Addition of salmeterol to low-dose fluticasone versus higher-dose fluticasone: An analysis of asthma exacerbations

Jonathan Matz, MD,[a] Amanda Emmett, MS,[b] Kathleen Rickard, MD,[b] and Christopher Kalberg, PhD[b] *Baltimore, Md, and Research Triangle Park, NC*

Background: Adding salmeterol to low-dose fluticasone propionate (FP) produces greater improvements in pulmonary function and symptom control than increasing the dose of FP in patients who remain symptomatic with low-dose FP.
Objective: We sought to compare the rates and characteristics of asthma exacerbations in patients after adding salmeterol to low-dose FP with the rates and characteristics of exacerbations in patients receiving higher dose FP.
Methods: In 2 multicenter, double-blind studies, 925 patients 12 years of age and older receiving 88 μg twice daily FP randomly received either 42 μg of salmeterol and 88 μg of FP or an increased dose of FP (220 μg) twice daily for 24 weeks. Exacerbation rates and clinical measures of asthma worsening were assessed for all patients who experienced an asthma exacerbation.
Results: The addition of salmeterol resulted in a significantly lower rate and number of exacerbations compared with higher dose FP. A total of 41 (8.8%) patients experienced 47 exacerbations with the addition of salmeterol compared with 63 (13.8%) patients with 75 exacerbations in the group receiving increased-dose FP ($P = .017$). Salmeterol plus low-dose FP was significantly more protective than increased-dose FP in preventing asthma exacerbations, as assessed by the time to first exacerbation ($P < .05$). In both groups clinical indicators of worsening asthma showed parallel changes before asthma exacerbation, and greater improvements were observed after exacerbation with salmeterol compared with higher dose FP.
Conclusion: Salmeterol plus low-dose FP was more effective than higher dose FP alone in reducing asthma exacerbations in patients with persistent asthma. The ability to detect deteriorating asthma and the severity of exacerbation was similar between groups. (J Allergy Clin Immunol 2001;107:783-9.)

From [a]Atlantic Asthma and Allergy Center, Inc, Baltimore; and [b]Glaxo Wellcome Inc, Research Triangle Park.
Supported by a grant from Glaxo Wellcome Inc, Research Triangle Park, NC.
Presented in part at the 56th Annual Meeting of the American Academy of Allergy, Asthma and Immunology, San Diego, Calif, March 2000.
Received for publication December 6, 2000; revised January 29, 2001; accepted for publication January 30, 2001.
Reprint requests: Jonathan Matz, MD, Atlantic Asthma & Allergy Center, Inc, 7939 Honeygo Blvd, #219, Baltimore, MD 21236.

0091-6749/2001 $35.00 + 0 **1/81/114709**
doi:10.1067/mai.2001.114709

Key words: *Salmeterol xinafoate, fluticasone propionate, long-acting β_2-agonist, inhaled corticosteroid, asthma exacerbations*

Current asthma treatment guidelines recommend the use of daily long-term controller medications to achieve and help maintain control of the symptoms of persistent asthma. Anti-inflammatory therapy with an inhaled corticosteroid (ICS) is considered the most effective treatment currently available for the long-term management of persistent asthma symptoms and has become the cornerstone of care for persistent asthma.[1,2]

Although ICSs are effective in controlling symptoms in many patients, some patients may remain symptomatic despite ICS therapy. In these patients the combination of an ICS with a long-acting β-agonist has been shown to be more effective than increasing the dose of ICSs, as assessed by improvements in pulmonary function and decreases in asthma symptoms and the need for rescue albuterol.[3-7]

In addition to the improvement in pulmonary function and symptom control, prevention of asthma exacerbations is a key goal of asthma therapy.[1] In this context early recognition and treatment is considered the best strategy for the management of asthma exacerbations.[1] For this reason, knowledge of the expected rates and characteristics of asthma exacerbations with the varied therapeutic regimens is an important factor in the selection of the most effective asthma therapy for optimal care of the asthmatic patient.

The purpose of this analysis was to compare the rates and characteristics of asthma exacerbations in the following groups of patients who remained symptomatic with a low dose of the ICS fluticasone propionate (FP): (1) patients who had the long-acting β_2-agonist salmeterol added to 88 μg of FP (lower dose FP) and (2) patients who had their dose of FP increased 2.5-fold (higher dose FP). This was a combined analysis of 2 identical studies. The clinical efficacy and safety results of these studies have been reported previously.[7,8] However, because asthma exacerbation rates in the individual studies were low, and the individual studies were not adequately powered to compare differences in exacerbation rates, combining the data allowed a more comprehensive analysis of asthma exacerbations with these different treatment options.

Abbreviations used
FP: Fluticasone propionate
ICS: Inhaled corticosteroid
MDI: Metered-dose inhaler
PEF: Peak expiratory flow

TABLE I. Patient characteristics

	Salmeterol 42 μg + FP 88 μg (n = 41)	FP 220 μg (n = 63)
Mean age, y (mean ± SE)	36.6 ± 2.5	39.0 ± 1.8
Male/female, %	46/54	46/54
White, %	80	86
Duration of asthma, % of patients ≥10 y	76	81
Predicted FEV_1, % (mean ± SE)	58.1 ± 1.7	59.1 ± 1.5
Reversibility, % (mean ± SE)	35.8 ± 2.7	31.5 ± 1.7

METHODS

Patients

Male and female patients (≥12 years of age) were eligible for enrollment if they had asthma, as defined by the American Thoracic Society, for at least 6 months[9]; had reversible airways disease, as demonstrated by a 15% or greater increase in FEV_1 from baseline after the inhalation of 180 μg of albuterol; had an FEV_1 of 40% to 85% of their predicted value; and used a short-acting bronchodilator on a regular basis for at least 3 months. The use of ICS therapy before screening was allowed. Patients were excluded if any of the following were present at screening: current tobacco use, a hospital admission for asthma in the past 30 days, or an upper or lower respiratory tract infection within 30 days. Female patients who had a positive pregnancy test result or were lactating were excluded. The following medications were not allowed for the indicated times before screening: oral or parenteral corticosteroid therapy within 30 days, oral or long-acting inhaled bronchodilators within 48 hours, and cromolyn or nedocromil within 30 days. Written informed consent was obtained from each patient or his or her guardian if applicable. The institutional review board for each study site approved the protocol.

Study design

Seventy-one research centers participated in these studies, which consisted of a 2- to 4-week screening period followed by a 24-week randomized, double-blind, double-dummy, parallel-group treatment period. During screening, all patients used 88 μg of open-label FP twice daily and albuterol on an as-needed basis to treat their asthma. Albuterol (Ventolin Inhalation Aerosol; Glaxo Wellcome Inc, Research Triangle Park, NC) and FP (Flovent Inhalation Aerosol, Glaxo Wellcome Inc) were supplied as metered-dose inhalers (MDIs) that delivered 90 μg and 44 μg per actuation, respectively.

Patients meeting all randomization criteria were randomly assigned to receive either salmeterol (42 μg twice daily) plus lower dose FP (88 μg twice daily) or higher dose FP alone (220 μg twice daily) by using a double-dummy design. Patients were given 2 MDIs containing either active drug or placebo and were instructed to take 2 inhalations from each MDI each morning and evening approximately 12 hours apart. The blinded inhalers in the salmeterol plus lower dose FP group consisted of an MDI that delivered 21 μg of salmeterol xinafoate (Serevent Inhalation Aerosol, Glaxo Wellcome Inc) per inhalation (total dose, 42 μg) and an MDI that delivered 44 μg of FP per inhalation (total dose, 88 μg). The higher dose FP group used a blinded MDI that delivered 110 μg of FP per inhalation (total dose, 220 μg) and a blinded MDI containing placebo. Inhalers were replaced every 4 weeks. The patients continued to use albuterol on an as-needed basis to relieve breakthrough symptoms.

During the double-blind treatment period, patients were evaluated at clinic visits at randomization (treatment day 1) and after 2, 4, 8, 12, 16, 20, and 24 weeks of treatment. Patients continued to record diary card evaluations throughout the treatment period. Before each clinic visit, patients were required to withhold morning doses of blinded drug and to withhold albuterol for 6 or more hours. At each clinic visit, clinical adverse events were assessed, pulmonary function tests were performed (between 6 and 10 AM), completed diary cards were collected and reviewed, and new diary cards were issued.

Asthma exacerbations were defined as any asthma event that required treatment with oral or parenteral corticosteroids. Patients were withdrawn if they experienced more than 2 study-defined asthma exacerbations or had 2 exacerbations within a 30-day period. When a patient experienced an asthma exacerbation during the study, the research physician determined the date of the onset of the exacerbation and recorded this information in the patient's study records. After completion of the study, the mean change from baseline in morning peak expiratory flow (PEF), rescue albuterol use, and daytime symptom scores at onset date and over the 14 days before and after the exacerbation onset date were determined for all patients who experienced an exacerbation of asthma. Baseline was defined as the average of values for morning PEF, rescue albuterol use, and daytime symptom scores obtained over the 14th, 13th, and 12th days before the onset date of exacerbation.

Data analysis

Data analysis was performed on the intent-to-treat population, consisting of all patients who were randomized to blinded study drug. A total sample size of 925 patients provided approximately 70% power in detecting a 5% difference between the treatment groups in the proportion of patients experiencing an asthma exacerbation. For all statistical comparisons, *P* values were based on 2-sided tests and were considered statistically significant at the .05 significance level. Frequency of exacerbations was compared between the salmeterol plus lower dose FP and the higher dose FP treatment groups by using χ^2 methods. The exacerbation rate was compared between the 2 treatment groups by applying a Poisson regression log-linear model, and time to exacerbation was compared between treatment groups by using a Kaplan-Meier test. ANOVA was used to test treatment differences in both mean duration of exacerbation and mean duration of oral corticosteroid treatment. Comparisons between the 2 treatment groups in daily morning PEF measurements, daytime symptom scores, and rescue albuterol use over the –14 to +14-day course of an exacerbation were made by using analysis of covariance on mean change from baseline values, with the pre-exacerbation baseline value as the covariate.

RESULTS

Patient characteristics

In these studies 925 patients whose asthma was not adequately controlled with low-dose FP were randomly assigned to receive either salmeterol (42 μg twice daily) plus low-dose FP (88 μg twice daily) or a 2.5-fold higher dose of FP (220 μg twice daily). During the 24-week

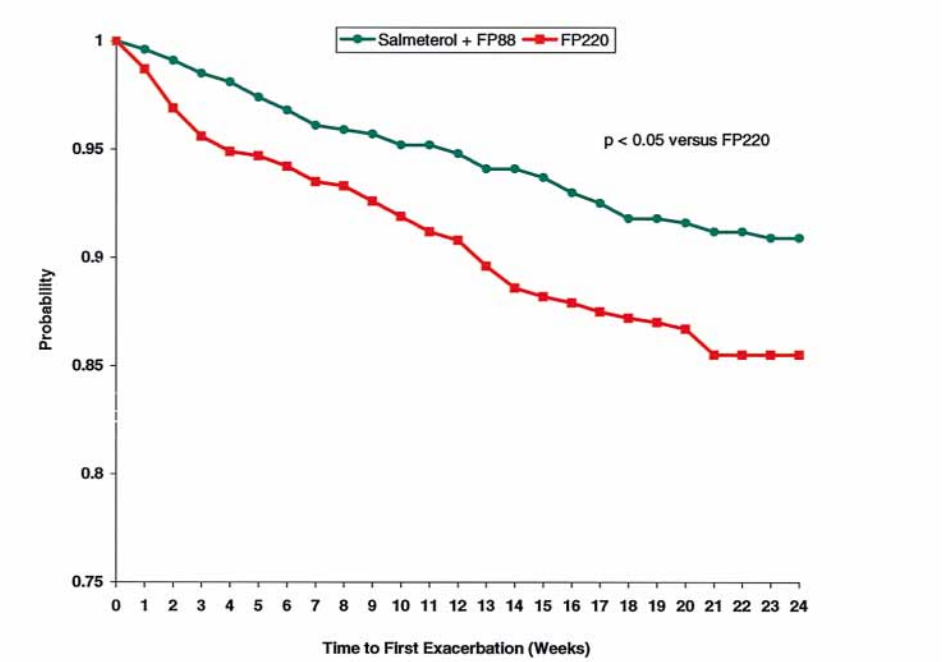

FIG 1. Analysis of time to first exacerbation. Between-treatment comparisons were completed by using Kaplan-Meier methods.

TABLE II. Asthma exacerbations

	Salmeterol 42 μg + FP 88 μg (n = 467)	FP 220 μg (n = 458)	*P* value
Patients with ≥1 exacerbation, n (%)	41 (8.8)	63 (13.8)	.017
Total No. of exacerbations	47	75	
Mean duration of exacerbation, d (mean ± SE)	8.4 ± 0.9	10.5 ± 1.2	.173
Mean duration of oral corticosteroid treatment, d (mean ± SE)	6.6 ± 0.5	7.5 ± 0.4	.120

treatment period, 104 patients experienced an asthma exacerbation (41 in the salmeterol plus lower dose FP group and 63 in the higher dose FP group). The characteristics of patients experiencing an asthma exacerbation from both treatment groups were similar (Table I). Mean compliance rates for the use of blinded study inhalers, as determined from patient diary records, were 99% in each group (range, 80%-117%).

Asthma exacerbations and time to first exacerbation

Significantly fewer patients treated with the salmeterol plus lower dose FP experienced asthma exacerbations compared with patients treated with higher dose FP alone (Table II). The mean duration of exacerbations, as determined by investigator-recorded dates of exacerbation onset and resolution, was shorter with salmeterol plus lower dose FP (8.4 days) compared with higher dose FP alone (10.5 days). Exacerbations in patients treated with salmeterol plus lower dose FP required similar doses of oral corticosteroids compared with the exacerbations in patients treated with higher dose FP (mean of 38.1 ± 3.7 mg vs 37.2 ± 2.6 mg, respectively). Annualized exacerbation rates were computed and were significantly lower for the salmeterol plus lower dose FP group (0.23 exacerbations per patient per year) compared with the higher dose FP group (0.39 exacerbations per patient per year; $P = .005$).

Salmeterol plus lower dose FP was significantly more protective ($P = .049$) than increased-dose FP in preventing asthma exacerbations, as assessed by the time to first exacerbation (Fig 1). When grouped according to the severity of baseline airway obstruction, patients with mild-to-moderate airway obstruction (baseline FEV_1 >60%-85% of predicted value) and patients with severe obstruction (FEV_1 of 40%-60% of predicted value) both experienced a lower number of exacerbations with salmeterol plus lower dose FP compared with higher dose FP alone (Fig 2).

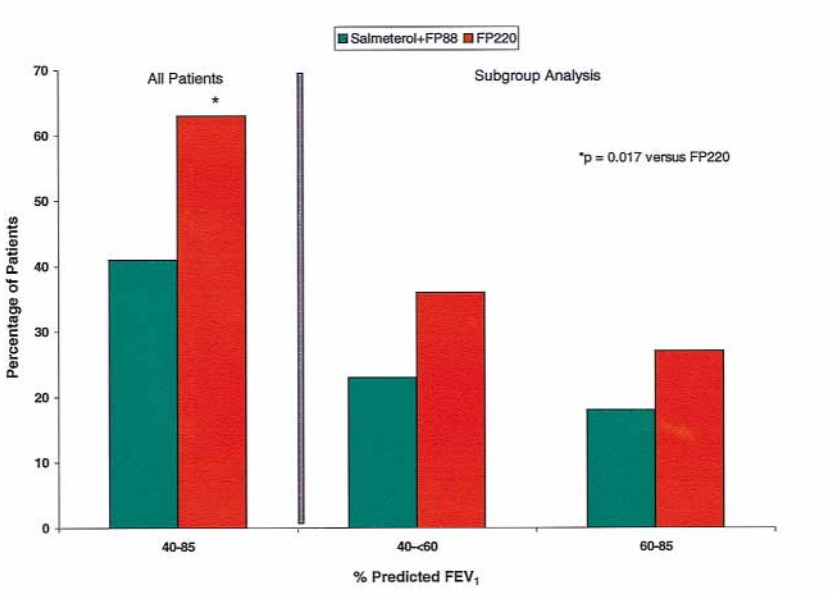

FIG 2. Effect of severity of airway obstruction on incidence of asthma exacerbation.

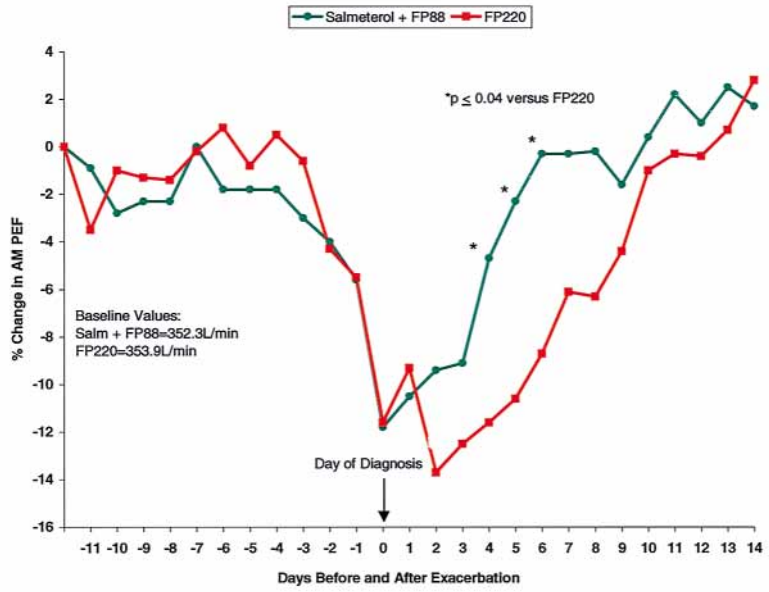

FIG 3. Change in morning PEF before and after exacerbation. Analysis of covariance methodology was used to compare the 2 treatments, with the pre-exacerbation baseline value as the covariate.

Change in PEF, albuterol use, and symptom scores before, during, and after exacerbation

Changes in morning PEF, rescue albuterol use, and asthma symptom scores in the 2 weeks before and during an asthma exacerbation were comparable in the 2 treatment groups (Figs 3-5). In the 2 weeks after an exacerbation, significantly greater improvements in morning PEF, symptom scores, and rescue albuterol use were observed with the addition of salmeterol compared with the higher dose FP group ($P \leq .04$, Figs 3-5).

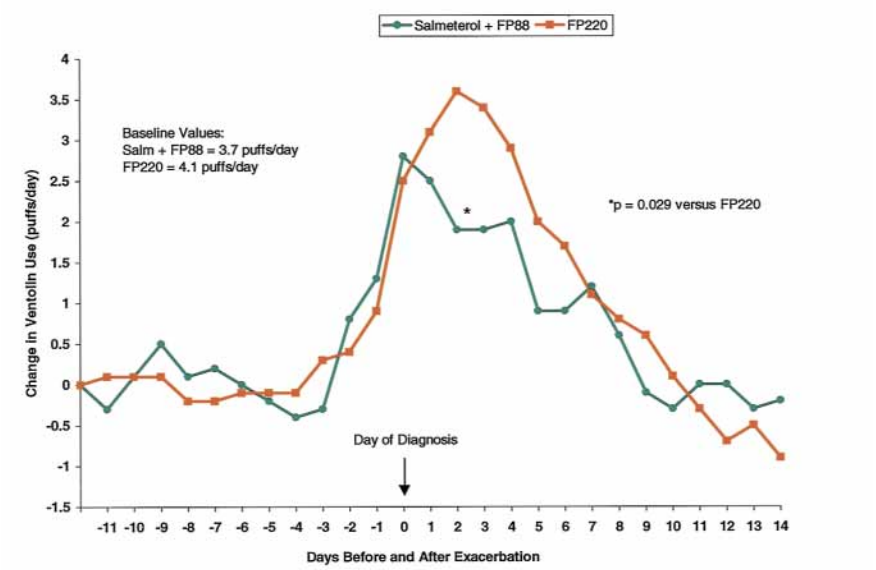

FIG 4. Change in supplemental albuterol use before and after exacerbation. Analysis of covariance methodology was used to compare the 2 treatments, with the pre-exacerbation baseline value as the covariate.

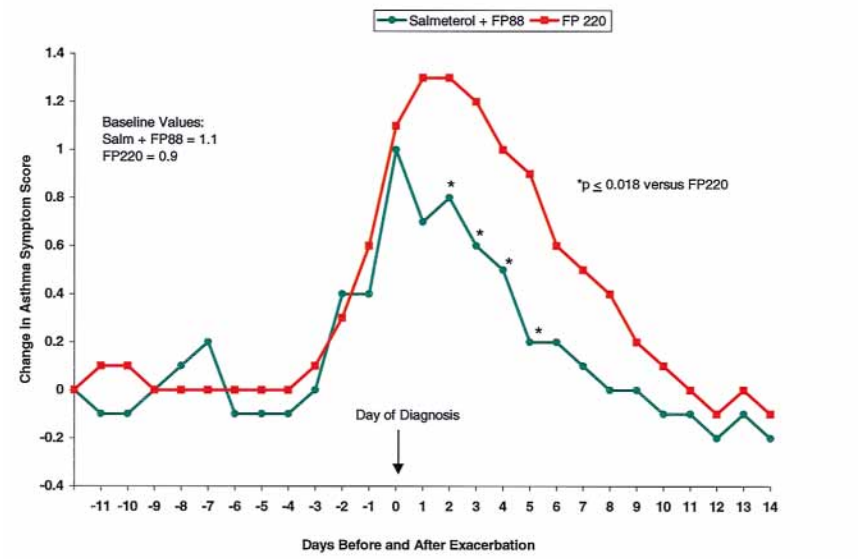

FIG 5. Change in asthma symptom score before and after exacerbation. Symptom scores were rated on a 5-point scale (0 = no symptoms to 4 = symptoms that caused significant discomfort and prevented normal daily activity). Analysis of covariance methodology was used to compare the 2 treatments, with the pre-exacerbation baseline value as the covariate.

DISCUSSION

This study indicates that the addition of a long-acting β_2-agonist to a low dose of FP results in significantly fewer asthma exacerbations than a higher dose of FP alone. In addition, this lower asthma exacerbation rate occurred without altering the ability to detect worsening asthma. A reduction in asthma exacerbation rate would not be expected to occur without effective control of the underlying airway disease. Thus the results of this study suggest that the addition of a long-acting β_2-agonist to FP may be a more effective way to help control the

underlying clinical and pathologic abnormalities associated with asthma than a higher dose of FP alone. Studies with a combined formulation of inhaled FP and the long-acting bronchodilator salmeterol have shown that this regimen offers significant clinical advantages over either of the products alone.[10-12]

The present study was a retrospective analysis of 2 identical, randomized, double-blind studies in which the rate of asthma exacerbations was not an efficacy endpoint. Exacerbations were defined as worsening asthma that required treatment with systemic corticosteroids. Specific criteria for worsening asthma were not defined, and systemic corticosteroid treatment was dependent on the clinical judgment of the individual study investigators. Similarly, data obtained regarding the duration of the exacerbations were obtained from investigator records that were subject to differences in interpretation between investigators.

Because exacerbation rates are very important measures of long-term asthma control, our finding of reduced exacerbation frequency with combination therapy has positive implications with regard to patients' quality of life and use of healthcare resources. Kemp et al[13] have shown that the addition of salmeterol to the treatment regimen of patients whose symptoms are not well controlled with ICSs provides significantly greater improvement in quality-of-life outcomes. In addition to improved quality of life, a decrease in exacerbations could have a significant effect on healthcare resources. Lanes et al[14] have shown a lower risk of emergency department treatment, intensive care unit stays, and hospitalizations with the use of salmeterol.

The results of the present study were similar to the findings of Pauwels et al[15] and Tattersfield et al,[16] who found that the addition of the long-acting β_2-agonist formoterol to inhaled budesonide therapy reduced the rate of severe and mild exacerbations and that the pattern of change in symptoms and PEF associated with an exacerbation was similar in patients receiving either formoterol and budesonide or budesonide alone. If a long-acting β_2-agonist masked symptom recognition, an increase in the frequency of exacerbations, increased severity of exacerbations, or both would be expected. At the very least, some change in the pattern of symptoms or short-acting β_2-agonist use would be expected to develop. The fact that neither occurred and that exacerbations were reduced in our study and the reports by Pauwels et al and Tattersfield et al clearly suggests that masking of worsening symptoms or underlying disease state does not occur when a long-acting β_2-agonist is added to ICS therapy.

Exacerbations of asthma are a measure of underlying airway inflammation. Li et al[17] and Sue-Chu et al[18] have evaluated the effect of adding a long-acting β_2-agonist to a low dose of an ICS versus a higher dose of an ICS on airway inflammatory cell numbers, as assessed with bronchial biopsy. Their results show that the numbers of mast cells, eosinophils, and CD4 lymphocytes are reduced or unchanged by adding a long-acting β_2-agonist to an ICS compared with an increased dose of an ICS. In addition, no significant differences in sputum eosinophil levels were observed during a 1-year treatment with a low dose of budesonide plus formoterol compared with a higher dose of budesonide in patients with persistent asthma.[19] Although these results cannot be extrapolated to the present study, they suggest that the addition of a long-acting β_2-agonist to an ICS is an effective approach in helping to control the clinical and pathophysiologic alterations that characterize asthma when compared with a higher dose of an ICS.

In conclusion, the addition of salmeterol to patients who remained symptomatic on low-dose FP therapy was a more effective treatment option for reducing asthma exacerbation rates than increasing the dose of FP. The ability to detect clinical markers of deteriorating asthma was not different between groups. This study further demonstrates that the use of a long-acting β-agonist with ICSs results in improvement in overall asthma control.

We thank Larry E. East for his assistance in the writing, editing, and review of this article.

REFERENCES

1. National Institutes of Health (National Heart, Lung, and Blood Institute). Expert panel report 2. Guidelines for the diagnosis and management of asthma. Bethesda (MD): National Institutes of Health. NIH Publication No. 97-4051; 1997.
2. Bleeker E. Inhaled corticosteroids: current products and their role in patient care. J Allergy Clin Immunol 1998;101:S400-2.
3. Greening AP, Ind PW, Northfield M, Shaw G. Added salmeterol versus higher-dose corticosteroid in asthma patients with symptoms on existing inhaled corticosteroid. Lancet 1994;344:219-24.
4. Woolcock A, Lundback B, Ringdal N, Jacques L. Comparison of addition of salmeterol to inhaled steroids with doubling of the dose of inhaled steroids. Am J Respir Crit Care Med 1996;153:1481-8.
5. Kelsen SG, Church NL, Gillman SA, Lanier BQ, Emmett AH, Rickard KA, et al. Salmeterol added to inhaled corticosteroid therapy is superior to doubling the dose of inhaled corticosteroids: a randomized clinical trial. J Asthma 1999;36:703-15.
6. Murray JJ, Church NL, Anderson WH, Bernstein DI, Wenzel SE, Emmett A, et al. Concurrent use of salmeterol with inhaled corticosteroids is more effective than inhaled corticosteroid dose increases. Allergy Asthma Proc 1999;20:173-80.
7. Condemi JJ, Goldstein S, Kalberg C, Yancey S, Emmett A, Rickard K. The addition of salmeterol to fluticasone propionate versus increasing the dose of fluticasone propionate in patients with persistent asthma. Ann Allergy Asthma Immunol 1999;82:383-9.
8. Kalberg CJ, Nelson H, Yancey S, Petrocella V, Emmett AH, Rickard KA, et al. A comparison of added salmeterol versus increased-dose fluticasone in patients symptomatic on low-dose fluticasone [abstract]. J Allergy Clin Immunol 1998;101(Suppl):S6.
9. American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease (COPD) and asthma. Am Rev Respir Dis 1987;136:225-44.
10. Shapiro G, Lumry W, Wolfe J, Given J, White MV, Woodring A, et al. Combined salmeterol 50μg and fluticasone propionate 250μg in the Diskus device for the treatment of asthma. Am J Respir Crit Care Med 2000;161:527-34.
11. Kavuru M, Melamed J, Gross G, LaForce C, House K, Prillaman B, et al. Salmeterol and fluticasone propionate combined in a new powder inhalation device for the treatment of asthma: a randomized, double-blind, placebo-controlled trial. J Allergy Clin Immunol 2000;105:1108-16.
12. Aubier M, Pieters WR, Schlosser NJ, Steinmetz KO. Salmeterol/fluticasone propionate (50/500 micrograms) in combination in the Diskus inhaler (Seretide) is effective and safe in the treatment of steroid-dependent asthma. Respir Med 1999;93:876-84.
13. Kemp JP, Cook DA, Incaudo GA, Corren J, Kalberg C, Emmett A, et al. Salmeterol improves quality of life in patients with asthma requiring inhaled corticosteroids. J Allergy Clin Immunol 1998;101:188-95.
14. Lanes SF, Lanza LL, Wentworth CE. Risk of emergency care, hospital-

ization and ICU stays for acute asthma among recipients of salmeterol. Am J Respir Crit Care Med 1998;158:857-61.
15. Pauwels RA, Lofdahl C-G, Postma DA, Tattersfield AE, O'Byrne P, Barnes PJ, et al. Effect of inhaled formoterol and budesonide on exacerbations of asthma. N Engl J Med 1997;337:1405-11.
16. Tattersfield AE, Postma DS, Barnes PJ, Svensson K, Bauer C, O'Byrne PM, et al. Exacerbations of asthma: a descriptive study of 425 severe exacerbations. Am J Respir Crit Care Med 1999;160:594-9.
17. Li X, Ward C, Thien F, Bish R, Bamford T, Bao X, et al. An antiinflammatory effect of salmeterol, a long-acting β_2 agonist, assessed in airway biopsies and bronchoalveolar lavage in asthma. Am J Respir Crit Care Med 1999;160:1493-9.
18. Sue-Chu M, Wallin A, Wilson S, Ward J, Sandstrom T, Djukanovic R, et al. Bronchial biopsy study in asthmatics treated with low and high dose fluticasone propionate (FP) compared to low dose FP combined with salmeterol [abstract]. Eur Respir J 1999;14:124S.
19. Kips JC, O'Connor BJ, Inman MD, Svensson K, Pauwels RA, O'Byrne P. A long-term study of the anti-inflammatory effect of low-dose budesonide plus formoterol versus high-dose budesonide in asthma. Am J Respir Crit Care Med 2000;161:996-1001.