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Does measuring BHR add to guideline derived clinical measures in determining treatment for patients with persistent asthma? ☆

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Summary
Rationale: Little is known about the use of biomarkers in guiding treatment decisions in routine asthma management. The objective of this study was to determine whether adding a LABA to an ICS would control bronchial hyperresponsiveness (BHR) at an overall lower dose of ICS when titration of medication was based upon the assessment of routine clinical measures with or without the measurement of BHR.
Methods: After a 2-week run-in period, subjects ($\geqslant$12 years) were randomized to one of three treatment groups. Two groups followed a BHR treatment strategy (based on clinical parameters [lung function, asthma symptoms, and bronchodilator use] and BHR) and were treated with either fluticasone propionate/salmeterol (FSC_{BHR} group) or fluticasone propionate (FP_{BHR} group) ($n = 156$ each). The third group followed a clinical treatment

Abbreviations: AMP, adenosine monophosphate; BAL, bronchoalveolar lavage; BDP, beclomethasone dipropionate; BHR, bronchial hyperresponsiveness; BUD, budesonide; eNO, exhaled nitric oxide; FP, fluticasone propionate; FEV_1, forced expiratory volume in 1 s; FP_{BHR}, fluticasone propionate utilizing a bronchial hyperresponsiveness strategy; FP_{REF}, fluticasone propionate utilizing a reference strategy; FSC, fluticasone propionate/salmeterol; FSC_{BHR}, fluticasone propionate/salmeterol utilizing a bronchial hyperresponsiveness strategy; ICS, inhaled corticosteroids; ITT, intent-to-treat; LABA, long-acting beta agonist; PC_{20}, provocative concentration of methacholine necessary to produce a decrease in FEV_1 of 20% from baseline; PEF, peak expiratory flow; TAA, triamcinolone acetonide.

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algorithm (based on clinical parameters alone) and were treated with fluticasone propionate (FP_{REF} group; $n = 154$). All treatments were administered via Diskus®. Treatment doses were adjusted as needed every 8 weeks for 40 weeks according to the subject's derived severity class, which was based on clinical measures of asthma control with or without BHR.

Results: The mean total daily inhaled corticosteroids (ICS) dose during the double-blind treatment period was lower, although not statistically significant, in the FSC_{BHR} group compared with the FP_{BHR} group (a difference of −42.9 mcg; $p = 0.07$). Compared with the FP_{REF} group, the mean total daily ICS dose was higher in the FSC_{BHR} group (a difference of 85.2 mcg) and was significantly higher in the FP_{BHR} group (a difference of 131.2 mcg, $p = 0.037$).

Conclusion: This study demonstrated that for most subjects, control of BHR was maintained when treatment was directed toward control of clinical parameters. In addition, there was a trend towards control of BHR and clinical measures at a lower dose of ICS when used concurrently with salmeterol.

Introduction

Asthma is a chronic disease of the airways characterized by inflammation, bronchoconstriction, and bronchial hyperresponsiveness (BHR).[1] Inhaled corticosteroids (ICS) are the gold standard in anti-inflammatory therapy since they are proven to improve asthma symptoms and lung function, and reduce BHR, inflammatory cells and mediators associated with asthma.[2] However, treatment with ICS alone does not adequately control clinical symptoms of asthma in many patients, and in such instances guidelines recommend the addition of controller medications such as inhaled long-acting beta$_2$-agonists (LABA). Treatment with ICS plus LABA improves the clinical status of asthma by attenuating airway inflammation and bronchoconstriction.[3–11] BHR is a predominant feature of asthma and is present in patients whose asthma may be active or in remission.[12] A number of studies suggest a positive correlation between increased asthma morbidity, exacerbations, airway inflammation and BHR.[13–15] Therefore, increased BHR may indicate the presence of under-treated airway inflammation and thus be a useful therapeutic target in asthma.

The clinician must often choose an asthma treatment management plan based solely on clinical presentation. However, lack of information about the degree of airway inflammation may lead to under-treatment with anti-inflammatory therapy, which may be associated with long-term progressive worsening of the disease.[16] Markers of inflammation, such as sputum eosinophils, BHR and exhaled nitric oxide (eNO), have been utilized in clinical trials and provide insight into the asthmatic inflammatory process.[15,17] Some studies suggest that low-dose ICS alone may adequately control clinical parameters, lung function and bronchial hyperreactivity (BHR)[18] while other studies suggest that higher doses of ICS are required to do the same.[15,17,19] The objective of this study was to determine whether adding a LABA to an ICS would control BHR at an overall lower dose of ICS when titration of medication was based upon the assessment of routine clinical measures with or without the measurement of BHR.

Methods

Patient selection

Male and female patients, 12 years of age and older, were eligible to participate in the study if they had asthma for at least 3 months and had been treated during the previous month with short-acting beta$_2$-agonists, anticholinergics, or ICS ($\leqslant$250 mcg daily of fluticasone propionate (FP) or equivalent). At the screening visit, all patients were required to have a forced expiratory volume in 1 s (FEV_1) between 60% and 95% of predicted normal (based on Crapo standards for patients 18 years and older[20] or Polgar and Promadhat standards[21] for patients 12–17 years, race-adjusted for African Americans).[22] They were also required to have either historical documentation of reversible airways disease within the last 24 months or an increase in FEV_1 of at least 12% within 30 min of inhalation of 2 puffs (180 mcg) of albuterol. At Visit 2, patients had to demonstrate a PC_{20} of $<$8 mg/mL of methacholine.

Exclusion criteria included the following: pregnancy, life-threatening asthma, hospitalization attributable to asthma within the last 6 months, current smoker or a $>$10 pack-year history of smoking, a recent (within 2 weeks) upper or lower respiratory tract infection, or significant concurrent diseases. Medications that could confound the evaluation of the study treatments or treatment strategies were prohibited before and throughout the study, including inhaled (up to 250 mcg FP allowed prior to randomization), oral, or parenteral corticosteroids (with the exception of protocol defined use of oral corticosteroids following second consecutive assignment to the highest dose of FP), theophylline or other bronchodilators, leukotriene modifiers, anticholinergics, cromolyn, and nedocromil.

Study design and intervention

This randomized, multicenter, double-blind, parallel group 40-week study (SAM40086) was conducted at 50 sites in the US, three sites in Latin American, and two sites in Latvia.

Patients underwent physical examination, pulmonary function testing, and other pre-study procedures at the screening visit (Visit 1).

Eligible patients entered a 2-week run-in period during which they continued their allowed short-acting beta$_2$-agonist, anticholinergic, or inhaled corticosteroid treatment. All inhaled short-acting beta$_2$-agonists were replaced with albuterol (Ventolin® HFA inhalation aerosol, GlaxoSmithKline, Research Triangle Park, NC) for the duration of the study. In addition to providing the baseline for efficacy and safety parameters, this period served to evaluate the patient's eligibility for randomization, compliance with study procedures, and asthma status.

Patients who met all eligibility criteria were randomly assigned to one of the following treatment arms at Visit 2: fluticasone propionate/salmeterol DISKUS® (FSC) BID utilizing the BHR strategy (FSC_{BHR}), FP DISKUS utilizing the BHR strategy (FP_{BHR}), or FP DISKUS utilizing the reference strategy (FP_{REF}). All double-blind study drugs were supplied in identical DISKUS devices to blind the treatment. In each treatment strategy the starting dose of treatment at randomization and adjustments to the dose, as needed, at each 8-week visit for a total of 40 weeks of treatment were made based on the patient's asthma Severity Class (Table 1). The Severity Class was derived by a computerized algorithm based on clinical measures of asthma control over the 14 days prior to a visit and PC_{20} on the day of the visit. The clinical measures of asthma control included asthma symptoms (rated on a four-point scale with 0 equal to no symptoms and 3 equal to severe symptoms), bronchodilator use, and mean PEF variability from daily diary records, and clinic lung function. Additionally, BHR was also assessed in all three groups (FSC_{BHR}, FP_{BHR} and FP_{REF} groups).

At each visit, a patient's Severity Class was determined to be one of four categories (Table 1) based on the highest level achieved for any of the clinical measures or BHR. BHR was not considered in determining Severity Class for patients in the FP_{REF} group.

Treatment for 8 weeks after each visit was based upon the Severity Class: Severity Class 1—no requirement for corticosteroid (placebo); Severity Class 2—FSC 100/50 mcg BID or FP 100 mcg BID; Severity Class 3—FSC 250/50 mcg BID or FP 250 mcg BID; Severity Class 4—FSC 500/50 mcg BID or FP 500 mcg BID. However a patient's treatment could not be reduced by more than one step even if they had a two step or greater improvement in their Severity Class on consecutive visits. If the patient remained in Severity Class 4 for two consecutive visits (a total of 16 weeks), an oral prednisone burst of 1 mg/kg per day for 4 days followed by half that dose for 3 days was added to the inhaled study medication at the second visit. An exacerbation was defined as worsening asthma for which treatment with medication other than the double-blind study drugs or study-provided albuterol was necessary, and was treated with the same dosing regimen for prednisone as above.

At each visit, treatment compliance was assessed by recording the number of doses remaining on the counter for the DISKUS.

Clinic measurements

FEV_1 was performed at each visit and measured using a standardized KoKo spirometer (Quantum Ferraris Group, Louisville, CO). BHR was measured through the 5-breath procedure methacholine challenge test[23] and was expressed as PC_{20} for FEV_1. All FEV_1 measurements were performed prior to the subject receiving their morning dose of study drug at clinic visits. Methacholine in doubling concentrations (0.031–16 mg/mL) was delivered from a DeVilbiss 646 nebulizer (DeVilbiss, Somerset, PA) connected to a KoKo DigiDoser (Quantum Ferraris Group, Louisville, CO). The challenge test was discontinued if FEV_1 fell by more than 20% from its baseline value, if the patient felt uncomfortable, or if the highest concentration of methacholine had been given. Spirometric and BHR results were transmitted electronically to a central data collection site (Quantum Ferraris Group, Louisville, CO).

Statistical analyses

The estimated mean daily dose of ICS for each group was derived from estimates of the overall expected proportions of the treatment period subjects would spend in each Severity Class (i.e., on each ICS dose). For the FSC_{BHR} group, the expected proportion of time by ICS dose was as follows: placebo: 2%, 100 mcg BID: 53%, 250 mcg BID: 43%, and 500 mcg BID: 2%; and for the FP_{BHR} group: placebo: 0%, 100 mcg BID 7%, 250 mcg BID: 85%, and 500 mcg BID: 8%. Based on these estimates, over the treatment period of 40 weeks, the expected mean daily dose for the FSC_{BHR} group was 170.5 mcg BID and for the FP_{BHR} group was 259.5 mcg BID (a difference of 89 mcg). Based on a two-group *t*-test with a significance level of 0.05, a sample size of 43 subjects in each group would have 90% power to detect a difference in mean daily ICS dose of 89 mcg (the difference between the FSC_{BHR} mean of 170.5 mcg and the FP_{BHR} mean of 259.5 mcg). In the absence of data to determine an accurate

Table 1 Severity Class markers.

Severity Class	Composite symptom score (0–3 scale)	Mean daily albuterol use (puffs)	Mean PEF variability (%)	FEV_1 (% of predicted)	PC_{20} (mg/mL)
4	3	$\geqslant 6$	>50	<50	<0.25
3	2	4–5.99	31–50	50–69	0.25–1.0
2	1	2–3.99	20–30	70–90	1.1–4.0
1	0	<2	<20	>90	>4.0

PEF variability was calculated for each of the 14 days prior to a visit as (morning PEF−evening PEF)/(evening PEF) × 100. The daily PEF% variability results from the 14 days preceding each visit were averaged to determine the mean PEF% variability.

estimate of the standard deviation of the mean daily dose of inhaled corticosteroid, the sample size estimate was based on a standard deviation equal to 125, which corresponds to one-fourth the range of possible doses (0–500 mcg). However, it was anticipated that the variability of these results could be greater than the rough estimate of 125 mcg. Therefore, the sample size for this study was increased to 100 subjects per group.

All efficacy and safety analyses were based on the intent-to-treat (ITT) population, which comprised all randomized patients. The analyses of the ITT population included all data available from these subjects, except in the case of the primary efficacy measure, the average daily ICS dose comparing FSC_{BHR} with FP_{BHR}, which required at least two on-treatment clinic visits in order to calculate a weighted average ICS dose.

The primary efficacy measure, the average daily ICS dose (averaged over the entire treatment period) comparing FSC_{BHR} with FP_{BHR}, was calculated as the area under the dose-by-time curve, and analyzed using van Elteren tests stratified by baseline Severity Class. The primary efficacy measure was evaluated at a significance level of 0.05. All statistical hypotheses were tested using two-tailed tests. Median treatment differences and their corresponding 95% confidence intervals were derived using Hodges–Lehmann estimation methods. Secondary efficacy measures and respective related measures (in parentheses) were as follows: morning PEF (evening PEF); morning pre-dose FEV_1; percentage of symptom-free days (number of nighttime awakenings and symptom scores); and daily albuterol use (percentage of albuterol-free days). Secondary and related measures were analyzed by 28-day intervals and at endpoint (the average of the data recorded over the last 7 days of study participation) in terms of change from baseline, using analysis of covariance models that included baseline (the average of the data recorded over the last 7 days prior to randomization) as a covariate and terms for treatment and baseline severity class.

Safety was assessed in terms of the frequency of clinical adverse events and asthma exacerbations by group.

For a given pairwise treatment comparison, secondary and related efficacy measures were assessed for statistical significance only if the primary measure was deemed to be statistically significant. The set of secondary efficacy measures was subject to the following disclosure-of-results scheme. Reporting the results of one measure in this set of secondary measures required reporting results of all other measures in the set, regardless of the statistical significance associated with the tests of the measures. Conversely, choosing not to report any one measure in the set required that none of the other measures in the set be reported. Each secondary efficacy measure was evaluated at a significance level of 0.05. In addition, no related efficacy measure was assessed for statistical significance unless its parent measure (i.e., the secondary measure to which it is related) was deemed to be statistically significant.

Results

A total of 466 subjects were randomly assigned to one of the three study drug treatment groups (FSC groups: FSC_{BHR}, FP_{BHR}, and FP_{REF}). The initial dose of ICS at randomization was determined by the BHR (clinical parameter plus BHR) or

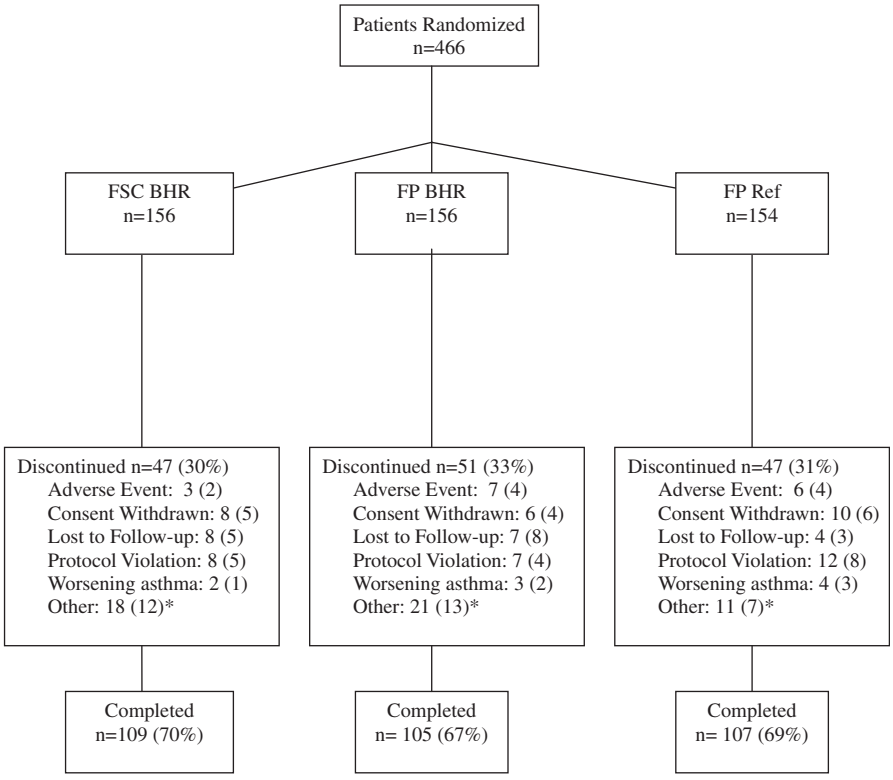

Figure 1 Patient flow diagram. *The ''Other'' reasons for subject withdrawal included sponsor discretion, non-compliance, move from area, dissatisfaction with medication, investigator discretion, positive pregnancy test, and inconsistent PFT efforts.

Table 2 Patient background characteristics.

	FSC_{BHR}, $N = 156$	FP_{BHR}, $N = 156$	FP_{REF}, $N = 154$
Male/female, %	38/62	36/64	49/51
Mean age, years (range)	34.8 (12–81)	34.8 (12–81)	33.2 (12–72)
Ethnic origin, no. (%)			
White	124 (79)	120 (77)	124 (81)
Black	18 (12)	24 (15)	16 (10)
Other	14 (9)	12 (8)	14 (9)
Mean FEV_1 at baseline (S.D.)			
% Predicted	77 (9.6)	79 (9.2)	79 (9.6)
% Reversibility	19 (7.9)	20 (11.0)	20 (9.7)

REF strategy (clinical parameters alone). A subject flow diagram is presented in Figure 1.

Randomization resulted in comparable treatment groups at baseline with respect to patient demographics and pulmonary function (Table 2).

Efficacy assessments

The results of the efficacy assessments are shown in Table 3. For the primary endpoint the mean total daily ICS dose taken during the double-blind treatment period was lower in the FSC_{BHR} group compared with the FP_{BHR} group (a difference of −42.9 mcg; although the difference was not statistically significant, $p = 0.07$) (Table 3). Compared with the FP_{REF} group, the mean total daily ICS dose was higher in the FSC_{BHR} group (a difference of 85.2 mcg) and was significantly higher

Table 3 Efficacy assessments.

	FSC_{BHR}, $N = 156$	FP_{BHR}, $N = 156$	FP_{REF}, $N = 154$
Primary efficacy			
Inhaled corticosteroid daily dose (mcg)			
Median (minimum–maximum)	368.7 (111.6–1000.0)	414.3 (80.1–1008.9)	254.0 (18.6–1000.0)
	FSC_{BHR} vs. FP_{BHR}	FSC_{BHR} vs. FP_{REF}	FP_{BHR} vs. FP_{REF}
Mean treatment difference (mcg)	−42.9	85.2	131.2
95% confidence interval	−89.6, 2.0	49.8, 125.4	83.2, 178.5
p-value	0.070	0.554	0.037
Secondary and related† efficacy*			
AM PEF (L/min)*			
Baseline least squares mean (S.E.)	401 (13.5)	409 (13.4)	407 (13.0)
Least squares mean change at endpoint (S.E.)	31.3 (9.1)	16.9 (9.0)	25.5 (8.9)
PM PEF (L/min)†			
Baseline least squares mean (S.E.)	416 (14.2)	423 (14.2)	427 (13.8)
Least squares mean change at endpoint (S.E.)	26.8 (8.7)	16.4 (8.7)	22.4 (8.6)
Pre-dose FEV_1 (L)*			
Baseline least squares mean (S.E.)	2.75 (0.08)	2.79 (0.08)	2.80 (0.08)
Least squares mean change at endpoint (S.E.)	0.14 (0.05)	0.06 (0.05)	0.11 (0.05)
% Symptom-free days*			
Baseline least squares mean (S.E.)	45.0 (4.07)	48.0 (4.07)	37.6 (3.95)
Least squares mean change at endpoint (S.E.)	19.9 (5.48)	13.0 (5.48)	18.1 (5.31)
Nighttime awakenings†			
Baseline least squares mean (S.E.)	0.3 (0.08)	0.3 (0.08)	0.3 (0.08)
Least squares mean change at endpoint (S.E.)	−0.2 (0.04)	−0.2 (0.04)	−0.1 (0.04)
24-h Asthma symptom scores†			
Baseline least squares mean (S.E.)	0.7 (0.07)	0.7 (0.07)	0.9 (0.07)
Least squares mean change at endpoint (S.E.)	−0.3 (0.08)	−0.2 (0.08)	−0.3 (0.08)
24-h Albuterol use (puffs/24 h)*			
Baseline least squares mean (S.E.)	1.6 (0.24)	1.2 (0.24)	2.2 (0.24)
Least squares mean change at endpoint (S.E.)	−1.2 (0.18)	−0.8 (0.18)	−0.7 (0.17)
% Albuterol-free days†			
Baseline least squares mean (S.E.)	54.2 (4.54)	53.4 (4.54)	45.6 (4.40)
Least squares mean change at endpoint (S.E.)	30.4 (5.03)	21.2 (5.01)	16.8 (4.87)

*Secondary efficacy measures.
†Related efficacy measures (related to preceding secondary measure).

Table 4 Baseline and mean change from baseline in methacholine PC_{20} (mg/mL).

	FSC_{BHR}, $N = 156$	FP_{BHR}, $N = 156$	FP_{REF}, $N = 154$
Baseline geometric mean (S.E.)	0.50 (1.25)	0.48 (1.25)	0.37 (1.26)
Week 8 mean change (S.E.)	2.01 (0.46)	1.60 (0.26)	1.45 (0.27)
Week 16 mean change (S.E.)	2.53 (0.41)	1.56 (0.28)	1.72 (0.38)
Week 24 mean change (S.E.)	2.45 (0.44)	1.56 (0.17)	1.75 (0.51)
Week 32 mean change (S.E.)	2.06 (0.37)	1.52 (0.18)	1.75 (0.35)
Week 40 mean change (S.E.)	1.86 (0.48)	1.75 (0.19)	1.98 (0.59)

in the FP_{BHR} group (a difference of 131.2 mcg, $p = 0.037$). There were no statistically significant differences between pairs of treatment groups for any secondary or related efficacy measures. During the treatment period, 5, 15, and 3 subjects remained at Severity Class 4 for two consecutive visits for the FSC_{BHR} group, FP_{BHR} group, and FP_{REF} group, respectively. Treatment compliance was high for all three treatment groups (96%, 94%, and 96%, respectively).

PC_{20} to methacholine

There were no differences in PC_{20} between treatments at baseline and any 8-week clinic visit over the 40-week treatment period. Compared with the other treatment groups, the concentration of methacholine relative to baseline required to effect a 20% fall in FEV_1 at each visit (except at Week 40, compared with the FP_{REF} group) was numerically greater in the FSC_{BHR} group, indicating greater improvements in airway hyperresponsiveness (Table 4).

Safety

All treatments were well tolerated during the 40-week study period. There were no non-fatal serious adverse events in any treatment group that were considered to be drug-related. One subject in the FP_{BHR} treatment group died due to convulsions and cardiac arrest following deep vein thrombosis. The death was not considered by the investigator to be related to study medication. The incidence of common and pharmacologically predictable adverse events was similar, with 81% of patients reporting one or more adverse events. Infections were the most frequently reported adverse events, but was similar across treatment groups (18–20%). Investigator-assessed drug-related adverse events occurred in 9% of patients. Drug-related adverse events that occurred in more than one patient in a treatment group were oral candidiasis, dysphonia, pharyngolaryngeal pain, insomnia, palpitations, and headache. The incidence of asthma exacerbations reported during treatment was 15% in the FSC_{BHR} group, 21% in the FP_{BHR} group, and 24% in the FP_{REF} group. An *ad-hoc* analysis showed no statistically significant differences between any pair of treatments or across all treatments ($p = 0.056$).

Discussion

To our knowledge, this is the first study to examine the effect of reducing BHR and controlling clinical asthma symptoms with either an ICS alone or adding a LABA to an ICS while titrating treatment using two different strategies, one based solely on clinical parameters (reference strategy) and the other based on clinical parameters plus optimizing control of BHR (BHR strategy). This study shows that asthma control using titration of clinical parameters alone or clinical parameters plus BHR is achieved at low doses of FP. The results also indicate that improvements in BHR and clinical measures of asthma control are achieved at even lower doses of FP when administered with salmeterol in the same device (FSC) compared with ICS alone, although these findings did not reach statistical significance.

Our results are qualitatively similar to the findings of Sont et al., a study that guided the design of the present study.[17] In their 2-year study, higher doses of either budesonide (BUD) or beclomethasone dipropionate (BDP) were required to optimize control of both BHR and clinical parameters, while lower doses of BUD or BDP adequately controlled clinical parameters, but not BHR. Similar findings have been reported with other biomarkers used to titrate asthma treatment.[15,24,25] For example, Green et al. used induced sputum eosinophil count rather than BHR to guide treatment titration, and reported a dose effect of ICS (with BDP, budesonide [BUD], or FP) in order to achieve control of sputum eosinophils.[15]

The studies reported by Sont and Green allowed for continuation of the specific baseline ICS, which consisted primarily of BDP, BUD, and FP. The present study standardized the treatment ICS, utilizing only FP, and recent studies have shown that maximal improvements in lung function and BHR can often be achieved with a dose of FP in the range of 200 mcg per day.[18,26] By contrast, higher doses of BDP and BUD are required to achieve a similar therapeutic response in lung function and BHR.[18] This may in part explain the relatively limited ICS dose response for these outcomes observed in the present study compared with those of Sont and Green.

The clinical benefits of salmeterol and concurrent ICS treatment have been repeatedly demonstrated.[7,27] For example, for patients symptomatic on low-dose ICS, adding salmeterol compared with increasing the dose of ICS has been shown to improve lung function, decrease symptoms and rescue albuterol use, improve BHR, and control both tissue and sputum markers of inflammation.[3,4,6,7,9,28,29] Additionally, in patients requiring medium doses of ICS for asthma stability, the addition of salmeterol allows a reduction in the dose of ICS without any loss of clinical asthma control parameters and without any increase in biopsy and bronchoalveolar lavage (BAL) markers of airway inflammation.[30–32]

It is also important to note that in the present study, although not designed to compare rates of exacerbation, a lower number of exacerbations occurred when salmeterol was added to FP relative to FP alone, regardless of treatment strategy. The highest incidence of exacerbations was seen in the FP_{REF} group followed by the FP_{BHR} group. The lowest incidence of exacerbations was seen in patients receiving both FP and salmeterol in the same device (FSC), for whom both clinical parameters and control of BHR were a target of the treatment strategy (FSC_{BHR} group). Thus, treatment with FSC to control BHR and symptoms reduced the incidence of exacerbations by 9 and 6 percentage points when compared with FP for patients treated using the clinical (FP_{REF} group) or BHR (FP_{BHR} group) strategies, respectively.

Another important design consideration in interpreting the results of this study is that the present study employed a flexible dosing scheme, whereas other studies comparing FSC and FP did not allow dose reduction once control was achieved[33] and others used a constant dosing scheme comparing FSC with adjustable dosing of budesonide/formoterol.[34] Although these studies differed in design and baseline characteristics of the study populations, the incidence of exacerbations in the studies reported by Bateman et al. and FitzGerald et al.[33,34] were lower than in the present study, suggesting that constant dosing over time provides better control of exacerbations. This supposition is also supported by studies that show a loss of asthma control when ICS are withdrawn[35] or tapered too rapidly.[36,37]

There are potential limitations of the present study. First, the schedule for dose alterations was every 8 weeks. Guidelines[1,38] suggest that once asthma control is achieved, treatment doses should not be altered for at least 12 weeks, although few studies have examined this directly. However, some studies have shown that maximal or near maximal ICS effects are achieved after 8 weeks.[18] Nonetheless, the fact that patients often lost control in the 8-week period following the downward titration in dose suggests that the flexible dosing strategy used in this study would not be optimal in clinical practice and that a strategy of longer term maintenance of control is appropriate. Second, methacholine challenge is one of several methods for assessing underlying airway inflammation; however, it may not define the inflammatory phenotype for all patients. As shown by Van Den Berge et al.,[39] changes in PC_{20} methacholine are related to changes in airway inflammation and caliber and was, therefore, felt to be appropriate for use in this study. In addition, in the study by Sont et al.,[13] study visits were every 12 weeks, whereas, in the current study, study visits were every 8 weeks. Although unlikely (because dose response to ICS is maximal in days, not weeks), the more frequent visits in the current study could have impacted the results compared with the study by Sont et al.[13]

To assess the use of methacholine responsiveness as a biomarker in determining treatment strategy (a measure that most clinicians do not have the opportunity to evaluate), we retrospectively examined whether BHR was an independent factor in driving dose changes when clinical parameters alone would not have resulted in a dose alteration. Notwithstanding the fact that we found a slightly higher dose of ICS was required in the BHR groups, only 9% of visits required an increased dose of ICS due to uncontrolled BHR that otherwise would not have been triggered by observation of clinical parameters alone (Table 5). The study suggests that clinicians can be confident that the assessment of clinical measures can predict the need for additional therapy in most patients. As discussed above, the fact that patients often lost control in the 8-week period following the downward titration in dose suggests that the dosing strategy used in this study would not be optimal in clinical practice and that a strategy of longer term maintenance of control is appropriate.

Table 5 Treatment changes triggered by BHR alone.

	BHR+clinical markers (%)	Clinical markers alone (%)
FP_{BHR}	43	57
FSC_{BHR}	40	60

With respect to pharmacotherapy, the current study supports that control of clinical markers and BHR can be achieved at a lower dose of ICS when used concurrently with salmeterol. In addition, this study suggests that the clinician can have confidence that BHR is controlled in most patients by monitoring clinical symptoms when using FSC. Finally, although it has been shown that asthma treatment directed at maintaining a high level of clinical asthma control is an effective strategy,[32] the current study suggests that frequent dose alterations may lead to uncontrolled asthma.

Conflict of interest statements

Dr. Koenig has received grants from GlaxoSmithKline, AstraZeneca, and Genentech/Novartis, honoraria from GlaxoSmithKline, Merck, Pfizer, Boehringer-Ingelheim, Abbott, Lilly, and Wyeth, and serves as a consultant for GlaxoSmithKline, Boehringer-Ingelheim, and Abbott.

Dr. Murray serves as a consultant for GlaxoSmithKline and he has received clinical research funding and honoraria from GlaxoSmithKline.

Dr. Wolfe receives an honoraria for the Speakers Bureau from GlaxoSmithKline.

Dr. Stauffer is a former employee of GlaxoSmithKline.

Ms. Andersen, Ms. Prillaman, Mr. Yancey and Dr. Dorinsky are employees of GlaxoSmithKline.

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