

Comparison of inhaled salmeterol and oral zafirlukast in patients with asthma

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Background: Salmeterol, a long-acting β_2 -agonist, and zafirlukast, a leukotriene receptor antagonist, are both indicated for the treatment of asthma in adolescent and adult patients. **Objective:** We sought to compare the effect of 4 weeks of treatment with inhaled salmeterol xinafoate versus oral zafirlukast in the treatment of persistent asthma.

Methods: This was a randomized, double-blind, double-dummy, parallel-group, multicenter clinical trial. Patients, over 80% of whom were on a concurrent inhaled corticosteroid regimen, were treated for 4 weeks with either inhaled salmeterol xinafoate 42 μ g twice daily administered by means of a metered-dose inhaler or oral zafirlukast 20 mg twice daily. The primary efficacy measure was morning peak expiratory flow (PEF); secondary efficacy measures included evening PEF, asthma symptom scores, supplemental albuterol use, nighttime awakenings, sleep symptoms, asthma exacerbations, and FEV₁.

Results: Both inhaled salmeterol and oral zafirlukast resulted in within-group improvements from baseline in measures of pulmonary function, asthma symptoms, and supplemental albuterol use. Salmeterol treatment resulted in significantly greater improvements from baseline compared with zafirlukast for most efficacy measurements, including morning PEF (29.6 vs 13.0 L/min; $P \leq .001$), percentage of symptom-free days (22.4% vs 8.8%; $P \leq .001$), and percentage of days and nights with no supplemental albuterol use (30.5% vs 11.3%; $P \leq .001$). There were no differences in safety profiles as assessed by adverse event monitoring.

Conclusion: In patients with persistent asthma, most of whom were concurrently using inhaled corticosteroids, treatment with inhaled salmeterol provided significantly greater improvement than oral zafirlukast in overall asthma control over the 4-week treatment period. (*J Allergy Clin Immunol* 1999;103:1075-80.)

Key words: Salmeterol xinafoate, zafirlukast, asthma, peak expiratory flow, β_2 -agonist, leukotriene receptor antagonist

Leukotriene modifiers are a new class of medications indicated for the treatment of asthma.¹ These drugs inhibit

Abbreviations used

ICS: Inhaled corticosteroid
PEF: Peak expiratory flow

the effects of proinflammatory leukotrienes by either inhibition of enzymatic production of leukotrienes or by antagonism of leukotriene receptor binding. The efficacy of the leukotriene receptor antagonist zafirlukast has been demonstrated in clinical trials that showed zafirlukast to be significantly superior to placebo in improving pulmonary function and decreasing asthma symptom scores, nocturnal awakenings, and supplemental albuterol use.²⁻⁴

The utility and placement of leukotriene antagonists within an asthma management program is unclear because little comparative data are available between these drugs and established long-term control therapies, such as inhaled corticosteroids (ICSs), methylxanthines, and long-acting β -agonists. Current National Institutes of Health Expert Panel Report 2 treatment guidelines of the National Asthma Education and Prevention Program include leukotriene modifiers among the long-term control medications but state that further clinical experience is needed to establish their roles in asthma therapy.¹

The selective, long-acting β -agonist salmeterol is indicated for long-term control of asthma. The prescribing information for salmeterol indicates that it may be used with or without concurrent use of ICSs, although most treatment guidelines indicate salmeterol should be used as adjunctive therapy in patients whose symptoms are not adequately controlled with ICSs.¹

This study was the first to compare the efficacy and safety of salmeterol and zafirlukast in the treatment of patients with persistent asthma, the majority of whom were using concomitant ICS therapy. Salmeterol has been reported to reach peak effectiveness as early as 4 days into treatment,⁵⁻⁷ and zafirlukast has been reported to reach peak effectiveness as early as 2 weeks into treatment.⁸ A study duration of 4 weeks was chosen to encompass the onset of peak efficacy for both agents.

METHODS

Study design and patients

This randomized, double-blind, double-dummy, parallel-group, multicenter clinical trial compared the efficacy and safety of inhaled salmeterol xinafoate (Serevent; Glaxo Wellcome Inc, Research Triangle Park, NC) at a dose of 42 μ g twice daily (2 puffs), administered by means of a metered-dose inhaler, with oral zafirlukast

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(Accolate; Zeneca Pharmaceuticals, Wilmington, Del) at a dose of 20 mg twice daily over a 4-week treatment period in adolescents and adults with persistent asthma. This study was conducted at 26 centers, with a patient population composed of patients who attended private practice clinics or responded to study advertisements.

Male and female patients 12 years of age and older were eligible for enrollment if they had a diagnosis of asthma as defined by the American Thoracic Society⁹ for at least 6 months, had a baseline FEV₁ of 50% to 80% of the Crapo¹⁰ (patients 18 years and older) or Polgar¹¹ (ages 12 to 17 years) predicted normal values after withholding bronchodilators, and had at least a 12% increase in FEV₁ within 30 minutes after inhalation of 180 µg of albuterol. Predicted FEV₁ values were race adjusted for African American subjects.¹² After a 7- to 14-day run-in period, patients were required to have an FEV₁ value within 50% to 70% of predicted normal value with or without asthma symptoms or an FEV₁ value of 70.1% to 80% of predicted normal value and 1 or more of the following criteria during the 6 days immediately before randomization: an average of 4 or more puffs/day of albuterol, a symptom score of 2 or greater on 2 or more days for any of the asthma symptom categories, 1 or more nights when the patient awakened because of asthma, or 2 or more days when evening to morning peak expiratory flow (PEF) variation was 20% or greater. Eligibility criteria further specified that before enrollment, patients were required to have used either an oral or inhaled short-acting β₂-agonist on a fixed schedule or as-needed basis for at least 6 weeks. At the time of enrollment, patients were supplied with albuterol inhalers (albuterol sulfate USP, Ventolin; Glaxo Wellcome Inc) to be used on an as-needed basis for relief of breakthrough symptoms. Use of all other bronchodilators was prohibited. Antihistamines, nasal decongestants, and other intranasal medications for the treatment of rhinitis were allowed. Concomitant treatment with a stable regimen of ICSs was permitted during the study. Concurrent use of theophylline or any medications that could interact with sympathomimetic amines or zafirlukast was not allowed (ie, β-blockers, polycyclic antidepressants, monoamine oxidase inhibitors, and warfarin). Patients were not eligible if they exhibited current evidence of pneumonia, pneumothorax, atelectasis, pulmonary fibrotic disease, chronic bronchitis, emphysema, or other respiratory abnormalities other than asthma. Patients were excluded if they had a greater than 10 pack-year history of cigarette smoking, had used any tobacco products within 1 year of enrollment, or both.

Eligible patients underwent screening assessments, including medical history, physical examination, pulmonary function testing (including FEV₁ reversibility assessment), pregnancy testing (females), and adverse event assessments. All patients provided written informed consent, and institutional review boards approved the study at the respective sites.

Patients used a hand-held Astech peak flowmeter (Center Laboratories, Port Washington, NY) to measure morning and evening PEF, recording the highest of 3 forced exhalations in the morning immediately after getting out of bed and before dosing with the blinded study drug. Evening measurements were completed before taking the last dose of study drug for the day. Patients also recorded nighttime awakenings caused by asthma, supplemental albuterol use, and daytime and nighttime asthma symptoms daily on diary cards. Symptom scores were recorded before any relief with supplemental albuterol. Daytime asthma symptoms of wheezing, chest tightness, and shortness of breath were rated according to the following scale: 0, no symptoms; 1, some symptoms present but no discomfort; 2, symptoms that caused discomfort but did not interfere with normal daily activities; 3, symptoms that caused discomfort and interfered with at least 1 normal daily activity; and 4, symptoms that caused significant discomfort and prevented normal daily activities. Sleep symptoms were rated according to the following

scale: 0, no symptoms; 1, some symptoms present but no discomfort; 2, symptoms that caused mild discomfort; 3, symptoms that caused moderate discomfort; and 4, symptoms that caused severe discomfort. Patients returned to the clinic for adverse event and FEV₁ assessments after 1 and 4 weeks of treatment. FEV₁ measurements were performed between 6 AM and 10 AM before administration of study medications.

Salmeterol and matching placebo were supplied in metered-dose inhalers and were administered by inhalation. Zafirlukast and matching placebo were supplied as hard gelatin capsules and were administered orally. Study medications were taken twice daily, once in the morning and once in the evening. Because the bioavailability of zafirlukast is reduced by food, patients were instructed to take their capsule 1 hour before or 2 hours after meals, as recommended in the product labeling.

Asthma exacerbations occurring during this study were defined as any worsening of asthma symptoms requiring a change in the patient's asthma therapy other than increased use of supplemental albuterol. Patients who experienced an asthma exacerbation were withdrawn from the study.

Statistical analysis

The primary efficacy measure was morning PEF. Secondary efficacy measures included evening PEF, asthma symptom scores, supplemental albuterol use, nighttime awakenings, FEV₁, and asthma exacerbations. A sample size of 125 patients per treatment arm was estimated to provide greater than 80% power to detect a significant difference of 18 L/min in morning PEF measurements at a significance level of .05.

Descriptive and inferential analyses of the PEF data were performed comparing the 2 treatment groups for each treatment week and for the entire 4-week treatment period. Inferential analyses of change in PEF from pretreatment baseline were performed comparing the 2 treatment groups by ANOVA and controlling for the investigator and baseline.

FEV₁ analyses were performed comparing the 2 treatment groups after week 1 and week 4 by ANOVA. Within-treatment analyses comparing treatment-week FEV₁ measurements to baseline were performed with paired *t* tests. Inferential analyses comparing treatment groups on the basis of change from pretreatment values for daytime and sleep symptoms, nighttime awakenings, and supplemental albuterol use were performed by using a van Elteren test and controlling for investigator. Comparisons of asthma exacerbation and adverse event frequencies between the 2 treatment groups were analyzed by using Fisher's exact test.

RESULTS

Demographics

A total of 144 patients received inhaled salmeterol and 145 received oral zafirlukast in this trial. Demographic and baseline disease characteristics were similar in the 2 treatment groups (Table I). Approximately 80% of the patients in each treatment group were on a stable regimen of ICSs.

Pulmonary function

PEF. Baseline morning and evening PEF were comparable between the 2 groups (371.8 and 392.1 L/min, respectively, in the salmeterol group; 368.5 and 398.3 L/min, respectively, in the zafirlukast group). Within-treatment increases from baseline (weeks 1 to 4) were noted in mean morning and evening PEF in both the salmeterol (29.6 and 21.8 L/min, respectively) and zafir-

TABLE I. Demographics and baseline disease characteristics

	Treatment group		<i>P</i> value*
	Salmeterol (n = 144)	Zafirlukast (n = 145)	
Age (y)			
Mean	38.6	36.9	.285
Range	12-73	12-71	
Sex, n (%)			
F	77 (53)	85 (59)	.350
M	67 (47)	60 (41)	
Ethnic Origin, n (%)			
White	125 (87)	134 (92)	.061
Black	11 (8)	8 (6)	
Asian	2 (1)	1 (<1)	
Hispanic	5 (3)	2 (1)	
Other	1 (<1)	0	
Asthma duration, n (%)			
<10 years	36 (25)	37 (26)	
≥10 years	108 (75)	108 (74)	
ICS use, n (%)			
No use†	23 (16)	29 (20)	
Constant dose‡	121 (84)	116 (80)	
FEV ₁ before bronchodilation (L)			
Mean (SEM)	2.35 (0.05)	2.37 (0.05)	.821
Percent predicted FEV ₁ at randomization			
Mean (SEM)	66.77 (0.67)	66.74 (0.69)	.986

*Probability (*P*) values for FEV₁ and age are based on ANOVA; *P* values for sex and ethnic origin are based on chi-square methods.

†No use of ICSs for 30 or more days before randomization.

‡Use of a constant dose of ICS for 30 or more days before randomization.

lukast (13.0 and 9.9 L/min, respectively) treatment groups. For the 4-week treatment period, salmeterol resulted in significantly greater increases in mean morning PEF ($P = .001$) and mean evening PEF ($P = .019$) compared with zafirlukast. There was a significantly greater decrease in mean evening/morning PEF differential over the 4 weeks in the salmeterol group (-8.2 L/min) than in the zafirlukast group (-4.6 L/min; $P = .016$).

When analyzed by treatment week, significantly greater improvements in morning PEF were noted in the salmeterol group than in the zafirlukast group after weeks 1, 2, 3, and 4 of treatment (Fig 1). Similarly, significant differences between the 2 groups in evening PEF were noted at weeks 1 through 3. The difference in improvement at week 4 was not significant.

FEV₁. Baseline mean FEV₁ values were similar in the 2 treatment groups (Table I). There were significant within-treatment increases from baseline in mean predose FEV₁ values in both the salmeterol and zafirlukast treatment groups at both week 1 and week 4 ($P < .001$). At week 1, the increase in mean predose FEV₁ was significantly greater in the salmeterol treatment group compared with the zafirlukast treatment group (0.29 ± 0.03 L vs 0.19 ± 0.03 L, respectively; $P = .023$). The difference between the treatment groups at week 4 (0.28 ± 0.04 L vs 0.22 ± 0.04 L, respectively; $P = .293$) was not significant.

Asthma symptom scores, nighttime awakenings, supplemental β -agonist use

Over the 4-week treatment period, patients treated with salmeterol experienced significantly greater ($P \leq$

.026) improvement in all patient-rated asthma symptom scores compared with patients treated with zafirlukast (Table II). In the salmeterol group patient-rated daytime symptom scores for chest tightness, shortness of breath, and wheezing decreased by 37%, 37%, and 35% from baseline, respectively, compared with decreases of 20%, 18%, and 16%, respectively, in the zafirlukast group. Similarly, the combined daytime symptom score for salmeterol decreased by 37% compared with a 19% decrease for zafirlukast.

Over the 4-week treatment period, patients treated with salmeterol experienced a significantly greater ($P < .001$) reduction in sleep symptoms compared with patients treated with zafirlukast (Table II). In the salmeterol group patient-rated sleep symptoms decreased by 46% from baseline compared with a decrease of 22% in the zafirlukast group. However, there was no significant difference in the reduction of nighttime awakenings between the 2 treatment groups (Table II). In the salmeterol group nighttime awakenings decreased by 45% from baseline compared with a decrease of 26% in the zafirlukast group.

Over the 4-week treatment period, patients treated with salmeterol experienced a significantly greater reduction in both daytime and nighttime supplemental albuterol use ($P = .004$ and $P = .013$, respectively) compared with patients treated with zafirlukast (Table II). In the salmeterol group daytime and nighttime albuterol use decreased by 42% and 32% from baseline, respectively, compared with decreases of 19% and 10%, respectively, in the zafirlukast group.

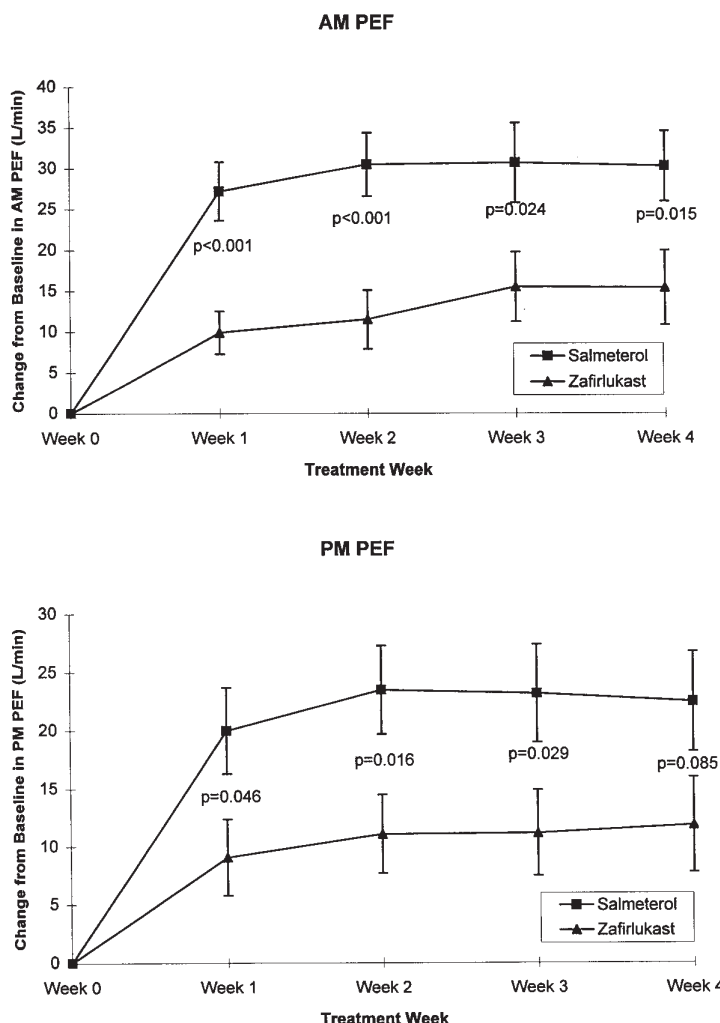


FIG 1. Mean changes from baseline in morning (top) and evening (bottom) PEF values at treatment weeks 1 through 4. Probability (*P*) values represent differences between treatment groups.

Asthma exacerbations

Seven patients (7 of 144 [5%]) in the salmeterol group and 9 patients (9 of 145 [6%]) in the zafirlukast group experienced asthma exacerbations during the 4-week treatment period. The most common suspected cause of exacerbation in both treatment groups was respiratory infection (3 of 8 [38%] and 5 of 9 [38%] in the salmeterol and zafirlukast groups, respectively).

Adverse events

The overall incidence of adverse events did not differ significantly between the 2 treatment groups. The percentage of patients reporting at least 1 adverse event in the salmeterol and zafirlukast groups was 40% and 42%, respectively. The most frequently reported adverse events in the salmeterol and zafirlukast groups were the common cold (6% and 8%, respectively) and headache (5% and 8%, respectively). There was 1 serious adverse event during the study. A 25-year-old female patient receiving salmeterol experienced a severe asthma exacerbation

related to allergen exposure and was withdrawn from the study. The event resolved within 10 days. Nine patients were withdrawn from the study because of adverse events (5 in the salmeterol group and 4 in the zafirlukast group). Two of the 9 patients had adverse events (1 patient with nervousness, tingling, and flushing; 1 patient with headache, sleeplessness, tension, and jitteriness) that were judged by the investigator to be study drug related. Both of these patients were in the zafirlukast treatment group.

DISCUSSION

This study is the first to compare a leukotriene receptor antagonist to a long-acting β -agonist. Previous studies have characterized the efficacy of zafirlukast in patients with mild-to-moderate persistent asthma who were not using concomitant inhaled steroids.²⁻⁴ The effects of zafirlukast in a patient population that is heterogeneous with regard to ICS use have not been studied.

TABLE II. Mean changes from baseline* in symptom scores, nighttime awakenings, and supplemental albuterol use over 4 weeks of treatment

Endpoint	Treatment group				P value†
	Salmeterol (n = 144)		Zafirlukast (n = 145)		
	Baseline (SEM)	Mean change (SEM)	Baseline (SEM)	Mean change (SEM)	
Subject-rated daytime symptoms					
Wheezing	1.06 (0.07)	−0.38 (0.05)	1.04 (0.07)	−0.18 (0.04)	.006
Shortness of breath	1.34 (0.07)	−0.49 (0.06)	1.34 (0.07)	−0.24 (0.05)	.003
Chest tightness	1.10 (0.07)	−0.42 (0.05)	1.28 (0.07)	−0.26 (0.05)	.026
All symptoms	1.17 (0.06)	−0.43 (0.05)	1.22 (0.06)	−0.23 (0.04)	<.001
Symptom-free days (%)	12.63 (2.09)	22.41 (2.53)	10.85 (2.08)	8.75 (1.85)	<.001
Subject-rated sleep symptoms	1.00 (0.07)	−0.46 (0.05)	1.00 (0.07)	−0.22 (0.05)	<.001
Nighttime awakenings	0.42 (0.05)	−0.20 (0.04)	0.38 (0.05)	−0.10 (0.03)	.142
Days and nights with no supplemental albuterol use (%)	11.66 (2.15)	30.45 (2.80)	10.42 (1.98)	11.26 (2.36)	<.001
Daytime supplemental albuterol use (no. of puffs)	3.37 (0.17)	−1.50 (0.15)	3.80 (0.19)	−0.93 (0.14)	.004
Nighttime supplemental albuterol use (no. of puffs)	0.82 (0.08)	−0.34 (0.08)	0.89 (0.10)	−0.16 (0.07)	.013

*Baseline is defined as an average for the 7 days immediately before treatment day 1.

†P values are based on a van Elteren test on change from baseline, controlling for investigator.

The current study included patients who were and patients who were not using ICSs. This was an appropriate population for a comparative study because zafirlukast has the potential to be used as an adjuvant therapy, and the product information for salmeterol indicates that salmeterol may be used alone or as concomitant therapy with ICSs.

The analysis of data from this randomized, double-blind, double-dummy, parallel-group, multicenter study demonstrated within-treatment group improvements in morning and evening PEF, FEV₁, daytime symptom scores, sleep symptoms, and daytime and nighttime supplemental albuterol use for both salmeterol and zafirlukast. Between-group comparisons showed that inhaled salmeterol provided significantly greater improvement in lung function (morning PEF and evening PEF), significantly greater relief from asthma signs and symptoms, and significantly greater increases in days and nights with no supplemental albuterol use than oral zafirlukast. The safety profiles were similar, and both treatments were well tolerated. An analysis of data from all of the patients who were using ICSs showed that clinical efficacy results for these patients were similar to those found in the patient population as a whole, an expected outcome because of the low number of patients not currently using an ICS (data not shown).

Cysteinyl leukotrienes have been shown to be potent inducers of airway smooth muscle contraction, and as proinflammatory mediators, they may be involved in some of the underlying inflammatory processes of asthma.¹³⁻¹⁵ Zafirlukast and other leukotriene modifiers likely exert their therapeutic effect by inhibition of leukotriene-induced bronchoconstriction and possibly through a reduction in proinflammatory cell infiltration.¹⁶ However, The clinical relevance of the anti-

inflammatory effect of the leukotriene modifiers requires further study. Previous studies have shown that maintenance treatment with the ICS beclomethasone was clinically superior to that found with the regular administration of the leukotriene receptor antagonist montelukast.¹⁷ Salmeterol exerts its therapeutic effect by binding to the β -adrenoreceptor, activating the receptor-Gs-protein complex, and stimulating the formation of cyclic adenosine monophosphate, which then acts as the intracellular mediator of the functional response to salmeterol. This response includes the relaxation of airway smooth muscle and, as has been shown in vitro, the inhibition of the release of proinflammatory mediators from mast cells derived from lung tissue.¹⁸⁻²⁰

In a 13-week study the effects of zafirlukast were observed within the first 2 days of treatment, reached significance by the first week of treatment, and were sustained throughout the treatment period.³ In this study improvements produced by salmeterol were significantly greater than those produced by zafirlukast after week 1 for all efficacy measures except nighttime awakenings and nighttime supplemental albuterol use. In general, between-group differences in clinical measures favoring salmeterol observed at week 1 were maintained throughout the study, with the exception of FEV₁, for which the difference tended to decrease after week 1.

Current National Institutes of Health Expert Panel Report 2 asthma treatment guidelines identify ICSs as the most potent and effective anti-inflammatory agents available for mild-to-severe persistent asthma and recognize that ICSs are well tolerated and safe at recommended doses.¹ The guidelines further recognize the addition of salmeterol to ICSs as a treatment option for patients with moderate-to-severe persistent asthma who are not optimally controlled by ICSs alone. The results of this

study demonstrate that in patients with persistent asthma, the majority of whom were receiving regular ICS therapy, salmeterol is significantly more effective than zafirlukast in improving pulmonary function and symptom control. Additional studies, particularly in comparison with ICSs, are needed to clarify the role of zafirlukast and other leukotriene modifiers in the therapeutic management of asthma.

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