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A M E R I C A N C O L L E G E O F
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Zafirlukast Treatment for Acute Asthma*

Evaluation in a Randomized, Double-Blind, Multicenter Trial

Robert A. Silverman, MD; Richard M. Nowak, MD; Phillip E. Korenblat, MD; Emil Skobeloff, MD†; Yusong Chen, PhD; Catherine M. Bonuccelli, MD; Christopher J. Miller, MStat; and Steven G. Simonson, MD, FCCP‡

Context: Acute asthma causes nearly 2 million hospital emergency department (ED) visits in the United States annually, and hospitalization after an ED visit and relapse after ED discharge are common.

Objective: To evaluate the adding of therapy with zafirlukast to standardized care for patients with acute asthma in the ED and a 28-day follow-up period.

Design and patients: A total of 641 patients presenting to the ED with acute asthma were randomized to receive either single-dose zafirlukast, 160 mg (Z160) [162 patients], zafirlukast, 20 mg (Z20) [158 patients], or placebo (321 patients) as adjunct treatment to standard care in this double-blind, multicenter trial. Assessments, including spirometry and symptom scores, were obtained before each albuterol treatment and at 4 h. Patients who were discharged from the ED after 4 h continued outpatient therapy over a 28-day period and received either Z20 bid (276 patients) or placebo (270 patients) in addition to prednisone, albuterol, and their previous asthma medications. FEV₁ was measured at clinic visits on days 10 and 28. Patients recorded outpatient clinical data twice daily on a home diary card.

Main outcome measures: the effect of zafirlukast on relapse after ED discharge. Other assessments were the rate of extended care (*ie*, ED stay for > 4 h or hospitalization), FEV₁, and symptoms.

Results: At the end of the outpatient period, 65 of 276 patients (23.6%) treated with zafirlukast and 78 of 270 patients (28.9%) treated with placebo relapsed ($p = 0.047$; absolute reduction, 5.3%; relative reduction, 18.3%). At the end of the ED period, 16 of 162 patients (9.9%) treated with Z160, 26 of 158 patients (16.5%) treated with Z20, and 48 of 321 patients (15.0%) treated with placebo required extended care ($p = 0.052$; absolute reduction with Z160 compared to placebo, 5.1%; relative reduction, 34%). These findings were supported by a significant improvement in FEV₁ and dyspnea in the ED with the use of Z160 therapy, and by greater improvement in FEV₁ and symptoms during the outpatient period for patients treated with Z20.

Conclusions: When added to standardized care, therapy with Z20 bid reduced the risk of relapse compared with placebo over a 28-day treatment period. One dose of Z160 in the ED also reduced the rate of extended care. (CHEST 2004; 126:1480-1489)

Key words: acute illness; asthma; leukotrienes; relapse; zafirlukast

Abbreviations: CI = confidence interval; ED = emergency department; ICS = inhaled corticosteroid; ITT = intent-to-treat; LTRA = leukotriene receptor antagonist; PEF = peak expiratory flow; Z20 = zafirlukast, 20 mg; Z160 = zafirlukast, 160 mg

Acute asthma is responsible for 2 million emergency department (ED) visits and nearly 500,000 hospital admissions in the United States annually.¹ Although most patients improve enough to be discharged from the ED after treatment, such improvement does not signify complete recovery. Often, asthma symptoms will persist for days or weeks.² Moreover, relapse after the acute asthma episode, requiring either urgent asthma treatment or hospitalization, is common. Relapse rates ranging from

10% within 7 days after ED discharge to 31% 10 to 21 days after ED discharge have been reported.³⁻⁷

Cysteinyl leukotrienes have been shown to be mediators of inflammation and bronchoconstriction in asthma patients,^{8,9} and marked elevations of these compounds may occur during acute asthma episodes.^{10,11} Evidence supports the use of leukotriene-modifying drugs in the treatment of chronic asthma, and a number of studies¹²⁻¹⁶ have indicated potential benefit in patients with acute asthma. The effects of

this drug class on relapse after an acute asthma episode have not yet been described.

Treatment guidelines include therapy with systemic corticosteroids and inhaled β_2 -agonists as ED treatment for acute asthma, and a course of oral corticosteroids after ED discharge to prevent relapse.^{17,18} Nevertheless, high ED admission and relapse rates persist.^{3-7,19-22} Findings that corticosteroids do little to decrease the production of cysteinyl leukotrienes after allergen challenges,^{23,24} that the beneficial effects of leukotriene-modifying agents are additive to inhaled β_2 -agonists, and that the bronchodilatory effects of β_2 -agonists may diminish during asthma exacerbation²⁵⁻²⁷ suggest that there may be a role for leukotriene-modifying agents in the current ED treatment of asthma.

In this multicenter trial, we studied the effect of zafirlukast, an oral leukotriene receptor antagonist (LTRA), when added to standardized care in a population of patients who presented to the ED with acute asthma. The main objective was to assess the effects of zafirlukast on relapse after discharge from the ED. Other assessments included the rate of extended care before ED discharge, and treatment effects on pulmonary function, symptoms, and other patient outcomes in both the ED and outpatient periods.

MATERIALS AND METHODS

This trial was conducted in 20 US hospital-affiliated EDs. Patients aged 12 to 65 years who presented to the ED with acute asthma were screened by study investigators for trial eligibility. Eligible patients were those with a history of asthma and a FEV₁ of < 70% predicted both at ED entry and 25 min after receiving a single aerosol treatment with 2.5 mg of albuterol. Patients with the following conditions were excluded from the study: history of smoking of > 10 pack-years; positive pregnancy test result; a recent history of oral corticosteroid use (*ie*, ≥ 5 days) or treat-

*From the Long Island Jewish Medical Center (Dr. Silverman), New Hyde Park, NY; the Henry Ford Health System (Dr. Nowak), Detroit, MI; Barnes-Jewish Hospital (Dr. Korenblat), St. Louis, MO; Crozer-Chester Medical Center (Dr. Skobeloff), Upland, PA; and AstraZeneca Pharmaceuticals LP (Drs. Chen, Bonuccelli, and Simonson, and Mr. Miller), Wilmington, DE.

†Currently with Consortium Clinical Research, Upland, PA.

‡A list of participating investigators and centers is located in the Appendix.

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Correspondence to: Robert A. Silverman, MD, Long Island Jewish Medical Center, 270-05 76th Ave, New Hyde Park, NY 11042; e-mail: aresilv@aol.com

ment with a leukotriene-modifying drug within 2 weeks of ED entry; a need for intubation before randomization; pneumonia or an elevated temperature (*ie*, > 38.9°C); chronic lung disease other than asthma; or diabetes mellitus or any other clinically significant medical condition that could affect the required evaluations. Additionally, patients had to be willing to stay in the ED for at least 4 h (*ie*, the ED period) and then to participate in a 28-day outpatient treatment program (Fig 1). The trial was conducted in compliance with the principles of good clinical practice, approval was obtained from each institutional review board, and informed consent was obtained from all patients.

Trial Design and Treatment

At ED entry, patients underwent spirometry and were treated with nebulized albuterol (2.5-mg unit-dose nebulers) [Ventolin; GlaxoSmithKline; Research Triangle Park, NC]. Spirometry was repeated 25 min after ED entry, and patients with FEV₁ values still < 70% of predicted were randomized, 1:1:2, respectively, to double-blind, single-dose treatment with zafirlukast, 160 mg (Z160), zafirlukast, 20 mg (Z20) [Accolate; AstraZeneca; Wilmington, DE], or matching placebo. Patients then received a 60-mg po dose of prednisone and a second dose of nebulized albuterol, with additional albuterol administered at 60, 120, and 180 min after ED entry. At the final ED assessment (210 min after trial drug administration), the investigator determined whether the patients were ready for ED discharge or needed extended care (*ie*, additional time in the ED or an observation unit, or hospital admission). Although not formally bound by National Asthma Education and Prevention Program disposition guidelines, investigators were encouraged to use them in making ED discharge decisions.

If a patient needed extended care at 4 h, the protocol ended. Patients discharged from the ED at 4 h entered the 28-day outpatient period and were treated as follows: patients treated with zafirlukast in the ED continued receiving Z20 bid; patients treated with placebo in the ED continued receiving matching placebo bid; and patients were placed on a 7-day course of prednisone (20 mg bid), were given albuterol inhalers (Ventolin) to use as needed, and were instructed to resume previously established regimens of asthma medication. During the outpatient period, study personnel contacted patients by telephone on days 3, 15, and 21 to assess asthma symptoms, medication compliance, whether patients had sought additional asthma treatment, and adverse events. Patients were scheduled for clinic visits on days 10 and 28 after ED discharge. They were given a 40-day supply of trial medication and were instructed to take the medication until their last clinic visit in the event they were unable to return on day 28 and needed to reschedule their final appointment. A follow-up telephone contact was made 14 days after the trial treatment ended (*ie*, 42 days after study entry), and patients described any medical interventions since leaving the trial. Patients who relapsed during the 28-day study period were not contacted at day 42.

The treatment given to individual patients during the ED and outpatient periods was determined by a computer-generated randomization schedule, and each site had its own separate randomization scheme. The randomization scheme used in the ED was in the ratio of 2:1:1 (placebo/Z20/Z160, respectively) to ensure an approximate 1:1 randomization of zafirlukast and placebo patients during the subsequent outpatient period. Patients who were randomized to receive a placebo loading dose in the ED were given placebo bid for the outpatient period of the trial, and patients randomized to receive either Z20 or Z160 as a loading dose in the ED were given Z20 bid for the outpatient period of the trial. Patients, all study investigators, and ED staff were blinded to the intervention.

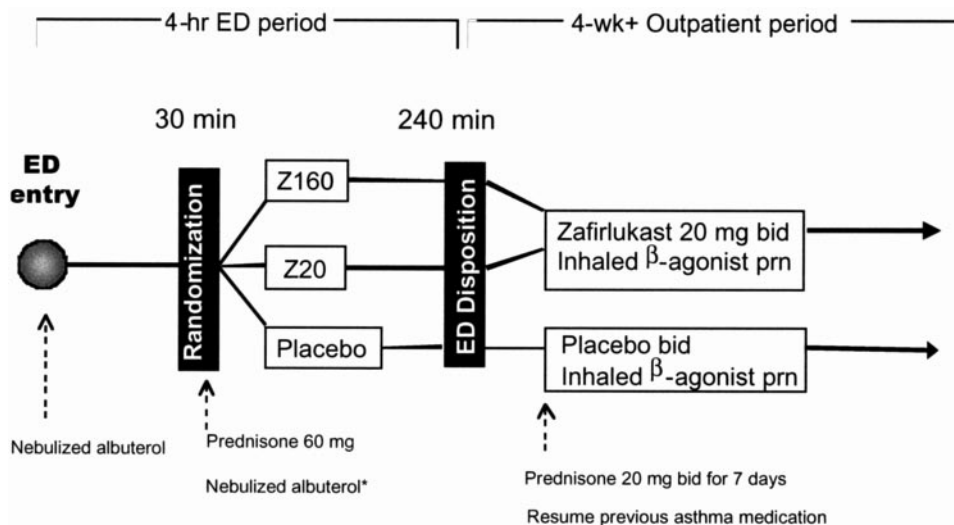


FIGURE 1. Trial design. pm = as needed. *Albuterol was also administered at 60, 120, and 180 min after ED entry.

Outcome Assessments

The time to relapse in the outpatient period was the primary outcome assessed. Relapse was defined as a deterioration in the patient's condition that required an unscheduled office visit or a return to the ED at any point up until the final outpatient clinic visit. Because protocol-prescribed clinic visits had the potential to influence when patients sought care for worsening asthma, additional relapse criteria were applied on visit days. Specifically, if patients indicated that they would have sought urgent care had their clinic visit not been scheduled, relapse was recorded. Additionally, relapses were recorded during clinic visits if patient FEV₁ values were $\leq 40\%$ of predicted, if the patient required additional oral corticosteroid treatment, or if two of the following three criteria were met: (1) the patient felt worse relative to the original ED visit; (2) the patient's FEV₁ was less than that measured before ED treatment; or (3) morning peak expiratory flow (PEF), β_2 -agonist use, nighttime awakenings, and daytime asthma symptoms, as recorded on diary cards, had all worsened (by the investigator's judgment) during the previous 72 h.

Secondary outcome assessments included the rate of extended care after single-dose treatment in the ED. FEV₁ was measured in the ED on arrival, before randomization, and at 30, 90, and 210 min after single-dose drug administration and at each outpatient clinic visit (days 10 and 28). Patients rated their dyspnea at ED entry, at randomization, and 210 min after drug administration. The method, a modified Borg method,²⁸ incorporated a visual analog scale, with verbal descriptors, ranging from 0 (no symptoms) to 10 (severe symptoms).

During the outpatient period, patients recorded PEF, daytime asthma symptoms (0, no symptoms; 1, mild symptoms; 2, moderate symptoms; and 3, severe symptoms), the number of nighttime awakenings, β_2 -agonist use, and the number of days when asthma interfered with work, school, or home activities on a diary card. Instructions on the use of the peak flow meters (Mini-Wright; Clement Clarke; Harlow, UK) and diary use were given before ED discharge.

Safety was monitored by reviews of adverse events, laboratory findings, and vital sign measurements. Clinical adverse events were identified either by the investigator or by scripted, open-ended questions that were asked during each clinic and phone contact. Blood samples for analyses of hematologic and biochem-

ical parameters were obtained before the first dose of randomized treatment in the ED and at the 28-day visit.

Spirometry

Spirometry methods were based on American Thoracic Society criteria²⁹ with modifications made for a trial population of acutely ill subjects. All centers used the same model spirometer and software (KoKo Spirometer; Pulmonary Data Services; Lewisville, CO), with the software specifically developed to facilitate both patient and investigator use. Investigators and trial personnel were trained on the use of the system as part of the certification process. Measured value-acceptability criteria for patient maneuvers included a forced expiratory effort of at least 2 s, a back-extrapolated volume of $< 5\%$, and a time to peak flow within the first 120 ms of forced expiration. FEV₁ values were considered to be reproducible if the two best efforts were within 10% of each other. An additional criterion, the absence of glottic closure in the first second, was evaluated when time-flow graphs were inspected visually. Completed data were captured on disk and sent for independent central (blinded) review within 24 h of acquisition, feedback on technique and adherence to criteria was returned to the site investigators, and retraining was provided as required.

Statistical Analysis

Sample size was calculated in conjunction with estimated relapse rates for patients who received standard care, as determined from Chapman et al¹⁹ Approximately 300 patients per treatment group would provide 80% power for a 0.05-level two-sided log-rank test of the time to first relapse.

The proportion of patients who required extended care was calculated per ED treatment group, and the proportions of patients who relapsed were calculated per outpatient treatment group. Patients who required extended care from the ED were not assigned to an outpatient treatment group since they did not undergo follow-up in the outpatient period. The rate of extended care was analyzed using logistic regression, and relapse was analyzed using a Cox proportional hazards regression model. Both the logistic regression and Cox models used FEV₁ percent predicted at ED entry as a covariate. FEV₁ was compared among

treatment groups using an analysis of covariance with the initial change in FEV₁ (from ED entry to just before randomization) and FEV₁ at randomization serving as covariates. Treatment effects on diary card variables and other outpatient outcomes, excluding FEV₁, were examined using an analysis of variance. For clinic visit and diary card measures, the last observations carried forward were used to define end point values.

Additional patient characteristics identified on ED arrival that may have influenced outcome or the response to the drug were placed into regression models, and characteristics included, but were not limited to, baseline Borg score, sex, recent use of oral steroids and inhaled steroids, past ED utilization, past asthma hospitalizations, and race/ethnicity. To determine whether the characteristics of the patients who were discharged from the ED at 4 h and entered the outpatient portion of the study may have influenced the outcome, propensity scores were calculated and multivariate regression analysis was performed using selected variables.

All statistical tests were two-sided with a statistical significance level of 0.05. The primary population for each analysis was the intent-to-treat (ITT) population, which included all patients who had received at least one dose of the trial drug and had undergone at least one posttreatment assessment. Per-protocol analyses, which excluded patients who had major protocol violations, were also performed. A statistical software package (SAS, version 6.11; SAS Institute; Cary, NC) was used to analyze the data.

RESULTS

Patients

During the ED period, 641 patients were randomized to treatment as follows: Z160, 162 patients; Z20,

158 patients; and placebo, 321 patients (Fig 2). Demographic and disease characteristics at ED entry are presented in Table 1. The mean age was 32 years, and the mean FEV₁ was 37.8% predicted. At the end of the ED period, 551 of 641 patients (86%) were discharged from the ED, and 546 patients entered the outpatient period. Of those, 276 were treated with Z20 bid and 270 were treated with placebo (Fig 2). Demographic and disease characteristics were generally similar between treatment groups (Table 2).

Four individuals with a prerandomization FEV₁ of > 70% predicted were randomized in error, two in the Z20 group and two in the placebo group. Five patients who were randomized in the ED were not continued in the outpatient portion of the study because of exclusion criteria that were missed at the baseline screening but were subsequently identified in the ED. Overall, 457 of 546 patients (84%) completed the outpatient protocol either through the end of treatment or to relapse. Reasons for withdrawal from the study are shown in Figure 2.

ED Outcomes

Rate of Extended Care: At the end of the ED period, 14.0% of all patients required extended care as follows: 16 of 162 patients (9.9%) treated with Z160; 26 of 158 patients (16.5%) treated with Z20;

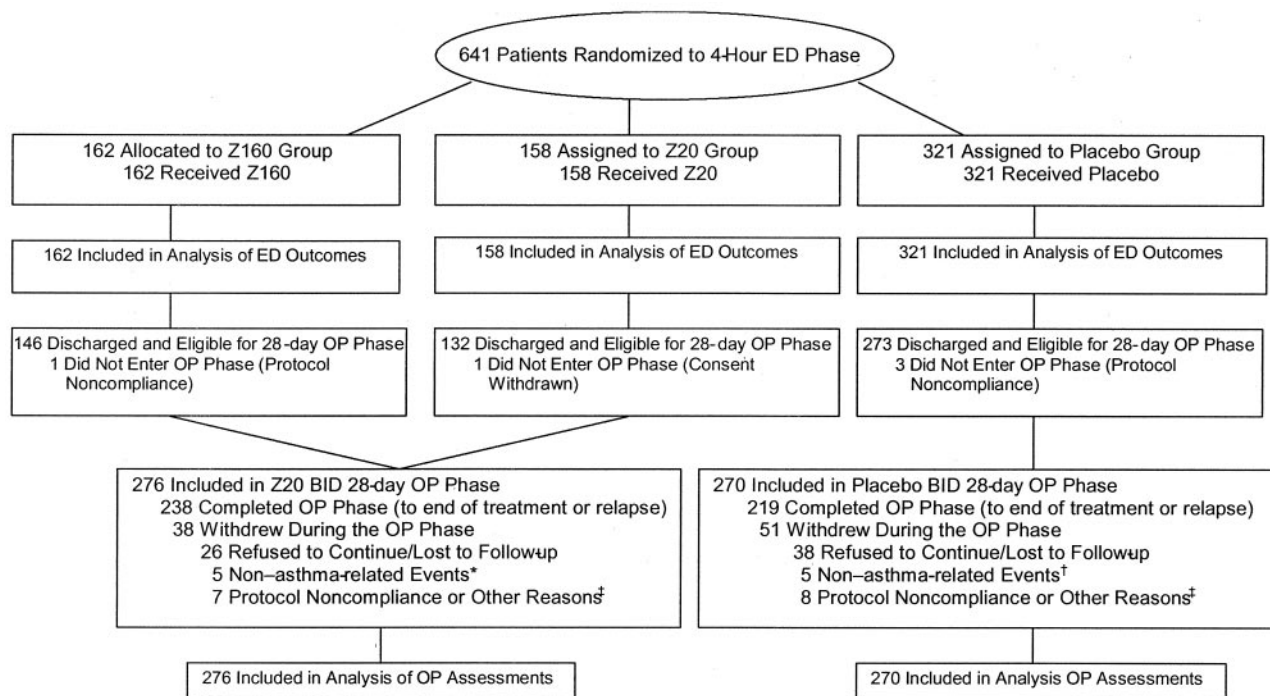


FIGURE 2. Patient disposition. OP = outpatient. *Lung infection (n = 2), pulmonary embolus (n = 1), abdominal pain (n = 1), malaise (n = 1). †Myocardial infarction (n = 1), atrial fibrillation (n = 1), lung infection (n = 1), abdominal pain (n = 1), and general edema and pruritis (n = 1). ‡Includes consent withdrawal, randomization in error, inability to adhere to protocol, positive pregnancy test, and elevated liver function test results at baseline.

Table 1—Demographic Characteristics and Disease-Related History for Patients Randomized to ED Treatment

Characteristics	Treatment Group		
	Z160 (n = 162)	Z20 (n = 158)	Placebo (n = 321)
Demographic			
Age,* yr	32.3 (12.6)	32.5 (11.4)	32.6 (11.7)
Sex, %			
Female	45.7	63.3	59.8
Male	54.3	36.7	40.2
Race, %			
Black	68.5	67.1	60.4
White	18.5	17.1	26.8
Hispanic	9.9	13.3	10.6
Asian/other	1.2/1.9	0.6/1.9	0.6/1.6
Smoking status, %			
Current	19	20	18
Former	22	25	26
Nonsmoker	59	54	56
Previously intubated for asthma†	22 (13.6)	15 (9.5)	39 (12.1)
Prior ED or urgent care visits past year			
Patients†	117 (72.2)	113 (71.5)	239 (74.5)
Median per patient, No.	2	1	2
Prior hospitalizations past year†	39 (24.1)	39 (24.7)	93 (29.0)
14-d medication history†			
Theophylline	16 (9.9)	16 (10.1)	38 (11.8)
Oral corticosteroids‡	10 (6.2)	16 (10.1)	15 (4.7)
ICSs	59 (36.4)	55 (34.8)	121 (37.7)
Long-acting inhaled β_2 -agonist	11 (6.8)	10 (6.3)	35 (10.9)
Inhaled β_2 -agonist use within 24 h of entry, puffs*	11 (15)	11 (21)	10 (13)
FEV ₁ ,*§ L	1.29 (0.50)	1.18 (0.53)	1.26 (0.46)
% predicted	38.0 (13.8)	35.7 (13.4)	38.7 (12.9)
Borg index score*§	6.6 (2.4)	7.0 (2.1)	6.6 (2.2)

*Values given as mean (SD).

†Values given as No. (%).

‡Use of oral corticosteroids was restricted to < 5 days (sporadic or consecutive) in the 14 days before trial entry.

§As determined at ED entry (30 min before trial treatment).

and 48 of 321 patients (15.0%) treated with placebo. Compared with placebo, Z160 reduced the absolute rate of extended care by 5.1%. This equates to a relative risk reduction of 34% ($p = 0.052$; odds ratio, 0.54; 95% confidence interval [CI], 0.29 to 1.00).

Spirometry: Baseline values can be found in Table 1. The mean values for the final FEV₁ measured in the ED (least squares means) were 2.12 L (64% predicted) with Z160, 2.09 L (62% predicted) with Z20, and 2.03 L (61% predicted) with placebo. Differences between Z160 and placebo were statistically significant at 90 min ($p = 0.02$), 210 min ($p = 0.04$), and at the end point ($p = 0.02$). Differences between Z20 and placebo did not reach statistical significance.

Dyspnea: From ED entry to just before randomization, median Borg values changed from 7 (mean, 6.68) to 5 (mean, 4.96). At 210 min, the final median Borg values were reduced to 1 (mean, 1.48) in the Z160 group, 2 (mean, 2.08) in the Z20 group, and 2

(mean, 2.02) in the placebo group. Compared with placebo, these differences were significant for Z160 ($p = 0.005$), but were not for Z20.

Outpatient Period Outcomes

Relapse: By the 28-day visit, 143 of 546 patients (26.2%) had relapsed (zafirlukast, 65 of 276 patients [23.6%]; placebo, 78 of 270 patients [28.9%]). Compared with placebo, treatment with zafirlukast reduced the absolute rate of relapse by 5.3%, which equates to a relative risk reduction of 18.3% ($p = 0.047$; hazards ratio, 0.714; 95% CI, 0.512 to 0.996). Figure 3 shows the Kaplan-Meier curves for the probability of time to relapse through the last dose of trial treatment. When zafirlukast-treated patients were considered by the ED dose of zafirlukast, relapse rates were similar (patients treated with Z160/Z20 bid, 22.8%; patients treated with Z20/Z20 bid, 24.4%). Through the 14-day follow-up period, cumulative postrandomization relapse rates were 27% in the zafirlukast treatment group and 32% in the placebo treatment group

Table 2—Disease-Related History for Patients Who Entered the Outpatient Period

Asthma History	Outpatient Period	
	Z20 bid (n = 276)	Placebo (n = 270)
14-day medication history†		
Theophylline	26 (9.4)	30 (11.1)
Oral corticosteroids‡	20 (7.2)	7 (2.6)
ICSs	103 (37.3)	101 (37.4)
Long-acting inhaled β_2 -agonist	21 (7.6)	27 (10.0)
Inhaled β_2 -agonist use within 24 h of entry,* puffs	11 (18)	9 (12)
FEV ₁ ,*§ L	1.28 (0.5)	1.30 (0.5)
% predicted	38.0 (13.8)	39.9 (12.3)
Borg index score*§	6.7 (2.3)	6.4 (2.1)
Previously intubated for asthma†	31 (11.2)	30 (11.1)

*Values given as mean (SD).

†Values given as No. (%).

‡Use of oral corticosteroids was restricted to < 5 days (sporadic or consecutive) in the 14 days before trial entry.

§Values given as mean (SD).

§As determined at ED entry (30 min before trial treatment).

(absolute reduction in relapse, 5%; relative reduction in risk of relapse with zafirlukast, 16%; $p = 0.048$; hazards ratio, 0.729; 95% CI, 0.533 to 0.997).

Most relapses occurred as patient-initiated, urgent, unscheduled office or ED visits (*ie*, they were not identified relative to the additional protocol-defined relapse criteria). Patient-driven relapses occurred in 60 of the 65 zafirlukast-treated patients who relapsed (92%) and in 74 of the 78 placebo-treated patients who relapsed (95%). Among patients who relapsed, the hospitalization rate was 6.2% (4 of 65) for zafirlukast-treated patients and 10.3% (8 of 78) for placebo-treated patients. Among the patients who were initially discharged from the ED, hospitalization rates were 1.4% (4 of 276) for zafirlukast-treated patients and 3.0% (8 of 270) for placebo-treated patients.

Spirometry: For patients who entered the outpatient period, mean FEV₁ values at the start of the outpatient period (*ie*, at ED discharge) were 2.23 L (65.8% predicted) for the zafirlukast treatment group and 2.14 L (64.7% predicted) for the placebo treatment group. At each outpatient clinic visit, patients who had been treated with zafirlukast had higher mean FEV₁ values than did patients treated with placebo, with significant differences between treatment groups occurring on both days (day 10: zafirlukast, 2.47 L; 74.0% predicted; placebo, 2.29 L; 69.1% predicted [$p = 0.008$]; day 28: zafirlukast, 2.49 L; 73.4% predicted; placebo, 2.27 L; 67.8% predicted [$p = 0.009$]; end point: zafirlukast, 2.41 L; 71.4% predicted; placebo, 2.26 L; 68.0% predicted [$p = 0.039$]) [Fig 4].

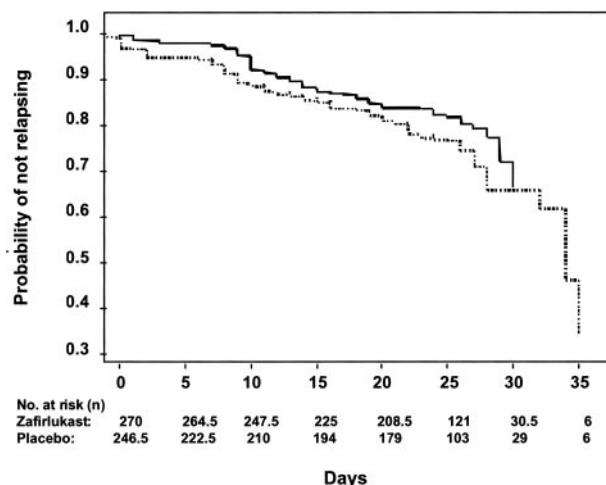


FIGURE 3. Kaplan-Meier probability estimates of being relapse-free during the outpatient period. Solid line, Z20; dotted line, placebo. The numbers under the graph represents the number of patients remaining in the trial who were at risk for a relapse.

Diary Card Indexes: Overall, the mean improvements were greater for many but not all diary card indexes among patients treated with zafirlukast. Zafirlukast-treated patients had lower mean daytime symptom scores (0.82 vs 1.01, respectively; $p < 0.01$), less daily β -agonist usage (3.3 vs 4.1 puffs per day, respectively; $p < 0.01$), and a trend toward a lower proportion of sleepless nights (0.32 vs 0.38, respectively; $p = 0.054$). Similarly, patients treated with zafirlukast had a smaller mean proportion of days on which asthma interfered with work, school, or home activities (zafirlukast, 20%; placebo, 26%; $p = 0.018$); the asthma-related absentee rate was 9% for patients treated with zafirlukast compared with 13% for patients treated with placebo ($p = 0.032$). There were no significant differences between groups in terms of PEF (zafirlukast group, 320 L/min; placebo, 312 L/min).

Per-Protocol Analysis

In the evaluation of outcomes for the per-protocol population, few patients were excluded (*ie*, the per-protocol population was similar to the ITT population) [excluded from the extended-care analysis, 9 patients; excluded from the relapse analysis, 26 patients (including 8 patients who were excluded from the extended-care analysis who continued as outpatients)]. A prerandomization FEV₁ of > 70% predicted was the most common reason for exclusion from the per-protocol analyses. The results of the per-protocol analyses were consistent with those of the ITT analyses.

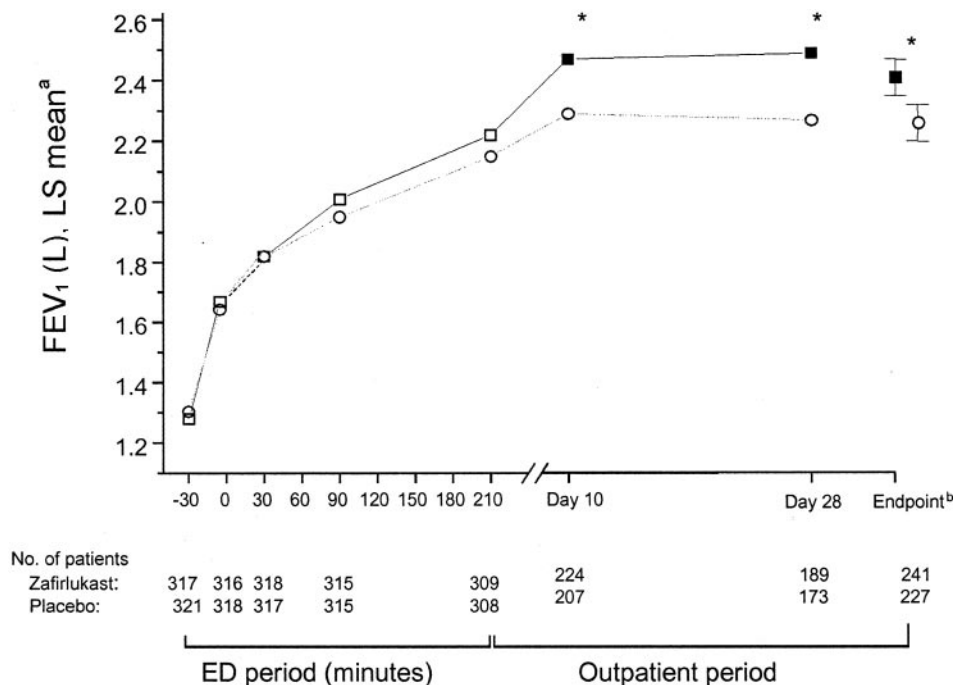


FIGURE 4. Mean FEV₁ (in liters) over time for patients who entered the outpatient period. □ = Z160 or Z20 mg (single dose); ■ = Z20 mg bid; ○ = placebo. Model includes center, change in FEV₁ from -30 to -5 min, and value of FEV₁ at -5 min. *p < 0.04 (analysis of covariance) for difference between zafirlukast (20 mg bid) and placebo. a = arithmetic means at -30 min and -5 min (before treatment); least-squares means from analysis of covariance model at all other points. b = end point values based on last observation carried forward.

Influence of Baseline Characteristics

For each outcome (*ie*, extended care and relapse), the effects of zafirlukast were not influenced by race, age, initial ED FEV₁, response to the initial ED β-agonist therapy, or the use of oral steroids within 14 days of ED enrollment. Gender did not influence either the need for extended care or the time to relapse in this study, and the greater number of men in the ED Z160 group did not impact the need for extended-care study results. Additional analysis revealed a relationship between therapy with inhaled corticosteroids (ICSs) and that with zafirlukast in the outpatient portion of the study, with patients not receiving ICSs responding better to zafirlukast. A similar relationship was not found in the ED portion of the study. Propensity analysis indicated that the effect of zafirlukast on relapse was not influenced by patient or clinical characteristics at the time of ED discharge.

Safety

The number of adverse events was similar between the zafirlukast and placebo treatment groups per trial period. The most common adverse event was headache. In the ED period, headache occurred

in two patients (1%) each in the Z160 and Z20 treatment groups, and in five patients (2%) in the placebo group. In the outpatient period, headache occurred in 40 patients (15%) treated with zafirlukast and in 33 patients (12%) treated with placebo. After 4 weeks of randomized treatment, four zafirlukast-treated patients (1%) and six placebo-treated patients (2%) had alanine aminotransferase levels greater than two times the upper limit of normal.

There was one patient in the placebo arm of the trial who died from asthma 11 days after ED discharge. The patient reportedly was not compliant with treatment or follow-up, and on autopsy additional factors contributing to his death, but unrelated to the protocol, were identified.

DISCUSSION

Previous studies^{10,11} have suggested that cysteinyl leukotrienes have a role in the pathophysiology of acute asthma. This multicenter trial showed that adding a leukotriene receptor antagonist to standardized ED therapy and routine discharge medication decreases the need for extended care in the ED and improves the 28-day outpatient relapse rate. Improvement in asthma symptoms and airway function

occurred with the first dose in the ED, and many secondary outcomes improved throughout the trial. Of the two zafirlukast doses (160 mg and 20 mg) evaluated during the ED period, the larger dose reduced the relative risk of extended care by 34%, a number that approached statistical significance ($p = 0.052$). The lower dose did not appear to have an impact in the ED. In the 28-day period after ED discharge, the addition of zafirlukast, 20 mg bid, to standard prednisone-based therapy reduced the relative risk of relapse by 18% compared with prednisone-based therapy alone. Given the overall findings, zafirlukast may be a useful adjunct for managing acute asthma episodes.

These trial results are consistent with observations made in patients with acute and chronic asthma of an early and additive LTRA- β_2 -agonist effect, and suggest that the direct blockade of leukotrienes improves the clinical effect.^{30–33} The effect of zafirlukast on the need for extended care is supported by a recent study³⁰ evaluating therapy with IV montelukast in ED patients. A single infusion of montelukast reduced the number of ED treatment failures (defined as hospitalizations, need for care for > 6 h, or need for additional medications) compared to usual care. There were also trends toward greater benefit in the higher dose of montelukast (14 mg) vs the lower dose of montelukast (7 mg), which is consistent with the dose-related effect noted in our study. To our knowledge, the effects of montelukast or other LTRAs on relapse after ED discharge have not been studied.

The ease of oral administration combined with a favorable time to improvement in clinical findings suggest that a single dose of zafirlukast is a useful ED treatment. Even though our overall extended care rates were lower than anticipated, we still found improvement when Z160 was administered. Because the CIs surrounding the need for extended care results were relatively wide, further study with a larger sample size is needed to more precisely identify a treatment effect.

The planned 28-day outpatient treatment and 14-day posttreatment follow-up periods gave us an opportunity to evaluate when outpatient treatment with zafirlukast first exerted its beneficial effect, and whether zafirlukast affected the probability of relapse only during treatment or whether relapse was simply postponed until after treatment ended. It was during the first week of treatment, when prednisone was coadministered, that the treatment effect seen throughout the study period first emerged (Fig 3, Kaplan-Meier curve). The treatment effect was maintained throughout the interventional portion of the trial. After treatment ended, the differential between treatments for the risk of relapse was

sustained at least through the 14-day follow-up period. To what extent zafirlukast maintained the poststudy differential is unknown, although the data indicate the lack of a rebound effect when zafirlukast treatment was discontinued.

Standardized ED treatment and assessment may have led to the relatively low ED admission rates despite patients generally having severe asthma on ED arrival. Relapse rates, however, were comparable to those in other studies even though fewer patients were hospitalized. Unlike previous studies that monitored patients after ED discharge, relapse in our trial occurred at a fairly consistent rate over time without early relapses dominating the pattern of events. This gradual emergence may have reflected, in part, the controlled and standardized ED treatment and assessments. Other factors that possibly influenced the pattern of relapse included patient knowledge of planned future contacts, the provision of peak flowmeters, and instructions on diary card usage at ED discharge. This idea seems to be supported by the similar pattern of graduated relapse seen in patients who received standard care alone.

Among the study limitations, we did not include standardized criteria for determining ED discharge decisions because there are no validated disposition criteria. We encouraged the use of National Asthma Education and Prevention Program guidelines but allowed clinicians to make the final determination for extended care. We standardized the duration of treatment for 210 min after zafirlukast treatment both to provide uniform care across sites and to allow time to observe for efficacy. In practice, treatment and disposition times vary widely, as does the use of observation or hold units for more prolonged treatment. Because of this, our results for “rate of extended care” may differ in other settings. The same limitations also may apply to relapse results, which may be influenced by the study definition as well as the protocolized outpatient portion of the study.

In an outpatient setting, regular treatment with ICSs is the first-line therapy for chronic persistent asthma.¹⁷ However, studies evaluating short-term relapse when therapy with ICSs is initiated as a component of ED discharge therapy have produced conflicting results. One study³⁴ showed that adding ICS therapy after ED discharge (budesonide, 1,600 $\mu\text{g}/\text{d}$) significantly decreased the 21-day relapse rate, improved quality of life, and improved symptom scores. In contrast, two other studies showed that ICSs (flunisolide, 2 mg/d³⁵ or fluticasone, 250 μg bid³⁶) were not beneficial in decreasing relapse rates or improving symptoms. A systematic review by the Cochrane group³⁷ from the three ICS trials (909 patients) yielded relapse results that were broadly similar to ours (odds ratio, 0.68; 95% CI, 0.46 to

1.02). Differences in study populations, medication and dosing equivalency, protocols, methods of analysis, and follow-up periods make direct comparisons difficult. Clinical trials directly comparing the efficacy and effectiveness of therapy with inhaled steroids to those with zafirlukast therapy in preventing short-term relapse after ED discharge, prescribed alone or in combination, are needed to determine the optimal treatment regimen.

There are potential advantages to prescribing an oral agent to patients discharged from the ED, as many asthmatic patients do not use their inhalers properly,^{38,39} ED staff may not be proficient in teaching inhaler technique,⁴⁰ and outpatient compliance may be better with oral agents.⁴¹ Our trial was not designed to compare the short-term benefit from therapy with oral zafirlukast with that with an inhaled steroid, although it does highlight the need for additional intervention following an ED visit. Starting therapy with a controller agent would represent a shift in strategy for many emergency physicians, who may be reluctant to prescribe up to a month course of outpatient treatment for patients they will not care for after ED discharge. Clinicians should, however, consider this approach because therapy with either ICSs or leukotriene modifiers has few short-term side effects, relapse is common following ED discharge even with prednisone-based treatment, and follow-up with a clinician immediately after the ED visit cannot be assured. Whether the introduction (and choice) of a controller agent into the course of treatment by an ED clinician also will lead to better follow-up, long-term controller usage and optimized outpatient management needs to be studied.

This trial suggests that zafirlukast is a useful treatment adjunct for acute asthma. Of particular interest is the potential for higher dose zafirlukast to decrease extended care in the ED, and this requires further study. The results also indicate that zafirlukast therapy could be studied in other settings or situations, for example, when patients are hospitalized for asthma.

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APPENDIX

Steering Committee

Robert Silverman, MD (Chair); Richard Nowak, MD; Emil Skobeloff, MD; Phillip Korenblat, MD; and Steven Simonson, MD.

Investigators

Leonard Altman, MD, Harbor View Medical Center, Seattle, WA; Paula J. Anderson, MD, University of Arkansas for Medical Sciences, Little Rock, AR; Raymond E. Brady, MD, Vancouver, WA; Ronald A. Charles, MD, Parkland Hospital, UT Southwestern Medical Center, Dallas, TX; William Calhoun, MD, Presbyterian University Hospital, University of Pittsburgh, Pittsburgh, PA; Charles Emerman, MD, The Cleveland Clinic Foundation, Cleveland, OH; James A. Feldman, MD, Boston Medical Center, Boston, MA; Fred Harchelroad, MD, Allegheny General Hospital, Pittsburgh, PA; Liudvikas Jagminas, MD, Rhode Island Hospital, Providence, RI; Phillip E. Korenblat, MD, Barnes-Jewish Hospital, St Louis, MO; James Larson, MD, University of North Carolina Hospitals, Chapel Hill, NC; Michael McDermott, MD, Cook County Hospital, Chicago, IL; Richard M. Nowak, MD, Henry Ford Hospital, Detroit, MI; Robert O'Conner, MD, Christiana Hospital, Newark, DE; Charles V. Pollack, Jr., MD, Maricopa Medical Center, Phoenix, AZ; Michael Silver, MD, Rush-Presbyterian-St. Luke's Medical Center, Chicago, IL; Robert A. Silverman, MD, Long Island Jewish Medical Center, New Hyde Park, NY; Emil Skobeloff, MD, Crozer-Chester Medical Center, Upland, PA; Brian Tiffany, MD, PhD, and Mark Rumbak, MD, Tampa General Hospital, Tampa, FL; and Archie Wilson, MD, University of California Irvine Medical Center, Orange, CA.

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Zafirlukast Treatment for Acute Asthma*

Robert A. Silverman, Richard M. Nowak, Phillip E. Korenblat, Emil Skobeloff,
Yusong Chen, Catherine M. Bonuccelli, Christopher J. Miller and Steven G.
Simonson

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