Asthma control can be maintained when fluticasone propionate/salmeterol in a single inhaler is stepped down

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Background: Asthma control is the goal of treatment, but little data exist to support treatment strategies for stepping down treatment once control has been achieved.
Objective: We assessed whether either the long-acting β_2-agonist or corticosteroid could be reduced without loss of asthma control once control had been attained with fluticasone propionate/salmeterol (FSC).
Methods: After 12 weeks of open-label treatment with FSC 250/50 μg twice daily, patients whose asthma was well controlled were randomized to FSC 100/50 μg twice daily or fluticasone propionate (FP) 250 μg twice daily. for 12 weeks. The primary endpoint was mean morning peak expiratory flow over the randomized study period. Secondary endpoints included symptom scores, rescue albuterol use, and asthma control.
Results: During open-label treatment, improvements from baseline were seen, and 435 of 641 patients (68%) achieved well controlled status during each of the last 4 weeks of this period. A total of 246 patients received FSC 100/50 μg twice daily and 238 FP 250 μg twice daily. The adjusted mean change in morning peak expiratory flow from the end of open-label treatment was −0.3 L/min for FSC and −13.2 L/min for FP (treatment difference, 12.9 L/min; 95% CI, 8.1-17.6; $P < .001$). Secondary efficacy endpoints also showed FSC 100/50 μg twice daily to be more effective than FP 250 μg twice daily alone. The majority of patients remained well controlled, but the proportion was higher with FSC.
Conclusion: In patients achieving asthma control with FSC 250/50 μg twice daily, stepping treatment down to a lower dose of FSC 100/50 μg twice daily is more effective than switching to an inhaled corticosteroid alone. (J Allergy Clin Immunol 2006;117:563-70.)

Key words: *Asthma, fluticasone propionate, fluticasone propionate/salmeterol, maintenance, control, step-down*

Although there is no cure for asthma, with effective controller treatment, it is possible for most patients to achieve clinical control of disease.[1] Although inhaled corticosteroids remain the reference medication, many studies have confirmed superior efficacy for the combination of a long-acting β_2-agonist and an inhaled corticosteroid on all components that are used to define clinical asthma control.[2]

In the international Global Initiative for Asthma guidelines,[1] control of asthma is defined as minimal (ideally no) chronic symptoms, minimal (infrequent) exacerbations, no emergency visits, minimal (ideally no) use of as-needed β_2-agonist, no limitations on activities including exercise, peak expiratory flow (PEF) circadian variation of less than 20%, (near) normal PEF, and minimal (or no) adverse effects from medicine. It has previously been argued[3] that to be clinically relevant, all of these should be achieved and maintained for significant periods and that assessment of single endpoints overestimates control. A recent study[4] has confirmed that control measured using a guideline-derived composite endpoint is achievable in a majority of patients with uncontrolled asthma. Significantly more patients achieved control with fluticasone propionate/salmeterol combination (FSC) than with fluticasone propionate (FP) alone, and control was achieved earlier and at a lower corticosteroid dose with the combination treatment. Furthermore, this high level of control was maintained in a large majority for as long as a year when treatment was maintained at a constant dose.

Asthma guidelines recommend that once asthma control has been achieved and maintained for 3 to 6 months, treatment should be reviewed and dose reduction attempted, with careful monitoring to ensure that control is not lost. However, relatively few studies have examined strategies for dose reduction and, in the case of combination therapies, which treatment should be reduced first. Reddel et al[5] have demonstrated continued improvement in measures of asthma control and airway hyperresponsiveness during progressive reduction of budesonide

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Abbreviations used
FP: Fluticasone propionate
FSC: Fluticasone propionate/salmeterol combination product
GOAL: Gaining Optimal Asthma ControL
ITT: Intent-to-treat
OR: Odds ratio
PEF: Peak expiratory flow
PP: Per protocol

dose, and Hawkins et al[6] showed that in primary care, inhaled corticosteroid doses could be reduced without detrimental effects on asthma control. We report here results of a prospective double-blind controlled study in which, using a very similar definition of asthma control to that used in the Gaining Optimal Asthma ControL (GOAL) study,[4] we compared the effects on features of asthma of reducing either the inhaled long-acting β_2-agonist or inhaled corticosteroid component once control had been attained with FSC in previously steroid-naive patients with chronic asthma. Our study did not attempt to define the optimal control level or interval after achieving control at which such a dose reduction should be commenced.

METHODS

Study design

After a 2-week run-in period, this multicenter study had 2 treatment phases (Fig 1). Patients whose asthma was assessed as well controlled in each of the last 4 weeks of 12 weeks of open-label treatment with FSC (ADVAIR/SERETIDE/VIANI; GlaxoSmithKline, Greenford, United Kingdom) 250/50 μg twice daily were randomized into a 12-week, double-blind, parallel-group phase (step-down phase) comparing FSC 100/50 μg twice daily (inhaled corticosteroid reduced) with FP 250 μg twice daily (long-acting β_2-agonist stopped).

The primary endpoint was mean morning PEF. Asthma control, symptoms, and rescue albuterol usage were secondary endpoints. Morning and evening PEF (best of 3 attempts) before use of study medication (or albuterol) was measured by using a Mini-Wright PEF meter (Clement Clark, Harlow, United Kingdom). Nighttime asthma symptoms were scored from 0 (no symptoms) to 4 (symptoms so severe patient did not sleep at all) and daytime symptoms from 0 (no symptoms) to 5 (symptoms so severe that patient could not perform normal daily activities). Lung function and moderate (requiring oral corticosteroids) and severe (requiring hospitalization) asthma exacerbations were recorded at clinic visits. Asthma control was assessed weekly by using a composite measure.[4] Patients were also assessed as having total control or being well controlled over weeks 5 to 12 of the step-down phase.[4]

Patients

The study was approved by local research ethics committees, and all patients (or their legal representatives) gave written informed consent. Patients aged 12 to 80 years with a ≥6 month history of asthma and ≤10 pack-year smoking history and treated with only inhaled short-acting β_2-agonists for the past 6 months were eligible. They had a prebronchodilator FEV_1 of ≥60% and <80% predicted, combined daytime and nighttime symptom scores of ≥2 on ≥4 of the last 7 days of the run-in, no exacerbations in the run-in, and demonstrated reversibility in lung function.

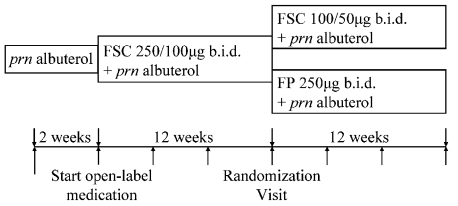

FIG 1. Study design. Patients were considered eligible for randomization if they fulfilled the criteria for well controlled asthma during each of the last 4 weeks of the open-label period. *prn,* As needed; *b.i.d.,* twice daily.

Statistical methods

Statistical analyses were performed by using SAS version 8.2 (SAS Institute Inc, Cary, NC) in a UNIX environment.

The open-label population was composed of all patients entered in the open-label phase who received at least 1 dose of FSC 250/50 μg. Changes in diary card data in the open-label phase (from the last 7 days of the run-in) were summarized for this population.

Patients were randomized to double-blind treatment by using a computer-generated centralized randomization schedule with a block size of 4. The blinded treatment comparison was designed to show noninferiority with a limit for PEF set a priori at −15 L/min. If the lower confidence limit (2.5% 1-sided significance) exceeded 0, then, using a separate closed testing procedure, superiority would be established. An intent-to-treat (ITT) population (all patients randomized who received at least 1 dose of double-blind study medication) and a per protocol (PP) population (ITT population excluding patients with major protocol violations) were defined. Both populations had equal importance to claim noninferiority[7]; the ITT population had greater importance to claim superiority. Mean morning PEF and secondary endpoints of mean symptom scores, albuterol use, and evening PEF were compared between randomized treatments using an Analysis of Covariates (ANCOVA) model allowing for effects caused by treatment, baseline, age, sex, and country. Baseline was defined as the last week of the open label phase. Comparisons between treatments for percentage of symptom-free and rescue-free days and nights and well controlled asthma were made by using logistic regression allowing for effects caused by treatment, baseline (prebronchodilator FEV_1 for well controlled asthma), age, sex, and country. The results of logistic regression analyses are expressed as odds ratios (ORs).

RESULTS

Patient characteristics

A total of 855 patients were screened, 641 patients were included in the open-label phase, and 484 patients (246 treated with FSC and 238 treated with FP) were included in the ITT population for the double-blind step-down phase (Fig 2). Two hundred eight patients treated with FSC and 188 treated with FP were included in PP analyses.

Baseline characteristics at study entry and during run-in were similar for all patients entering the open-label phase and for randomized patients (Table I). The mean baseline percent predicted FEV_1 was 70.4% (±7.8). The low percentages of days and nights with no symptoms or rescue