Budesonide/Formoterol Maintenance Plus Reliever Therapy: A New Strategy in Pediatric Asthma

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Budesonide/Formoterol Maintenance Plus Reliever Therapy*

A New Strategy in Pediatric Asthma

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Objectives: **A fixed combination of long-acting β_2-agonists (LABA) plus inhaled corticosteroids (ICS) has never been proven to reduce asthma exacerbations vs ICS alone in children. This 12-month, double-blind, randomized study in 341 children (age range, 4 to 11 years) with asthma uncontrolled on ICS investigated whether a novel regimen using budesonide/formoterol for maintenance and reliever therapy (Symbicort maintenance and relief therapy [SMART]) [Symbicort; AstraZeneca R&D; Lund, Sweden] could reduce exacerbations.**

Methods: **Patients received SMART (budesonide/formoterol 80/4.5 μg qd maintenance plus additional inhalations for symptom relief), budesonide/formoterol 80/4.5 μg qd for maintenance (fixed combination), or higher-dose budesonide 320 μg qd (fixed-dose budesonide). Blinded as-needed medication (terbutaline 0.4 μg) was provided in both fixed-dose groups.**

Results: **SMART prolonged the time to first exacerbation vs fixed-dose budesonide ($p = 0.02$) and fixed-dose combination ($p < 0.001$). Rates of exacerbation requiring medical intervention were reduced by 70 to 79% with SMART vs fixed-dose budesonide and fixed-dose combination (0.08/patient vs 0.28/patient and 0.40/patient, respectively; both $p < 0.001$). Mild exacerbation days and awakenings were significantly lower with SMART; yearly growth improved by 1.0 cm vs fixed-dose budesonide ($p < 0.01$).**

Conclusion: **The SMART regimen using budesonide/formoterol for both maintenance and as-needed symptom relief reduces the exacerbation rate compared with both fixed-dose combination and higher fixed-dose ICS alone in children with asthma.** ***(CHEST 2006; 130:1733–1743)***

Key words: asthma; budesonide/formoterol; inhaled corticosteroids; long-acting β_2-agonist; pediatric; Symbicort

Abbreviations: ACTH = adrenocorticotrophic hormone; AE = adverse events; ANOVA = analysis of variance; ED = emergency department; ICS = inhaled corticosteroids; LABA = long-acting β_2-agonists; PEF = peak expiratory flow; SMART = Symbicort maintenance and relief therapy

The benefit of asthma control from adding long-acting β_2-agonists (LABA) remains unclear in children.[1–4] Previous pediatric studies[1–8] found no protection against asthma exacerbations from fixed-combination therapy with inhaled corticosteroids (ICS)/LABA. This may partly be because pediatric

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asthma is often an episodic disease with a particular strong seasonality, associated with few symptoms and near-normal lung function for long periods punctuated by periods of increases in symptoms and exacerbations.[9] Children therefore often move in and out of the classical disease severity categories. Traditional dosing strategy emphasizes fixed dosage that is decided based on the history and therefore inevitably lags behind variation in disease activity, and carries a risk of overtreatment or undertreatment. Instead, new pediatric management strategies should consider fluctuations in disease activity and proactively adjust therapy to periods of worsening. Furthermore, compliance is a well-recognized flaw in any fixed treatment strategy of chronic diseases in children and adolescents.[10] Written management plans are recommended[11] but rarely applied,[12] and adherence to such plans is generally poor[13] and of limited effectiveness.[14] Indeed, the general recommendation to double the dose of ICS during exacerbations is without convincing evidence.[15,16]

We therefore challenged the current treatment paradigm of fixed dosing of ICS/LABA for moderate-to-severe persistent asthma in pediatrics, instead emphasizing intermittent use in addition to the regular low-dose use titrating the steroid dose dynamically to the disease activity. The treatment approach in which patients receive ICS/LABA (budesonide/formoterol) for maintenance and reliever therapy in response to symptoms differs from traditional treatment regimens, as it involves patients using one inhaler to control and treat their asthma symptoms without the requirement for a separate short-acting rescue inhaler. We suggest a simplified ICS/LABA dosing strategy as a new strategy for persistent pediatric asthma.

We initially presented this new concept at the International Pediatrics Respiratory and Allergy Congress in 2001 and recently reported the compiled results of both the pediatric and adult protocols in a 1-year study[17] in $>$ 2,700 asthma patients. This novel treatment strategy substantially reduced the incidence of exacerbations and repeat exacerbations, improved lung function, and reduced symptoms to a greater extent than a fourfold-higher dose of ICS alone.[17] This is in contrast to the Formoterol and Corticosteroids Establishing Therapy study,[18] which demonstrated that ICS plus LABA improved symptom control but was less effective at controlling exacerbations in comparison to a fourfold-higher dose of budesonide. The acronym SMART (Symbicort maintenance and reliever therapy) [Symbicort; AstraZeneca R&D; Lund, Sweden] was suggested for this novel strategy.

Pediatric patients should be given medicines that have been appropriately evaluated for their use in those populations. Too often, clinical asthma trials involving children and adults do not benefit children as a class because they rarely provide subset analysis of child subjects.[4,19] Established safety and efficacy in a predominantly adult population may not apply to children,[20] which recently caused both the US Food and Drug Administration[21,22] and European Union[23] to request separate pediatric assessment. This is particularly pertinent in view of the apparent discrepancy between the efficacy of LABA in pediatrics and adults.[2,3] Therefore, we prospectively planned a separate pediatric protocol and subanalysis within the main study.

The pediatric subgroup comprises 341 children 4 to 11 years of age. In this 12-month study in pediatric patients, the efficacy and safety of SMART were compared with that of two alternative regimens: budesonide/formoterol once daily (fixed combination) plus blinded terbutaline for rescue medication, or a fourfold-higher maintenance dose of budesonide (fixed-dose budesonide), plus blinded terbutaline.

Materials and Methods

Patients

Children aged 4 to 11 years with an asthma history $\geq$ 6 months and at least one clinically important asthma exacerbation in the 12 months before study entry were enrolled. All patients had used ICS (any brand) at a constant dose for $\geq$ 3 months (200 to 500 μg/d). At enrollment, patients had a prebronchodilator FEV_1 60 to 100% of predicted and $\geq$ 12% reversibility from baseline in FEV_1 15 min after inhalation of terbutaline (1 mg). To be eligible for randomization, patients had to have used eight or more inhalations of terbutaline in the last 10 days of run-in and up to seven inhalations on any 1 day. Any patient who had an exacerbation or required a change in ICS during the run-in was excluded.

The study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Approval from ethics committees was obtained from all centers. Written informed consent was obtained from all parents as well as written or oral consent from all children.

Study Design

The study (study code SD-039–0673) included a prospectively planned analysis of pediatric data from the pediatric protocol in a 12-month, randomized, double-blind, and parallel-group trial conducted at 41 centers in 12 countries. Data for the full study population of patients aged 4 to 80 years have been published previously.[17] Following a run-in period during which patients used their previous ICS plus terbutaline as needed, patients were randomized to one of three treatments: budesonide/formoterol (Symbicort via Turbuhaler; AstraZeneca R&D) 80/4.5 μg qd plus additional doses as needed (SMART); budesonide/formoterol 80/4.5 μg qd plus terbutaline 0.4 mg for rescue medication (fixed combination); or a fourfold-higher maintenance dose of budesonide 320 μg qd plus terbutaline 0.4 mg for rescue medication (fixed-dose budesonide). All maintenance and rescue medications were administered

via blinded Turbuhaler. Reliever medication was to be taken whenever the patients judged that it was needed. During the treatment period, however, the patients were not allowed to use more than eight inhalations of the study medication during 1 single day (*ie*, not more than seven as-needed inhalations per day in addition to their daily maintenance treatment). If the patient needed more medication, the investigator had to be contacted in order to decide what action should be taken.

The randomization schedule was generated using a computer program (RandLink; AstraZeneca; Lund, Sweden). Eligible patients were randomized to treatment in balanced blocks by consecutive patient number. All medications were administered from separate blinded inhalers; patients were able to differentiate between their maintenance and rescue medication by inhaler color and the labeling "maintenance" or "relief." The use of medications that might affect the study results was not permitted. This included the use of leukotriene receptor antagonists, which had to be discontinued at least 72 h before study visit 1, and ICS, which had to be discontinued from visit 2 (except for the treatment of severe asthma exacerbations).

Efficacy Assessments

The primary efficacy outcome was the time to first exacerbation. An asthma exacerbation was defined as a deterioration in asthma resulting in any one of the following: hospitalization/emergency department (ED) treatment; treatment with oral steroids; an increase in ICS (via a separate inhaler, *ie*, not study medication) and/or any other additional treatment; or morning peak expiratory flow (PEF) $\leq$ 70% of the baseline mean on 2 consecutive days. Exacerbations requiring medical intervention (hospitalization/ED treatment, treatment with oral steroids, an increase in ICS [via a separate inhaler], and/or other additional treatment) were analyzed separately.

A mild exacerbation day was defined as a day with morning PEF $\geq$ 20% below the average run-in value, as-needed medication use two or more inhalations a day above baseline, or awakenings due to asthma. A mild exacerbation was 2 consecutive mild exacerbation days of the same criterion.

Patients recorded their daily morning and evening pretreatment PEF measured using a PEF meter (Mini-Wright; Clement Clark, Harlow, UK), nighttime and daytime symptom scores (on a 3-point scale, with 0 indicating no symptoms and 3 indicating incapacitating symptoms), awakenings, as-needed medication use, and intake of study medication on diary cards. For patients who were unable to make their own judgments and recordings, the parent/guardian was responsible for completing the diary. FEV_1 was assessed by spirometry at the beginning and end of run-in and at 1, 3, 6, 9, and 12 months.

Safety Assessments

Safety was assessed at clinic visits by adverse events (AEs), ECG, vital signs, clinical chemistry, hematology, and urinalysis.

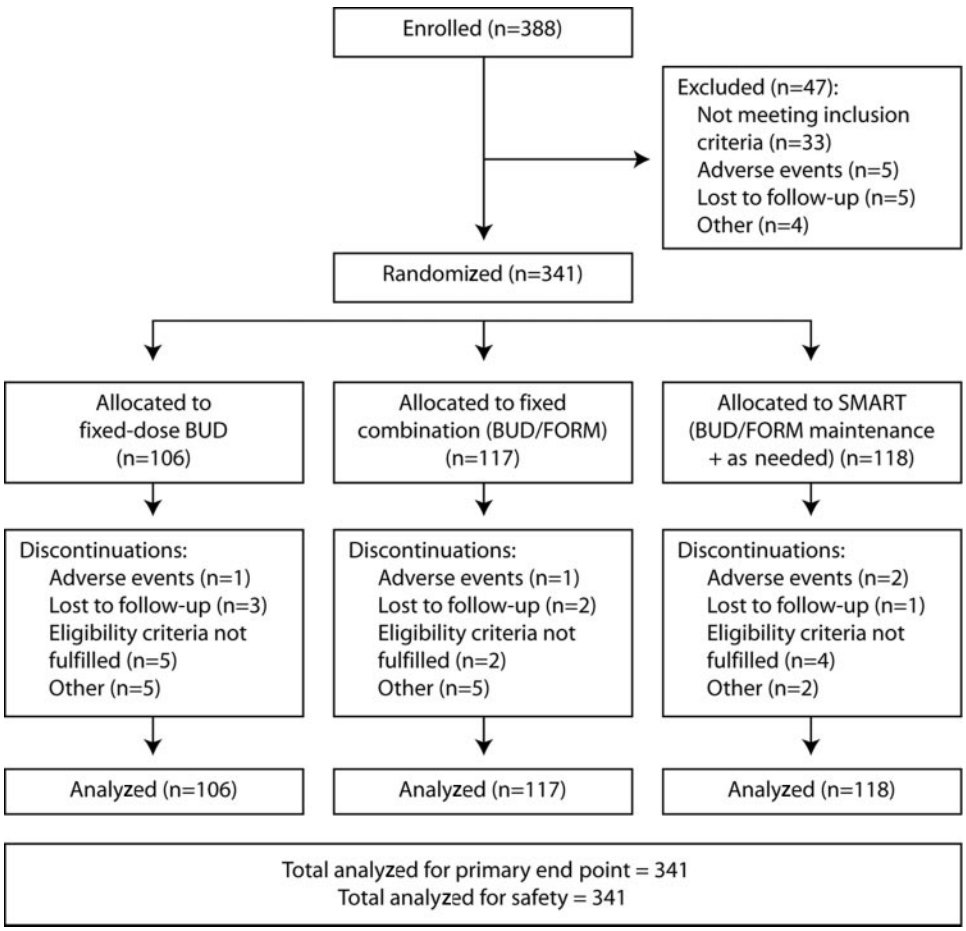

FIGURE 1. Patient flow. BUD = budesonide; FORM = formoterol.

Patient height was measured using local procedures before run-in and at 6 months and 12 months. As the same methods were used across all three groups, no bias would be expected. Morning cortisol levels were assessed in all patients at baseline and at 6 months and 12 months, and an adrenocorticotrophic hormone (ACTH) stimulation test was performed in a subgroup. Blood samples were analyzed by CRL Medinet (Breda, the Netherlands). For the ACTH test, a baseline plasma cortisol sample was obtained at 8:00 AM (± 30 min), immediately before IV injection of 0.25 mg tetracosactide; thereafter, plasma cortisol samples were analyzed at 30 min and 60 min after injection.

Data Analysis

The study was powered to detect differences in exacerbations in the overall population and not in the pediatric subgroup. However, 100 patients aged 4 to 11 years were planned to be recruited per group in order to compare the safety and efficacy of each treatment regimen in children. All analyses were performed on an intention-to-treat basis. All hypothesis testing was two sided; p values < 0.05 were considered statistically significant. Time to first exacerbation was described using Kaplan-Meier plots, and treatment groups were compared using a log-rank test. Analysis of the instantaneous risk of an exacerbation was performed using a Cox proportional hazards model with treatment as a factor. The total number of exacerbations was compared using a Poisson regression model with time in study as an offset variable.

Changes in diary card variables from baseline (average value over the last 10 days of run-in) were compared using analysis of variance (ANOVA), with treatment and country as factors and the baseline value as a covariate. Change in FEV_1 was analyzed using a similar ANOVA with the end of run-in value as a covariate.

Growth was calculated as change in height between enrollment and after treatment, divided by the time between the visits and multiplied by 1 year. Growth was compared between treatments using ANOVA with height at enrollment as a covariate. Changes in morning plasma cortisol and maximal plasma cortisol levels after ACTH stimulation from run-in to the end of the study were analyzed using a multiplicative (log transformation of data) ANOVA model and an additive ANOVA model, respectively.

Results

Of the 388 pediatric patients enrolled, 341 were randomized to receive one of the following: SMART (n = 118), fixed-dose combination (n = 117), or fixed-dose budesonide (n = 106). Patient flow is shown in Figure 1. Baseline characteristics were comparable between groups (Table 1). There were 34 patients with one or more protocol deviations, with no difference between treatments. None of the protocol deviations justified exclusion of data from the analysis, and all data were included where available.

Exacerbations

Overall, 14% of patients receiving the SMART regimen had an exacerbation, vs 38% and 26% of patients in the fixed-dose combination and fixed-dose budesonide groups, respectively (Fig 2; Table 2). The SMART regimen significantly prolonged the time to first exacerbation vs fixed-dose combination ($p < 0.001$) and fixed-dose budesonide ($p = 0.02$). The instantaneous risk of having an exacerbation was 66% lower with SMART vs fixed-dose combination

Table 1—*Baseline Characteristics

Characteristics	Fixed-Dose Budesonide (n = 106)	Fixed-Dose Combination (n = 117)	SMART (BUD/FORM Maintenance Plus as Needed) [n = 118]
Male/female gender	70/36	82/35	85/33
Age, yr	8 (4–11)	8 (4–11)	8 (4–11)
White race/other ethnicity	90/16	101/16	100/18
Asthma duration, yr†	3 (0–10)	3 (0–11)	3 (1–10)
ICS dose at entry, μg	321 (100–500)‡	302 (200–500)	319 (200–500)
FEV_1, L	1.6 (0.7–3.1)	1.5 (0.7–2.9)	1.6 (0.9–2.7)
FEV_1, % predicted normal	76 (60–100)	76 (54–99)‡	76 (57–108)‡
FEV_1, % reversibility	23 (11–58)‡	24 (12–70)	23 (12–89)
Morning PEF, L/min	221 (93–407)	216 (97–396)	226 (101–357)
Evening PEF, L/min	226 (98–393)	221 (85–390)	231 (101–360)
As-needed use, No. of inhalations over 24 h	1.6 (0.1–4.0)	1.6 (0.3–5.6)	1.7 (0.7–5.9)
As-needed-free days, %	17.4 (0–70)	17.2 (0–80)	15.3 (0–80)
Asthma symptom score (scale 0–6)	1.2 (0.0–3.4)	1.1 (0.0–3.5)	1.1 (0.0–4.4)
Symptom-free days, %§	28.9 (0–100)	36.4 (0–100)	35.3 (0–100)
Nighttime awakenings, %	11.0 (0–100)	12.8 (0–100)	10.8 (0–70)
Asthma control days, %‖	12.8 (0–70)	14.0 (0–80)	12.5 (0–80)

*Data are presented as mean (range) or absolute value unless otherwise indicated. See Figure 1 for expansion of abbreviations.
†Data are presented as median (range).
‡Deviation from inclusion criteria (included in the intention-to-treat population).
§Defined as a day and night with no asthma symptoms and no awakenings due to asthma symptoms.
‖A symptom-free day with no as-needed medication.

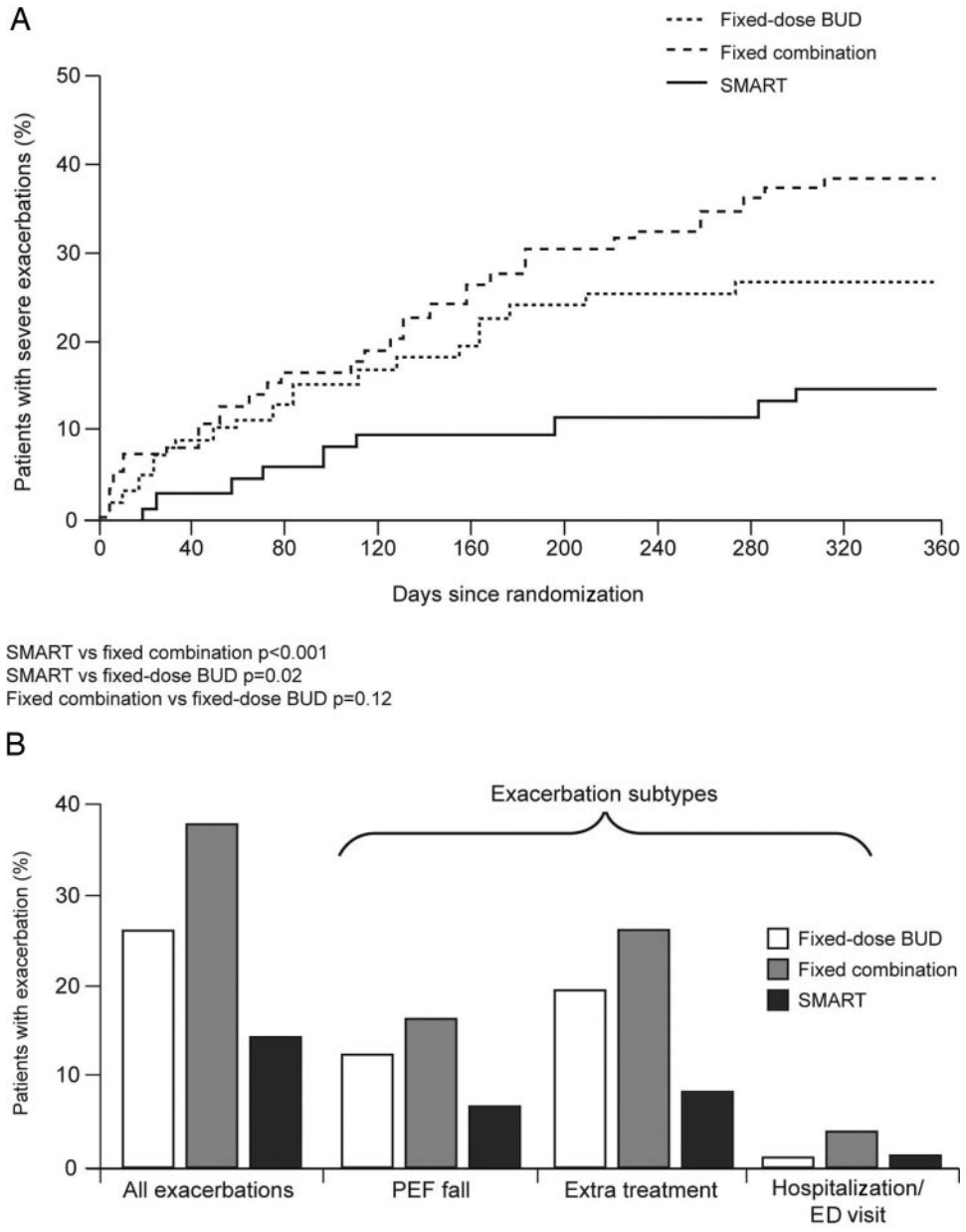

FIGURE 2. *Top*, *A*: Kaplan-Meier survival plot of time to first asthma exacerbation (defined as a deterioration in asthma resulting in any of: morning PEF $\leq$ 70% of baseline on 2 consecutive days; treatment with oral steroids; an increase in inhaled corticosteroids [via a separate inhaler] and/or other additional treatment; or hospitalization/ED treatment). *Bottom*, *B*: Exacerbation incidence (percentage of patients with event) by subtype. Patients received either fixed-dose budesonide (320 μg qd), fixed combination (budesonide/formoterol 80/4.5 μg qd) or SMART (budesonide/formoterol 80/4.5 μg qd plus as needed). See Figure 1 for expansion of abbreviation.

and 51% lower vs fixed-dose budesonide. The number of events per patient was significantly lower on SMART vs fixed-dose combination ($p = 0.017$); and lower on fixed-dose budesonide vs fixed-dose combination ($p = 0.073$).

Exacerbations requiring medical intervention occurred in 8% in SMART, 31% in fixed combination, and 20% fixed-dose budesonide; *ie*, SMART significantly reduced the instantaneous risk by 75% vs fixed-dose combination ($p < 0.001$), and by 60% vs fixed-dose budesonide ($p = 0.016$) [Table 2]. Similarly, the relative rate of exacerbations requiring intervention was reduced by 70 to 79% with SMART vs the two fixed-dose groups (Table 2). Figure 3 shows the incidence of exacerbations requiring medical intervention over time. The reduction in exacerbations provided by SMART over time was reflected by numerically fewer days requiring oral steroid days

Table 2—*Clinical Outcomes*

Variables	Mean Treatment Values			Between-Group Difference p Values		
	Fixed-Dose Budesonide (n = 106)	Fixed-Dose Combination (n = 117)	SMART (BUD/FORM Maintenance Plus as Needed)# [n = 118]	SMART vs Fixed-Dose Budesonide	SMART vs Fixed-Dose Combination	Fixed Combination vs Fixed-Dose Budesonide
All exacerbations (including PEF falls)						
Patients with event, No. (%)*	28 (26)	44 (38)	17 (14)	0.022	< 0.001	0.12
Hazard ratio				0.49	0.34	1.45
95% confidence interval				0.27–0.90	0.19–0.60	0.90–2.33
Events per patient†	0.48	0.76	0.41	0.59	0.017	0.073
Exacerbations requiring medical intervention						
Patients with event, No. (%)*	21 (20)	36 (31)	10 (8)	0.016	< 0.001	0.098
Events per patient†	0.28	0.40	0.08	< 0.001	< 0.001	0.12
Mild exacerbations						
Patients with event, No. (%)*	77 (75)	98 (84)	74 (63)	0.03	< 0.001	0.081
Mild exacerbation days, %‡	20.0	22.9	16.6	0.025	< 0.001	0.057
Daily symptom control§						
Night-time awakenings, %	4.6	4.4	2.4	0.003	0.0039	0.87
Asthma symptom score (scale 0–6)	0.81	0.54	0.60	0.098	0.53	0.024
Symptom-free days, %‖	56.2	68.0	63.4	0.28	0.31	0.041
Daytime as-needed use, No. of inhalations	0.59	0.59	0.49	0.16	0.066	0.71
Night-time as-needed use, No. of inhalations	0.15	0.17	0.09	0.067	0.024	0.73
As-needed use, No. of inhalations/24 h	0.74	0.76	0.58	0.1	0.038	0.72
As-needed-free days, %	64.0	67.5	69.4	0.12	0.48	0.39
Asthma-control days, %¶	50.8	60.6	57.0	0.14	0.6	0.047
Lung function§						
Morning PEF, L/min	238	242	255	0.0019	0.22	0.053
Evening PEF, L/min	241	243	256	0.0036	0.18	0.1
FEV_1 L	1.76	1.70	1.86	0.39	0.094	0.43

*p Values based on the instantaneous risk of at least one exacerbation (Cox proportional hazards model).
†p Values based on relative rate analysis (Poisson regression).
‡A mild exacerbation was defined as two consecutive days with morning PEF ≥ 20% below the average run-in value; relief medication use of two or more inhalations above baseline in 24 h; or awakenings due to asthma symptoms.
§Values presented as raw means with p values for statistical comparisons of adjusted mean difference.
‖A symptom-free day was defined as a day and night with no asthma symptoms and no awakenings due to asthma symptoms.
¶An asthma-control day was a symptom-free day with no as-needed medication use.
#See Figure 1 for expansion of abbreviations.

(32 days vs 230 days and 141 days for fixed-dose combination and fixed-dose budesonide, respectively) and low levels of emergency treatment (hospitalization/ED visits: one event in the SMART and fixed-dose budesonide groups vs eight events in the fixed-dose combination group).

Mild exacerbations occurred in 63% in SMART, 84% in fixed-dose combination, and 75% in fixed-dose budesonide regimen. The instantaneous risk of having a mild exacerbation was reduced by 30 to 46% with SMART vs both fixed-dose regimens ($p < 0.05$) [Table 2]. The number of mild exacerbation days was also significantly reduced with SMART vs both fixed-dose groups (Table 2). These differences in exacerbations in favor of the SMART regimen were driven predominantly by a reduction in awakenings and excessive as-needed medication use, and to a lesser extent by preventing PEF falls.

Symptoms and Lung Function

Nighttime awakenings were significantly reduced with SMART compared with the other two groups (Table 2). No differences in symptom-free days and asthma control days were seen between the groups receiving SMART and the fixed-dose combination; however, differences were apparent between the two fixed-dose groups for both parameters (Table 2). Patients receiving the SMART regimen had significantly greater increases in morning and evening PEF than those receiving fixed-dose budesonide; no between-group differences were seen with SMART vs

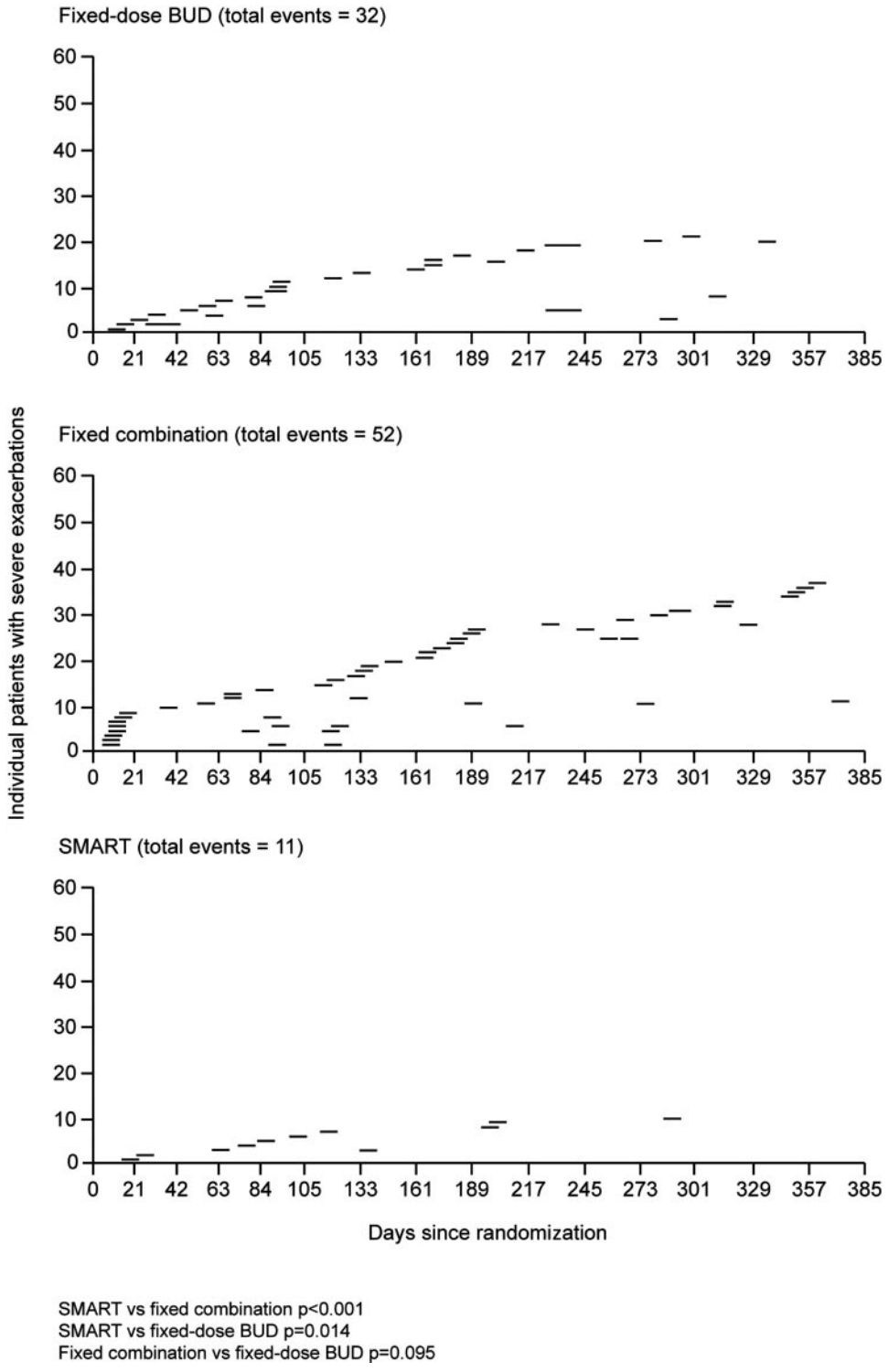

FIGURE 3. Exacerbations requiring medical intervention over time for each individual patient. The *x*-axis on each plot represents time, and each point on the y-axis represents an individual patient in each treatment group. Each single line (—) represents one exacerbation for an individual patient. Exacerbations > 10 days in duration were considered as multiple events. Individual patients with more than one exacerbation are shown as broken or extended lines in the same horizontal plane. Patients received either fixed-dose budesonide (320 μg qd), fixed combination (budesonide/formoterol 80/4.5 μg qd), or SMART (budesonide/formoterol 80/4.5 μg qd plus as-needed additional inhalations for symptom relief). Statistical analysis is from the log-rank test of time to first exacerbation requiring medical intervention. See Figure 1 for expansion of abbreviation.

fixed-dose combination (Table 2). Mean FEV_1 was similar in all groups (Table 2).

Study Drug Use

The mean number of as-needed inhalations was lower for patients receiving the SMART regimen than for fixed-dose combination or fixed-dose budesonide (0.58, 0.76, and 0.74 inhalations per day, respectively; Table 2). High level as-needed use (seven or more as-needed inhalations on any 1 day) was uncommon in all groups. Only six patients in the SMART group (5%) received this level of as-needed medication; this occurred on < 0.1% of treatment days and was not temporally associated with an exacerbation on any occasion. In contrast, 27 patients (23%) and 15 patients (15%) in the groups receiving fixed-dose combination and fixed-dose budesonide used seven or more inhalations of rescue medication on any single day, with a greater than fivefold-higher incidence than that with SMART (0.7% and 0.5% of treatment days for fixed-dose combination and fixed-dose budesonide, respectively). Overall, 40 to 45% of these days were temporally associated with an exacerbation.

The majority of patients (83%) receiving SMART had a mean daily ICS dose (maintenance and as-needed) ≤ 160 μg; 97% of patients had a dose ≤ 320 μg/d. Only three patients in this group had a daily dose > 320 μg. The combined mean daily dose of budesonide and formoterol used for maintenance plus as-needed relief in the SMART group was 126/7.1 μg. In contrast, the daily ICS dose was 80 μg/d in the group receiving the fixed-dose combination and 320 μg/d in the group receiving fixed-dose budesonide.

Safety

Patients receiving the SMART regimen grew significantly more than patients in the fixed-dose budesonide group (Table 3). There was an adjusted mean difference in growth of 1 cm between patients receiving SMART vs those receiving fixed-dose budesonide (95% confidence interval, 0.3 to 1.7; p = 0.0054) and a similar difference of 0.9 cm was seen between the fixed-dose combination and fixed-dose budesonide groups (95% confidence interval, 0.2 to 1.6; p = 0.0099).

The number of patients with abnormal (< 400 nmol/L) pre–ACTH- and post–ACTH-stimulated plasma cortisol levels were similarly low in all groups (2 of 51 patients vs 1 of 55 patients vs 3 of 41 patients in the SMART, fixed-dose combination, and fixed-dose budesonide groups, respectively). Baseline and posttreatment ACTH-stimulated cortisol levels are shown in Table 3. Changes over time in clinical laboratory and vital signs data were minimal, and there were no notable differences between groups.

A total of 24 serious AEs were reported in 23 patients (2, 16, and 5 patients in the SMART, fixed-dose combination, and fixed-dose budesonide groups, respectively). No patients in the SMART group had serious AEs related to asthma worsening/exacerbation, compared with 6% of patients receiving fixed-dose combination therapy and 2% of patients receiving fixed-dose budesonide. Other serious AEs reported by ≥ 1% of the total patient sample were fracture (1% vs 3% and 0% of patients in the SMART, fixed-dose combination, and fixed-dose budesonide groups, respectively) and pneumonia (0% vs 2% and 0% of patients in the SMART, fixed-dose combination, and fixed-dose budesonide

Table 3—*Growth and Plasma Cortisol Response to ACTH-Stimulation Test at Baseline and After 12 Months of Treatment

Variables	Fixed-Dose Budesonide (n = 106)	Fixed-Dose Combination (n = 117)	SMART (BUD/FORM Maintenance Plus as Needed) [n = 118]
Height at baseline, cm	133 (101–162)	131 (105–167)	134 (103–159)
Height after 6 mo of treatment, cm	135 (105–165)	133 (109–172)	136 (105–160)
Height at end of treatment, cm	136 (105–168)	136 (113–175)	139 (105–163)
Growth at end vs baseline, cm	4.3 (− 2.0–15.0)	5.4 (− 4.0–12.0)†	5.3 (1.0–14.0)†
ACTH response at baseline, maximal plasma cortisol, nmol/L‡	627 (298–1,010)	619 (145–1,040)	617 (345–1,280)
ACTH response at the end of treatment, maximal plasma cortisol, nmol/L‡	571 (320–1,240)	620 (294–997)	598 (288–1,090)

*Data are presented as mean (range). See Figure 1 for expansion of abbreviations.
†p < 0.01 vs budesonide qd.
‡Performed in a subgroup of patients (n = 55–59 per group). A normal response to ACTH stimulation is a maximal plasma cortisol concentration ≥ 400 nmol/L.

groups, respectively). Class-related effects, such as tremor, dysphonia, and tachycardia, were rare and evenly distributed between the three groups.

Discussion

This is the first pediatric protocol to assess the SMART regimen (budesonide/formoterol for maintenance plus additional inhalations as needed for symptom relief). In contrast to other studies[1–8] performed in children with fixed-dose combination ICS plus LABA, the SMART regimen greatly reduced exacerbations compared with a fourfold-higher maintenance dose of budesonide. This novel treatment regimen also improved lung function and reduced nocturnal symptoms compared with fixed-dose budesonide. In addition, as the SMART regimen was associated with an increased yearly growth rate vs fixed-dose budesonide, we suggest that this regimen improved asthma control while minimizing systemic effects compared with a higher dose of budesonide. The superior efficacy of the SMART regimen compared with the fixed-dose regimens demonstrated here is in line with our previous report[17] from the compiled data. The need for separate pediatric evaluation of the long-term effects of add-on therapy to ICS in children with poorly controlled asthma has been emphasized previously.[2–4,19–23] Our study represents the first 12-month protocol to assess the SMART regimen in children.

SMART reduced the rate of exacerbations requiring medical intervention by 70 to 79% vs both fixed-dose regimens. This benefit was attained with the novel regimen while using less than half the daily dose of budesonide compared with the fixed-dose budesonide group. The benefit of reducing exacerbations requiring medical intervention using SMART was reflected by 77 to 86% fewer oral steroid days compared with the two fixed-dose regimens. Given the higher incidence of exacerbations associated with pediatric vs adult patients,[9] this finding could have major implications for future guideline recommendations in children.

Pediatric asthma is episodic in nature, and the majority of patients recruited for this study were poorly controlled on their existing ICS treatment at study entry. The mean number of as-needed inhalations decreased from 1.7 inhalations per day during run-in to 0.58 inhalations per day over the 12 months with the novel budesonide/formoterol regimen. Although similar reductions from run-in were seen for the other two groups, there was an additional 30% reduction in as-needed use with SMART compared with fixed-dose combination therapy. Furthermore, overuse of as-needed budesonide/formoterol by patients in the SMART group was rare. On average, approximately 70% of days were as-needed free in the SMART group; high as-needed medication use (more than seven inhalations on any one day) was at least fivefold less common with this novel regimen compared with both fixed-dose regimens. Nevertheless, clinicians should be aware of the potential for overuse and the resultant safety concerns that might occur in a larger, less "monitored" population outside of the clinical trial situation. Patient education and careful monitoring of prescription refills will be important components of the SMART approach. Throughout the treatment period, there was no evidence of tolerance to the SMART regimen, as the advantage was at least maintained during the 12-month study period.

The SMART regimen was well tolerated compared with both fixed-dose regimens and also had a potentially more favorable safety profile compared with the fourfold-higher maintenance dose of budesonide. Growth in the children using both SMART and fixed-dose combination was approximately 1 cm greater over 12 months compared with the fixed-dose budesonide group. This growth inhibition from the fixed dose of budesonide is similar to results reported previously for a comparable dose of budesonide compared with placebo.[24]

The regular use of ICS/LABA in fixed regimens plus short-acting β_2-agonist as rescue has been studied in a number of pediatric trials; however, to date, no evidence has suggested that such a regimen protects against exacerbations in this population. Indeed, increased exacerbation rates have been suggested.[1–8] In line with this, we found an increased risk of exacerbations and correspondingly increased number of associated ED visits and hospitalizations and need for oral prednisolone in children on the fixed budesonide/formoterol combination compared with the fourfold-higher budesonide dose group, as well as compared with the SMART group. The improved control with SMART in comparison with the fixed-dose combination therapy is probably not due to the small increase in budesonide, from 80 to 126 μg/d. Only three children received, on average, $>$ 320 μg/d during the study. Previous studies[14,15] indicate that doubling the dose of ICS does not appear to reduce the risk of exacerbations, and it is therefore more likely that with SMART the timing of the increased steroid dose in close proximity to asthma worsening or exacerbation is key to the effectiveness rather than this extra daily dose of 46 μg. In addition, issues related to compliance could have been an important contributory factor. Children's adherence to regular asthma therapy tends to be erratic, and nonadherence has been associated with an increased need for oral steroid therapy.[10]

Adhering to prescribed regular daily treatments may even be more problematic in pediatric patients, who tend to have episodic asthma characterized by a higher exacerbation rate than adults, despite fewer days with symptoms. Letting the need for rescue drive adjustment in controller therapy using SMART has the potential to address this current problem of pediatric asthma therapy. SMART simplifies asthma therapy by one inhaler for both maintenance and rescue. This also reduces the potential for patients to overrely on their β_2-agonist rescue medication, which does not treat the underlying inflammation. Additionally, concerns that LABA alone may mask subclinical airway inflammation[25] is reduced with SMART because the regular LABA is used at its minimal dosage and in combination with ICS.

Treatment guidelines state that the minimum daily steroid dose sufficient to control symptoms should be used in patients with persistent asthma.[11] The SMART regimen mirrors this recommendation. Patients receiving this novel regimen automatically increased the dose of budesonide/formoterol with each as-needed inhalation, to obtain timely increases in ICS early during periods of worsening symptoms. When control was regained, this treatment group was able to maintain control with their regular daily dose and no rescue use of budesonide/formoterol on 70% of treatment days. In conclusion, the use of the SMART regimen—budesonide/formoterol for maintenance plus additional inhalations as needed for symptom relief—is an effective and well-tolerated treatment approach that may greatly simplify pediatric asthma management in the future.

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Appendix

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