ORIGINAL PAPER

Effect of budesonide/formoterol maintenance and reliever therapy on asthma exacerbations

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SUMMARY

This randomised, double-blind, 6-month study compared budesonide/formoterol for maintenance and relief with salmeterol/fluticasone and a fixed maintenance dose of budesonide/formoterol, both with terbutaline for relief. Following a 2-week run-in, 3335 symptomatic adults and adolescents (mean FEV_1 73% predicted, mean inhaled corticosteroid dose 745 μg/day) received budesonide/formoterol 160/4.5 μg one inhalation bid plus additional inhalations as needed, salmeterol/fluticasone 25/125 μg two inhalations bid plus as-needed terbutaline or budesonide/formoterol 320/9 μg one inhalation bid plus as-needed terbutaline. Budesonide/formoterol for maintenance and relief prolonged the time to first severe exacerbation requiring hospitalisation, emergency room treatment or oral steroids (primary variable) vs. fixed-dose salmeterol/fluticasone and budesonide/formoterol (p = 0.0034 and p = 0.023 respectively; log-rank test). Exacerbation rates were 19, 16 and 12 events/100 patients/6 months for salmeterol/fluticasone, fixed-dose budesonide/formoterol and budesonide/formoterol for maintenance and relief, respectively, [rate reduction vs. fixed-dose salmeterol/fluticasone (0.61; 95% CI 0.49–0.76, p < 0.001) and vs. fixed-dose budesonide/formoterol (0.72; 95% CI 0.57–0.90, p = 0.0048)]. Budesonide/formoterol maintenance and relief patients used less inhaled corticosteroid vs. salmeterol/fluticasone and fixed-dose budesonide/formoterol patients. All treatments provided similar marked improvements in lung function, asthma control days and asthma-related quality of life. Budesonide/formoterol for maintenance and relief reduces asthma exacerbations and maintains similar daily asthma control at a lower overall drug load compared with fixed-dose salmeterol/fluticasone and budesonide/formoterol.

What's known

Clinical evidence has shown that asthma management using budesonide/formoterol (Symbicort®) maintenance and reliever therapy (SMART) provides a simpler and more effective treatment strategy than traditional approaches with short-acting β_2-agonist (SABA) therapy. SMART improves daily symptom control and prevents severe exacerbations more effectively than higher doses of inhaled corticosteroid (ICS) plus SABA or the same maintenance dose of budesonide/formoterol plus as-needed terbutaline or formoterol. The SMART approach has been recommended in the recent GINA guidelines.

What's new

The evidence within this manuscript confirms that patients randomised to receive SMART therapy have greater protection from severe asthma exacerbations, including hospitalisations and emergency room treatment, than those treated even with higher traditional fixed-dose ICS/long-acting β_2-agonist (LABA) treatment. Similar levels of daily asthma symptom control were observed compared with treatment with salmeterol/fluticasone or fixed-dose budesonide/formoterol. The observed improvements in overall asthma control occurred despite a 50% reduction in regular maintenance doses of ICS/LABA with the SMART approach.

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Introduction

The current treatment recommended by guidelines for persistent asthma is a fixed-dose inhaled corticosteroid (ICS) or an ICS/long-acting β_2-agonist (LABA) combination administered twice daily (bid), plus a short-acting β_2-agonist (SABA) as needed for symptom relief. The two ICS/LABA combination inhalers currently available – budesonide/formoterol and salmeterol/fluticasone – are highly effective at providing early and sustained improvements in asthma control for patients symptomatic on ICS alone (1–3).

Even with such treatments, asthma control remains suboptimal (4). Residual asthma symptoms can

persist, even in patients using regular ICS or ICS/LABA maintenance therapy, with exacerbations ranging from mild increases in symptoms to events requiring medical intervention or hospitalisation (1,5,6). Consequently, asthma management plans have been developed that specify treatment changes in response to increasing symptoms or deteriorating lung function. These effectively reduce the rate of exacerbations (7), but require detailed physician guidance and patient adherence. Despite strong advocacy and evidence of effectiveness, the use of asthma management plans remains disappointingly low (8).

A new approach to asthma therapy is budesonide/formoterol (Symbicort®) maintenance and reliever therapy (SMART) using one inhaler, without the

requirement for a separate SABA (9–12). This novel treatment approach has also been endorsed in the latest Global Initiative for Asthma (GINA) guidelines (13). The simple substitution of budesonide/formoterol for SABA allows the dose of controller medication, LABA and ICS, to be increased quickly in response to symptoms, while simultaneously offering rapid symptom relief. A previous study has shown that SMART is more effective at reducing exacerbations and improving daily asthma control than the same maintenance dose of budesonide/formoterol plus as-needed SABA (9). In that study, however, SMART patients used, on average, a higher daily dose of budesonide/formoterol than fixed-dose budesonide/formoterol patients. Therefore, a comparison of the efficacy of SMART with that of a higher maintenance dose of ICS/LABA was needed to answer two remaining questions: could SMART be as effective at reducing exacerbations as a higher fixed maintenance dose of combination therapy and would SMART result in greater day-to-day fluctuations in asthma control?

Using a double-blind approach, we hypothesised that SMART (budesonide/formoterol 160/4.5 µg one inhalation bid plus additional as-needed inhalations for relief) would prevent exacerbations more effectively than a fixed dose of salmeterol/fluticasone (25/125 µg two inhalations bid) plus terbutaline or a comparable fixed maintenance dose of budesonide/formoterol (320/9 µg one inhalation bid) plus terbutaline as needed (1,14), and that this important benefit would not be achieved at the expense of daily asthma control.

Methods

In this study (study code SD-039-0735), outpatients aged ≥ 12 years with a diagnosis of asthma [as defined by the American Thoracic Society (15)] for ≥ 6 months and using ICS for ≥ 3 months [≥ 500 µg/day of budesonide or fluticasone (or ≥ 1000 µg/day of another ICS) for ≥ 1 month] were eligible for enrolment. Patients had to have a forced expiratory volume in 1 s (FEV$_1$) $\geq 50\%$ predicted normal with $\geq 12\%$ reversibility following terbutaline 1 mg and ≥ 1 asthma exacerbation in the previous 1–12 months. Patients using reliever medication on ≥ 5 of the last 7 days of the 2-week run-in were randomised; those with > 10 as-needed inhalations in any day of run-in and patients who experienced an asthma exacerbation during run-in were not randomised. Patients using systemic corticosteroids or with respiratory infections affecting asthma control within 30 days of study entry were excluded.

Study design

This 6-month, randomised, double-blind, double-dummy, parallel-group study was conducted according to the Declaration of Helsinki and Good Clinical Practice guidelines. Independent ethics committees approved the study protocol, patient information and consent forms. All patients and parents/guardians of adolescents gave written informed consent. The first patient was enrolled on 19 December 2003 and the last patient completed the study on 11 March 2005.

Patients attended the clinic at the beginning and end of run-in (visits 1–2), and after 8, 16 and 24 weeks of treatment (visits 3–5 respectively). During run-in, patients used their regular ICS for maintenance and terbutaline (Bricanyl® Turbuhaler®; AstraZeneca, Lund, Sweden) for symptom relief. ICS/LABA combination inhalers were stopped 72 h before study entry and the corresponding ICS dose used. Following run-in, eligible patients were randomised to one of three treatment groups for 24 weeks (Figure 1): budesonide/formoterol (Symbicort® Turbuhaler®; AstraZeneca, Sweden) 160/4.5 µg one inhalation bid for maintenance plus additional inhalations as needed (Symbicort SMART®), fixed-dose salmeterol/fluticasone [Seretide™/Advair™ Evohaler™ (pressurised metered-dose inhaler, pMDI), GlaxoSmithKline, Uxbridge, UK] 25/125 µg two inhalations bid plus terbutaline as reliever medication or budesonide/formoterol 320/9 µg one inhalation bid plus terbutaline. The salmeterol/fluticasone dose, delivered via a dry-powder inhaler (DPI), has been shown in previous studies to have similar clinical efficacy to the fixed dose of budesonide/formoterol used in this study (1,14). In addition, therapeutic equivalence has been reported for salmeterol/fluticasone delivered via either DPI or pMDI (16,17).

At the start of the study, all patients were instructed in the correct use of the Turbuhaler and the Evohaler devices. As an additional safety precaution, any patient who required > 10 inhalations of reliever medication on any 1 day was asked to contact the investigator for reassessment.

Randomisation and blinding

The randomisation schedule was computer-generated at AstraZeneca Research and Development, Charnwood, UK. Within each centre, patients were randomised strictly sequentially as they became eligible. Individual treatment codes and code envelopes (indicating the treatment allocation for each randomised patient) were provided, but code envelopes were to be opened only in case of medical emergencies.

To maintain the blinding, all patients received three inhalers. Patients were instructed to take one
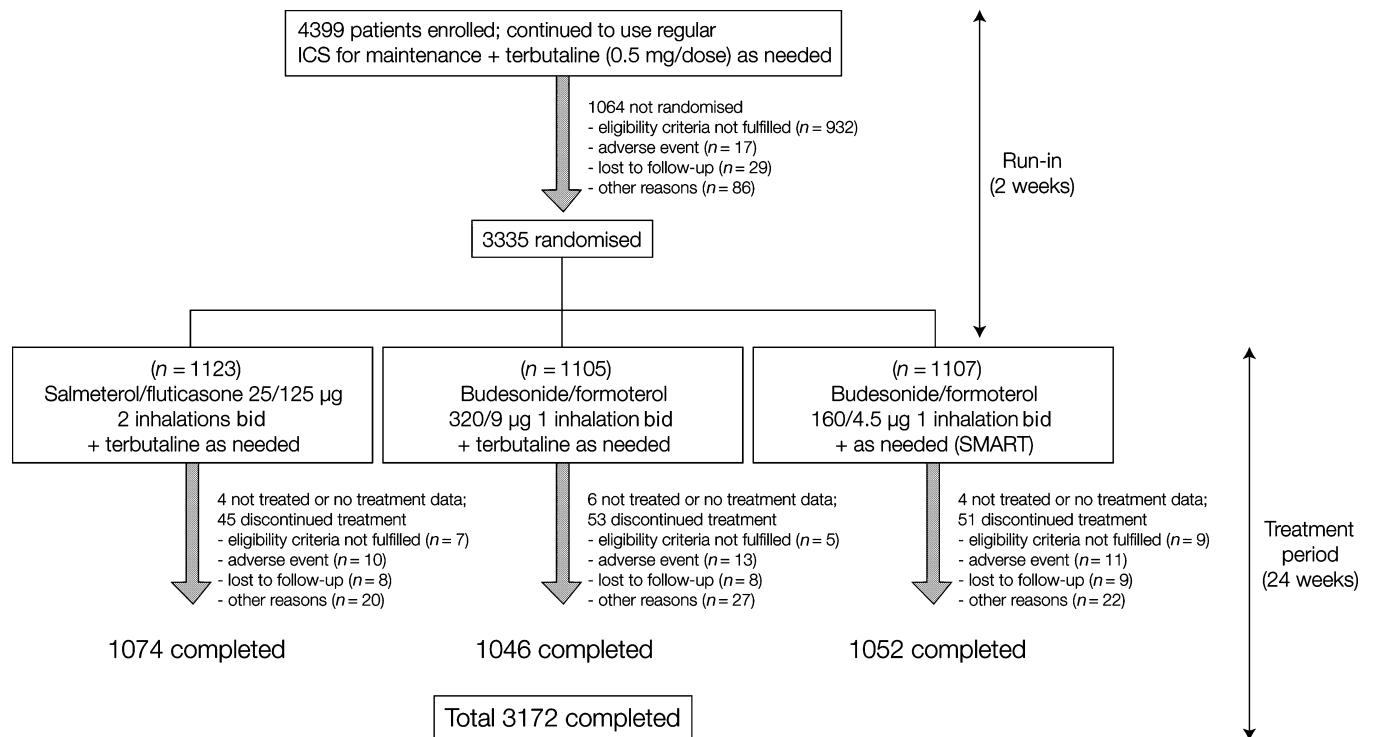
Figure 1 Patient flow. bid, twice daily; ICS, inhaled corticosteroid; SMART, Symbicort® maintenance and reliever therapy. Terbutaline dose expressed as 0.5 mg/inhalation metered dose corresponds to 0.4 mg/inhalation delivered dose

inhalation from the inhaler with the red grip (budesonide/formoterol or placebo Turbuhaler) and two inhalations from the pMDI (salmeterol/fluticasone or placebo Evohaler) upon rising and before going to bed; for symptom relief, as-needed inhalations were to be taken from the inhaler with the white grip (budesonide/formoterol or terbutaline Turbuhaler).

Efficacy measures

The primary objective of this study was to compare the efficacy of SMART [budesonide/formoterol (160/4.5 μg one inhalation bid) plus additional inhalations as needed], with salmeterol/fluticasone (25/125 μg two inhalations bid) plus terbutaline (0.4 mg/inhalation as needed). The primary variable was the time to first severe exacerbation. Severe exacerbations were defined as deterioration in asthma resulting in hospitalisation or emergency room (ER) treatment, or the need for oral steroids for ≥ 3 days (as judged by the investigator). To ensure that the results obtained were not specific to choice of ICS/LABA combination therapy or delivery device, predefined secondary objectives investigated were a combination of the efficacy of SMART vs. budesonide/formoterol (320/9 μg one inhalation bid) plus terbutaline (0.4 mg/inhalation as needed) both delivered by Turbuhaler, with an additional comparison of the efficacy between the two fixed-dose ICS/LABA

regimen. Secondary outcome variables were the total numbers of severe exacerbations; inhalations of as-needed medication; change in morning and evening peak expiratory flow (PEF), FEV$_1$, asthma symptom score, nights with awakenings caused by asthma, symptom-free days, as-needed-free days, asthma-control days and the number of mild exacerbations.

Patients completed a daily diary throughout the study in which they recorded PEF, symptoms, reliever use and intake of maintenance medication. Adherence to prescribed treatment was checked by the investigator at every visit. Daytime and night-time asthma symptom scores, measured on a scale of 0–3 (where 0 = no symptoms and 3 = incapacitating symptoms), were also recorded; these scores were summed to obtain the total daily score (range 0–6). The percentage of symptom-free days, nights free of awakenings, reliever-free days and asthma control days (a night and a day without asthma symptoms, no night-time awakenings caused by asthma and no reliever use) were calculated from diary-card data. Mild exacerbation days, defined as a day with any one of the following: morning PEF ≥ 20% below baseline, daily as-needed medication use ≥ 2 inhalations above baseline or a night with an asthma-related awakening, were also calculated from diary-card data. A mild exacerbation was defined as two consecutive mild exacerbation days satisfying the same criterion.

FEV_1 was assessed by spirometry, performed as recommended by the European Respiratory Society (18), at each clinic visit. The best of three satisfactory FEV_1 tests was recorded (18,19). Following instruction, patients recorded morning and evening PEF using a Mini-Wright® peak flow meter (Clement Clarke, Harlow, UK). Measurements were to be carried out before inhalation of the study medication. The highest of three consecutive measurements was recorded.

The Asthma Control Questionnaire (ACQ) 5-item version (ACQ-5) (20,21) and Asthma Quality of Life Questionnaire [standardised version; AQLQ(S)] (22) were self-administered at clinic visits.

Tolerability was assessed by the recording of adverse events at clinic visits. Investigators were provided with a set of instructions to be used for the interpretation of causality judgement.

Overall ICS treatment load was compared between groups by converting ICS doses to beclomethasone dipropionate (BDP)-equivalent ICS doses. These calculations were based on the GINA (13) estimates of equipotence of ICS doses as metered doses: fluticasone 500 µg = budesonide 800 µg = beclomethasone 1000 µg; 800 µg budesonide metered dose = 640 µg delivered dose.

Statistical analysis

The study was powered to detect a difference in the primary end-point (time to first severe exacerbation). With a total of 1000 patients/group, a log-rank test (at the two-sided 5% significance level) had a 90% chance of detecting a difference between treatment groups, assuming a true difference of 20% vs. 14.5% in the proportion of patients experiencing a severe exacerbation (23). All patients with data after randomisation were included in the intention-to-treat population for all efficacy analyses. The safety analyses were based on all patients who received ≥ 1 dose of study drug.

The time to first severe exacerbation was described using Kaplan–Meier plots and was compared between treatments using a log-rank test. Further description of treatment differences was obtained using a Cox proportional hazards model stratified by country, with treatment as a factor. The total number of severe exacerbations was compared between treatment groups using a Poisson regression model, with treatment and country as factors and time in the study as an offset variable.

Changes in diary-card variables from the average value during run-in (average value over the last 10 days of run-in) to the average value during the treatment period were compared between treatments using an analysis of variance (ANOVA) model, with treatment and country as fixed factors and the run-in

means as a covariate. Change in FEV_1 from baseline to the average value during visits 3–5 was analysed using a similar ANOVA, with baseline values as a covariate. The ACQ and AQLQ(S) overall scores were analysed in the same way as FEV_1, with the exception that, for AQLQ(S), the change from baseline to the last visit on treatment was used.

Results

Patient profile

Patient flow is summarised in Figure 1. Of the 4399 patients enrolled at 235 centres in 16 countries, 3335 were randomised to treatment. The most common reasons for exclusion from randomisation were failure to meet defined criteria for asthma severity, specifically spirometry criteria and use of as-needed medication during the run-in period. There were 409 protocol deviations in 327 patients, none of which justified exclusion of data from the analysis. Patient demographics are shown in Table 1. Self-reported adherence to maintenance medication was high; 99% of patients in all groups reported taking more than 81% of their maintenance medication.

Severe exacerbations

SMART prolonged the time to first severe exacerbation compared with fixed-dose salmeterol/fluticasone and budesonide/formoterol (log-rank test p = 0.0034 and p = 0.023 respectively; Figure 2). There was a 33% reduction in the hazard ratio (HR) for a first severe exacerbation with SMART compared with salmeterol/fluticasone [HR 0.67; 95% confidence interval (CI) 0.52–0.87; p = 0.003] and a 26% reduction compared with fixed-dose budesonide/formoterol (HR 0.74; 95% CI 0.56–0.96; p = 0.026). The two fixed-dose groups did not differ with respect to time to first severe exacerbation (Table 2). The total number of severe asthma exacerbations was reduced by 39% [relative rate (RR) 0.61; 95% CI 0.49–0.76; p < 0.001] in the SMART group compared with fixed-dose salmeterol/fluticasone and by 28% (RR 0.72; 95% CI 0.57–0.90; p = 0.0048) compared with fixed-dose budesonide/formoterol. The total number of exacerbations was similar in the two fixed-dose groups (Figure 3a).

The total number of hospitalisations/ER treatments was reduced in both budesonide/formoterol groups compared with the fixed-dose salmeterol/fluticasone group: there was a 39% rate reduction in the SMART group (RR 0.61; 95% CI 0.44–0.83; p = 0.0015) and a 32% reduction in the fixed-dose budesonide/formoterol group (RR 0.68; 95% CI 0.51–0.92; p = 0.013; Figure 3b). The difference between the two budesonide/formoterol groups was not statistically significant.

Table 1 Patients' baseline characteristics

Characteristic	Salmeterol/fluticasone (n = 1123)	Budesonide/formoterol (n = 1105)	SMART (n = 1107)
Male, n (%)	484 (43)	448 (41)	479 (43)
Mean age, years (SD)	38 (17)	38 (17)	38 (17)
Age, n (%)			
≥ 18 years	912 (81)	892 (81)	908 (82)
12–17 years	211 (19)	213 (19)	197 (18)
Smoking status			
Never, n (%)	904 (80)	865 (78)	873 (79)
Previous, n (%)	165 (15)	169 (15)	178 (16)
Current, n (%)	54 (5)	71 (7)	56 (5)
Mean FEV_1, % predicted (SD)	73 (14)	73 (14)	72 (14)
Mean FEV_1 reversibility, % (SD)	23 (12)	25 (14)	24 (12)
Mean ICS at study entry, μg/day (SD)	744 (230)	750 (262)	740 (240)
LABA use at study entry, n (%)	525 (47)	518 (47)	509 (46)

SMART, Symbicort® (budesonide/formoterol) maintenance and reliever therapy; FEV_1, forced expiratory volume in 1 s; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist.
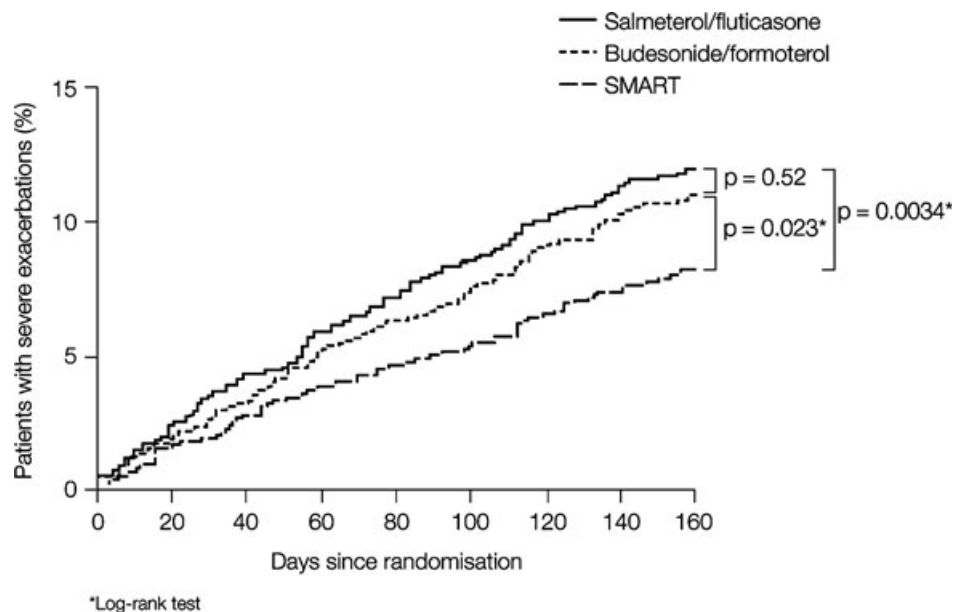

Figure 2 Time to first severe exacerbation (deterioration in asthma resulting in hospitalisation/emergency room treatment, or the need for oral steroids for ≥ 3 days). SMART, Symbicort® (budesonide/formoterol) maintenance and reliever therapy

The total exacerbation burden in days is shown in Table 2. The total number of days with exacerbations requiring oral steroid use was reduced by 41–45% with SMART compared with both fixed-dose regimens. Moreover, compared with fixed-dose treatment, SMART reduced the number of days with exacerbations requiring hospitalisation/ER treatment by 38–61% (Table 2).

A *post hoc* analysis, based on interaction between age-class and treatment, indicated that the size of the reduction in the overall exacerbation rate in the SMART group was consistent for adults (aged ≥ 18 years) and adolescents (aged < 18 years) (p =

0.84, interaction test). Adults treated with SMART had a 39% and 29% reduction in severe exacerbations vs. fixed-dose salmeterol/fluticasone (p < 0.001) and fixed-dose budesonide/formoterol (p = 0.0043) respectively. Similarly, the small number of adolescents treated with SMART had non-statistically significant reductions in severe exacerbations of 42% and 24% respectively.

Mild exacerbations

No significant differences were seen between the SMART group and the two fixed-dose regimens in the number of mild exacerbation days or the time to

Table 2 Exacerbation burden

Exacerbation burden	Salmeterol/ fluticasone	Budesonide/ formoterol	SMART	Treatment comparison of hazard ratios (95% CI)		
				SMART vs. salmeterol/ fluticasone	SMART vs. budesonide/ formoterol	Budesonide/formoterol vs. salmeterol/ fluticasone
All event types						
No. patients having at least one severe exacerbation (%)*	138 (12)	126 (11)	94 (9)	0.67 (0.52, 0.87); p = 0.003	0.74 (0.56, 0.96); p = 0.026	0.91 (0.72, 1.16); p = 0.45
Rate/100 patients/6 months†	19	16	12	0.61 (0.49, 0.76); p < 0.001	0.72 (0.57, 0.90); p = 0.0048	0.85 (0.69, 1.04); p = 0.1
Total no. severe exacerbations (total no. days with event)	208 (1327)	173 (1143)	125 (692)			
Hospitalisation/ER treatment						
No. patients having at least one hospitalisation/ER treatment (%)*	70 (6)	50 (5)	48 (4)	0.69 (0.48, 0.99); p = 0.047	0.97 (0.65, 1.44); p = 0.87	0.71 (0.49, 1.02); p = 0.066
Rate/100 patients/6 months†	8	5	5	0.61 (0.44, 0.83); p = 0.0015	0.88 (0.63, 1.24); p = 0.47	0.68 (0.51, 0.92); p = 0.013
Total no. events (total no. days with event)	106 (278)	72 (174)	64 (108)			

*Cox proportional hazards model of time to first severe exacerbation; †Comparisons of relative rates from a Poisson regression. SMART, Symbicort® (budesonide/formoterol) maintenance and reliever therapy; ER, emergency room.

a mild exacerbation (two consecutive mild exacerbation days). There was an average of 27 mild exacerbation days/patient/6 months in the salmeterol/ fluticasone group, 29 in the fixed-dose budesonide/ formoterol group and 27 in the SMART group. Overall, 660 (59%), 689 (63%) and 674 (61%) salmeterol/fluticasone, budesonide/formoterol and SMART patients, respectively, experienced a mild exacerbation.

Asthma symptoms

SMART provided similar improvements to fixed-dose budesonide/formoterol and salmeterol/fluticasone in all symptom-control measures used to assess daily variability in asthma control (Table 3).

Asthma questionnaires

Patients in all three treatment groups reported similar improvements in AQLQ(S) and ACQ-5 scores. Changes of 0.5 units from run-in indicate clinically relevant improvements in both scores (21,24). These improvements were indicated by an increase in AQLQ(S) score of 0.76–0.78 (Figure 4a) and the reduction in ACQ-5 score of 0.74–0.79 in the three treatment groups (Figure 4b).

Lung function

FEV_1 and PEF values during the run-in and treatment periods are presented in Table 3. No differences between the three treatment groups in any of these measures were detected.

Overall treatment load

As-needed reliever medication use is shown in Table 3. As-needed use was similar in the SMART and fixed-dose groups, decreasing by 8–9 inhalations/week compared with baseline in all three groups. The range of daily mean BDP-equivalent ICS doses [calculations based on GINA estimations of equipotence of ICS in metered doses: fluticasone 500 μg = budesonide 800 μg = beclomethasone 1000 μg (13)] for the three treatment groups are summarised in Figure 5. While individual mean doses varied in SMART patients as a consequence of the treatment concept, there was an overall reduction in mean ICS dose in the SMART group compared with both fixed-dose groups. The overall number of days per treatment group when oral corticosteroids were required for asthma was 619 days in the SMART group, 1044 days with budesonide/formoterol and 1132 days with salmeterol/fluticasone.

Safety

All three treatments were well tolerated and there were no notable between-group differences in the number or severity of adverse events. The most frequently reported adverse events were upper respiratory tract infection, pharyngitis and nasopharyngitis. The incidence of pharmacologically predictable adverse events related to ICS and LABA use was low and comparable in all treatment groups.
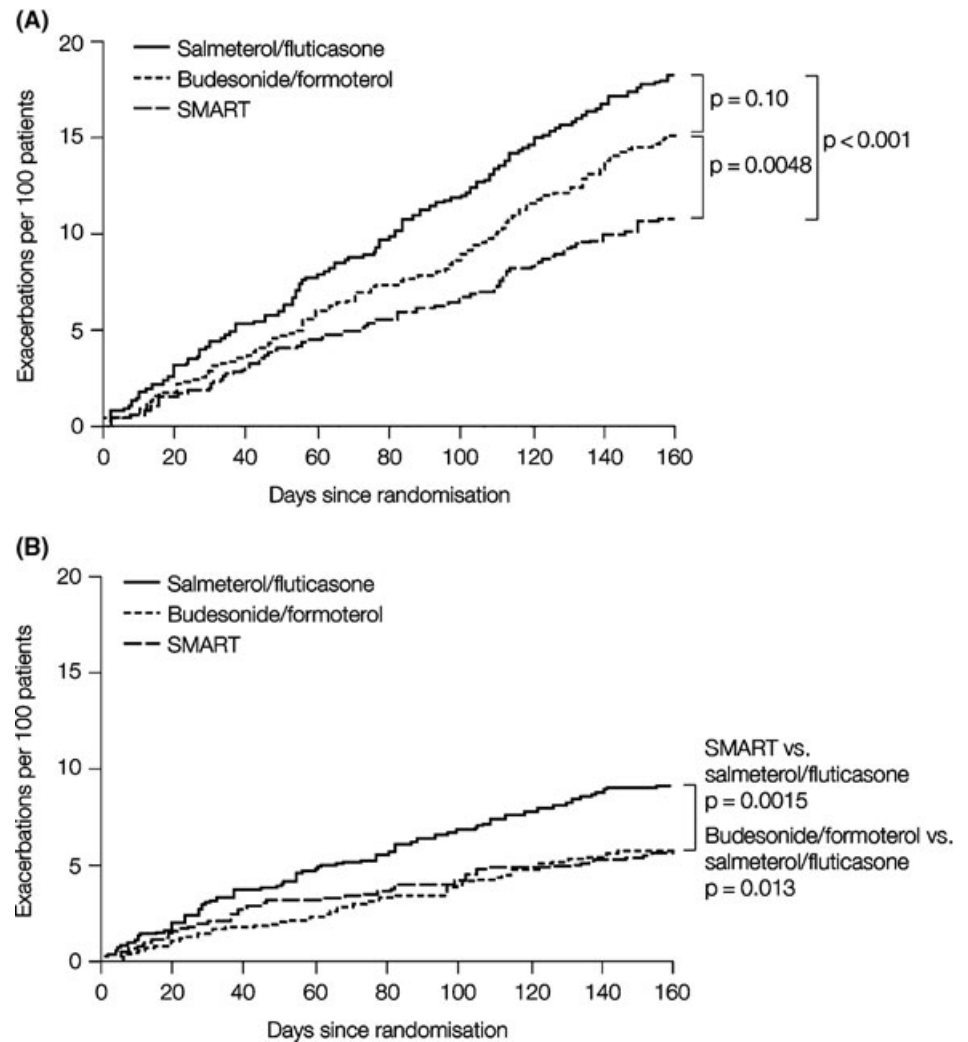
Figure 3 Cumulative rate of (A) severe exacerbations and (B) hospitalisations/ emergency room treatments caused by asthma; p-values are derived from relative rate analysis (Poisson regression analysis). SMART, Symbicort® (budesonide/ formoterol) maintenance and reliever therapy

Serious adverse events were uncommon and their incidence was comparable across all three treatment groups: 32 patients (3%) in the salmeterol/fluticasone group, 39 patients (4%) in the fixed-dose budesonide/ formoterol group and 31 patients (3%) in the SMART group experienced such events. Four serious adverse events were considered by the investigator to be causally related to the study drug: three in the SMART group (pneumonia, gastritis and asthma) and one in the salmeterol/fluticasone group (asthma).

Two deaths occurred during the study, one in the SMART group (respiratory failure) and one in the salmeterol/fluticasone group (cardiac failure). Neither death was considered by the investigator to be causally related to the study drug.

Discussion

This study validates the concept of SMART. Reducing the maintenance dose of budesonide/formoterol by 50% and using budesonide/formoterol as reliever medication instead of terbutaline reduces the risk and rate of severe exacerbations in adults and adolescents with asthma compared with a higher maintenance dose of fixed-dose budesonide/formoterol or salmeterol/fluticasone. Other measures of daily asthma control were similar across the three treatment groups. This improvement in the outcome of asthma treatment was seen even though the total dose of ICS administered using the SMART regimen was 25% lower in BDP equivalents than those administered in the fixed-dose regimens. Thus, while conventional fixed-dose combination therapy can provide well-controlled asthma for many patients, similar improvements can be achieved with the SMART approach while further reducing exacerbations and drug load.

The reduction in exacerbations and associated medical care was substantial. Patients in the SMART group had 28–39% fewer exacerbations than those in the fixed-dose groups. Extrapolating these 6-month data to a 1-year period suggests

Table 3 Clinical outcomes

Efficacy end-point	Salmeterol/fluticasone	Budesonide/formoterol	SMART	Treatment comparison of clinical outcomes: mean difference (95% CI)		
				SMART vs. salmeterol/fluticasone	SMART vs. budesonide/formoterol	Budesonide/formoterol vs. salmeterol/fluticasone
Asthma symptoms						
Total score (0–6)						
Run-in	1.93	1.93	1.91	0.04 (−0.03, 0.10)	0.00 (−0.07, 0.06)	0.04 (−0.02, 0.11)
Treatment	1.03	1.07	1.06			
Symptom-free days (%)						
Run-in	8.6	8.8	9.3	−2.5 (−5.3, 0.3)	−0.8 (−3.6, 2.0)	−1.6 (−4.4, 1.2)
Treatment	46.0	44.6	44.2			
Asthma-control days* (%)						
Run-in	5.7	5.9	5.8	−2.6 (−5.4, 0.2)	−0.7 (−3.6, 2.1)	−1.9 (−4.7, 1.0)
Treatment	43.7	42.2	41.3			
Night-time awakenings (%)						
Run-in	31.5	32.8	33.7	−0.8 (−2.4, 0.9)	−1.0 (−2.6, 0.7)	0.2 (−1.4, 1.8)
Treatment	14.0	14.6	14.1			
Use of as-needed medication						
Total no. inhalations/day						
Run-in	2.33	2.31	2.29	0.07 (−0.02, 0.16)	−0.03 (−0.12, 0.06)	0.10 (0.01, 0.19)†
Treatment	0.96	1.05	1.02			
As-needed-free days (%)						
Run-in	8.8	8.8	8.9	−3.2 (−6.0, −0.5)†	−1.8 (−4.6, 1.0)	−1.4 (−4.2, 1.4)
Treatment	59.1	57.8	56.0			
Lung function						
FEV_1 (l)						
Visit 2	2.43	2.42	2.44	0.006 (−0.025, 0.037)	0.005 (−0.026, 0.037)	0.000 (−0.031, 0.031)
Visit 3–5 (mean)	2.67	2.66	2.69			
Morning PEF (l/min)						
Run-in	338	335	337	−3.2 (−6.9, 0.4)	−0.7 (−4.5, 3.0)	−2.5 (−6.2, 1.2)
Treatment	367	362	363			
Evening PEF (l/min)						
Run-in	347	344	346	−1.3 (−4.9, 2.3)	−0.6 (−4.3, 3.0)	−0.7 (−4.3, 3.0)
Treatment	370	366	368			

*Asthma-control days were defined as a day with no symptoms (day or night), no awakenings caused by asthma and no as-needed medication use; †Statistically different at the 5% level of significance. SMART, Symbicort® (budesonide/formoterol) maintenance and reliever therapy; FEV_1, forced expiratory volume in 1 s; PEF, peak expiratory flow; CI, confidence interval.

that treating 100 matched patients for 1 year with SMART compared with fixed-dose salmeterol/fluticasone and fixed-dose budesonide/formoterol would prevent 15 and 9 severe exacerbations respectively (the number needed to treat to prevent one exacerbation was 7 and 11 respectively). There were fewer exacerbations requiring hospitalisation or ER treatment in the SMART group, with such events occurring on 61% fewer days compared with salmeterol/fluticasone and on 38% fewer days compared with fixed double-dose budesonide/formoterol. Exacerbations leading to ER treatment or hospitalisation were approximately 1 day longer on average (based on the number of days with these events) in the fixed-dose salmeterol/fluticasone vs. the SMART group.

It seems unlikely that the reduced number of SMART patients who still experienced exacerbations did so as a result of using a maintenance dose that was too low. All patients using fixed-combination ICS/LABA in our study received the equivalent of the maximally effective dose used in the landmark FACET exacerbation study (25). With SMART, the average dose used approached 75% of the FACET dose. Nevertheless, SMART resulted in further reductions in exacerbations of all types vs. both fixed-dose groups. This suggests that the SMART approach has exceeded a previous gold standard for exacerbation control, while reducing overall steroid and LABA doses.

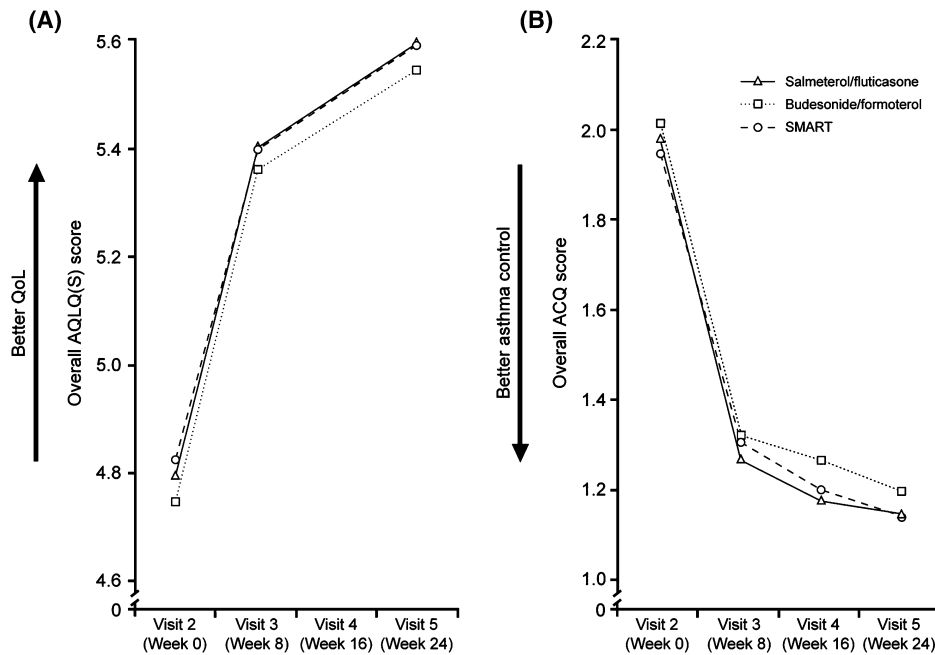The precise reason for the overall reduction in exacerbations with the SMART approach remains to

Figure 4 Mean overall (A) Asthma Quality of Life Questionnaire (standardised version) [AQLQ(S)] and (B) Asthma Control Questionnaire (ACQ) scores over the duration of the study. QoL, quality of life; SMART, Symbicort® (budesonide/formoterol) maintenance and reliever therapy
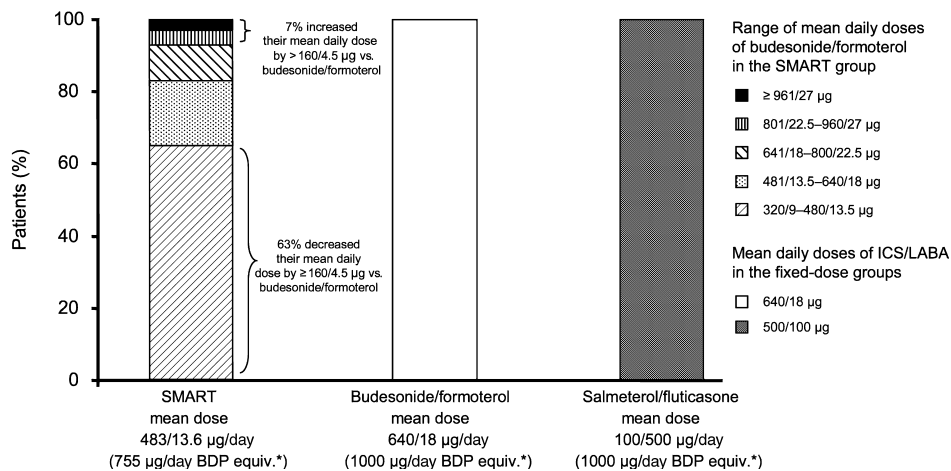

Figure 5 Range of daily mean doses of ICS/LABA reported by individual study patients. *Mean ICS doses converted to BDP equivalents based on GINA (13) guidelines. Compared with fixed-dose budesonide/formoterol treatment, 9 : 1 (ratio: 63% divided by 7%) SMART-treated patients reduced their mean daily dose by at least 160/4.5 μg than increased their dose by at least 160/4.5 μg. SMART, Symbicort® (budesonide/formoterol) maintenance and reliever therapy; BDP, beclomethasone dipropionate

be fully elucidated. Temporary dose increases resulting from as-needed formoterol and budesonide are likely to contribute to the overall efficacy of this treatment. As-needed treatment immediately following exposure to environmental triggers that lead to a temporary loss of symptom control is likely to result in an increase in controller therapy in line with disease activity. During periods when asthma control is stable, with no need for symptom relief (56% of study days), patients using the SMART approach default solely to maintenance budesonide/formoterol, but at half the daily dose compared with the fixed-dose regimen. Thus, maintenance plus as-needed budesonide/formoterol responds more effectively and efficiently to the natural variations in asthma control that are evident even when using an ICS/LABA regimen at a higher daily dose.

Timely increases in the ICS dose have been suggested as the defining feature of SMART (9,26,27). Thus, budesonide-containing reliever therapy can ensure that an increase in anti-inflammatory therapy is delivered as required during periods of deteriorating symptoms and increased need for reliever medication (28). In our study, SMART patients used more budesonide/formoterol than the fixed-dose budesonide/formoterol group on only 13% of days, with half the dose used on 56% of days. This suggests that the timing of the dose increase, not the overall dose, is of greater importance. Whether this benefit is related to dose clustering of the as-needed ICS over a spread of days, or to the more efficient spread of the dose throughout the day during periods of poor control, is not clear.

Studies have shown that increasing the dose and frequency of administration of ICS improves asthma control in patients with acute worsenings (29). As lung tissue concentrations of ICS decline between maintenance doses (30,31), as-needed ICS may restore concentrations when the level of ICS can be suboptimal. In contrast, approaches that rely on a significant deterioration in asthma symptoms and action plans that instruct patients to double their ICS dose without an increase in dose frequency have been demonstrated to be wholly ineffective at preventing exacerbations (32,33).

Marked improvements in daily symptom control were seen in all three treatment groups, despite patients in the SMART group using a lower maintenance dose of ICS/LABA. Compared with run-in, patients in all groups experienced similar improvements in asthma control and quality of life (assessed by questionnaires) and more asthma-control days and fewer asthma-related awakenings (assessed by daily diaries). The increase in day-to-day asthma control seen in all three groups can be extrapolated to at least 130 extra days per year with full symptom control without the use of reliever medication and at least 64 extra nights per year without awakenings. There was no evidence of any clinically relevant between-group differences in any of these control measures. Numbers of days with symptom flares (mild exacerbation days) were equally distributed among the three treatment groups. Furthermore, no differences in lung function were detected between the treatment groups, despite lower use of bronchodilator therapy (maintenance and as needed) in the SMART group. The mean daily ICS dose in BDP equivalents (13) was approximately 750 µg in the SMART group vs. 1000 µg in both fixed-dose groups. In total, only eight SMART patients (< 1%) used a mean dose of budesonide equivalent to > 2000 µg/day of BDP. The majority of SMART patients used less ICS and less LABA than in the fixed-dose budesonide/formoterol group, i.e. for every SMART patient who took 160/4.5 µg/day of budesonide/formoterol more than in the fixed-dose group, there were nine SMART patients using at least 160/4.5 µg/day less. The fact that day-to-day symptom control was similar in all three groups, even with the clear difference observed in severe exacerbation rates, serves as a reminder that these measures reflect different aspects of asthma control, both of which need to be considered when evaluating asthma management programmes. Our results show the improved control seen with as-needed budesonide/formoterol using the SMART concept vs. fixed-dose ICS/LABA + SABA therapy is greater for exacerbations than for minor symptoms. Minor symptoms dictate the need for an increase in as-needed therapy to a similar extent in all treatment groups, but with the SMART asthma management approach this leads to an increase in anti-inflammatory therapy at the right time, resulting in fewer exacerbations.

Although there were no clinically important differences between the two fixed-dose groups in the majority of outcomes, one clinically relevant and statistically significant advantage of budesonide/formoterol was observed. Patients treated with fixed-dose budesonide/formoterol had 32% fewer exacerbations requiring hospitalisation/ER treatment vs. those in the salmeterol/fluticasone group. It is noteworthy that this is the largest study ever performed with two fixed-dose ICS/LABA combinations and, as such, may be the first study able to detect such differences. A similar trend was seen in a smaller study (approximately 200 patients in each group) in which three vs. eight events required hospitalisation/ER treatment in patients treated with the same fixed dose of budesonide/formoterol or salmeterol/fluticasone respectively (1). The reasons for this difference remain unclear and may require further exploratory analysis. One possible reason may be that formoterol, a full β_2-agonist, is more efficacious than salmeterol, a partial β_2-agonist, during periods of increased inflammation or challenge (34,35). Another factor may be the beneficial effects on neutrophilic inflammation that have been described for formoterol but to a lesser extent for salmeterol (36).

In a controlled clinical setting, SMART has previously been shown to improve asthma control compared with the same maintenance dose of budesonide/formoterol plus terbutaline for relief (9). In a study allowing titration of the maintenance dose as judged appropriate by the treating physician, SMART patients had fewer exacerbations and better asthma control than those receiving salmeterol/fluticasone up to a dose of 50/500 µg bid (40% of

patients) (12). Together these studies suggest that SMART is uniquely effective at reducing exacerbations and their associated morbidity compared with fixed-dose ICS/LABA, even at a higher daily dose. The study by Vogelmeier et al. was performed open label to allow easier maintenance-dose titration; we have now demonstrated in a very large double-blind study that SMART leads to fewer exacerbations with no increase in fluctuations of daily asthma control compared with a twofold higher maintenance dose of budesonide/formoterol or a corresponding dose of salmeterol/fluticasone. The SMART approach has also been demonstrated to deliver significant cost savings compared with the higher maintenance dose of budesonide/formoterol or salmeterol/fluticasone plus terbutaline as needed, when applying 2004 UK unit costs to the present dataset (37).

In the present study, patients who were infrequent users of reliever medication were excluded after the run-in period. This may have excluded a small minority of patients for whom the benefit of SMART is unknown. Nonetheless, a recent survey of 1921 patients using regular ICS or ICS/LABA medication has highlighted that 71% of these patients used their reliever medication every day and 47% had experienced one or more exacerbations in the previous year (7), suggesting that the results of the present study have wide-reaching applicability to real-life asthma. Finally, this study, in addition to previous research (9–11), has confirmed that the SMART treatment approach is well tolerated with no increase in asthma-related events of any type compared with higher doses of ICS alone or an alternative combination ICS/LABA regimen.

In conclusion, compared with a twofold higher fixed maintenance dose of budesonide/formoterol or a corresponding dose of salmeterol/fluticasone plus SABA for relief, SMART reduces the incidence of severe asthma exacerbations and maintains similar daily asthma control at a lower overall drug load. With this combination of increased efficacy and simplicity, the SMART approach represents a significant improvement over fixed, twice-daily combinations of higher-dose ICS/LABA, which have until now been regarded as the most effective way to manage moderate and severe persistent asthma.

Acknowledgements

Supplementary material

The following supplementary material is available for this article online:

Slideshow S1. Effect of budesonide/formoterol maintenance and reliever therapy on asthma exacerbations.

This material is available as part of the online article from http://www.blackwell-synergy.com

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