Zafirlukast in Clinical Practice
Results of the Accolate Clinical Experience and Pharmacoepidemiology Trial (ACCEPT) in Patients with Asthma

James P. Kemp, MD; Phillip E. Korenblat, MD; Joseph E. Scherger, MD, MPH; and Margaret Minkwitz, PhD
San Diego, California; St. Louis, Missouri; Irvine, California; and Wilmington, Delaware

BACKGROUND. Zafirlukast is an oral leukotriene receptor antagonist used in the treatment of patients with mild to moderate asthma. To investigate its effects in a clinical practice setting, we evaluated zafirlukast in a heterogeneous group of patients who had asthma of different degrees of severity and who were receiving concomitant asthma medications.

METHODS. A total of 3759 patients were enrolled at 924 sites. Patients received zafirlukast 20 mg twice a day for 4 weeks. Pulmonary function was measured twice a day, and overall asthma symptom scores, number of nighttime awakenings, severity of morning asthma symptoms, and β_2-agonist use were recorded daily.

RESULTS. In the efficacy analysis (3207 evaluable patients), all parameters showed statistically significant improvement that continued throughout the 4 weeks of the trial. A total of 71% of patients had improved pulmonary function and 72% had improved asthma symptoms. Improvement was consistent regardless of asthma severity category and regardless of concomitant asthma medication category. More than 70% of both physicians and patients indicated there was clinical improvement in pulmonary measures as well as in asthma symptoms. Common adverse events reported were headache (3.7%), nausea (1.4%), pharyngitis (1.4%), and sinusitis (1.1%).

CONCLUSIONS. Zafirlukast 20 mg twice a day is well tolerated and improves pulmonary function and asthma symptoms, regardless of asthma severity category and regardless of concomitant asthma medication category.

KEY WORDS. Asthma; receptors, leukotriene; respiratory function tests; zafirlukast (non-MeSH); bronchoconstriction. *(J Fam Pract 1999; 48:425-432)*

Asthma currently affects more than 14 million people in the United States.[1] This chronic disease is characterized by airway obstruction, inflammation, and heightened airway responsiveness to a variety of stimuli.[2] Successful management of long-term asthma involves the application of anti-inflammatory medications to control symptoms. The development of the class of asthma medications known as the antileukotrienes has provided a new form of chronic therapy for the treatment of asthma.[3,4] Controlled clinical trials[5-8] have demonstrated that antileukotriene-directed therapy produces clinical benefits in asthmatic patients.

Zafirlukast is an oral leukotriene receptor antagonist indicated for the chronic treatment of patients with mild to moderate asthma. Controlled clinical trials designed for regulatory approval have shown that up to 13 weeks of zafirlukast therapy improves pulmonary function parameters, reduces the need for β_2-agonist rescue medications, and improves overall asthma symptoms when used in patients with mild to moderate[7-11] or severe[12] asthma. One 13-week trial of zafirlukast has also demonstrated an improved quality of life in patients with moderate reversible airflow obstruction.[11] In addition, interim results from an open-label extension trial[13] have demonstrated the long-term efficacy and safety of zafirlukast in patients with mild to moderate asthma. The majority of patients enrolled in those trials had mild or moderate asthma and were prohibited from receiving concurrent medications other than short-acting β_2-agonists. Moreover, most of the patients were treated by specialists in the fields of asthma or allergy.

The Accolate Clinical Experience and Pharmacoepidemiology Trial (ACCEPT) was designed to evaluate a different group of patients from those enrolled in the clinical trials for regulatory approval. The purpose of ACCEPT was to study zafirlukast in a population of asthmatic patients in a clinical practice setting. With an enrollment of 3759 patients, including 3207 evaluable patients, this clinical practice study represents the largest investigation of zafirlukast to date.

Submitted, revised, March 8, 1999.
From the Department of Pediatrics (Allergy), University of California, San Diego (J.P.K.); Washington University, St. Louis, Missouri (P.E.K.); the Department of Family Medicine, University of California–Irvine (J.E.S.); the Medical Affairs Department, Zeneca Pharmaceuticals, Wilmington, Delaware (M.M.). Requests for reprints should be addressed to James P. Kemp, MD, Allergy & Asthma Medical Group and Research Center, 9610 Granite Ridge Drive, Suite B, San Diego, CA 92123.

METHODS

Objectives and Study Design

The primary objectives of the trial were to determine patient response to 4 weeks of zafirlukast therapy, identify pharmacoepidemiologic factors predictive of response to zafirlukast, determine patient and physician global evaluations of zafirlukast therapy, and identify any adverse events of zafirlukast not previously observed.

Participating investigators were identified by geographic region; 4 primary care physicians and 1 specialist from each region were invited to participate. Participating investigators were permitted to enroll up to 5 patients at each site. A total of 3759 patients were enrolled at 924 sites in the United States and Puerto Rico between December 1996 and June 1997.

After a 3-day lead-in period during which baseline pulmonary function values were obtained and diary card assessments were performed, patients received zafirlukast 20 mg twice a day for 4 weeks. Pulmonary function testing was performed twice a day, and daily diary cards were used to document asthma symptoms. Investigators evaluated patients at a baseline visit, and again at 2 and 4 weeks after beginning the study. At the baseline visit, patients provided a medical and smoking history and underwent a complete physical examination. Each patient received an AirWatch Airway Monitor System (Enact Health Management Systems, Inc, Mountain View, Calif) and was instructed in the use of this device. The AirWatch monitor is an electronic spirometry device that measures peak expiratory flow (PEF) and forced expiratory volume in 1 second (FEV_1) in accordance with American Thoracic Society standards.[14]

To obtain baseline data, patients performed pulmonary function testing using the AirWatch monitor twice a day (in the morning before β_2-agonist use and again 12 hours later) for 3 days after the initial visit. Patients recorded overall asthma symptoms, nighttime awakenings, morning asthma symptoms, and β_2-agonist use on daily diary cards. Asthma symptoms were scored on a 4-point scale where 0 = no symptoms, 1 = mild symptoms that did not interfere with activities, 2 = moderate symptoms that interfered with some activities, or 3 = severe symptoms that interfered with many activities. Nighttime awakening was recorded as a yes or no according to whether the patient was awakened during the previous night because of asthma. β_2-agonist use was recorded as number of puffs per day.

After the baseline period, zafirlukast 20-mg tablets were supplied to each patient. The first 20-mg dose of zafirlukast was taken on the morning of day 4 of the trial, and treatment with zafirlukast continued for 4 weeks. Participants in the study were instructed to take zafirlukast 20 mg twice a day, either 1 hour before or 2 hours after meals, 12 hours apart. All prescription and nonprescription medications for asthma treatment were allowed as long as they had not been stopped or started within 4 weeks of screening; modification of dosages, substitutions, and additions of any asthma medication were discouraged.

Each patient performed pulmonary function testing using the AirWatch monitor twice a day—once in the morning before β_2-agonist use and again 12 hours later. In addition, patients recorded overall asthma symptom scores, nighttime awakenings, morning asthma symptoms, and β_2-agonist use daily on diary cards.

Patient compliance, response to treatment, and adverse events were assessed at visits week 2 and week 4. At each of these visits, patients were asked if they had had any unusual symptoms (ie, symptoms other than allergy or asthma symptoms) since the previous visit. A description of each reported event and its severity was recorded. Investigators also recorded their assessment of the relationship of each reported event to the use of study medication. At the final study visit, both physicians and patients answered specific questions on overall safety, effectiveness, and other issues regarding zafirlukast therapy.

Patient Population

Patients 12 years and older were eligible to participate in the trial if they had symptoms of asthma within the preceding month and were candidates for prophylactic or chronic asthma therapy. An FEV_1 value that was between 45% and 85% of predicted value after at least a 4-hour abstinence from β_2-agonist use was required for study participation. PEF was evaluated both before and after β_2-agonist use. Patients had to have been nonsmokers for at least 6 months and have a smoking history of no more than 10 pack-years (ie, packs per day times total number of years smoked). There were no restrictions on concurrent asthma medications, but therapeutic regimens must have been stable within the 4 weeks before study entry. Patients with newly diagnosed asthma were eligible to participate in the study if they met the above criteria.

Patients were excluded if they had any chronic lung or airway problem other than asthma, if they had an acute asthma exacerbation at the time of screening, or if they had received more than 10 days of treatment with oral corticosteroids in the 4 weeks before screening. Patients with known active hepatic dysfunction, those being treated with warfarin or β-blockers, those who had participated in a trial with an investigational drug within the preceding 30 days, and women who were pregnant or lactating were also ineligible to participate.

Study approval was obtained through a centralized institutional review board (Institutional Review Board, Inc, San Clemente, Calif); local institutional review board approval was obtained when required. All patients provided written informed consent. For patients aged 12 through 17 years, a parent or legal guardian had to also sign the consent form.

STATISTICAL METHODS

The evaluable patient population was defined as all patients who (1) received at least 7 consecutive days of trial medication; (2) had 3 days of baseline data and 7 consecutive days of post-baseline pulmonary function data (ie, morning and evening PEF and morning and evening FEV_1) obtained via the AirWatch Airway Monitoring System; and (3) had a completed patient case report form, including 1 week of asthma scores.

Eight pulmonary function and diary card measures were analyzed for efficacy. Descriptive statistics were calculated and a paired *t* test was applied to each of the 8 variables to assess the magnitude and statistical significance of the changes from baseline to the end of the 4 weeks of therapy. A last-observation-carried-forward procedure was used to form complete data sets for analysis, and significance was defined as $P < .05$. Percentage change from baseline was derived as a function of the ratio between the mean baseline values and the mean end-of-study values.

Efficacy analyses were also done for subgroups based on severity of disease and reported concomitant asthma medication use at entry. Severity of disease was assessed according to consensus asthma guidelines[15] current when the trial commenced. The categories of concomitant asthma medications to which zafirlukast was added included: short-acting inhaled β_2-agonists, long-acting inhaled β_2-agonists, oral β_2-agonists, inhaled steroids, xanthine, and mast cell stabilizers. Differences between subgroups were assessed using an analysis of covariance model, and significance was defined as $P < .05$.

The safety analysis was based on all enrolled patients and included assessment of adverse events and asthma worsening, defined as a 25% reduction in pulmonary function or an increase in asthma symptoms associated with an increase in the dose of any concomitant asthma medication, or the addition of an asthma medication to a patient's background regimen.

TABLE 1

Demographic Characteristics of Study Patients with Mild to Moderate Asthma

Characteristic	Enrolled Patients (N = 3759) n	(%)	Efficacy Patients (N = 3207) n	(%)
Age, years				
<18	312	(8.3)	263	(8.2)
18-65	3021	(80.4)	2602	(81.1)
>65	384	(10.2)	321	(10.0)
Not recorded	42	(1.1)	21	(0.7)
Sex				
Male	1320	(35.1)	1130	(35.2)
Female	2429	(64.6)	2073	(64.6)
Not recorded	10	(0.3)	4	(0.1)
Race				
White	3119	(83.0)	2723	(84.9)
Black	300	(8.0)	215	(6.7)
Hispanic	208	(5.5)	170	(5.3)
Other*	132	(3.5)	99	(3.1)
Asthma severity†				
Mild	363	(9.7)	363	(11.3)
Moderate	2129	(56.6)	2129	(66.4)
Severe	647	(17.2)	647	(20.2)
Not recorded	620	(16.5)	68	(2.1)
Duration of asthma, years				
1 to 5	849	(22.6)	718	(22.4)
6 to 10	742	(19.7)	620	(19.3)
11 to 20	881	(23.4)	759	(23.7)
> 20	1259	(33.5)	1095	(34.1)
Asthma medications at entry‡				
Short-acting inhaled β_2-agonist	3288	(87.5)	2835	(88.4)
Long-acting inhaled β_2-agonist	1330	(35.4)	1146	(35.7)
Oral β_2-agonist	398	(10.6)	333	(10.4)
Inhaled steroid	2578	(68.6)	2238	(69.8)
Xanthine	974	(25.9)	846	(26.1)
Mast cell stabilizer	536	(14.3)	471	(14.7)
Comorbid conditions‡				
Allergic rhinitis	2606	(69.3)	2273	(70.9)
Chronic sinusitis	662	(44.2)	1440	(44.9)
Urticaria	814	(21.7)	704	(22.0)
Arthritis	628	(16.7)	544	(17.0)
Atopic dermatitis	558	(15.6)	523	(16.3)
Nasal polyps	455	(12.1)	410	(12.8)
History of childhood asthma	1385	(36.8)	1171	(36.5)
History of remitting adolescent asthma	854	(22.7)	730	(22.8)
ED visit in past year	997	(26.5)	812	(25.3)
Intubated in past year	233	(6.2)	188	(5.9)
Hospitalized in past year	482	(12.8)	385	(12.0)

ED denotes emergency department.
*Includes Native American or Alaska native, Asian or Pacific Islander, other, and race missing.
†Assessed by 1991 consensus asthma guidelines.[15]
‡ Categories not mutually exclusive.

RESULTS

Eighty-three percent (3120) of the 3759 patients enrolled completed the trial, but 85.3% (3207) were deemed eligible for the efficacy analysis. Of the 639 (17%) patients

TABLE 2

Efficacy Results: Pulmonary Function and Diary Card Measures by Week Changes (n=2796)

Measure	Baseline Mean (SD)	Change in Mean (SD)*	% Change
PEF, liters per minute†			
Morning	348 (115)	35 (88)	10
Evening	367 (114)	30 (90)	8
FEV_1, liters†			
Morning	2.28 (0.91)	0.22 (0.81)	10
Evening	2.36 (0.88)	0.21 (0.84)	9
Asthma symptoms score‡	8.84 (4.60)	-2.66 (4.63)	-30
Nighttime awakenings§	1.93 (2.58)	-0.91 (2.49)	-47
Mornings with asthma symptoms	3.88 (2.89)	-1.52 (2.93)	-39
β_2-agonist use‖	5.99 (5.17)	-1.44 (3.63)	-24

SD denotes standard deviation; PEF, peak expiratory flow; FEV_1, forced expiratory volume in 1 second.
*Significant difference from baseline (P <.001) through week 4 for all values.
†Measured before β_2-agonist use.
‡Total symptoms score per week.
§Days per week.
‖ Puffs per day.

TABLE 3

Change from Baseline in Pulmonary Function and Diary Card Measures by Asthma Severity Category

Assessment	Mild Mean (SD)*	Moderate Mean (SD)*	Severe Mean (SD)*
PEF, liters per minute			
Morning	34.5 (95.1)	36.8 (88.9)	26.6 (81.3)
Evening	36.5 (94.3)	31.6 (90.1)	25.1 (90.4)
FEV_1, liters			
Morning	0.19 (0.85)	0.24 (0.84)	0.17 (0.69)
Evening	0.18 (0.86)	0.23 (0.85)	0.18 (0.81)
Asthma symptoms score†	-2.8 (4.5)	-2.7 (4.6)	-2.6 (5.0)
Nighttime awakenings‡	-0.8 (2.2)	-0.9 (2.5)	-1.1 (2.7)
Mornings with asthma symptoms‡	-1.5 (2.7)	-1.5 (3.0)	-1.6 (3.0)
β_2-agonist use§	-1.2 (3.0)	-1.5 (3.6)	-1.5 (3.9)

Note: Assessed by 1991 consensus asthma guidelines.[15]
SD denotes standard deviation; PEF, peak expiratory flow; FEV_1, forced expiratory volume in 1 second.
*Significant difference from baseline (P <.001) through week 4 for all values.
†Total symptoms score per week.
‡Days per week.
§Puffs per day.

who did not complete the trial, 4.9% were lost to follow-up or patient decision (ie, patient decided not to continue in the study). Reasons for withdrawal from the study also included adverse events (2.3%), protocol violation (1.7%), worsening asthma (0.6%), concurrent illness (0.5%), pregnancy (0.1%), and other reasons (0.3%). The reason for discontinuation was not reported for 6.6% of the patients.

Patient Demographic Information and Baseline Characteristics

Table 1 summarizes the demographic information for all enrolled patients and those included in the efficacy analysis. The majority were white women who had moderate asthma of long-standing duration (>10 years). Most of the patients were taking one or more concomitant medications at the time of trial entry and had one or more comorbid conditions. Approximately 40% of patients were primarily treated by a family practice physician. The mean percentage of predicted FEV_1 was 74%.

Efficacy of Zafirlukast

Pulmonary Function

Significant improvement (P <.001) was observed for each pulmonary function measure within 1 week of beginning treatment with zafirlukast, and the improvement increased weekly over the treatment period. After 4 weeks, mean morning PEF and FEV_1 had increased 10% compared with baseline values (Table 2); evening values showed slightly less but similar improvement. By the end of therapy, pulmonary function had improved from baseline by at least 30 liters per minute in PEF or by at least 15% in FEV_1 in 63% of patients and by at least 20 to 29 liters per minute in PEF or at least 10% from baseline in FEV_1 in 71% of patients.

Asthma Symptoms, Nighttime Awakenings, and β_2-Agonist Use

Significant changes from baseline (P < .001) were observed by week 1, and values continued to improve weekly over 4 weeks. After 4 weeks, mean asthma symptoms score had improved by 30%, nighttime awakenings by 47%, mornings with asthma by 39%; use of β_2-agonists had declined by 24% (Table 2). By the end of therapy, 52% of patients had at least a 50% reduction in asthma symptoms score, and 72% of patients had at least a 10% improvement in that measure.

Subgroup Analysis for Severity Category

Significant changes from baseline ($P < .001$) were seen in pulmonary function measurements and asthma symptoms, regardless of severity category (Table 3). Figure 1 shows the mean percentage change from baseline for selected pulmonary measures and for pulmonary diary card assessments according to category of asthma severity.

At the end of the 4-week study period, changes in morning and evening FEV_1 were similar across all 3 categories of asthma severity. Change from baseline in morning and evening PEF, however, was significantly greater ($P < .05$) for patients with mild and moderate asthma than for those with severe asthma. Decreases in asthma symptoms scores, nighttime awakenings, and β_2-agonist use were also significantly greater ($P < .05$) for patients with mild or moderate asthma. All other subgroup comparisons based on severity of asthma were similar with respect to the mean change from baseline for each efficacy parameter at week 4.

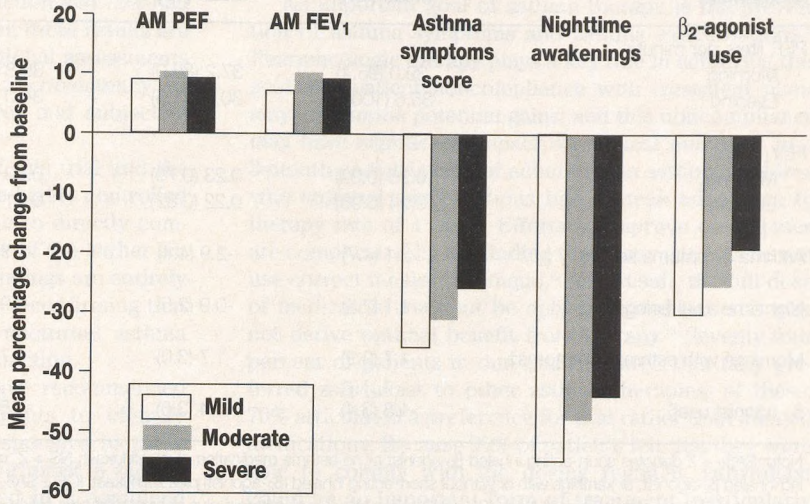
Subgroup Analysis for Concomitant Asthma Medication Category

Significant improvement from baseline ($P < .05$) was evident for all pulmonary function measurements and diary card assessments for all patients, regardless of concomitant asthma medication category (Table 4). Figure 2 shows the mean percentage change from baseline for selected pulmonary measures and diary card assessments when zafirlukast was added to each concomitant medication group.

After 4 weeks of treatment, the changes in morning and evening FEV_1 and morning PEF were similar for all concomitant medication groups, but patients using only β_2-agonists or no concomitant asthma medication showed

FIGURE 1

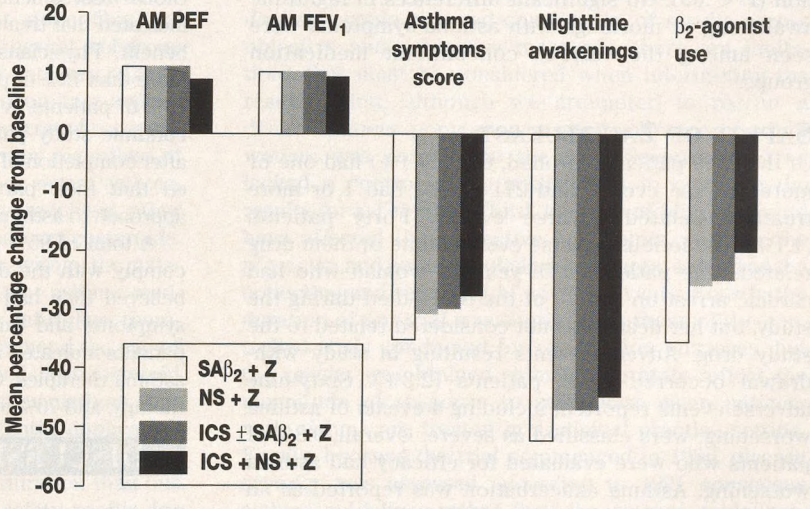
Mean percentage change from baseline at end point in morning (AM) pulmonary function (PEF and FEV_1) asthma symptoms score, nighttime awakenings, and β_2-agonist use according to category of asthma severity using 1991 consensus asthma guidelines.



From the National Asthma Education and Prevention Program.[15]

FIGURE 2

Mean percentage change from baseline at end point in morning (AM) pulmonary function (PEF and FEV_1) asthma symptoms score, nighttime awakenings, and β_2-agonist use according to category of concomitant medication to which zafirlukast was added.



Note: $SA\beta_2 + Z$ denotes short-acting inhaled β_2-agonist or no asthma medication plus zafirlukast; NS + Z, nonsteroidal (mast cell stabilizer, oral or long-acting inhaled β_2-agonist, or xanthine with or without short-acting inhaled (β_2-agonist) plus zafirlukast; ICS ± $SA\beta_2$ + Z, inhaled corticosteroid with or without short-acting inhaled β_2-agonist plus zafirlukast; ICS + NS + Z; inhaled corticosteroid plus nonsteroidal plus zafirlukast.

TABLE 4

Change from Baseline in Pulmonary Measures and Asthma Symptoms by Concomitant Medication Category

Assessment	SAβ_2+ Z Mean (SD)*	NS + Z Mean (SD)*	ICS ± SAβ_2+ Z Mean (SD)*	ICS + NS + Z Mean (SD)*
PEF, liters per minute				
Morning	39.0 (95.4)	37.2 (86.0)	36.8 (92.1)	31.3 (84.0)
Evening	35.6 (100.9)	30.9 (91.5)	34.0 (89.5)	26.4 (86.6)
FEV_1, liters				
Morning	0.25 (0.92)	0.23 (0.79)	0.23 (0.80)	0.20 (0.78)
Evening	0.24 (0.95)	0.22 (0.82)	0.21 (0.78)	0.20 (0.82)
Asthma symptoms score†	-3.1 (4.7)	-2.9 (4.4)	-2.7 (4.7)	-2.4 (4.6)
Nighttime awakenings‡	-1.1 (2.6)	-0.9 (2.5)	-0.9 (2.5)	-0.8 (2.4)
Mornings with asthma symptoms‡	-1.7 (2.9)	-1.7 (3.0)	-1.7 (3.0)	-1.3 (2.9)
β_2-agonist use§	-1.8 (3.4)	-1.4 (3.6)	-1.5 (3.7)	-1.3 (3.7)

Note: SAβ_2 + Z denotes short-acting inhaled β_2-agonist or no asthma medication plus zafirlukast; NS + Z, nonsteroidal (mast cell stabilizer, oral or long-acting inhaled β_2-agonist, or xanthine with or without short-acting inhaled (β_2-agonist) plus zafirlukast; ICS ± SAβ_2 + Z, inhaled corticosteroid with or without short-acting inhaled β_2-agonist plus zafirlukast; ICS + NS + Z; inhaled corticosteroid plus nonsteroidal plus zafirlukast.
SD denotes standard deviation; PEF, peak expiratory flow; FEV_1, forced expiratory volume in 1 second.
*Significant difference from baseline (P <.05) through week 4 for all values.
†Total symptoms score per week.
‡ Days per week.
§ Puffs per day.

significantly more improvement than patients receiving inhaled corticosteroids and nonsteroidal medication (P < .05). No significant differences in nighttime awakening or mornings with asthma symptoms were seen among the various concomitant medication groups.

Safety of Zafirlukast

Of the 3759 patients enrolled, 642 (17.1%) had one or more adverse events, and 271 (7.2%) had 1 or more treatment-related adverse events. Forty patients (1.1%) had serious adverse events, none of them drug related. One patient—a 55-year-old woman who had cardiac arrest on day 20 of the trial—died during the study, but her death was not considered related to the study drug. Adverse events resulting in study withdrawal occurred in 85 patients (2.3%). Sixty-nine adverse events reported, including 4 events of asthma worsening, were classified as severe. Overall, 9.3% of patients who were evaluated for efficacy had asthma worsening. Asthma exacerbation was reported as an adverse event for 46 patients (1.2%). The most common adverse events were headache (3.7%), nausea (1.4%), pharyngitis, (1.4%), and sinusitis (1.1%). No clinically meaningful differences with regard to adverse events were noted between patients who were using inhaled corticosteroids and those who were not.

Physician and Patient Global Assessment of Therapy

Global assessments from both physicians and patients indicated that treatment with zafirlukast provided clinical benefit. Physicians perceived clinical improvements in more than 72% of patients for pulmonary measures and in 78% of patients. A total of 77% of physicians planned to continue study participants on therapy with zafirlukast after completion of the trial, and 80% of physicians reported that their participation in the trial changed their approach to asthma treatment.

A total of 95% of patients felt that they were able to comply with the dosing regimen of the study, and 78% believed they had experienced improvement in asthma symptoms and pulmonary function. Moreover, 74% of patients indicated a preference for zafirlukast over other asthma therapies. Of these, 81% felt better on zafirlukast therapy, and 70% had a preference for oral medication.

DISCUSSION

The results of this clinical practice study demonstrate that zafirlukast was effective in treating a heterogeneous population of asthmatic patients, regardless of asthma severity category and concomitant medications received. Patients had significant improvements (P < .001) in both morning and evening FEV_1 and PEF

values, as well as in overall asthma symptoms score, morning asthma symptoms, nighttime awakenings, and β_2-agonist use. Improvements occurred as early as 1 week after initiation of drug use, and continued throughout the 4-week treatment period. A total of 71% of patients had improved pulmonary function and 72% had improved asthma symptoms. Moreover, these results are similar to the physician and patient global assessments of zafirlukast therapy, indicating a consistency of response for both objective measures and subjective assessments.

Because the patient population of this trial and the trial design differed from those of the highly controlled trials of zafirlukast, it is inappropriate to directly compare the results of our trial with those of the earlier trials of zafirlukast. Nevertheless, our findings are entirely consistent with those of earlier trials,[7-12] confirming that zafirlukast diminishes daytime and nocturnal asthma symptoms and improves pulmonary function.

Consensus asthma guidelines[16] have recommended further study of antileukotriene agents to identify patients who may be particularly responsive to these therapies. To that end, the effect of zafirlukast in various patient subgroups has been examined in 2 combined analyses of 13-week controlled trials.[10,12] Tashkin and colleagues[10] reported that zafirlukast is similarly efficacious in different sex, racial, and age groups and provides a benefit to patients with either mild or moderate persistent asthma. Further, they found that zafirlukast appears to be incrementally beneficial for patients with more moderate disease. Kemp et al[12] reported that steroid-naive patients with severe persistent asthma had clinically significant improvements across all efficacy measures after treatment with zafirlukast alone. Our trial population was sufficiently large to permit subgroup analyses of patients according to their category of asthma severity and their category of concomitant asthma medication use. These analyses demonstrated a consistent improvement with zafirlukast therapy regardless of whether patients had mild, moderate, or severe asthma, and regardless of whether they were receiving other asthma medications, including inhaled corticosteroids. Thus, we could identify no subgroup within the categories of asthma severity or concomitant asthma medication that did not derive benefit from zafirlukast therapy. Given that current guidelines recommend the use of zafirlukast as an alternative to inhaled corticosteroid therapy for patients with mild persistent asthma, our results suggest that zafirlukast has potential application in a broader range of patients than is currently indicated.

Placebo-controlled trials of longer duration than our trial have demonstrated a favorable safety profile for zafirlukast that is clinically indistinguishable from that of placebo.[7-13] Few serious adverse events occurred during this study, and zafirlukast was well tolerated, confirming this overall safety conclusion. No new or unexpected side effects were seen in this broad population of asthma patients who were permitted to use concomitant asthma medications. Common adverse events such as headache, nausea, pharyngitis, and sinusitis occurred with a similar or lower frequency in our trial than in the controlled trials of zafirlukast.[7-13]

An important goal of asthma therapy is the prevention of asthma symptoms and asthma exacerbations.[16] Pharmacologic therapy plays a key role in achieving this goal, but patient noncompliance with treatment plans may undermine potential gains, and this noncompliance may have significant impact on clinical outcome. In a 3-month pediatric trial of adherence in asthma, children who suffered exacerbations had a mean adherence to therapy rate of 13.8%.[17] Efforts to improve compliance are complicated by the finding that many patients do not use correct inhaler technique.[18] As a result, the full dose of medication may not be delivered, and patients may not derive optimal benefit from therapy.[19] Seventy-four percent of patients in our trial indicated that they preferred zafirlukast to other asthma therapies; of these, 70% articulated a preference for oral rather than inhaled medications. Because 95% of patients felt that they were able to comply with the dosing regimen, zafirlukast could be an important form of treatment, particularly in patients who are less than fully compliant with inhaler therapy. These high levels of compliance with zafirlukast were confirmed in a clinical trial using an electronic monitoring device to precisely assess patient compliance. The mean numerical compliance was 80% for the patients who completed that trial.[20]

LIMITATIONS

While the strengths of this trial relate to its large and diverse sample size and consistency of results across objective and subjective measures, there are limitations that must be considered when interpreting the results. First, although we attempted to recruit a diverse patient population, a predominance of white women was enrolled in the trial. Second, the trial lacked a control group with which to compare the results for zafirlukast. Third, the lack of blinding could have affected the subjective end points, such as the physician and patient global assessments, as well as the collecting and reporting of adverse events. Fourth, the duration of our trial was shorter than those of the controlled trials conducted for registration purposes, but the results we obtained should accurately reflect the magnitude of response to zafirlukast when patients with asthma are treated in a clinical practice setting. Finally, because the trial commenced in 1996, disease severity was assessed according to 1991 consensus asthma guidelines rather than the current guidelines. However, because the current guidelines primarily affect the categorization of patients with mild asthma; the percentage of patients in our trial with moderate or severe asthma would be similar under the former, even if categorized by current guidelines.

CONCLUSIONS

We conclude that zafirlukast 20 mg twice a day is well tolerated and effective in a heterogeneous population of asthma patients, regardless of asthma severity category and regardless of concomitant medication category to which zafirlukast was added. Although these findings require confirmation in a randomized controlled study, they suggest a broader range of indication for zafirlukast therapy than that recommended in the current consensus asthma guidelines.[16] Moreover, the availability of zafirlukast for oral administration may provide advantages in terms of patient compliance and acceptance when compared with inhaled asthma therapies.

ACKNOWLEDGMENTS

This study was supported by a grant from Zeneca Pharmaceuticals, Wilmington, Delaware. Accolate is a trademark, the property of Zeneca Limited.

The authors gratefully acknowledge the participating ACCEPT investigators for conducting the trial and MEDEX Clinical Trial Services for clinical operations and statistical reporting support. Acknowledgment is given to Kendall Wills Sterling and Gary Dorrell for editorial assistance and Oliver Yeh for graphics support.

REFERENCES

1. Adams P, Marano M. Current estimates from the National Health Interview Survey, 1994. Vital Health Stat 1995; 10:94.
2. Leff A. Pharmacologic management of asthma. J Allergy Clin Immunol 1998; 101:S397-9.
3. O'Byrne P. Leukotrienes in the pathogenesis of asthma. Chest 1997; 111:27S-34S.
4. Wenzel S. New approaches to anti-inflammatory therapy for asthma. Am J Med 1998; 104:287-300.
5. Israel E, Cohn J, Dubé L, Drazen J. Effects of treatment with zileuton, a 5-lipoxygenase inhibitor, in patients with asthma. JAMA 1996; 275:931-6.
6. Reiss TF, Chervinsky P, Dockhorn RJ, Shingo S, Seidenberg B, Edwards TB. Montelukast, a once-daily leukotriene receptor antagonist, in the treatment of chronic asthma: a multicenter, randomized, double-blind trial. Arch Intern Med 1998; 158:1213-20.
7. Spector SL, Smith LJ, Glass M. Effects of 6 weeks of therapy with oral doses of ICI 204,219, a leukotriene D_4 receptor antagonist, in subjects with bronchial asthma. Am J Respir Crit Care Med 1994; 150:618-23.
8. Fish JE, Kemp JP, Lockey RF, Glass M, Hanby LA, Bonuccelli CM. Zafirlukast for symptomatic mild-to-moderate asthma: a 13-week multicenter study. Clin Ther 1997; 19:675-90.
9. Nathan RA, Minkwitz MC, Bonuccelli CM. Two first-line therapies in the treatment of mild asthma: use of peak flow variability as a predictor of effectiveness. Ann Allergy Asthma Immunol. In press.
10. Tashkin DP, Nathan RA, Howland WC, Minkwitz MC, Simonson S, Bonuccelli CM. An evaluation of zafirlukast in the treatment of asthma with exploratory subset analyses. J Allergy Clin Immunol 1999; 103:246-54.
11. Nathan RA, Bernstein JA, Bielory L, et al. Zafirlukast improves asthma symptoms and quality of life in patients with moderate reversible airflow obstruction. J Allergy Clin Immunol 1998; 102:935-42.
12. Kemp JP, Minkwitz MC, Bonuccelli, CM, Warren MS. Therapeutic effect of zafirlukast as monotherapy in steroid-naive patients with severe persistent asthma. Chest 1999;115:336-42.
13. Grossman J, Smith LJ, Wilson AM, Thyrum PT. Long-term safety and efficacy of zafirlukast in the treatment of asthma: interim results of an open-label extension trial. Ann Allergy Asthma Immunol. In press.
14. American Thoracic Society. Standardization of spirometry: 1994 update. Am J Respir Crit Care Med 1995; 152:1107-36.
15. National Asthma Education and Prevention Program. Guidelines for the Diagnosis and Management of Asthma. US Department of Health and Human Services, Public Health Service, National Institutes of Health, National Heart, Lung, and Blood Institute, Bethesda, Md. NIH Publication No. 91-3042.
16. National Asthma Education and Prevention Program. The Expert Panel Report 2: Guidelines for the Diagnosis and Management of Asthma. US Department of Health and Human Services, Public Health Service, National Institutes of Health, National Heart, Lung, and Blood Institute, Bethesda, Md. NIH Publication No. 97-4051.
17. Milgrom H, Bender B, Ackerson L, Bowry P, Smith B, Rand C. Noncompliance and treatment failure in children with asthma. J Allergy Clin Immunol 1996; 98:1051-7.
18. Poelman M, Bogels A, Chisholm SL, Dekker FW. Effects of instruction by practice assistants on inhaler technique and respiratory symptoms of patients. A controlled randomized videotaped intervention study. Fam Pract 1998; 13:35-40.
19. Fabbri L, Piattella M, Caramori G, Ciaccia A. Oral vs. inhaled asthma therapy. Drugs 1996; 52(suppl 6):20-8.
20. Chung KF, Kennelly JC, Summerton L, Harris A. Compliance with an oral asthma treatment: electronic monitoring of twice daily dosing with zafirlukast. Allergy Clin Immunol International 1997; 9(suppl 4):241. Abs 880.