Safety and Clinical Efficacy of Zileuton in Patients with Chronic Asthma

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Abstract

Zileuton, a leukotriene pathway inhibitor used to treat asthma, improves lung function, relieves symptoms, and is well tolerated. The purpose of this 12-month, parallel-group, open-label study was to assess the efficacy of zileuton and evaluate liver function in patients treated with this drug (approximately 2% of patients treated with zileuton in controlled trials had reversible liver enzyme elevations). A total of 2,947 patients at 233 centers in the United States were randomly assigned in a 5:1 ratio to treatment with zileuton plus usual asthma care or usual asthma care alone. Efficacy variables included asthma exacerbations; need for alternative treatment, steroid rescue, emergency care, and hospitalizations; forced expiratory volume in 1 second (FEV_1); and asthma symptom scores. The safety evaluation included measurement of alanine aminotransferase levels. Patients treated with zileuton had significantly fewer corticosteroid rescues ($P < 0.001$), required less emergency care ($P < 0.05$), had fewer hospitalizations, and had greater increases in FEV_1 ($P = 0.048$). They also had significantly greater improvements in asthma symptoms. Increases in alanine aminotransferase levels to three times or more the upper limit of normal occurred in 4.6% of patients treated with zileuton and 1.1% of those receiving usual care ($P < 0.001$); most increases occurred during the first 2 to 3 months. Alanine aminotransferase levels decreased to less than two times the upper limit of normal or to baseline levels during zileuton treatment or after drug cessation. Jaundice or chronic liver disease did not develop in any patient. Adding zileuton to the therapeutic regimens of patients with asthma is likely to improve asthma control and lower utilization of healthcare resources.

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Inflammation, bronchoconstriction, and edema play important roles in the chronic airway obstruction experienced by patients with asthma. Increasingly, leukotrienes are recognized as major mediators in the pathophysiology of inflammation.[1] Derived from arachidonic acid by the action of the enzyme 5-lipoxygenase, leukotrienes cause bronchoconstriction,[2-8] changes in vascular permeability and edema,[9,10] mucus secretion,[11,12] and chemotaxis of inflammatory cells.[9,13-15]

Zileuton (Zyflo™, Abbott Laboratories, North Chicago, IL), a compound that blocks 5-lipoxygenase, is the first commercially available leukotriene pathway inhibitor to undergo extensive clinical testing in patients with asthma.[16-19] In two randomized, placebo-controlled clinical trials (one 3-month and one 6-month study),[16,19] patients with chronic asthma who were treated with zileuton had a statistically significant improvement in pulmonary function, required fewer corticosteroid rescues, used beta-agonist inhalers significantly less often, and had a greater improvement in quality of life indices compared with patients given placebo. In these studies, zileuton was well tolerated. Approximately 2% of patients treated with zileuton had transient but statistically significant elevations of liver enzymes, particularly alanine aminotransferase (ALT), a sensitive measure of liver injury.

Our 12-month study was designed to assess the effect of zileuton on liver function and to evaluate the benefit of zileuton under conditions simulating actual clinical practice. Because studies suggest that 40% to

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50% of the direct costs of asthma care are associated with emergency room visits and hospitalizations,[20] we specifically examined the effect of zileuton on the frequency of acute asthma exacerbations, systemic corticosteroid rescues, emergency room visits, and hospitalizations to augment our previous observations demonstrating the ability of zileuton to reduce the need for systemic corticosteroid rescue.[16]

··· METHODS ···

To enter the study, patients had to have a history of chronic asthma and a baseline forced expiratory volume in 1 second (FEV_1) at least 35% of the predicted value, measured at least 4 hours after albuterol inhalation and 12 hours after salmeterol inhalation. Reversibility of the patient's asthma had to be demonstrated by either a 15% or greater improvement in FEV_1 after albuterol inhalation at screening or a history of positive response to a methacholine or histamine challenge. In addition, patients had to be at least 16 years old, weigh within 30% of the upper limit of the Metropolitan Life tables, have no clinically significant abnormalities other than asthma, and be a nonsmoker for at least 6 months before enrollment. Women had to be postmenopausal, be surgically sterile, or use an effective method of contraception. Patients had to agree to limit their alcohol consumption to 2 ounces or less per day during the study. Screening examinations and tests included a physical examination, full blood chemistry panel, complete blood count, and liver function tests.

All patients gave signed, informed consent before any study procedures were initiated, and the institutional review board of each participating center approved the protocol.

Study Design

This 12-month, randomized, parallel-group, open-label study was conducted at 233 sites throughout the United States, including allergy and pulmonary clinics, private physicians' offices, research centers, and academic teaching institutions. Patients were randomly assigned in a ratio of approximately 5 to 1 to receive either zileuton (600 mg four times daily) plus usual asthma care or usual asthma care alone. Randomization to treatment groups was performed at a central randomization center (Abbott Laboratories).

Patients taking stable doses of concomitant asthma medications could continue using these drugs so that study conditions reflected treatment in a general clinical setting. Specifically, patients could use inhaled corticosteroids, nedocromil, cromolyn sodium, or salmeterol if the dose had been stable for at least 4 weeks before study entry. Patients assigned to the zileuton plus usual care group who were taking theophylline had their theophylline dose decreased by half before zileuton was started because zileuton inhibits the hepatic clearance of theophylline.[21] Subsequently, the theophylline dose was titrated to maintain serum levels in the therapeutic range (8 to 15 mg/L). Immunotherapy (antigen injection) was allowed if the dose was stable for at least 3 months before study entry or if therapy was seasonal. Patients were allowed limited treatment with systemic corticosteroids for an asthma exacerbation, but chronic steroid therapy was not permitted.

Objective measures of efficacy included the number of acute asthma exacerbations, additional or alternative asthma treatment (see below) for exacerbations, systemic corticosteroid rescue, emergency room visits, and hospitalizations. The Asthma Symptom Assessment Scale and the Borg Dyspnea Assessment were used for subjective measures of efficacy.[22,23] In addition, patients recorded symptoms and adverse events in a daily diary.

An acute asthma exacerbation was defined as worsened asthma symptoms (increased dyspnea, cough, wheezing) requiring a 50% or greater increase in beta-agonist use or a 100% or greater increase in inhaled steroid use for 3 consecutive days (additional asthma therapy) or the need for emergency room care or hospitalization. If the exacerbation appeared to be due to a respiratory tract infection, investigators could prescribe an antibiotic. For asthma exacerbations that did not respond to either the additional asthma treatments described above or alternative therapy (including nebulized beta-agonists), oral corticosteroids could be prescribed. Although the decision to prescribe corticosteroid rescue was left to the individual investigators, guidelines for such use were described in the protocol.

Study Procedures

At each visit, patients in the zileuton group were provided with a supply of 600-mg tablets, sufficient to last until the next visit; compliance was monitored by tablet count at each visit. In addition to an initial screening visit, study visits were scheduled for all patients on day 1 of treatment, at week 2, and at months 1, 2, 3, 4, 5, 7, 10, and 12.

Patients were assessed for safety at every visit, both by interview and through clinical and laboratory monitoring. Laboratory investigations included hematology measures (except at month 2), blood chemistry,

and liver function tests. Monitoring for adverse events included a review of the patients' daily diaries, in which they recorded any adverse or unusual physiologic events (including acute exacerbations of asthma symptoms). Investigators documented the dates, duration, severity, and intermittence of the events. In addition, investigators recorded any treatment required for all adverse events, as well as the likely causes and whether the event was potentially related to zileuton treatment.

The FEV_1 was measured in triplicate on study day 1 before the first dose of zileuton and at month 12. However, values for month 12 (or the final visit for patients who withdrew early) were not available for all patients, since FEV_1 testing was a late addition to the protocol. Patients were instructed to withhold albuterol for at least 4 hours and salmeterol for at least 12 hours before FEV_1 determinations.

Patients who had an acute asthma exacerbation were allowed a short course of systemic corticosteroids consisting of oral, intramuscular, or intravenous prednisone or its equivalent in a dose of 60 mg or less per day for no more than 7 days, after which tapering was permitted. Patients who required more than two systemic corticosteroid rescues could continue in the study only after review by a medical monitor. If asthma exacerbations were not severe enough to warrant systemic steroid therapy, more conservative treatment, such as short- or long-acting beta-agonists or inhaled steroids (defined in this study as alternative therapy), could be prescribed at the discretion of the investigator.

The Asthma Symptom Assessment Scale, modeled after similar scales used in asthma trials to assess the impact of asthma symptoms on the patient's daily life,[24] was administered as a questionnaire on study day 1 and at week 2 and months 1, 3, 4, 5, and 10. The symptoms evaluated covered multiple areas of the patient's life, including emotional function, social and work activities, quality of sleep, and the amount of beta-agonist inhaler use (scoring system shown in Table 1). Patients' ratings covered the 2-week interval before the study visit. The Borg Dyspnea Assessment, performed at each visit, consisted of an analog scale from 0 to 10, with 0 representing the patient's best breathing day and 10 the worst breathing day.

Patients with elevated alanine aminotransferase (ALT) values were monitored using an algorithm that evaluated the relative elevation of ALT compared with the upper limit of normal in conjunction with the presence or absence of symptoms. Asymptomatic patients with an ALT ≥3 times the upper limit of normal but ≤5 times the upper limit of normal could continue taking zileuton but were retested weekly until values returned to baseline levels. Zileuton was discontinued if ALT levels exceeded 5 times the upper limit of normal or if patients became symptomatic; these patients were followed up every 2 to 7 days until resolution.

Statistical Analyses

The sample size of 2,500 patients in the zileuton group provided a two-sided 95% confidence interval

Table 1. Scoring for the Asthma Symptom Assessment Scale

	Points Scored					
	1	2	3	4	5	6
Emotions (feeling anxious, depressed, or irritable)	Not at all	Slightly	Moderately	Quite a bit	Extremely	–
Interference with social activities	Not at all	Slightly	Moderately	Quite a bit	Extremely	–
Time missed from usual activities	None	1-3 days	4-7 days	1-2 weeks	2-3 weeks	3-4 weeks
Impairment in activity performance	None	1-3 days	4-7 days	1-2 weeks	2-3 weeks	3-4 weeks
Sleep interruption	Never	<1 time/week	1-4 nights/week	>5 nights/week	>1 time/night	–
Beta-agonist use	Never	Less than usual	Usual	More than usual	–	–

with a width of approximately 2% for the percentage of patients who develop an ALT elevation of 3 times the upper limit of normal.

Baseline values for patients randomly assigned to zileuton were defined as the final measurement taken before administration of the first dose of study drug. For patients in the usual care group, baseline values were the last measurement obtained before the start of the study. Continuous variables were analyzed using a *t* test and analysis of variance, as appropriate. Categoric data were analyzed using the Pearson chi-square tests of the Cochran-Mantel-Haenszel statistic, allowing for stratification by investigative site. Although zileuton was well tolerated, drop-outs were more frequent in the zileuton group. Therefore, Kaplan-Meier survival curves were chosen post hoc as the most appropriate method of analyzing differences in the rates of occurrence of asthma exacerbations and exacerbations resulting in emergency visits and hospitalizations. Final mean values were calculated using the last observation carried forward convention.

··· RESULTS ···

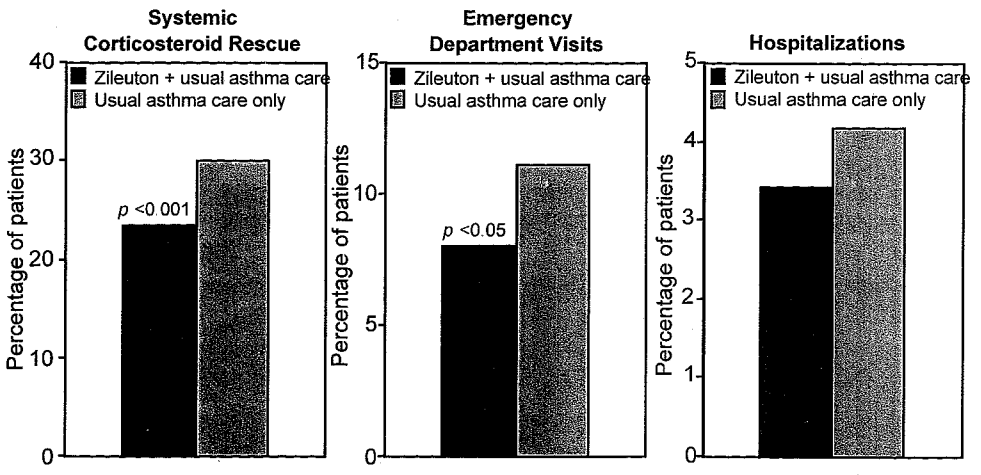
A total of 2,947 patients were enrolled at 233 centers throughout the United States, with 2,458 patients assigned to zileuton plus usual care and 489 to usual care alone. The enrollment period began in September 1994 and ended in January 1995. The study was completed in March 1996. The data represent an accumulated 1,518 patient-years of zileuton exposure.

The treatment groups were comparable demographically and medically (including medication use, tobacco use, incidence of allergic rhinitis, baseline FEV_1, Asthma Symptom Assessment Scale scores, and Borg Dyspnea Assessment scores). Approximately 61% of patients were female and 39% male; the mean age was 43 years (range, 15 to 86 years). The ethnic mix was similar to that in other zileuton studies: 91% white, 7% black, and 2% other. The mean FEV_1 at baseline was 64% of the predicted value in the zileuton group and 66% of the predicted value in the usual care group. Inhaled beta-agonists were used by 96.3%, inhaled corticosteroids by 56.5%, theophylline by 31.4%, and nedocromil by 11.4% of patients in the zileuton group; the corresponding percentages in the usual care group were 95.7%, 60.9%, 32.3%, and 11.9%.

Clinical Efficacy

Asthma exacerbations occurred in 49.4% of the usual care group and 45.1% of the zileuton group ($P = 0.12$; Kaplan-Meier). Despite the similar incidence in the two groups, patients treated with zileuton plus usual care appeared to have less severe exacerbations than those receiving usual care alone since fewer exacerbations required additional treatment. Compared with patients in the usual care group, 24% fewer patients treated with zileuton required systemic corticosteroid rescues for asthma exacerbations (23.0% versus 30.3%; $P < 0.001$) (Figure 1). The percentage of patients who required a hospital emergency department visit for asthma exacerbation was 33% lower in the zileuton group than in the usual care group (7.7% versus 11.5%; $P < 0.05$, Kaplan-Meier) (Figure 1). In addi-

Figure 1. Percentage of Patients with Acute Asthma Exacerbations Who Required Systemic Corticosteroid Rescue, Emergency Department Visits, or Hospitalization



tion, 22% fewer patients in the zileuton group required inpatient care for asthma (3.2% versus 4.1%), although the difference was not statistically significant (Figure 1).

There was no significant difference between groups in mean baseline FEV_1. The data for the 1,752 patients for whom final FEV_1 measurements were available (1,395 in the zileuton group and 357 in the usual care group) showed a significantly greater increase in FEV_1 from baseline to the final visit for patients treated with zileuton than for patients in the usual care group: 0.28 L versus 0.21 L ($P = 0.048$), an increase of 15.1% and 12.8%, respectively.

In addition to significant improvements in objective measures, including reductions in health resource utilization, the zileuton group showed statistically significantly greater improvements in subjective measures of efficacy. On the Asthma Symptom Assessment Scale, improvements in the zileuton group were greater than those in the usual care group at nearly every visit for all domains: negative emotions (anxiety, depression, or irritation), interference with social activities, time missed from usual activities, impairment in performance of activities, interruption of sleep, and frequency of beta-agonist use (Figure 2). The zileuton group also had significantly greater mean improvement in scores on the Borg Dyspnea Assessment compared with the usual care group for all visits except that on day 29.

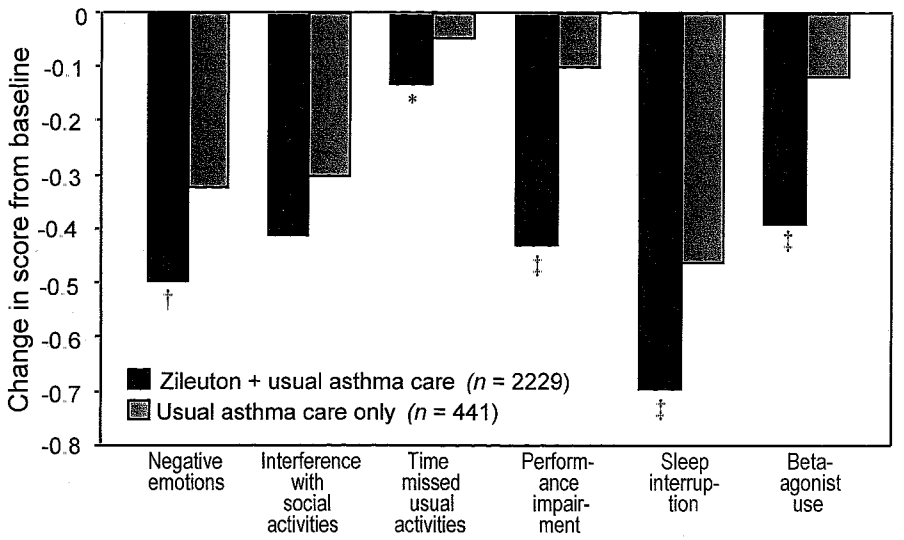
Adverse Events

Elevations of ALT greater than 3 times the upper limit of normal occurred in 109 of 2,358 patients in the zileuton group (4.6%) and 5 of 446 patients in the usual care group (1.1%) ($P < 0.001$). Only patients for whom samples were available after day 1 were evaluated. Approximately 70% of ALT increases occurred during the first 3 months of treatment. By the third month, the incidence of ALT elevations in the two treatment groups did not differ significantly. Spontaneous decreases in ALT to baseline or below 2 times the upper limit of normal were observed in 52% of patients who continued to receive zileuton and had ALT elevations between 3 and 5 times the upper limit of normal. All other cases of ALT elevations decreased to these levels within a mean of 4 weeks after cessation of therapy. Patients with ALT elevations were generally asymptomatic and had no associated elevations in alkaline phosphatase or bilirubin. No patient developed jaundice or chronic liver disease, and no deaths were associated with elevated liver enzymes.

Dyspepsia, nausea, and sinusitis were reported by 10% or more of patients in the zileuton group. Dyspepsia was significantly more frequent in the zileuton group than in the usual care group (16.6% versus 9.8%; $P < 0.001$). Nausea also occurred more frequently in the zileuton group (11.8% versus 5.7%; $P < 0.001$). However, sinusitis was more common in the usual care group than in the zileuton group (19.2% versus 13.5%; $P = 0.001$). Rates of infections were similar in both groups (46% in the zileuton group and 49% in the usual care group).

A total of 19.8% of patients in the zileuton group and 2.2% of those in the usual care group withdrew

Figure 2. Mean Improvement from Baseline to Last Visit on the Asthma Symptom Assessment Scale



*$P < 0.05$; †$P < 0.01$; ‡$P < 0.001$

early because of adverse events. The most common adverse events associated with premature withdrawal in the zileuton group and the usual care group were asthma exacerbations (3.7% and 1.0%, respectively), ALT elevations (2.7% and 0.2%), nausea (2.4% and 0%), and dyspepsia (1.6% and 0%). Miscellaneous adverse events accounted for withdrawals by an additional 9.3% of patients treated with zileuton and 1.0% of those receiving usual care. The withdrawal rate for personal and administrative reasons was equivalent in the two groups at 23.7%. Five deaths occurred during the study, none of which was considered related to treatment or associated with abnormal liver function test results.

··· DISCUSSION ···

In this 12-month study, patients treated with zileuton plus usual asthma care had more favorable subjective outcomes and significantly less need for systemic corticosteroid rescue and hospital emergency room visits than did patients who received usual asthma care alone. Patients in both groups had baseline FEV_1 values similar to those observed in previously published double-blind studies.[16,19] However, the patients in this study required more concomitant asthma medications at study entry (only concomitant beta-agonists were permitted in the protocols of the previous trials), indicating that these patients had more severe asthma than did patients in prior studies. Efficacy data from this and previous studies suggest that zileuton is a useful alternative or addition to existing "controller" agents in patients with asthma. With increased knowledge about the pathogenesis of asthma, national and international consensus groups have emphasized the need for chronic therapy with such agents in patients with persistent mild, moderate, or severe asthma.[25,26] Our findings suggest that zileuton has a role in effective maintenance therapy.

The long-term beneficial effects of zileuton on symptoms and clinical outcomes are most likely related to a complex effect of zileuton on the inhibition of leukotrienes in the inflamed asthmatic airway. In addition to their direct bronchoconstrictive effect on the smooth muscle of the airway, the cysteinyl leukotrienes LTC_4, LTD_4, and LTE_4 can alter the microvasculature,[9,10] leading to airway edema, and may increase mucus secretion.[11,12] Another 5-lipoxygenase product, LTB_4, is a potent chemotactic factor for neutrophils and eosinophils.[9,14,15] Zileuton alters the biochemical and inflammatory milieu of the airway to reduce the severity of asthma exacerbations by inhibiting the formation of both cysteinyl leukotrienes and LTB_4.

The higher rate of early withdrawal in the zileuton group because of adverse events may reflect the caution practiced by many clinicians and study subjects when participating in a protocol involving an investigational drug. Because both the investigators and patients were aware of treatment assignment in this open-label study, it was more likely that withdrawal would follow an adverse event in patients treated with zileuton. Since patients in the usual care group continued to receive their standard asthma treatment, discontinuation for adverse events was less likely. When outcome data other than corticosteroid rescue were analyzed, we used the Kaplan-Meier method to take into account the differential withdrawal rate for each group. Furthermore, in two previously reported placebo-controlled trials of zileuton in patients with asthma, the rate of discontinuation for adverse events in the zileuton groups was no higher than that in the placebo groups.[16,19]

Liver function studies were of particular interest in our assessment of adverse events. Overall, 4.6% of patients in the zileuton group had ALT levels that exceeded three times the upper limit of normal. However, these values later decreased to less than twice the upper limit of normal either spontaneously or on cessation of therapy, and no patient developed jaundice or chronic liver disease. The incidence of elevations in ALT was within the ranges reported with several other commonly used drugs (lovastatin, ketoconazole, and diclofenac)[27] and was substantially less than that associated with isoniazid[28] and tacrine.[29] Among patient-reported adverse events, dyspepsia and nausea were significantly more common in patients treated with zileuton, while sinusitis was more common in patients who received usual asthma care. The rate of infections did not differ between the two groups. Thus zileuton, which modulates the immune system, does not appear to increase the risk of infections.

Although our study was a prospective, randomized trial, it had certain limitations, the primary one being its open-label design. The clinical response of patients in the zileuton plus usual care group may have been enhanced because the patients knew they were receiving a new drug. Also, compliance with the therapeutic regimen may have been higher because of the added motivation conferred by participation in a study involving a "breakthrough" medication. On the other hand, the physicians may have been more attentive to adverse events because a new drug was involved, with clinical caution resulting in a higher proportion of premature withdrawals.

The data from this trial indicate that zileuton, when added to an existing therapeutic regimen,

improves asthma control in many patients. This study was not designed to collect economic outcomes data. However, published reports of the high average costs of emergency department visits ($800 to $1,409)[30,31] and of hospitalizations for asthma ($2,550 to $10,998 for 3 days)[30-32] suggest that even modest cost reductions in these areas may significantly reduce the costs of asthma care. We observed a decreased need for systemic corticosteroid rescue, emergency care, hospitalizations, and physician services in patients treated with zileuton. These data suggest that zileuton therapy may reduce healthcare costs associated with acute asthma exacerbations in patients with moderately severe asthma. A formal cost analysis study is required to confirm an economic benefit.

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