

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 argued³ 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 study⁴ 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 al⁵ 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 al⁶ 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-naïve 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; GlaxoSmith-Kline, Greenford, United Kingdom) 250/50 μ g twice daily were randomized into a 12-week, double-blind, parallel-group phase (step-down phase) comparing FSC 100/50 μ g twice daily (inhaled corticosteroid reduced) with FP 250 μ g 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 FEV₁ of $\geq 60\%$ and $<80\%$ predicted, combined daytime and nighttime symptom scores of ≥ 2 on ≥ 4

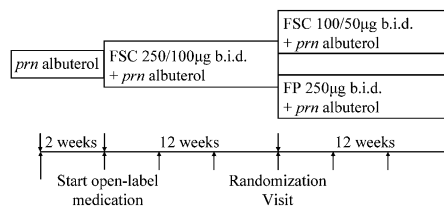


FIG 1. Study design. Patients were considered eligible for randomization if they fulfilled the criteria for well controlled asthma during each of the last 4 weeks of the open-label period. *prn*, As needed; *b.i.d.*, twice daily.

of the last 7 days of the run-in, no exacerbations in the run-in, and demonstrated reversibility in lung function.

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 μ g. 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 noninferiority⁷; 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 FEV₁ 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 FEV₁ was 70.4% (± 7.8). The low percentages of days and nights with no symptoms or rescue

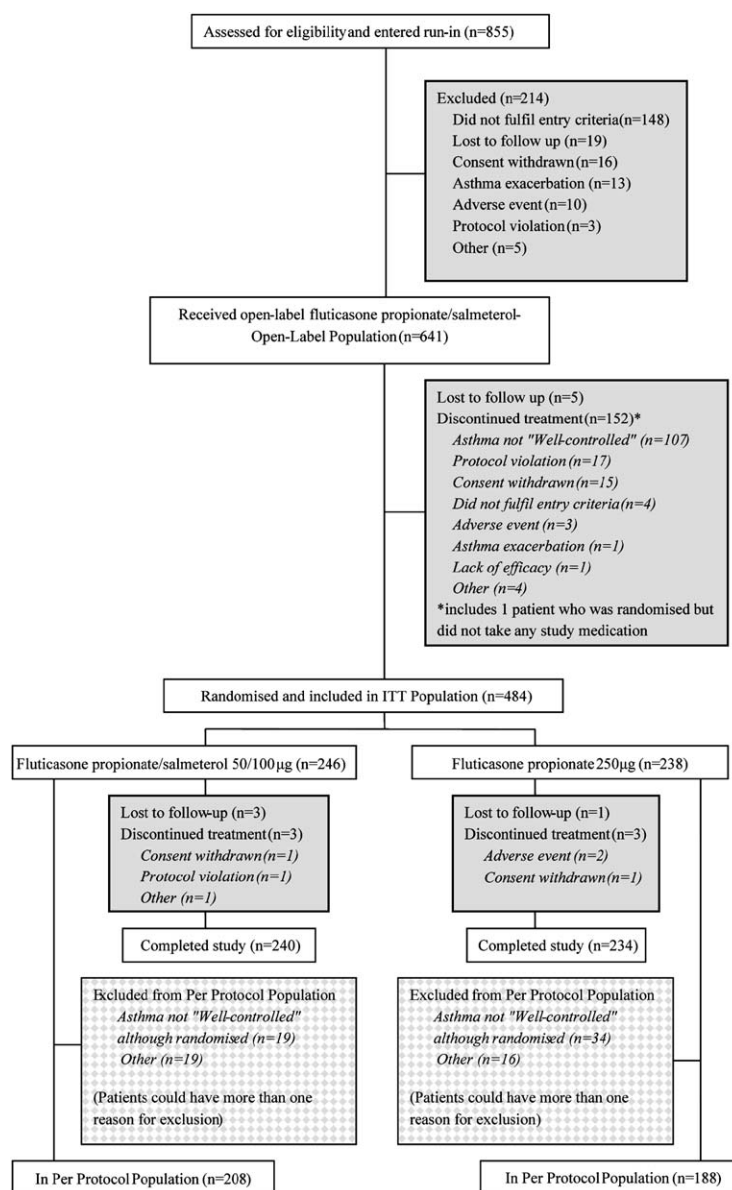


FIG 2. Flow of patients in study.

usage confirmed poor asthma control during run-in. Baseline characteristics of the PP and ITT populations were similar (data not shown).

Effect of open-label treatment with FSC 250/50 µg

Peak expiratory flow values and symptoms improved and use of rescue medication decreased during the 12-week open-label treatment with FSC 250/50 µg twice daily (Table II). The number of patients with totally controlled and well controlled asthma increased throughout this treatment phase; the proportion of patients achieving a well controlled or totally controlled week increased from <1% and 0%, respectively, during the last week of run-in to 83% and 48%, respectively, in week 12 of the

open-label period. During the 4-week asthma control assessment period at the end of the open-label phase to determine eligibility for randomization, 435 of 641 patients receiving open-label treatment (68%) were well controlled in all 4 weeks, and 193 patients (30%) achieved total control. Of the 484 patients subsequently randomized, 431 (89%) were well controlled, with 53 randomized patients having been incorrectly assessed as well controlled by recruiting investigators and randomized in error. These patients were included in all ITT analyses.

Effect of stepping down treatment

The improvement in mean morning PEF during open-label treatment achieved with FSC 250/50 µg was maintained in patients whose treatment was reduced to

TABLE I. Characteristics of all patients treated with open-label medication (open-label population) and of those subsequently randomized (ITT population)

	Open-label population	ITT population	
	FSC 250/50 μ g	FSC 100/50 μ g	FP 250 μ g
Mean (SD) age, y	41.3 (15.4)	40.3 (15.9)	40.7 (15.1)
Male/female, %	40/60	39/61	42/58
N (%) of subjects with exacerbations*	58 (9)	22 (9)	23 (10)
Baseline† lung function			
Mean (SD) FEV ₁ , L	2.22 (0.57)	2.22 (0.56)	2.23 (0.57)
Mean (SD) % predicted FEV ₁	70.4% (7.8)	69.6% (6.4)	70.5% (6.4)
Mean (SD) reversibility in FEV ₁	23.5% (14.2)	24.4% (14.8)	22.2% (14.0)
Baseline‡ diary card data			
Mean (SD) morning PEF, L/min	328 (91)	327 (89)	332 (92)
Mean (SD) daytime symptom score§	1.7 (0.8)	1.7 (0.8)	1.6 (0.8)
Mean (SD) nighttime symptom score§	1.3 (0.7)	1.3 (0.7)	1.2 (0.6)
Mean (SD) % symptom-free days	9.0% (18.2)	8.9% (17.4)	11.0% (20.5)
Mean (SD) % symptom-free nights	19.2% (28.6)	17.7% (28.2)	19.6% (27.7)
Mean (SD) daytime rescue use	1.8 (1.3)	1.8 (1.2)	1.7 (1.2)
Mean (SD) nighttime rescue use	1.3 (1.0)	1.4 (1.1)	1.2 (1.0)
Mean (SD) % rescue-free days	17.0% (28.3)	18.0% (29.5)	19.6% (29.4)
Mean (SD) % rescue-free nights	26.9% (35.0)	26.1% (35.3)	28.2% (34.8)

*Exacerbations treated with antibiotics or oral corticosteroids in the last year.

†Recorded at end of run-in visit; FEV₁ reversibility recorded at screening visit.

‡Mean of last 7 days of run-in period.

§The possible range of symptom scores is 0 to 4 for nighttime symptoms and 0 to 5 for daytime symptoms.

||Number of occasions.

TABLE II. Mean changes from last week of run-in ($\pm$ SD) in PEF, symptoms, and rescue usage during open-label treatment with fluticasone propionate/salmeterol 250/50 μ g

	Open-label population (N = 641)
Mean change (SD) in morning PEF, L/min	+63 (56) (from 328 to 392)
Mean change (SD) in daytime symptom score*	−1.3 (0.8) (from 1.7 to 0.4)
Mean change (SD) in nighttime symptom score*	−1.0 (0.7) (from 1.3 to 0.3)
Mean change (SD) in % of symptom-free days	+60.3 (30.6) (from 9 to 70)
Mean change (SD) in % of symptom-free nights	+58.5 (33.2) (from 19 to 78)
Mean change (SD) in daytime rescue† use	−1.4 (1.2) (from 1.8 to 0.4)
Mean change (SD) in nighttime rescue† use	−1.1 (1.0) (from 1.3 to 0.2)
Mean change (SD) in % of rescue-free days	+57.0 (34.0) (from 17 to 74)
Mean change (SD) in % of rescue-free nights	+54.7 (36.5) (from 27 to 82)

*The possible range of symptom scores is 0 to 4 for nighttime symptoms and 0 to 5 for daytime symptoms.

†Number of occasions.

FSC 100/50 μ g (adjusted mean change from end of open-label period, -0.3 L/min from 411 L/min). In contrast, mean morning PEF decreased in patients treated with FP 250 μ g (adjusted mean change, -13.2 L/min from 415 L/min). The estimated treatment difference between therapies in the randomized phase was 12.9 L/min (95% CI, 8.1-17.6; $P < .001$). Results were similar for the PP population (estimated treatment difference, 16.0 L/min; 95% CI, 10.8-21.2; $P < .001$). Because the lower bound of the 95% CI was above -15 L/min in both populations and was also greater than 0 in the ITT population, FSC was superior to FP alone in maintaining improvements in mean morning PEF after stepping down treatment from FSC 250/50 μ g.

For each week of the double-blind treatment period, the proportion of patients with asthma assessed as well

controlled or totally controlled was slightly lower than that seen during the last week of open-label treatment with FSC 250/50 μ g for the ITT population (Fig 3, A and B), but the proportion controlled each week with FSC 100/50 μ g remained higher than with FP 250 μ g. During week 12 of the step-down period, 86% in the FSC 100/50 μ g group and 79% in the FP 250 μ g group were well controlled, and 56% and 48%, respectively, were totally controlled.

Assessments of sustained control were made during an 8-week assessment period (weeks 5-12) of the step-down period. Of the 484 patients included in the ITT population (including the 53 patients not well controlled in the last 4 weeks of the open-label period and incorrectly randomized), 77% of patients in the FSC group (ie, inhaled corticosteroid dose reduced) had well controlled asthma,

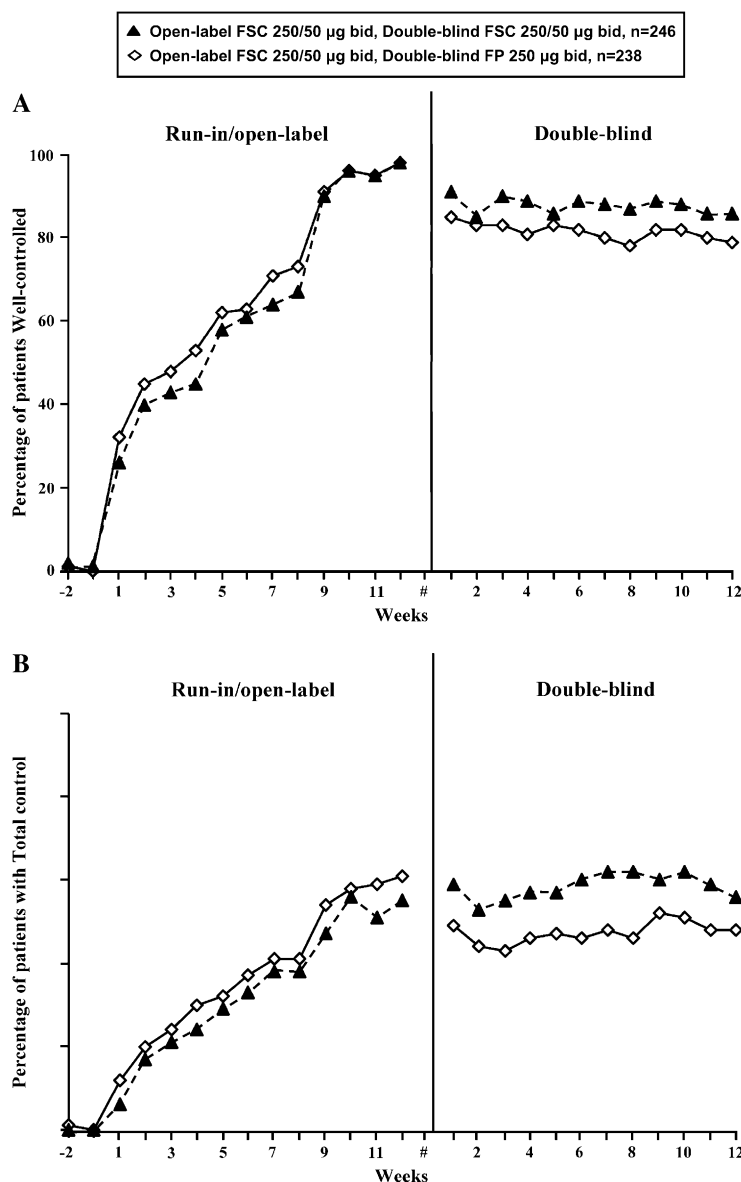


FIG 3. Percentage of subjects achieving asthma control during each week of the study (ITT population). **A**, Well controlled asthma. **B**, Total control of asthma. Only patients who were randomized to double-blind treatment are presented. Includes 53 patients who were randomized even though they had not achieved well-controlled asthma over weeks 9-12 of the open-label phase. *bid*, Twice daily.

compared with 69% in the FP group (ie, long-acting β_2 -agonist stopped). The odds of having well controlled asthma were 46% greater with FSC than with FP, but this finding was not statistically significant (OR, 1.46; 95% CI, 0.96-2.23; $P = .078$). The odds of achieving total control were 62% greater with FSC compared with FP, a statistically significant finding (OR, 1.62; 95% CI, 1.09-2.40; $P = .017$), with 49% of patients in the FSC group achieving total control over weeks 5 to 12, compared with 38% in the FP group.

Similar results were seen in the PP population, which excluded patients who had been incorrectly randomized. In this population, well controlled asthma over weeks 5 to

12 was maintained by 79% of patients in the FSC group and by 72% of patients in the FP group (OR, 1.57; 95% CI, 0.97-2.56; $P = .068$), and total control was achieved by 51% and 38%, respectively, in the 2 treatment groups (OR, 1.81; 95% CI, 1.16-2.82; $P = .008$).

Post hoc sensitivity analyses of asthma control over weeks 5 to 12 of the double-blind step-down phase were performed for 292 patients (60%, 145 receiving FSC, 147 receiving FP) who were well controlled over a period of 8 weeks of the open-label phase, rather than over the 4-week control period required for study entry. In this subset, 129 patients (89%) treated with FSC maintained well controlled asthma over weeks 5 to 12 of the step-down period.

TABLE III. Asthma symptoms and rescue albuterol use through double-blind treatment (ITT population)*

	Adjusted mean change from end of open-label period (SE)		Difference, FSC – FP	
	FSC	FP	(95% CI)	P value
Daytime symptom score†	0.03 (0.02)	0.09 (0.02)	–0.05 (–0.11, 0.00)	.042
Nighttime symptom score†	0.05 (0.01)	0.06 (0.01)	–0.02 (–0.05, 0.02)	.348
Daytime rescue‡ use	0.02 (0.02)	0.09 (0.02)	–0.07 (–0.13, –0.01)	.016
Nighttime rescue‡ use	0.03 (0.02)	0.07 (0.02)	–0.04 (–0.08, 0.00)	.065
	N (%) patients with 100% days/ nights symptom/rescue-free		OR (FSC/FP)	
	FSC	FP	(95% CI)	P value
100% symptom-free days	139 (57%)	108 (46%)	1.80 (1.21, 2.68)	.004
100% symptom-free nights	179 (74%)	140 (60%)	1.95 (1.31, 2.91)	.001
100% rescue-free days	150 (62%)	126 (54%)	1.61 (1.07, 2.41)	.021
100% rescue-free nights	172 (71%)	144 (62%)	1.61 (1.08, 2.41)	.019

*An OR is the odds of having 100% symptom/rescue-free days/nights in the FSC treatment group relative to the odds in the FP treatment group.

An OR >1 is in favor of FSC.

†The possible range of symptom scores is 0 to 4 for nighttime symptoms and 0 to 5 for daytime symptoms.

‡Number of occasions.

The comparative figure for patients treated with FP was 113 patients (77%). The odds of maintaining well controlled asthma were more than 2-fold greater with FSC than with FP (OR, 2.36; 95% CI, 1.20–4.63; $P = .013$). The odds of achieving total control after step-down were 90% greater with FSC compared with FP (OR, 1.90; 95% CI, 1.15–3.15; $P = .013$), with 62% of patients in the FSC subset totally controlled over weeks 5 to 12 of the double-blind step-down phase, compared with 45% in the FP subset.

Reasons for failure to maintain asthma control on dose reduction were generally similar in the 2 treatment groups. The well controlled asthma criteria that failed most commonly during the double-blind treatment period were those for nighttime awakenings and PEF. For patients who were not well controlled over weeks 5 to 12 of the double-blind step-down period, 80% in the FSC group and 83% in the FP group did not meet the nighttime awakenings criterion, and 59% and 56%, respectively, did not meet the PEF criterion.

There was no evidence for an increase in symptom scores or rescue use when treatment was stepped down, with only small changes seen from the end of the open-label period (Table III). Statistically significant differences in daytime symptom score and rescue usage and in the percentage of symptom-free and rescue-free days and nights in favor of FSC were seen. Ten patients, 5 (2%) in each treatment group, had an exacerbation during randomized treatment.

Adverse events

All treatments were well tolerated. During open-label treatment with FSC 250/50 μg , 164 patients (26%) reported an adverse event, and similar proportions of subjects reported adverse events during the blind treatment period (57 patients [23%] treated with FSC 100/50

μg and 61 [26%] treated with FP 250 μg). The number of patients experiencing drug-related adverse events was low (5% during FSC 250/50 μg , 2% during FSC 100/50 μg , and 3% during FP 250 μg). The most commonly reported drug-related events were hoarseness, reported by 1% during open-label treatment, and oral candidiasis during double-blind treatment (reported by 2% in each group).

DISCUSSION

Current international asthma guidelines¹ recommend that once asthma control has been achieved and maintained for 3 to 6 months, treatment should be reviewed and dose reduction of controller medication should be attempted, with careful monitoring to ensure that control is not lost. This advice is largely based on clinical experience, and few studies have examined the options and most favorable conditions for stepping down treatment. Questions that need to be addressed include whether step-down of controller can be achieved without loss of control of asthma, in whom and when is it safe to attempt it, how patients should be monitored when step-down is attempted, the size of the dosing steps, and, in an era of use of combination controllers (for example, inhaled corticosteroid combined with long-acting β_2 -agonist), which controller should be reduced first. Our study set out to examine some aspects of these questions, and principally whether, in patients on a combination of inhaled corticosteroids and long-acting β_2 -agonist, it is preferable to reduce the dose of inhaled corticosteroid in the combination or stop the long-acting β_2 -agonist.

The results of our study confirm that FSC with a lower corticosteroid dose (ie, reducing the dose of corticosteroid) is a better treatment option than continuing FP alone (ie, stopping long-acting β_2 -agonist treatment) when a dosage

reduction is indicated in patients whose asthma has been controlled by FSC 250/50 μg twice daily. On the basis of the primary endpoint of mean morning PEF, FSC 100/50 μg twice daily was shown to be more effective than FP 250 μg twice daily using the tests defined a priori for noninferiority and then superiority. These findings are supported by secondary endpoints confirming a lower level of asthma symptoms and rescue albuterol usage after corticosteroid dose reduction than was seen when the salmeterol was removed.

The majority of patients retained asthma control whether judged on a week-by-week basis or using the stringent 8-week assessment period described in the GOAL study.⁴ More patients treated with FSC than treated with FP alone retained control, but there was no evidence for a difference between treatments in the reasons for no longer being controlled. Specifically, in the light of the fact that a bronchodilator had been removed in the FP group, failure did not simply relate to measures of airway caliber (PEF) but was seen in nighttime awakenings, daytime symptom scores, and rescue usage.

Unique features of the study were that we enrolled patients with uncontrolled asthma and then defined a minimum level of control (well controlled asthma, defined in terms of a previously used composite control measure⁴), which served as the criterion for randomization, and a minimum duration of control (4 weeks) that each patient had to fulfill before dose reduction was commenced. We selected as primary endpoint morning predose PEF, because PEF is easily performed and is a well-established outcome measure for monitoring asthma¹ for which clinically important treatment differences are recognized.^{8,9} This was chosen in preference to a comprehensive measure of asthma control because, when the study was designed, the concept of using such measures was not well researched and their validity had not been established. The study was designed and powered for noninferiority of treatments, and rules for establishing superiority if noninferiority was demonstrated were also defined a priori. The noninferiority limit selected (95% lower CI bound of -15 L/min) has been used in previous studies,^{8,9} and, in line with European clinical trial guidelines,⁷ noninferiority had to be demonstrated in both ITT and PP populations before testing for superiority of a treatment in the ITT population. However, in the light of the recent emphasis and demonstrated benefits of using comprehensive composite measures of asthma control,^{3,4,10,11} we also used control criteria very similar to those used in the GOAL study to examine the effects of dose reduction. The assessment used differed from the GOAL measure only in respect to the criterion for rescue bronchodilator use; in this study, use had to be on ≤ 2 days per week, whereas in the GOAL study, use had to be on ≤ 2 days and also ≤ 4 occasions per week.

It is relevant to consider the effect of some of the features of the study design on the outcomes and interpretation of results. The patients selected for study had uncontrolled asthma of moderate severity,¹ and, contrary to guideline recommendations, were receiving only inhaled short-acting β_2 -agonists, and had not received

controller treatment for the preceding 6 months. Although not satisfactory, community-based surveys suggest that this is not an uncommon situation among patients with asthma.^{12,13} Not surprisingly, the patients demonstrated rapid and great clinical improvements when FSC 50/250 μg was commenced, with improvements in lung function and symptoms seen and increasing numbers achieving the well controlled status each week of the open label phase.

The optimal period that control should be maintained before treatment reduction is attempted is not known, and this question was not addressed in this study. It can be debated whether patients were treated for long enough before dose reduction was attempted. Step-down was commenced after only 4 consecutive well controlled weeks. The results suggest that the combination treatment step-down option was superior, and that in the majority, step-down after 4 weeks is satisfactory and not associated with loss of control. What, then, might be the benefits of maintaining patients on the higher dose for longer before stepping down? Results from other studies and most notably the GOAL study confirm that with sustained treatment, more patients will achieve higher levels of control (that is, total control), and that achievement of control is a function of both dose and duration of treatment.^{4,5} It is speculated that this benefit might be attributable to more complete suppression of airway inflammation¹⁴ or reversal of airway remodeling.¹⁵ In the current study, we performed a post hoc sensitivity analysis in a subset of patients who had achieved well controlled asthma for 8 weeks of the open-label phase. Higher proportions of patients maintained control after step-down in the subset of patients who had been controlled for an 8-week period (as defined in the GOAL study) than in patients who satisfied only the 4-week eligibility definition in the open-label period. This suggests that control may be better maintained in those patients in whom control is achieved for a longer period before step-down, although this difference might simply reflect differences in treatment responsiveness between patients rather than the benefit of prolonging treatment before step-down. Although the current study suggests that in the majority of patients, step-down may be commenced after only 4 weeks of established control, it was of relatively short duration (12 weeks after step-down), and effects on asthma exacerbation rates could not be examined. It is possible that over a longer period of follow-up, slow but steady deterioration might occur. These considerations might steer clinicians toward a more cautious policy on timing of dose reductions. Prospective evaluation of the optimal treatment period before step-down in studies of appropriate design is required.

In conclusion, the recently published GOAL study⁴ showed that with individualized incremental treatment, comprehensive asthma control could be achieved in the majority of patients, but it did not address whether control could be maintained if treatment was reduced. The current study provides some guidance on how best to reduce therapy when treatment reduction is indicated, although it has not assessed the optimal treatment or treatment duration to

achieve maximal levels of control before a dose reduction is attempted. It confirms that treatment with a lower dose of inhaled corticosteroid and a long-acting β_2 -agonist is a more effective treatment option than treatment with a higher dose of inhaled corticosteroid alone, an approach that is potentially advantageous with respect to minimizing the chance of corticosteroid-related side effects.^{1,16} When a decision has been taken to reduce a patient's therapy, stepping treatment down from FSC 250/50 μg to FSC 100/50 μg (reducing the corticosteroid dose) is more effective than stepping down to treatment with FP 250 μg alone (stopping treatment with salmeterol) in maintaining asthma control.

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