

Low-dose inhaled fluticasone propionate versus oral zafirlukast in the treatment of persistent asthma

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Background: Few studies have compared the efficacy of inhaled corticosteroids and leukotriene modifiers for the treatment of persistent asthma.

Objective: Our purpose was to compare the efficacy of a low dose of inhaled fluticasone propionate (FP) with that of oral zafirlukast in the treatment of persistent asthma previously treated with short-acting β_2 -agonists alone.

Methods: A 12-week, randomized, double-blind, double-dummy, multicenter study was conducted in 451 patients aged 12 years and older with asthma who were symptomatic on short-acting β_2 -agonists alone. After an 8- to 14-day run-in period, patients were randomized to treatment with FP 88 μ g twice daily or zafirlukast 20 mg twice daily.

Results: Treatment with FP was more effective than treatment with zafirlukast in increasing morning FEV₁ (by 0.42 L vs 0.20 L over baseline, $P < .001$), morning peak expiratory flow (by 49.94 L/min vs 11.68 L/min over baseline, $P < .001$), and evening PEF (by 38.91 L/min vs 10.50 L/min over baseline, $P < .001$). Statistically significant differences between the two treatments in FEV₁ were noted after the first observation (week 4) and in morning and evening peak expiratory flow by week 2. Mean change in percentage of symptom-free days was greater with FP than with zafirlukast (28.5% of days vs 15.6% of days, $P < .001$) and FP significantly increased the percentage of rescue-free days by 40.4% of days compared with 24.2% of days with zafirlukast ($P < .001$). Treatment with FP significantly reduced albuterol use by 2.39 puffs per day compared with 1.45 puffs per day ($P < .001$) and increased the percentage of nights with no awakenings by 21.2% of nights compared with 8.0% of nights with zafirlukast ($P < .001$).

Conclusion: The clinical effectiveness of a low dose of FP as first-line therapy in patients with persistent asthma who are symptomatic on β_2 -agonists alone is superior to that of zafirlukast. (*J Allergy Clin Immunol* 2000;105:1123-9.)

Key words: Fluticasone propionate, asthma, inhaled corticosteroids, leukotriene modifiers, zafirlukast

Abbreviations used

BID: Twice daily
FP: Fluticasone propionate
PEF: Peak expiratory flow

Guidelines from the National Institutes of Health for the treatment of asthma currently recommend the daily use of anti-inflammatory medications for the long-term control of persistent asthma.¹ These guidelines recognize inhaled corticosteroids as the most effective anti-inflammatory medications for the treatment of mild, moderate, and severe persistent asthma. The guidelines also suggest that a new class of medication, the leukotriene modifiers, may be considered as a potential alternative to low-dose inhaled corticosteroids as first-line controller therapy, although additional studies are needed to establish their position in asthma management. The leukotriene modifiers that are currently available worldwide include the leukotriene receptor antagonists, zafirlukast, pranlukast, montelukast, and the 5-lipoxygenase inhibitor zileuton. The relative merits of inhaled corticosteroids and leukotriene modifiers as first-line controller therapies in asthma should be based on the results of clinical trials that evaluate clinical efficacy and safety, disease-modifying properties, convenience of use, and anti-inflammatory properties.^{2,3} However, there have been few published studies comparing the clinical efficacy and safety of inhaled corticosteroids with that of leukotriene modifiers.^{4,5}

In this study the efficacy and safety of the lowest recommended dose (88 μ g twice daily [BID]) of the inhaled corticosteroid fluticasone propionate (FP) was compared with that of the recommended dose of oral zafirlukast (20 mg BID). The efficacy and safety of low-dose (as defined by the National Asthma, Education, and Prevention Program [National Heart, Lung, and Blood Institute] guidelines for the diagnosis and treatment of asthma) FP 88 μ g BID and zafirlukast 20 mg BID in patients previously treated with inhaled β_2 -agonists alone have previously been established.^{1,6-12} The purpose of this study was to provide comparative data on important objective (eg, pulmonary function tests, peak expiratory flow [PEF], rescue albuterol use, and asthma exacerbations) and subjective (eg, asthma symptom scores) measures related to clinical efficacy of these two asthma therapies as first-line treatment for persistent asthma.

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TABLE I. Patient demographics, characteristics, and disposition

	Zafirlukast 20 mg BID (n = 220)	FP 88 µg BID (n = 231)
Mean age (y [range])	31 (12-66)	31 (12-68)
Sex (No. [%])		
Male	107 (49)	119 (52)
Female	113 (51)	112 (48)
Ethnic origin (No. [%])		
White	183 (83)	191 (83)
African American	17 (8)	19 (8)
Other	20 (9)	21 (9)
Mean screening % predicted FEV ₁	68	67
No. (%) completed	170 (77)	200 (87)
No. (%) withdrawn	50 (23)	31 (13)
Consent withdrawn	1 (<1)	3 (1)
Lost to follow-up	6 (3)	7 (3)
Protocol violation	5 (2)	4 (2)
Asthma exacerbation*	14 (6)	6 (3)
Adverse event	12 (5)	8 (3)
Other†	12 (5)	3 (1)

Based on intent-to-treat population.

*Several patients who had an asthma exacerbation and withdrew from the study were listed as having been withdrawn for other reasons that precipitated an asthma exacerbation (ie, adverse event, treatment failure, noncompliance).

†Includes failure to meet entrance criteria, noncompliance, lost medications, and treatment failure.

METHODS

Patients

Patients 12 years of age and older with a diagnosis of persistent asthma for at least 6 months before screening were eligible for the study if they demonstrated a predose FEV₁ of 50% to 80% of predicted normal and an increase in FEV₁ of 12% or greater from baseline after inhalation of 180 µg of albuterol.¹³⁻¹⁵ Eligible patients were required to have used albuterol on a scheduled or as-needed basis during the 4 weeks immediately before screening. Patients were not permitted to receive montelukast, zafirlukast, or zileuton within 2 weeks of screening, and inhaled corticosteroids or systemic corticosteroids were not allowed within 2 months of screening. Patients who had a history of life-threatening asthma or who had received more than 3 bursts of oral or parenteral corticosteroids within 1 year were excluded. Other exclusion criteria included use of tobacco products within the previous year or a smoking history of greater than 10 pack-years, a respiratory infection within 2 weeks of screening, current evidence of significant respiratory disorders other than asthma, or other significant uncontrolled disease states. Concurrent use of medications, which might affect the course of asthma (eg, salmeterol, theophylline) or interact with zafirlukast (eg, terfenadine, warfarin) were prohibited. Antihistamines, decongestants, and intranasal medications for the treatment of allergic rhinitis were allowed.

Study design

All patients (or parent/guardian) gave written informed consent before undergoing any study procedures, and the institutional review board at each site approved the protocol (FAS40023). After the screening visit (visit 1), patients entered an 8- to 14-day run-in period during which all patients used rescue albuterol (Ventolin Inhalation Aerosol, GlaxoWellcome, Research Triangle Park, NC) to relieve symptoms of asthma. The purpose of the run-in period was to confirm each patient's eligibility for the study, to obtain

baseline diary card assessments of asthma symptom scores and rescue albuterol use, and to assess patient compliance in completing diary cards. At the conclusion of the run-in period (visit 2), patients had to have a morning predose FEV₁ between 50% to 80% of predicted normal that was within 15% of the baseline FEV₁ obtained at visit 1 and, on the basis of a diary card review of the 7 days before visit 2, demonstrate the use of Ventolin on ≥5 days or an asthma symptom score of ≥2 (on a 0-5 point scale) on ≥3 days. Thus patients selected for this study had persistent asthma, were receiving inadequate asthma therapy (ie, short-acting β₂-agonists alone) on the basis of current asthma treatment guidelines,¹ and were appropriate candidates for the use of chronic controller therapy.

Patients were randomly assigned to receive treatment twice daily (morning and evening) with either inhaled FP aerosol 88 µg (Flovent Inhalation Aerosol, GlaxoWellcome) or oral zafirlukast 20 mg (Accolate, Astra Zeneca, Wilmington, Del) for 12 weeks with use of a double-blind, double-dummy design. Treatment assignments were generated in blocks of 4 by a computer-based random code system. Because the bioavailability of zafirlukast is reduced by food, patients were instructed to take their capsules 1 hour before or 2 hours after meals. Throughout the double-blind treatment period, patients used albuterol as needed to relieve breakthrough asthma symptoms. On the morning of each clinic visit, the morning dose of study medication was withheld, and the visit was rescheduled if the patient had used albuterol within the 6 hours preceding the visit. Patients who had an asthma exacerbation during the study were withdrawn. An asthma exacerbation was defined as a worsening of asthma that required the use of oral or parenteral corticosteroids.

Procedures

Clinic visits at randomization and after 4, 8, and 12 weeks of study treatment were scheduled between 6 and 10 AM. At each clinic visit (or early withdrawal visit when applicable), spirometric determination of FEV₁ was performed, adverse events and concurrent medications were assessed, and diary cards were reviewed. Study investigators determined whether there was a reasonable possibility that any reported adverse events were caused by study medication.

Each morning and evening during both the run-in and treatment periods, patients rated asthma symptoms, measured PEF, and recorded the information on diary cards along with the number of puffs of albuterol used. PEF measurements were obtained before taking the morning and evening doses of blinded study medication, and the highest of 3 PEF measurements was recorded on a diary card. Symptoms of chest tightness, wheeze, shortness of breath, and cough were assessed before relief with albuterol and were rated on a 6-point scale: 0 = no symptoms to 5 = symptoms that caused discomfort and prevented normal daily activities.

Statistical analyses

The intent-to-treat population (defined as all patients randomly assigned to study drug) was used for all safety and efficacy analyses. The sample size in this study (at least 200 completed patients per treatment group) was determined to provide at least 80% power to detect a difference in FEV₁ of 0.175 L between the two treatment groups on the basis of a 2-sample *t* test with a significance level of .05 and an SD of 0.55 L. All statistical tests were 2-sided with a significance level of .05.

The primary measure of efficacy was mean morning premedication FEV₁ obtained at each clinic visit. Mean change from baseline at end point was the primary analysis for FEV₁ and all diary measures. Baseline FEV₁ was defined as the measurement obtained at randomization (visit 2) and baseline for all other measurements was defined as the mean from the 7 days before randomization for each diary measure. Mean change from baseline in FEV₁ was analyzed at each clinic visit and at end point, and mean change in each diary

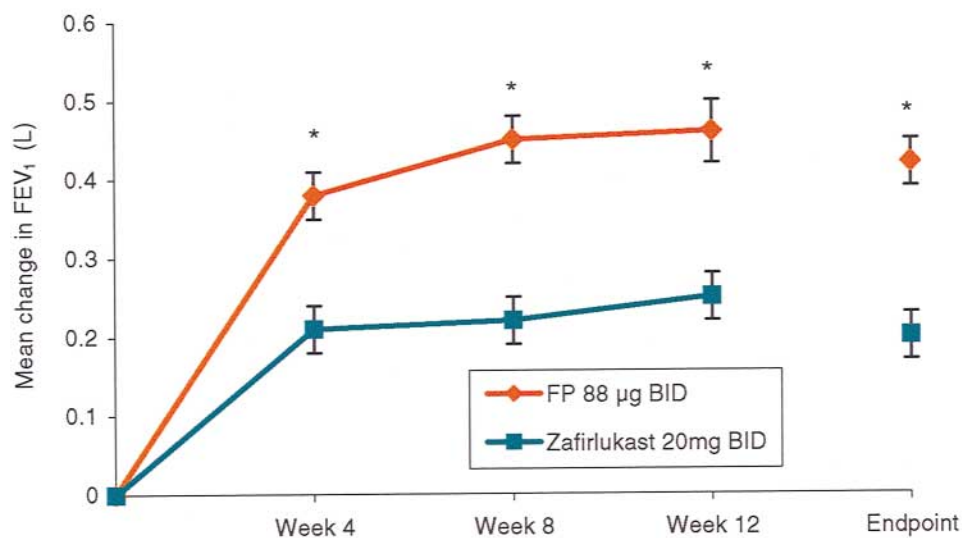


FIG 1. Mean change from baseline in FEV₁ over 12 weeks and at end point. Asterisk, $P < .001$ versus zafirlukast.

measure was analyzed at each week and at end point. End point was defined as the last postbaseline observation for FEV₁ and as the last postbaseline week of diary measurements. Analyses of covariance adjusting for site and baseline were conducted for FEV₁ and each diary measure to test for treatment differences.

The frequencies of patients in each treatment group who had an asthma exacerbation were compared with the Fisher exact test. Adverse events were tabulated by treatment group; no statistical analyses of adverse events were planned or performed.

RESULTS

Five hundred ninety-two patients were screened for participation at 41 study sites. Four hundred fifty-one patients met the inclusion criteria and were randomly assigned to treatment. Randomization resulted in comparable treatment groups at baseline with respect to patient demographics and pulmonary function. The characteristics of the patients in the two treatment groups are reported in Table I. Patient-reported compliance with the metered-dose inhaler and with the oral capsules was approximately 92% in both the FP and zafirlukast groups.

Efficacy

Table II reports baseline values and the changes at end point for efficacy measures.

Pulmonary function. Treatment with FP resulted in significantly greater increases in FEV₁ compared with zafirlukast. After week 4 (first treatment assessment), week 8, week 12, and at end point treatment with FP resulted in increases in FEV₁ of 0.38, 0.45, 0.46, and 0.42 L from baseline, respectively, compared with increases of 0.21, 0.22, 0.25, and 0.20 L with zafirlukast ($P < .001$ at all assessments, Fig 1). Similar changes in forced expiratory flow at 25% to 75% of forced vital capacity and in forced vital capacity were found.

Greater improvements in morning and evening PEF

were observed with FP compared with zafirlukast (Table II). Statistical differences between treatment groups in favor of FP in morning and evening PEF were found by week 2 and were maintained throughout the study. After 2 weeks of treatment, improvements in morning PEF of 33.52 L/min and 15.16 L/min were found in the FP and zafirlukast groups, respectively ($P < .001$), and after 12 weeks increases of 54.45 L/min and 17.18 L/min were observed ($P < .001$). The mean change from baseline at end point in morning PEF stratified by severity of airway obstruction (FEV₁, mean percent predicted) is reported in Fig 2. Treatment with FP resulted in significantly greater increases in morning PEF compared with zafirlukast ($P \leq .001$) regardless of the level of baseline airway obstruction.

Asthma symptoms and nighttime awakenings. Days in which patients reported no symptoms (ie, a symptom score of 0) were used to determine the percentage of symptom-free days during treatment with FP or zafirlukast. At baseline patients in both treatment groups reported a low number of symptom-free days ($7.4\% \pm 1.1\%$ of days and $5.1\% \pm 0.9\%$ of days for FP and zafirlukast groups, respectively). Treatment with FP resulted in a significantly greater improvement in the mean percentage of symptom-free days compared with zafirlukast (Fig 3). Statistical differences in favor of FP were noted by week 1 ($P = .021$).

The combined asthma symptom score measured patient evaluations of the severity of their daytime symptoms of chest tightness, wheeze, shortness of breath, and cough. A significantly greater decrease in the combined symptom score was observed after the first week of FP treatment compared with zafirlukast and throughout the study ($P = .026$ at week 1).

At baseline, the FP and zafirlukast groups reported 67.0% ($\pm 2.3\%$) and 66.5% ($\pm 2.3\%$) of nights with no awakenings, respectively. Treatment with FP significantly

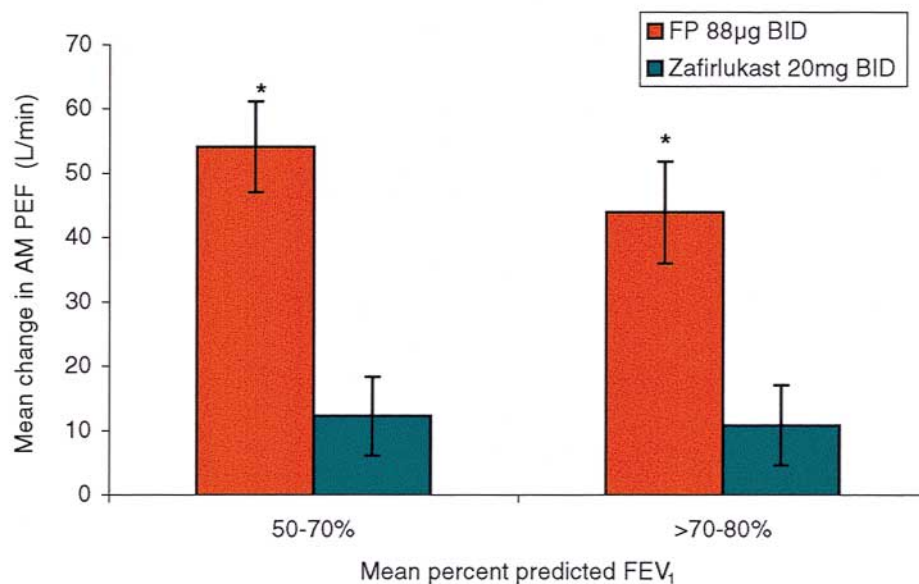


FIG 2. Mean change from baseline at end point in morning PEF stratified by severity of airway obstruction. Asterisk, $P \leq .001$ versus zafirlukast.

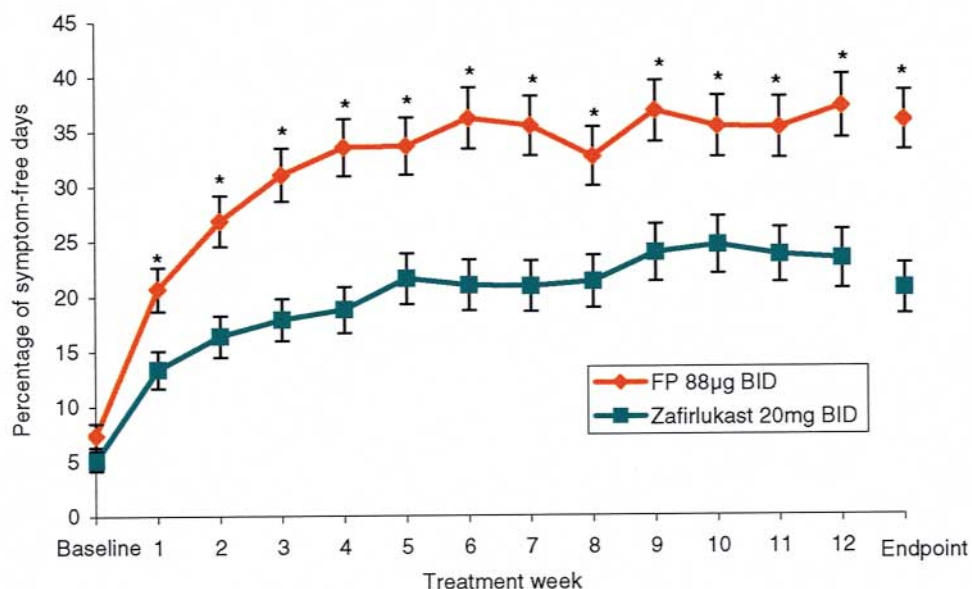


FIG 3. The percentage of symptom-free days over 12 weeks of treatment and at end point. Asterisk, $P \leq .021$ versus zafirlukast.

increased the percentage of nights with no awakenings by 21.2% ($\pm 2.3\%$) of nights compared with 8.0% ($\pm 2.1\%$) of nights with zafirlukast (end point, $P < .001$); statistical differences were noted between treatment groups in favor of FP by week 1 ($P < .001$). Similarly, the mean number of nighttime awakenings was significantly reduced with FP treatment compared with zafirlukast ($P < .001$ at end point, Table II).

Rescue albuterol use. Statistical differences in rescue albuterol use were noted in favor of FP by week 1 and throughout the study ($P < .001$). Albuterol use by treat-

ment week is shown in Fig 4. Similarly, treatment with FP resulted in significantly greater increases in the percent of days where patients did not use any rescue albuterol (ie, rescue-free days). Statistical differences in rescue-free days, noted in favor of FP by week 1 ($P = .009$ vs zafirlukast), were maintained throughout the study (Table II).

Physicians' global assessments. A significantly greater percentage of physicians rated treatment with FP as either "effective" or "very effective" compared with zafirlukast (56% vs 41%, $P < .001$). A significantly greater percent-

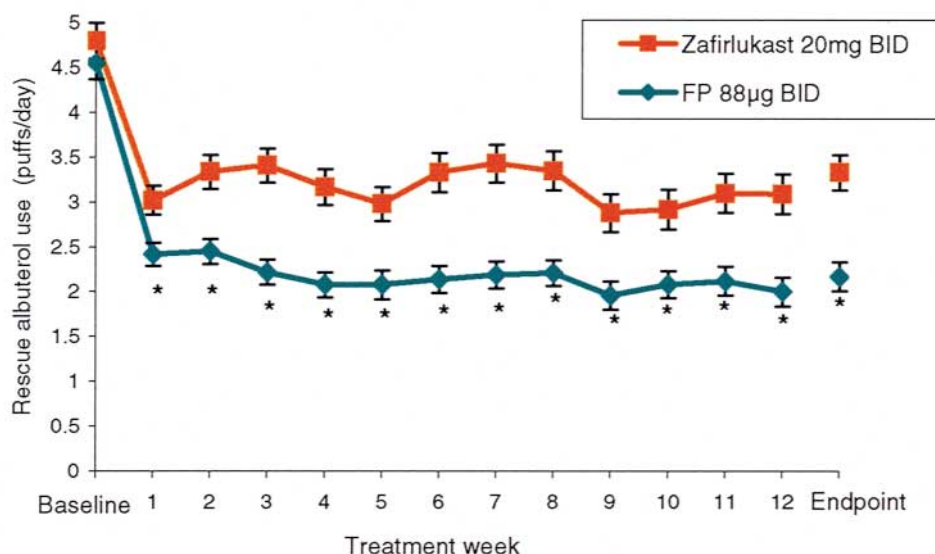


FIG 4. Rescue albuterol use over 12 weeks of treatment and at end point. Asterisk, $P < .001$ versus zafirlukast.

TABLE II. Mean change from baseline (SE) at end point for efficacy variables

Variable	FP 88 µg BID (n = 231)		Zafirlukast 20 mg BID (n = 220)	
	Baseline (SE)	Change at end point (SE)	Baseline (SE)	Change at end point (SE)
Morning FEV ₁ (L)	2.47 (0.04)	+0.42 (0.03)*	2.46 (0.04)	+0.20 (0.03)
Forced expiratory flow at 25%-75% of vital capacity (L)	1.77 (0.04)	+0.54 (0.05)*	1.74 (0.04)	+0.27 (0.04)
Forced vital capacity (L)	3.63 (0.06)	+0.36 (0.03)*	3.61 (0.06)	+0.15 (0.03)
Morning PEF (L/min)	357.3 (6.71)	+49.94 (5.28)*	366.5 (6.48)	+11.68 (4.37)
Evening PEF (L/min)	393.0 (6.81)	+38.91 (4.95)*	398.9 (6.96)	+10.50 (4.10)
Combined symptom score	1.17 (0.05)	-0.46 (0.05)*	1.12 (0.05)	-0.19 (0.05)
Symptom-free days (%)	7.4 (1.1)	+28.5 (2.6)*	5.1 (0.9)	+15.6 (2.3)
Albuterol use (puffs/d)	4.55 (0.18)	-2.39 (0.19)*	4.80 (0.20)	-1.45 (0.19)
Rescue-free days (%)	7.2 (1.1)	+40.4 (2.5)*	7.4 (1.2)	+24.2 (2.3)
Nights with no awakenings (%)	67.0 (2.3)	+21.2 (2.3)	66.5 (2.3)	+8.0 (2.1)
Nighttime awakenings (No.)	0.44 (0.04)	-0.28 (0.04)*	0.49 (0.05)	-0.15 (0.04)

End point was defined as the last postbaseline observation for FEV₁ and as the last postbaseline week of diary measurements.

* $P < .001$, FP versus zafirlukast.

age of physicians rated treatment with zafirlukast as “ineffective” (27% vs 16%, $P < .001$).

Safety

Asthma exacerbations. Asthma exacerbations were defined as worsening asthma that required treatment with oral or parenteral corticosteroids. Eight (4%) patients treated with FP had an exacerbation compared with 14 (6%) patients treated with zafirlukast; however, the difference between groups was not statistically significant ($P = .191$).

Adverse events. The overall incidence of adverse events was similar between groups. Twenty-three patients (10%) in each treatment group had at least one adverse event during the study that was considered by the investigator to be potentially related to treatment (“drug

related”). The most commonly reported drug-related adverse events ($\geq 1\%$ in any group) were headache (3% with FP and 1% with zafirlukast), dry mouth (1% in the FP group), and hoarseness (2% in the FP group). Two patients treated with FP withdrew because of adverse events potentially related to treatment (headache and rash). Four patients treated with zafirlukast withdrew because of adverse events potentially related to treatment (acne, generalized body rash, cough, and itching/rash). Two patients in the zafirlukast group had serious adverse events that resulted in withdrawal (one patient had an asthma exacerbation associated with pneumonia; the second patient had an asthma exacerbation associated with bronchitis). No patient in the FP group had a serious adverse event that resulted in withdrawal.

DISCUSSION

The results of this study demonstrated that a low dose of FP (88 µg BID) is more effective than zafirlukast (20 mg BID) as first-line therapy for patients with persistent asthma. Patients enrolled into this study were receiving inadequate asthma therapy (ie, short-acting β_2 -agonists alone) on the basis of current asthma treatment guidelines¹ and were appropriate candidates for the use of chronic controller therapy. Treatment with FP resulted in significantly greater improvements in all subjective and objective measures of clinical efficacy compared with zafirlukast. At end point, improvements in measures of pulmonary function (FEV₁ and PEF), asthma symptom control (symptom scores and the percent of symptom-free days), and rescue albuterol use were generally 2- to 4-fold greater with FP compared with zafirlukast. Physicians' ratings of effectiveness of treatment complemented these results. Improvements in forced expiratory flow of 25% to 75% of forced vital capacity, which may reflect changes in more peripheral airway function, were also greater with FP and were similar to results observed for FEV₁. Statistically significant differences in favor of FP compared with zafirlukast were noted by week 1 for asthma symptom measures and rescue albuterol use, by week 2 for PEF, and by week 4 for FEV₁ (the first treatment assessment). Both treatment regimens were well tolerated over the 12-week study with similar safety profiles assessed by similar occurrence of adverse events.

These data corroborate the results of other investigators who demonstrated the efficacy and safety of low doses of FP in patients previously treated with β_2 -agonists alone.⁷⁻⁹ In those studies the mean change from baseline at end point in FEV₁ was 0.42 to 0.54 L. In addition, Sorkness et al⁶ and Li et al⁸ demonstrated the safety of low-dose FP (88 µg BID); the adrenal response to 6-hour cosyntropin infusion was similar to that of placebo, suggesting minimal or no effect on the hypothalamic-pituitary-adrenal axis.

The results of the current study are similar to preliminary data reported by Busse et al,⁵ which showed greater improvements in pulmonary function and asthma symptoms after 12 weeks of treatment with FP 88 µg BID compared with zafirlukast 20 mg BID in a similar patient population. These results are also consistent with those from a study with montelukast, another leukotriene receptor antagonist.⁴ In that study, treatment with beclomethasone dipropionate 200 µg BID significantly increased FEV₁ (13.1% vs 7.4%, $P < .01$) and reduced asthma symptom scores (-0.62 vs -0.41, $P < .01$) compared with montelukast 10 mg once daily in patients with asthma treated with short-acting bronchodilators only. Thus these data confirm that inhaled corticosteroids, even at low doses, are more effective in controlling asthma than leukotriene modifiers alone.

In this study asthma exacerbations were defined as worsening asthma requiring treatment with oral corticosteroids. Patients treated with FP had fewer exacerbations than patients treated with zafirlukast; however, the

difference between groups was not statistically significant. With a less-stringent definition of an asthma exacerbation (based on PEF variation, rescue albuterol use, symptoms, oral steroid use, physician visits, or hospitalizations), Malmstrom et al⁴ reported that treatment with beclomethasone dipropionate resulted in significantly fewer days with asthma exacerbations compared with montelukast. Because of low occurrence rates, studies of longer duration (eg, ≥ 1 year) are optimal for analysis of asthma exacerbation and hospitalization rates. Such studies have demonstrated that the use of inhaled corticosteroids results in significant protection against acute exacerbations of asthma leading to hospitalization and reduced hospital readmission for asthma.^{16,17} Similar long-term studies comparing the rates of hospitalization for worsening asthma in patients receiving inhaled corticosteroids and leukotriene modulators are required to determine the relative benefits of these medications on long-term outcomes.

The anti-inflammatory properties of inhaled corticosteroids in the airways are well documented and include an extensive range of actions such as inhibitory effects on airway inflammatory cells and proinflammatory cytokines.¹⁸ The primary mechanism of action of the leukotriene modifiers, both leukotriene receptor antagonists (eg, zafirlukast and montelukast) and leukotriene synthesis inhibitors (eg, zileuton), is to prevent the action of a single class of mediators (ie, the leukotrienes) on airway cells and vascular permeability.¹⁹ Although we did not directly measure index values of inflammation in this study, the markedly greater improvements in measures of pulmonary function and symptom control observed with FP compared with zafirlukast may be a result of a broader range of anti-inflammatory activity afforded by FP in the treatment of asthma. Alternatively, expression of a genetic variant of 5-lipoxygenase in a subset of patients may have resulted in decreased leukotriene production and clinical response to treatment with zafirlukast.²⁰

In summary, treatment with inhaled FP (88 µg BID) produced significantly greater improvements in asthma control than zafirlukast (20 mg BID), as measured by improvements in pulmonary function, asthma symptom control, and rescue albuterol use in patients not well controlled on β_2 -agonists alone. Both treatments were well tolerated. These results support current asthma treatment guidelines¹ that recognize inhaled corticosteroids as the most effective long-term controller medications for the treatment of persistent asthma.

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