design in addition to the different degrees of freedom to adjust therapy as noted previously. The treatment allocation following randomisation was open label, as this is part of the design to test the concept in an effectiveness study. There was potential for bias in the

TABLE 5 Subjects with an adverse event in any category[#]

	Budesonide/formoterol maintenance and reliever therapy	Conventional best practice
Subjects n	772	766
Any adverse events	474 (61.4)	491 (64.1)
Total serious adverse events	17 (2.2)	15 (2.0)
Serious adverse events leading to death	1 (0.1)	2 (0.3)
Serious adverse events not leading to death	16 (2.1)	13 (1.7)
Discontinuations of study treatment		
Due to adverse events	27 (3.5)	7 (0.9)
Due to asthma worsening or exacerbation	9 (1.2)	3 (0.4)
Due to a severe asthma exacerbation	4 (0.5)	3 (0.4)
Due to a serious adverse event	3 (0.4)	3 (0.4)

Data are presented as n (%), unless otherwise stated. [#]: subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than one category are counted once in each of those categories.

judgement of a severe exacerbation, discontinuation from the study or in the choice of additional healthcare resources utilised. Despite the emphasis in the Canadian Asthma Consensus Guidelines [2] to establish control with minimal medication, physicians may have been reluctant to reduce ICS use in the CBP arm, preferring to maintain stability, leading to higher ICS usage in this arm. If this was so, the benefit of the new strategy, where such potential instability is rectified by the additional ICS in the as-needed doses of budesonide/formoterol, is evident. PEF was not measured regularly to guide treatment step-up or step-down, as this would not reflect real-world asthma management.

The number of asthma-related serious adverse events was not different between the treatment arms. The higher number of discontinuations in the budesonide/formoterol maintenance and reliever therapy arm likely reflects the open nature of the study. Patients receiving a new open-label treatment (or using a new strategy) who have increased symptoms as part of usual variability of asthma may be more likely to want to return to their previous therapy, which in the budesonide/formoterol maintenance and reliever arm required discontinuation from the study, whereas those in the comparator arm were free to make any desired changes without withdrawing from the study, thus introducing a bias in favour of CBP. In five large studies [6, 8–11], no differences in adverse events leading to discontinuation were observed between budesonide/formoterol maintenance and reliever therapy and comparator treatments, with the exception of a lower incidence of discontinuations due to asthma for the budesonide/formoterol maintenance and reliever therapy arm. Overall, the results indicate that budesonide/formoterol maintenance and reliever therapy is as safe and well tolerated as CBP.

In conclusion, budesonide/formoterol maintenance and reliever therapy achieved similar effectiveness compared with guideline-directed conventional best practice with regards to time to first severe exacerbation and rate of severe exacerbations. Clinical control with budesonide/formoterol maintenance and reliever therapy was maintained with significantly lower inhaled corticosteroid use, decreased use of oral steroids, a numerical but not statistically significant reduction in the number of emergency room visits and/or hospitalisations, and lower cost. Eosinophilic airway inflammation was similarly controlled by both strategies. Treatments in both groups were well tolerated and no safety concerns were identified.

ACKNOWLEDGEMENTS

The present authors would like to thank the study investigators and study coordinators for their work in conducting the clinical trial. They would also like to thank C. Macpherson (MediTech Media Ltd, London, UK) who provided editing assistance.

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