

# A Randomized Controlled Trial Comparing Zileuton With Theophylline in Moderate Asthma

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**Background:** Zileuton, a leukotriene pathway inhibitor, was compared with slowly absorbed theophylline in a randomized, double-blind study of patients with chronic asthma. The primary efficacy measure was improvement in forced expiratory volume in 1 second (FEV<sub>1</sub>).

**Methods:** Eligibility criteria included FEV<sub>1</sub> of 40% to 80% of predicted, documented reversibility of airway disease, and age 18 to 60 years. Initially, the theophylline dosage was titrated to achieve trough concentrations of 8 to 15 µg/mL. After washout and 1-week placebo lead-in, patients were randomly assigned to 13 weeks of the appropriate theophylline dose or zileuton, 400 or 600 mg 4 times daily. The FEV<sub>1</sub> was measured before the morning dose at 2-week intervals and serially after the dose on days 36 and 92. Patients kept daily diaries of asthma symptoms, β-agonist usage, and peak expiratory flow rate; on days 36 and 92, they completed quality-of-life questionnaires.

**Results:** Of 471 eligible patients at 38 centers, 377 were

randomly assigned to the study; 313 completed the study. On first-dose administration, all groups showed 11% to 13% improvement in FEV<sub>1</sub> within 30 minutes. Patients who received zileuton, 400 mg, had significantly greater improvement at several points than did theophylline-treated patients. The range of long-term maximum improvement in FEV<sub>1</sub> in the groups was 30% to 34% ( $P=.40$  for zileuton 600 mg;  $P=.90$  for zileuton 400 mg vs theophylline). Initially, the theophylline group improved significantly more in symptom scores, β-agonist usage, and peak expiratory flow rate, but at maximal effect there was no significant difference. All groups showed significant improvement in quality of life. No overall differences were observed between the zileuton dosage groups. Adverse events were comparable in all groups.

**Conclusion:** Zileuton appears as effective and safe as theophylline in patients with chronic asthma.

*Arch Intern Med.* 1998;158:141-148

**F**OR MORE than 50 years, theophylline has been one of the principal drugs used in the treatment of asthma.<sup>1</sup> However, it has a narrow therapeutic range and a wide variety of side effects, so dosage must be individualized and serum trough levels repeatedly monitored.<sup>2</sup> The search for alternative treatments has resulted in the use of inhaled corticosteroids, which reduce the airway inflammation in asthmatic patients. More recently, compounds that inhibit the synthesis of leukotrienes have been studied. Leukotrienes are products of the 5-lipoxygenase pathway of arachidonic acid metabolism, and have been shown to play a prominent role in the pathogenesis of asthma. They cause bronchoconstriction<sup>3,4</sup> and mediate permeability of the microvasculature, mucus secretion, and neutrophil recruitment, all of which have been found to be abnormal in asthmatic patients.<sup>5</sup>

Among the compounds that inhibit the action of 5-lipoxygenase is zileuton, a substituted hydroxylate. Zileuton is the first leukotriene pathway inhibitor to undergo extensive clinical testing. In a controlled clinical trial, zileuton was shown to reduce asthmatic response to cold dry air and decrease the generation of leukotriene B<sub>4</sub> by 74% in treated patients.<sup>6</sup> In another controlled trial in patients with mild to moderate asthma, zileuton significantly improved pulmonary function, and mean urinary leukotriene E<sub>4</sub> levels decreased by up to 39%.<sup>7</sup> This report describes a multicenter trial of the efficacy and safety of zileuton vs theophylline in patients with moderate asthma.

## RESULTS

Of 471 patients who initially enrolled in the study at 38 study sites, 377 entered the double-blind phase of the trial: 129 in the 400-mg zileuton group, 124 in the 600-mg

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## PATIENTS AND METHODS

### PATIENTS

To be eligible for enrollment, patients had to be 18 to 60 years old and could not have smoked for at least 1 year. Enrollment criteria included a history of chronic, stable asthma (mild, moderate, or severe); documented reversibility of airway obstruction (an increase in forced expiratory volume in 1 second [FEV<sub>1</sub>] of  $\geq 15\%$  within 15-30 minutes after  $\beta$ -agonist inhalation); and FEV<sub>1</sub> of 40% to 80% of predicted value 48 hours or more after the last theophylline dose and 8 hours after the last  $\beta$ -agonist use. Exclusion criteria included severe airway obstruction (FEV<sub>1</sub>,  $< 50\%$  of predicted during use of maintenance medication); hospitalization for asthma in the month preceding enrollment or more than once in the previous 6 months; a concurrent major medical illness; or abnormal findings on electrocardiogram. Women had to be sterile or of nonchildbearing potential (ie, practicing effective contraception). The study was approved by the institutional review boards of all participating institutions, and patients provided written informed consent before entering the study.

### STUDY DESIGN

This multicenter trial had a randomized, double-blind, active-controlled parallel-group study design (**Table 1**). The primary outcome variable was the mean percentage change in FEV<sub>1</sub> from baseline to the maximum improvement observed on study days 36 and 92 during postdose pulmonary function testing. Secondary outcome variables included changes in morning and evening peak expiratory flow rate (PEFR),  $\beta$ -agonist use, asthma symptom scores, quality-of-life indexes, and drug tolerability.

Initial screening was followed by an open theophylline titration period lasting from 2 days (minimum) to 71 days (maximum), depending on the time required to achieve a trough serum concentration of 8 to 15  $\mu\text{g/mL}$ . This was followed by a washout period of 1 to 22 days, then a 1-week single-blind placebo lead-in period, at the beginning of which theophylline was discontinued and placebo begun. The double-blind portion of the trial lasted 13 weeks. Detailed criteria for washout periods for antiasthma drugs and other commonly used medications were included in the study protocol.

On the first day of the placebo lead-in period, patients began keeping a daily diary of asthma symptoms,  $\beta$ -agonist usage, and PEFR. They were supplied with a flowmeter (Mini-Wright Peak Flow Meter, Armstrong Medical Supply, Lincolnshire, Ill) and instructed in its use. Patients entered the 13-week double-blind treatment phase of the study if all of the following applied: (1) patient completed titration of theophylline to attain a trough concentration of 8 to 15  $\mu\text{g/mL}$ , as measured before the morning dose of theophylline; (2) compliance in taking the single-blind medication was at least 75% and the patient diary was completed satisfactorily; (3) best FEV<sub>1</sub> values remained between 40% and 80% of that predicted at the end of the placebo lead-in phase; (4) total 7-day score on the Daytime Symptom Index (described

below) was at least 7 of a possible 21 during placebo lead-in; (5) patient used a  $\beta$ -agonist inhaler, albuterol (Ventolin, Allen & Hanburys, Research Triangle Park, NC) on at least 14 occasions during the lead-in period; and (6) pregnancy test results at screening and on double-blind day 1 were negative.

Zileuton, 400 and 600 mg, and matching placebo tablets (Abbott Laboratories, North Chicago, Ill) were supplied as identical-appearing tablets and were dispensed in blister packs containing an 8-day supply of the drug. The packs had labels indicating the day and time for each dose. Theophylline (Slo-Bid, Rhone-Poulenc Rorer Pharmaceuticals, Collegeville, Pa) was supplied as iron-gray, opaque, 100-mg capsules that were repackaged without alteration at Abbott Laboratories. Identical-appearing placebo capsules were supplied by Abbott Laboratories. Both were dispensed in bottles containing a 1-week supply. Thus, each patient received both tablets and capsules. Each patient was given an albuterol inhaler, the only  $\beta$ -agonist allowed during the study. Compliance with the drug regimen was monitored by tablet and capsule counts. To additionally monitor compliance and assess the adequacy of the dose estimated for the run-in period, theophylline levels were also measured during the double-blind phase on days 22, 50, and 92, just before the morning dose of theophylline.

Randomization was performed on day 1 of the double-blind treatment phase, with the use of a randomization scheme designed to ensure the participation of at least 120 patients per treatment group: zileuton, 400 mg 4 times daily; zileuton, 600 mg 4 times daily; or theophylline, 200 to 400 mg twice daily (the latter depending on the dosage necessary to maintain trough theophylline concentrations of 8 to 15  $\mu\text{g/mL}$ ). Randomization was performed separately at each study center by the assignment of sequential patient identification numbers corresponding to numbered sets of double-blind drug supplies. The computer-generated randomization schedule used a block of 6, with each of the 3 treatment groups represented twice in random order within each block. Study drugs were dispensed in boxes, each with 2-part labels. One part remained on the box and included the patient's identification number; the other, with the same information, was removed from the box and attached to the case report form. It contained a sealed scratch-off label containing the study drug assignment.

During the treatment phase, visits to the study center were scheduled for double-blind days 1, 8, 22, 36, 50, 64, and 92. At each visit, pulmonary function was assessed, the patients were examined for vital signs, their diaries were reviewed and new ones dispensed, compliance with study medications was monitored by pill count, and patients were questioned about the use of concomitant medications and the occurrence of any adverse events since the previous visit. Serum theophylline level was measured at 4 visits during the double-blind phase (Table 1), more often if any symptoms or signs suggestive of toxic reactions occurred. Results were not made available to the study centers. Theophylline levels were reviewed by an unblinded, third-party monitor, and physicians were told to adjust dosages accordingly. For zileuton-treated patients, mock theophylline dosage adjustment was performed in a randomly selected subset.

## PULMONARY FUNCTION STUDIES

The mean percentage change from the last FEV<sub>1</sub> measurement in the baseline period (just before the first dose of study drug) to the maximum improvement observed on double-blind days 36 and 92 was determined during a 6-hour period of pulmonary function testing. The test period began at least 8 hours after the last dose of  $\beta$ -agonist and 48 hours after the last dose of antihistamines. The FEV<sub>1</sub> value recorded for each interval was the best of 3 measurements.

Four-hour pulmonary function testing for response to  $\beta$ -agonist inhalation, consisting of 2 puffs of albuterol taken 1 minute apart, was performed on single-blind days 1 and 64. Pulmonary function was measured immediately before and 15 to 20 minutes after inhalation of albuterol. Spirometry machines at each site were to be calibrated daily, and the same machine was used on all study patients at each site. Patients also measured their PEFR each morning and evening and recorded the results in the patient diary.

Each patient maintained a diary that was structured for reporting the observations and self-evaluations described below. Patients were instructed to contact the investigator with any complaints or worsening of asthma symptoms. Acute asthma exacerbation was defined as 1 or more of the following: (1) increase of inhaler use by one third or more, (2) decline of 20% or more in the best of 3 FEV<sub>1</sub> measurements since the previous visit, and (3) decrease in morning PEFR of 25% or more.  $\beta$ -Agonist usage was recorded in the patient's diary (number of occasions used and number of puffs daily).

## SYMPTOM SCALES

In addition, patients rated their symptoms each day by means of an Asthma Symptom Scale developed by investigators at Abbott Laboratories. The scale consisted of 2 indexes: Daytime Symptom Index (all waking hours) and Nocturnal Symptom Index (time in bed sleeping or trying to sleep). Scores ranged from 0 to 3 on each index. On the Daytime Index, 0 indicated no symptoms and unrestricted activity; 3 indicated severe symptoms with little relief from inhaler use, the need for additional medications, and/or a visit to a physician. On the Nocturnal Index, 0 indicated good quality of sleep with no asthma symptoms, and 3 indicated no sleep at all, with use of the inhaler required. Also, the Juniper et al questionnaire<sup>8</sup> was used. This 32-item quality-of-life index was administered at the screening visit and on double-blind days 36 and 92, during scheduled office visits. The self-administered questionnaire covered 4 domains: activities, symptoms, emotional changes, and exposure to potential allergens.

## SAFETY MONITORING

Patients were monitored for adverse events at each visit by review of their diaries and specific questioning during the office interview. They were also instructed to contact their investigator between visits if a severe or worrisome adverse event occurred. Adverse events were reported by the

investigator in detail on case report forms, and patients were followed up until the condition was resolved. The investigator rated both the severity of the adverse event and its relationship to the study drug by means of scales provided in the study protocol. Adverse events were classified as "mild" (transient and easily tolerated), "moderate" (uncomfortable and causing interruption in the patient's usual activities), or "severe" (causing considerable interference in usual activities and possibly incapacitating or life threatening). Adverse events were also categorized by their relationship to study drug administration. "Probably related" described an event with a temporal relationship to study drug administration and no other apparent cause. "Possibly related" described an event with a temporal relationship to study drug administration but for which another possible cause was noted. "No relationship" described an adverse event for which definite evidence was available for another cause. Follow-up on adverse events continued after termination of the study until a resolution was reached.

Vital signs were monitored at every visit. A 12-lead electrocardiogram was made at initial screening and on double-blind days 8, 36, and 92 (the last day of the study). Clinical laboratory tests were performed at initial screening, on day 1 of placebo lead-in, and on double-blind treatment days 1, 22, 50, and 92. Complete batteries of hematologic tests and blood chemistry evaluations were performed, as were urinalyses.

## STATISTICAL ANALYSIS

All analyses were performed with the intent-to-treat principle. Data from the pulmonary tests performed before the morning dose at a particular visit were used for analysis of morning FEV<sub>1</sub> regardless of the time since the most recent double-blind drug dose. All pulmonary function tests were performed in triplicate, with the highest value used for statistical analysis. The values for data recorded in patients' diaries were averaged over 2-week intervals. Data for  $\beta$ -agonist usage as recorded in the patients' diaries were statistically analyzed in 2-week intervals by carry-forward 2-way analysis of variance. The baseline for diary variables was taken as the mean of all values recorded during the placebo lead-in week. Results were based on 2-way analysis of variance with effects for centers, treatments, and center-by-treatment interaction. Values were "carried forward" for patients who were discontinued prematurely from the study. The percentages of patients with an increase of at least 15% in pulmonary function were compared between treatment groups by Cochran-Mantel-Haenszel methods, with study site as the stratification variable.

All *P* values were based on 2-tailed tests, with *P*  $\leq$  .05 considered to be statistically significant. When patients left the study prematurely, their most recent values were carried forward to the subsequent time points. It was calculated that a sample size of approximately 120 patients per treatment group would be required to achieve 80% power at the 2-sided .05 level for a pairwise comparison between treatment groups, assuming a treatment difference of 0.175 L for the expected change from baseline in the morning predose measurement of FEV<sub>1</sub>.

**Table 1. Study Schematic**

	Screen	Titration	Placebo Lead-in*	Day 1 (wk 1)	Day 8 (wk 2)	Day 22 (wk 4)	Day 36 (wk 6)	Day 50 (wk 8)	Day 64 (wk 10)	Day 92 (wk 14)
Physical examination	X			X			X			X
Electrocardiogram†	X				X		X			X
Vital signs	X	X	X	X	X	X	X	X	X	X
Pulmonary function testing‡	X		X	X	X	X	X	X	X§	X
β-Agonist inhalation test	X		X						X	
Quality-of-life questionnaire	X						X			X
Laboratory tests	X		X	X		X		X		X
Theophylline level	X	X	X	X		X		X		X
Pregnancy test	X		X	X		X		X		X
Adverse event		X	X	X	X	X	X	X	X	X
Concomitant medications		X	X	X	X	X	X	X	X	X
Dispense diary, medications			X	X	X	X	X	X	X	X
Inventory study medications		X	X	X	X	X	X	X	X	X

\*Placebo lead-in period was single blind and lasted 7 days. Randomization was performed on study day 1.

†If initial findings on electrocardiogram were abnormal, it was repeated.

‡Testing was done just before the morning dose at all visits. On days 1, 36, and 92, postdose testing was done at 30, 60, 120, 180, 240, 300, and 360 minutes. Measurements were also done at these intervals after β-agonist usage at the start of placebo lead-in and on day 64, but only through 240 minutes.

§Testing was also done before β-agonist use.

||Results of urine pregnancy tests were confirmed by serum testing.

group, and 124 in the theophylline group. The groups were comparable in age, with group means ranging from 34.6 to 36.1 years. The percentages of women in the 3 groups ranged from 56% to 61%. The racial distribution was 6% to 10% African American, 85% to 91% white, and 2% to 5% other racial groups. Nonsmokers comprised 77% of each group; the remaining 23% were ex-smokers (for ≥1 year). Eleven percent of patients in the trial were ex-smokers older than 40 years; they were evenly divided among the 3 treatment groups. The mean (± SEM) percentages of predicted FEV<sub>1</sub> values in the 3 treatment groups were 59.6%±1.24% in the theophylline group, 59.2%±1.25% in the 400-mg zileuton group, and 61.7%±1.10% in the 600-mg zileuton group. Thirty percent of the patients enrolled had mild asthma, with baseline FEV<sub>1</sub> values greater than 70% of predicted; 44% had moderate asthma (50%-70% of predicted FEV<sub>1</sub>); and 26% had severe asthma (≤50% of predicted FEV<sub>1</sub>). The asthma histories were similar in the 3 groups (patients with allergic rhinitis, those with asthma symptoms worsened by various stimuli, time since asthma diagnosis, and number of acute exacerbations requiring intervention in the previous year). However, the 3 groups differed significantly in the proportions of patients who had used 1 or more asthma medications besides theophylline and albuterol in the 6 months preceding the study ( $P=.008$ ,  $\chi^2$  test). The difference was caused primarily by the higher proportion of patients in the 400-mg zileuton group taking an oral β-agonist or methylxanthines (14% and 50%, respectively) than in the 600-mg zileuton group (10% and 35%) and the theophylline group (4% and 37%). Antihistamines were used by 111 patients (29%) at some time during the trial.

Of the 377 patients who entered the double-blind treatment phase, 313 (83%) completed the full 13 weeks. The dropout rates were similar in the 3 groups: 19 in the 400-mg zileuton group (n=12 because of lack of drug efficacy and/or an adverse event), 21 in the 600-mg group

(n=10 for these reasons), and 24 in the theophylline group (n=15 for these reasons).

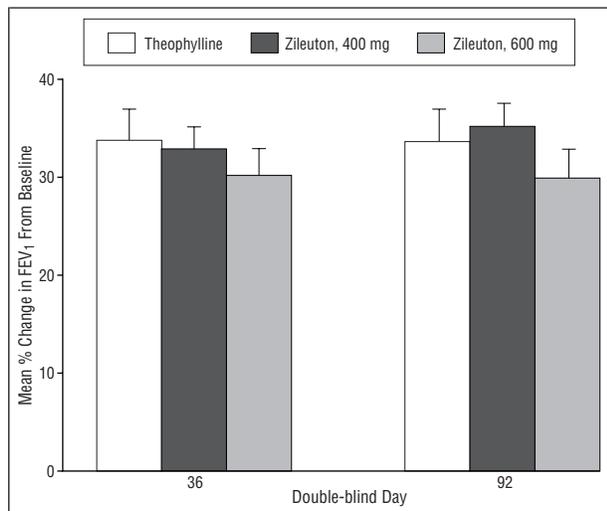
#### PULMONARY FUNCTION TESTS

The FEV<sub>1</sub> values before the morning dose of study drug (trough values) during scheduled visits improved significantly over baseline values in all groups. These improvements persisted throughout the trial. On double-blind day 92, an improvement of at least 15% in mean trough values for FEV<sub>1</sub> was observed between baseline and the morning predosing value in 43% of the 400-mg zileuton group, 41% of the 600-mg zileuton group (95% confidence limits, 32%, 50%), and 46% of the theophylline group (95% confidence limits, 37%, 55%). In addition, maximum FEV<sub>1</sub> values were determined during the serial 6-hour measurements (0- to 6-hour maximum) on days 36 and 92 (**Table 2**); at both visits, no significant differences were found between treatment groups for mean percentage change from double-blind baseline values in the 0- to 6-hour maximum FEV<sub>1</sub> (**Figure 1**). **Figure 2** displays the serial 6-hour measurements on day 36. No significant differences were found between treatment groups in mean percentage change from double-blind baseline values to any post-dose time point. Differences in mean improvement in FEV<sub>1</sub> were significantly in favor of theophylline only on the predose measurement; once the morning study drug dose had been administered, there was no statistically significant difference between the theophylline group and the 2 zileuton groups. While the theophylline group had significantly greater mean improvement in morning predose FEV<sub>1</sub> levels than either of the zileuton groups, this finding may be attributable to the substantially different half-lives of the drugs. There were no statistically significant differences in the mean percentage change from baseline in the 0- to 6-hour maximum FEV<sub>1</sub> among the 3 groups on days 36 and 92 (**Figure 1**).

**Table 2. Maximum Improvements in FEV<sub>1</sub> From Baseline to Days 36 and 92\***

	n	FEV <sub>1</sub> , L		Mean Maximum % Change	Difference, Zileuton–Theophylline, %	95% Confidence Limits
		Baseline Mean	6-h Maximum			
Day 36						
Zileuton, 400 mg	116	2.17	2.81	32.9	-0.9	-8.6, +6.9
Zileuton, 600 mg	108	2.23	2.85	30.2	-3.5	-11.5, +4.6
Theophylline	105	2.11	2.75	33.7	...	...
Day 92						
Zileuton, 400 mg	116	2.17	2.83	34.3	+0.6	-7.4, +8.6
Zileuton, 600 mg	108	2.23	2.86	30.2	-3.6	-11.8, +4.6
Theophylline	105	2.11	2.73	33.7	...	...

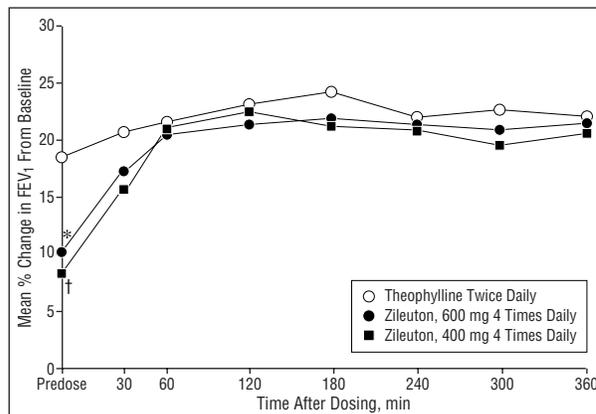
\*Pulmonary function testing was performed during a 6-hour period on both days. FEV<sub>1</sub> indicates forced expiratory volume in 1 second.



**Figure 1.** Change in maximum forced expiratory volume in 1 second (FEV<sub>1</sub>) (mean±SEM) observed between pretreatment and 6 hours after dosing on study days 36 and 92. There were 105 patients in the theophylline group, 116 in the 400-mg zileuton group, and 108 in the 600-mg zileuton group.

Within 30 minutes after administration of the first dose of study drug on day 1 of the double-blind treatment phase, the FEV<sub>1</sub> values in all groups increased by more than 10%, with additional increases throughout the first 120 minutes of spirometry. The first-dose effect persisted through the remainder of the 6 hours (**Figure 3**). The 400-mg zileuton group had significantly greater improvement than the theophylline group at 3 measurement points—2, 5, and 6 hours after dosing.

Analysis of PEFR data, which were recorded in the patients' diaries and averaged over 2-week intervals for the double-blind phase, showed that all groups experienced small but consistent improvement over baseline in both morning and evening PEFRs, starting with the first 2-week interval. Overall mean changes in evening PEFRs ranged from around 5% for the zileuton groups and 7% for the theophylline group. Morning PEFR improvements were higher, being about 8%, 6%, and 12% in the 400-mg zileuton, 600-mg zileuton, and theophylline groups, respectively. In the last measurement period of the double-blind phase, the theophylline group had an improvement in morning PEFR 8.7 L greater than that in the 400-mg zileuton group and 14.3 L greater than that in the 600-mg group, but the differences were not



**Figure 2.** Long-term improvement in forced expiratory volume in 1 second (FEV<sub>1</sub>) between the predose, baseline value on study day 1 and values measured before dosing and up to 6 hours after dosing on study day 36. Note that the data are similar to those observed during the same postdose interval on study day 1 (see Figure 3). Asterisk indicates a significant change vs theophylline ( $P \leq .05$ ; dagger, significant change vs theophylline ( $P \leq .01$ )).

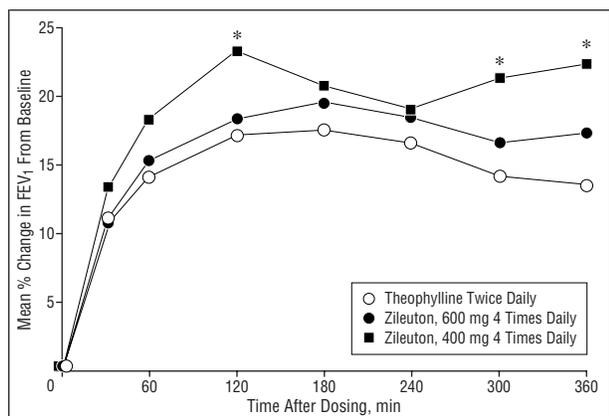
statistically significant. The 95% confidence limits around the latter difference were -33.5 and 4.9. The differences between groups in mean morning change were not statistically significant after the day 58 to 85 interval. The mean evening change was somewhat greater in the theophylline group than in either zileuton group, but the difference was statistically significant only for the first 2-week comparison with the 600-mg zileuton group.

At baseline and on day 64 of the double-blind phase, a  $\beta$ -agonist inhalation test was administered. The response was less on the second test in all 3 treatment groups, at which time the mean maximum percentage change in FEV<sub>1</sub> after  $\beta$ -agonist inhalation was 30% in the 400-mg zileuton group, 21% in the 600-mg zileuton group, and 23% in the theophylline group. The difference between theophylline and 400-mg zileuton on day 64 was significant ( $P = .01$ ).

When a subset analysis was performed, from which ex-smokers older than 40 years were removed from analyses, no differences in outcomes were noted.

#### EFFECT ON EOSINOPHILS

The mean eosinophil counts of patients in all groups decreased from baseline during the double-blind phase. The



**Figure 3.** Changes in forced expiratory volume in 1 second ( $FEV_1$ ) from the predose, baseline value on study day 1 to the values measured up to 6 hours thereafter. Asterisks indicate a statistically significant difference ( $P \leq .05$ ) between the 400-mg zileuton group and the theophylline group.

baseline mean was  $0.361 \times 10^9/L$  in the 400-mg zileuton group,  $0.301 \times 10^9/L$  in the 600-mg group, and  $0.313 \times 10^9/L$  in the theophylline group. The mean changes from baseline to the final visit were  $-0.076$ ,  $-0.032$ , and  $-0.005 \times 10^9/L$ , respectively. The difference between the 400-mg zileuton and theophylline groups was significant ( $P = .03$ ). Other results of laboratory tests indicated no clinically significant findings.

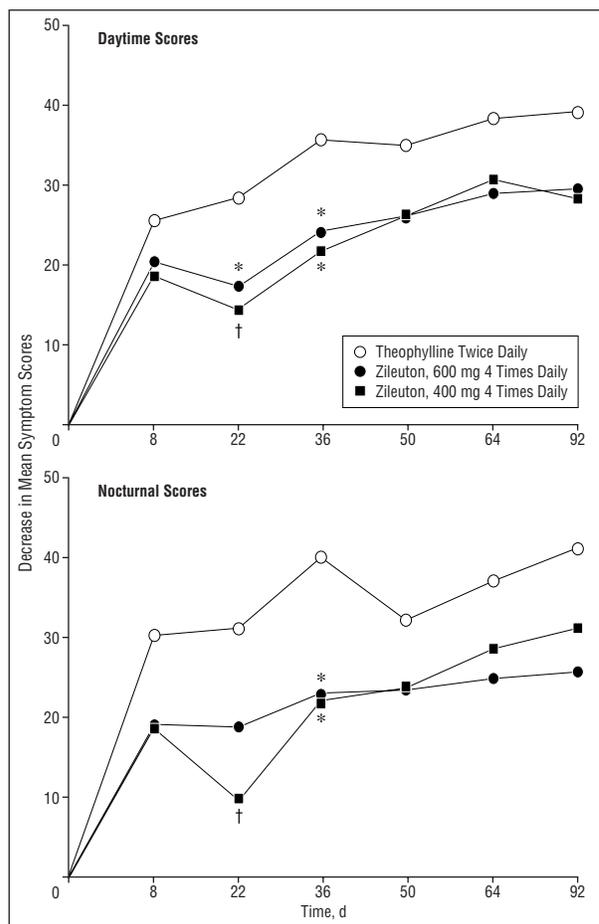
#### THEOPHYLLINE LEVELS

Monitoring of theophylline levels on days 22, 50, and 92 showed that 87 patients receiving theophylline did not achieve a serum concentration within the target range on at least 1 occasion. On day 22, 66 patients were below the target range; on days 50, 39, and 92, there were 29 below that range. Four patients had theophylline levels greater than  $20 \mu g$  at 1 time during the study; they were monitored closely, and 2 experienced adverse effects (listed below).

#### ASTHMA SYMPTOMS AND $\beta$ -AGONIST USE

All 3 treatment groups demonstrated consistent improvement in both daytime and nocturnal symptom indexes (**Figure 4**). At 2 points, the theophylline group showed significantly more improvement than 1 or both of the zileuton groups, both in daytime and nocturnal symptoms. On the final determination, however (which was generally the point of maximum improvement), there was no statistically significant difference among the groups. On the quality-of-life questionnaire administered at 2 visits, all groups showed significant improvement, with no significant differences among groups on any of the 4 domains (activity, symptoms, emotional changes, and exposure to allergens).

From the first 2 weeks onward, use of the  $\beta$ -agonist inhaler declined significantly in all groups. In the 400-mg zileuton group, baseline mean was 7.2 puffs per day; in the 600-mg zileuton group, it was 6.1 puffs per day; and in the theophylline group, it was 6.4 puffs per day. At the end of the study, respective means were 5.8, 4.6, and 4.4 puffs per day. None of the comparisons among treatment



**Figure 4.** Changes in scores on the Daytime and Nocturnal Symptom Indexes from baseline to study's end. Baseline values were determined from patients' diaries during single-blind lead-in. Asterisk indicates  $P \leq .05$  for theophylline vs zileuton; dagger,  $P \leq .001$ .

groups for reductions in usage was significant: at the final visit, confidence limits around the difference between zileuton, 600 mg, and theophylline were  $-0.47$  and  $1.35$ . However, during the first 10 weeks of the study, the theophylline group had intermittent reductions in puff usage significantly greater than those in 1 or both zileuton groups. Forty-five patients required the use of 1 or more courses of oral or injected corticosteroids because of worsening of asthma. No significant differences were found in the proportions of patients requiring corticosteroid rescue among the 3 treatment groups.

#### ADVERSE EVENTS

Of the 377 patients randomly assigned to treatment, 121 in the 400-mg zileuton group, 117 in the 600-mg zileuton group, and 110 in the theophylline group reported 1 or more treatment-emergent adverse events. Adverse events (excluding episodes of asthma exacerbation) reported by 5% or more of the patients are listed in **Table 3**. Approximately three fourths of the patients among all 3 treatment groups reported 1 or more episodes of acute worsening of asthma symptoms (asthma exacerbation) at some point in the 13-week double-blind phase. Thirty-two patients left the study prematurely at least in part

because of treatment-emergent adverse events that had their onset during the double-blind portion of the study or within 14 days after discontinuation of drug treatment. Eighteen of the 32 patients left at least in part because of exacerbation of their asthma. Eleven of the 32 patients had adverse events leading to termination that were considered probably or possibly related to study drug administration: 3 in the 400-mg zileuton group (insomnia in 1, elevated liver enzyme levels in 2), 3 in the 600-mg zileuton group (dyspepsia in 1, elevated liver enzyme levels in 2), and 5 in the theophylline group (1 case each of vomiting, nausea with palpitations, dyspepsia, upper respiratory tract infection, and insomnia with nervousness). All patients with adverse events were followed up to a satisfactory resolution of the events.

Overall, 25 patients had elevation of liver enzyme levels above twice the upper limit of normal: 8 in the 400-mg zileuton group, 9 in the 600-mg zileuton group, and 8 in the theophylline group. In the 400-mg zileuton group, 6 patients had mild abnormality (<3 times the upper limit of normal), 1 had moderate abnormality (3-8 times the upper limit), and 1 had severe abnormality (>8 times the upper limit). In the 600-mg zileuton group, comparable numbers were 5, 2, and 2, respectively, and in the theophylline group the numbers were 3, 4, and 1, respectively. Patients were followed up until assay values declined to normal, nearly normal, or baseline levels. No patient had overt hepatotoxic reactions, ie, no specific symptoms (clinical jaundice) were associated with observed biochemical changes.

#### COMMENT

In this 13-week multicenter study of people with moderate asthma, patients in all 3 treatment groups showed significant improvement in lung function, as well as reduced use of  $\beta$ -agonists and improved symptom profiles over the course of the study. In the acute first-day dosing situation, zileuton in both doses showed an acute bronchodilatory effect that was greater than that observed with theophylline. The results in the theophylline group were better in a long-term situation, although the gap between treatment groups narrowed toward the end of the study because of steady improvement in the zileuton groups. The differences in both directions achieved conventional statistical significance at only a few points; for most comparisons, no statistically significant differences were observed between the 3 treatments, and the sizes of the differences between treatments were small. Possibly the most telling measure of improvement (and of comparison of interventions) was the proportion of patients who achieved a clinically relevant improvement of at least 15% in FEV<sub>1</sub> on day 92. As reported, these proportions lay within a narrow range: 43% and 41% in the 400-mg and 600-mg zileuton groups, respectively, and 46% in the theophylline group (not statistically significantly different). Zileuton appeared to have the same efficacy in older patients with significant smoking histories as in the overall patient population; when ex-smokers older than 40 years were excluded from analyses, the outcomes were similar and did not alter interpretation of the study. In

**Table 3. Adverse Events Reported by 5% or More of Patients in Any Treatment Group**

Adverse Event*	Zileuton, No. (%)		Theophylline, No. (%)
	400 mg	600 mg	
Back pain	5 (4)	8 (7)	9 (7)
Dyspepsia	6 (5)	9 (7)	12 (10)
Influenza syndrome	11 (9)	8 (7)	8 (7)
Headache	35 (27)	24 (19)	36 (29)
Infection	30 (23)	28 (23)	26 (21)
Insomnia	7 (5)	4 (3)	3 (2)
Myalgia	11 (9)	7 (6)	5 (4)
Nausea	6 (5)	8 (7)	17 (14)
Pain	6 (5)	8 (7)	6 (5)
Pharyngitis	13 (10)	8 (7)	7 (6)
Sinusitis	8 (6)	3 (2)	7 (6)

\*This list does not include episodes of acute exacerbation of asthma. Adverse events were categorized by Coding Symbols for Thesaurus of Adverse Reaction Terms.

addition, when FEV<sub>1</sub> data were analyzed with exclusion of patients who took antihistamines at any point during the trial (n=111, 29%) to evaluate any favorable or unfavorable impact on results, no differences in outcomes were observed.

A feature in the design of the trial that may have affected the contrast between the zileuton and theophylline groups was the difference in approaches to setting dosages. Theophylline dosage was individualized by titration before randomization, while zileuton dosages were set arbitrarily at either 1.6 or 2.4 g/d (ie, 400 or 600 mg $\times$ 4). This could have optimized the effectiveness of theophylline in comparison with zileuton, maximizing the value of the theophylline-treated group as a positive control group.

The superiority of long-acting theophylline in the predose FEV<sub>1</sub> measurement of the day (see Figure 3) was not surprising. The last dose of the day was taken at bedtime, and this form of theophylline is a long-acting compound with a half-life of up to 15 hours and a time to maximum concentration of 7 to 9.8 hours.<sup>9</sup> In contrast, zileuton has a half-life of 2.5 hours and a mean time to maximum concentration of 1.7 hours. Therefore, comparisons of FEV<sub>1</sub> values were made between 0 and 6 hours after dosing, when levels were optimum for both drugs. Within 30 minutes after the morning dose, the FEV<sub>1</sub> values in the zileuton groups were approximately equal to those in the theophylline group.

A striking finding in the zileuton-treated groups was marked eosinopenia. Eosinophilia is a yardstick of asthma severity,<sup>10</sup> and eosinopenia is useful as a measure of the anti-inflammatory effectiveness of corticosteroid therapy.<sup>11</sup> Horn et al<sup>10</sup> reported that blood eosinophil counts measured in a group of asthmatic patients paralleled disease severity. Total eosinophil counts were inversely related to pulmonary function. The degree of eosinophilia was associated with increasing airflow obstruction as measured by changes in midexpiratory flow rates, first recoil forced expiratory volume, specific airway conductance, and lung volumes.

Asthma therapy produces significant decreases in total eosinophil counts and in levels of both eosinophil cationic protein and eosinophil peroxidase, paralleled by improved expiratory flow rates.<sup>12,13</sup> Corticosteroids cause eosinopenia, and the degree of eosinopenia is correlated with clinical improvement in asthma.<sup>10</sup> The risk of relapse in asthma may be related to blood eosinophil counts.<sup>14</sup> Failure of eosinopenia to emerge reflects ongoing tissue inflammation, for which most clinicians prescribe corticosteroid therapy. The combined bronchodilator and eosinopenia effects seen with zileuton suggest a multiplicity of pharmacological action beneficial for the average asthmatic patient.

The finding that results in the 400-mg zileuton group were frequently better than those in the 600-mg zileuton group cannot be readily explained except by random variation. Although this study does suggest that the 1.6-g daily dose of zileuton may be sufficient for some patients, results from placebo-controlled studies have previously shown the higher dose of zileuton to have greater efficacy than the lower one.<sup>15</sup> Those receiving the 2.4-g dosage did not experience an increase of adverse events at this higher dose.

Adverse events, excluding episodes of asthma exacerbation, occurred in similar percentages in the groups: 73% in the 600-mg zileuton group, 74% in the 400-mg zileuton group, and 75% in the theophylline group. Six patients (2 in each treatment group, including theophylline) left the study prematurely because of liver function abnormalities. The proportion of patients leaving the study because of abnormalities in liver enzyme levels was small and was similar in all 3 treatment groups; also, no treatment-emergent hepatotoxic reactions were observed.

The PEFr data recorded by patients twice daily at home were consistent with FEV<sub>1</sub> findings. Improvements over baseline values in the 3 groups averaged between 5% and 9% in the morning measurements and 4% to 6% in the evening measurements. Similar degrees of improvement have been documented in previous studies of zileuton (5%-10% in the mornings and 5%-7% in the evenings).<sup>15</sup> All treatment groups showed substantial decreases in the use of the  $\beta$ -agonist inhaler. Also, the percentages of patients with acute exacerbations of asthma, requiring oral or intravenous administration of corticosteroids, were similar in the 3 groups (11%-15%).

Zileuton is as effective as theophylline in the treatment of patients with moderate asthma, without the development of tachyphylaxis or the need for blood level therapeutic drug monitoring. Further studies are needed to investigate the reasons for its somewhat more modest performance in reducing symptom scores (without the same effect on quality-of-life measures). More data are also needed to determine the best timing of zileuton administration and optimal fine-tuning of the dosage.

Accepted for publication May 29, 1997.

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