

Benefits from Adding the 5-Lipoxygenase Inhibitor Zileuton to Conventional Therapy in Aspirin-intolerant Asthmatics

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From bronchoprovocation studies and investigations of the acute effects of drugs that inhibit leukotrienes (LT), the hypothesis has emerged that leukotrienes are important mediators of airway obstruction and other symptoms in aspirin-intolerant asthma (AIA). However, it has yet not been shown if subjects with AIA respond favorably to clinical treatment with leukotriene inhibitors. Therefore, in a double-blind placebo-controlled crossover study, we examined the effects of 6 wk of treatment with the leukotriene-pathway inhibitor zileuton (600 mg, four times daily) in 40 patients with well-characterized AIA. The treatment was added to existing therapy, which included medium to high doses of inhaled (average daily dose 1,030 μ g of beclomethasone or budesonide) or oral glucocorticosteroids (4 to 25 mg/d) for all but one of the patients. On top of this treated baseline, there were no significant effects of adding placebo, indicating that their asthma was kept relatively stable. However, there was an acute and chronic improvement in pulmonary function after treatment with zileuton, expressed both as increased FEV₁ from baseline compared with placebo, and higher morning and evening peak expiratory flow rate (PEFR) values on zileuton treatment compared with placebo. The improvements occurred despite lower use of rescue bronchodilator with zileuton. Zileuton also diminished nasal dysfunction, which is one of the cardinal signs of AIA. There was a remarkable return of smell, less rhinorrhea, and a trend for less stuffiness and higher nasal inspiratory flow during treatment with zileuton. Zileuton caused a small but distinct reduction of bronchial hyperresponsiveness to histamine and inhibited aspirin-induced bronchoconstriction. Zileuton inhibited urinary excretion of LTE₄ but did not change airway reactivity to inhaled LTD₄, supporting that zileuton specifically inhibited leukotriene biosynthesis. The findings indicate that leukotrienes are important mediators of persistent airway obstruction and chronic nasal dysfunction in AIA. The study also suggests that addition of a leukotriene pathway inhibitor such as zileuton may bring about greater control of asthma than what is achieved by treatment with medium to high doses of glucocorticosteroids alone. Dahlén B, Nizankowska E, Szczeklik A, Zetterström O, Bochenek G, Kumlin M, Mastalerz L, Pinis G, Swanson LJ, Boodhoo TI, Wright S, Dubé LM, Dahlén S-E. Benefits from adding the 5-lipoxygenase inhibitor zileuton to conventional therapy in aspirin-intolerant asthmatics.

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Intolerance to aspirin and related nonsteroidal anti-inflammatory drugs (NSAIDs) is a significant clinical problem among asthmatics (1, 2). Aspirin-intolerant asthmatics often suffer from a particularly severe form of asthma (2). Characteristically, in adult life the subjects develop chronic rhinosinusitis and recurrent polyposis, asthma, and intolerance to aspirin-like drugs (2). Ingestion of NSAIDs precipitates acute bronchoconstriction, which often is accompanied by extrapulmonary symptoms such as rhinorrhea, conjunctivitis, and skin rash, and occasionally nausea and vomiting (2). In severe cases circulatory shock and death may occur (2). It has been

established that all NSAIDs that inhibit the formation of prostaglandins and thromboxane induce the intolerance reaction in susceptible individuals (3), but it remains a mystery why only certain asthmatics are affected and the precise mechanism behind the reactions is unknown. However, in recent years observations have accumulated to suggest that leukotrienes have a central role in aspirin-intolerant asthma (AIA).

The leukotrienes (LT) are a group of mediators generated by 5-lipoxygenation of arachidonic acid when inflammatory cells such as mast cells and eosinophils are activated (4). The cysteinyl-leukotrienes (LTC₄, LTD₄, and LTE₄) are potent inducers of airway obstruction, causing bronchoconstriction, plasma exudation, mucus secretion, and activation of eosinophils (4–7). The chemoattractant LTB₄, which is the main 5-lipoxygenase product in polymorphonuclear leukocytes, is also able to cause stimulation and recruitment of inflammatory cells (4). Antileukotriene drugs have recently been introduced as new treatment for asthma because treatment trials have established therapeutically beneficial effects (4).

Different antileukotrienes have been shown to inhibit bronchoconstriction induced in aspirin-intolerant asthmatics by inhaled (8, 9) or oral challenge (10–12) with aspirin or other NSAIDs, supporting the hypothesis that leukotrienes mediate the intolerance reaction to NSAIDs. There are several observations suggesting that leukotrienes mediate spontaneous airflow obstruction in aspirin-intolerant asthmatics. Thus, aspirin-intolerant asthmatics have a basal overproduction of cysteinyl-leukotrienes, as demonstrated by increased baseline urinary excretion of LTE₄ (8, 13, 14). Aspirin-intolerant asthmatics may also be particularly sensitive to the bronchoconstrictive effects of inhaled leukotrienes (15). Furthermore, acute administration of an antileukotriene caused prompt bronchodilation in aspirin-intolerant asthmatics (16), and the improvement in pulmonary function correlated with the sensitivity to aspirin (16).

In view of these indications of a central role for leukotrienes in this syndrome, we decided to study the effect of treating aspirin-intolerant asthmatics with the 5-lipoxygenase inhibitor zileuton (in U.S. registered as Zylflo) (17). The effect of leukotriene pathway inhibition has previously not been investigated in a trial comprising only this particular patient population. From the hospital registers of the two collaborating centers (Stockholm and Cracow), a group of 40 well-characterized aspirin-intolerant asthmatics was selected. The patients suffered from long-standing asthma, but were considered to be relatively well-controlled on conventional treatment which for all but one subject consisted of medium to high doses of inhaled or oral glucocorticosteroids. To this baseline, zileuton (600 mg, four times daily) or placebo was added for 6 wk in a double-blind, two-period crossover design with 4 wk washout in between.

Because nasal application of leukotrienes induces swelling of the nasal mucosa (18, 19), it was hypothesized that leukotrienes may contribute to the chronic nasal problems in this group of asthmatics. Observations during a previous study of the acute influence of a leukotriene antagonist on aspirin-intolerant asthmatics (16) provided circumstantial support of this hypothesis. Therefore, in addition to assessment of drug effects on asthma-related variables, the subjects' nasal function was evaluated by different means.

METHODS

Patients

Twenty Polish and 20 Swedish subjects (28 females, 12 males) were recruited from each center's registers of aspirin-intolerant asthmatics, all showing the typical triad of chronic asthma, chronic nasal mucosal disease, and NSAID intolerance in combination (Table 1). The diag-

TABLE 1
PATIENT CHARACTERISTICS

	Mean ± SE	
Age, yr	44.1 ± 1.7	
Height, cm	167 ± 1.4	
Weight, kg	68.2 ± 2.3	
FEV ₁ , L	2.57 ± 0.13	
FEV ₁ , % of predicted	80.4 ± 3.4	
Histamine PD ₂₀ , µg	63.4 (51.9–77.5)*	
Nasal symptoms (0–10) [†]		
Loss of smell	6.9 ± 0.65	
Rhinorrhea	2.7 ± 0.47	
Congestion	3.3 ± 0.42	
	(n)	(%)
Duration of asthma		
0–5 yr	10	25
5–15 yr	21	52.5
> 15 yr	9	22.5

* Geometric mean.

[†] 0 = none, 10 = most severe on a visual analog scale.

nosis of aspirin intolerance was documented by previous provocations with oral and/or inhaled aspirin on several occasions, and with falls in FEV₁ of at least 20% as criterion for significant airway response. Three cases were admitted in the study on the basis of a long-standing clinical history of aspirin-intolerant asthma including emergency room visits after NSAID ingestion. In addition, the Polish subjects underwent a screening lysine–aspirin provocation prior to the study start to assess their current sensitivity to aspirin. For inclusion at least 12% reversibility after beta-agonist inhalation was required. The majority (75%) had suffered from asthma for more than 5 yr, and nine subjects (23%) for more than 15 yr (Table 1). All patients but one were receiving concomitant treatment with inhaled (38 subjects) and/or oral (14 subjects) glucocorticosteroids (Table 2), whereas long-acting beta-agonists, long-acting antihistamines, or theophylline were not used throughout the study. At inclusion, the patient's medications had remained unchanged for at least 4 wk.

Study Design

Approval from the ethics committees and medical product agencies were obtained at each center, and the subjects gave informed consent. The study was a 16-wk double-blind, placebo-controlled trial with a randomized crossover design and 4-wk washout between the 6-wk study periods (Figure 1). Zileuton (600 mg) or matching placebo were

TABLE 2
CONCOMITANT THERAPY

Medication	(n)	(%)	Dose/day* (mean ± SD)	Range
Short-acting inhaled beta-agonist	40	100	3.31 ± 3.05 puffs [†]	0–11.3
Inhaled corticosteroids (ICS) [‡]	38	95	1,030 ± 540 µg	300–2,400
Oral corticosteroids (OCS) [§]	14	35	11.2 ± 6.4 mg	4–25
Nasal corticosteroids (NCS) [‡]	21	53	190 ± 86 µg	50–400
Inhaled cromolyn	6	15	113 ± 33 mg	60–160
Corticosteroid treatment				
ICS only	7			
ICS + NCS	18			
OCS only	1			
OCS + ICS	10			
OCS + ICS + NCS	3			

* Mean within group receiving respective treatment.

[†] Calculated from individual means during the first 2 wk of placebo treatment. Salbutamol MDI, 100 µg/dose.

[‡] Budesonide or beclomethasone.

[§] Prednisone.

given orally as add-on treatment four times daily. The patients visited the clinic 1 wk before each treatment period, and on the first day, after 2 and 4 wk, and on the last day of each 6-wk treatment period. All visits were scheduled in the morning for each patient at the same time of the day throughout the study.

The patients were not allowed to take short-acting beta-agonist for at least 8 hr before each visit. Baseline pulmonary function was measured as FEV₁ using standard spirometers (Vitalograph MDI Compact; Förbandsmaterial, Stockholm, Sweden; Pneumoscreen; E. Jaeger, Wuerzburg, Germany), and the best of three efforts was recorded. In addition, during the first day of each period, FEV₁ was measured prior to and every hour after ingestion of the first tablet up to 4 h postdose.

Additionally, peak expiratory flow rates (PEFRs) were measured (mini-Wright; Clement Clarke, Harlow, UK) twice daily in triplicate and the best effort recorded in diaries supplied to the patients. Measurements were performed before use of beta-agonist; in the morning immediately prior to the first daily dose of study drug, and in the afternoon before the third dose of study drug. Daily beta-agonist use (number of puffs from a standard Salbutamol MDI, Glaxo Plc, Middlesex, UK; 100 µg per puff, supplied to all patients) and symptom assessments were also recorded by the patients. The severity of daytime symptoms was evaluated each evening using a subjective symptom score (0–3; none to severe). Nocuturnal symptom scores were similarly recorded (0–3; slept well to awake all night) in the mornings.

The diary cards also included daily morning and evening measurement of peak nasal inspiratory flow rate (PNIFR, Youlten Peak Nasal Inspiratory Flow Meter; Airmed Ltd, UK), where the best of three efforts was recorded immediately after the determination of PEFR. In addition, at each clinic visit during the treatment periods, the occurrence of three different nasal symptoms in the preceding 2-wk period was assessed using a visual analogue scale (VAS). The evaluation was made on a scale from zero (no symptoms) to 10 (severe symptoms) and included loss of smell, rhinorrhea, and nasal congestion. Accordingly, the recordings on Day 1 reflected baseline symptoms in the fortnight immediately before each study period.

The patients were considered to have had an asthma exacerbation if physicians decided on clinical grounds to give a 1-wk course of oral glucocorticosteroids, or to increase the dose of oral or inhaled glucocorticosteroids for 1 wk.

Bronchoprovocation Procedures

Bronchoprovocations with lysine–aspirin were conducted in Poland, and LTD₄ bronchoprovocations in Sweden. Histamine challenges were performed at both centers. The bronchoprovocations were performed in subjects whose baseline FEV₁ was greater than 60% of predicted normal. It was possible to assess sensitivity to inhaled aspirin in

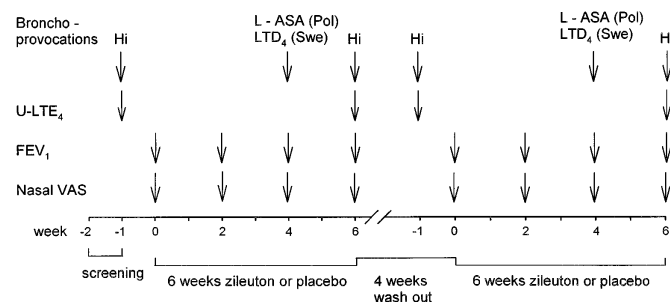


Figure 1. Study scheme showing the clinic visits. The study was a 16-wk double-blind, placebo-controlled trial with a randomized crossover design and a 4-wk washout between the 6-wk treatment periods. The patients visited the clinic 1 wk before each treatment period, on the first day, after 2 and 4 wk, and on the last day of each 6-wk period. Bronchoprovocations with lysine–aspirin were conducted in Poland, and LTD₄ bronchoprovocations in Sweden after 4 wk of treatment with zileuton and placebo, respectively. Histamine challenges were performed at both centers 1 wk before and on the last day of each treatment period. Urine was sampled and nasal symptoms were assessed in all subjects as indicated.

17 of 20 subjects in Poland, and sensitivity to inhaled LTD₄ in 18 of the 20 subjects from Sweden. Both bronchoprovocations were made after 4 wk of treatment with zileuton and placebo respectively. Histamine challenges were performed in 38 of the subjects on four occa-

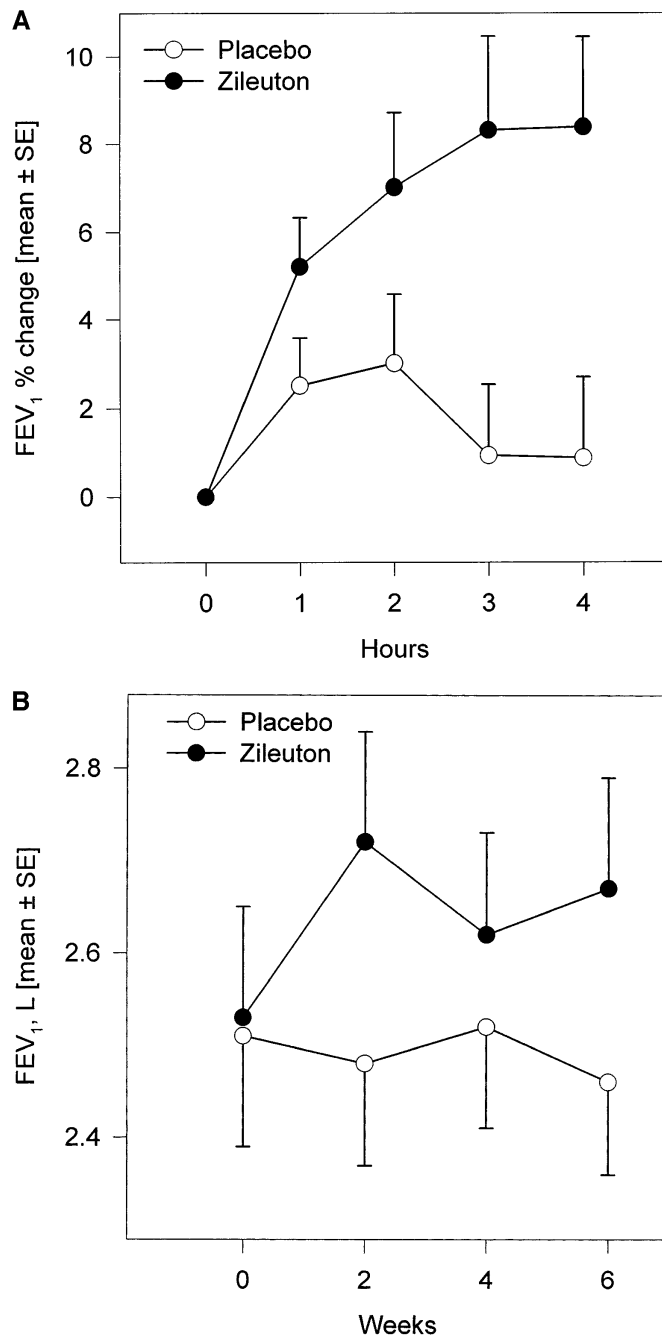


Figure 2. (A) Percent change in FEV₁ (treatment mean ± SE) after a single dose of zileuton (600 mg) or matching placebo. The increase in FEV₁ was significant compared with placebo at 1, 3, and 4 h ($p < 0.05$, $p < 0.01$, and $p < 0.01$, respectively). The maximum increase in FEV₁ during the first 0–4 h was 12.7% for zileuton and 6.8% for placebo; the difference between the two treatments was 5.9% (95% CI 1.9–9.9; $p < 0.01$). Likewise, at 4 h postdose an increase in FEV₁ was seen only on zileuton treated days, the treatment difference being 7.5% (95% CI 3–12; $p < 0.01$). (B) Improvement in lung function over baseline after 2, 4, and 6 wk of zileuton treatment (600 mg, four times daily) corresponding to, respectively, 9, 3, and 7% differences from placebo in FEV₁ ($p < 0.001$, $p = 0.16$, and $p < 0.01$).

sions, 1 wk before and on the last day of each treatment period. All provocation agents were administered by inhalation from a dosimeter-controlled jet nebulizer (Spira Elektro 2; Respiratory Care Center, Hämeenlinna, Finland). Challenges always began with inhalation of the respective diluent. Provided the postdiluent FEV₁ did not decrease by more than 10%, the provocative agent was administered in

approximately half-log increments of the cumulated dose until FEV₁ had fallen by at least 20% from postdiluent baseline. The solutions of histamine diphosphate were prepared by the Karolinska Hospital Pharmacy whereas solutions of lysine-aspirin (Aspisol; Bayer AG, Leverkusen, Germany) were made on each challenge day. The protocol for the lysine-aspirin challenge has been described elsewhere (8).

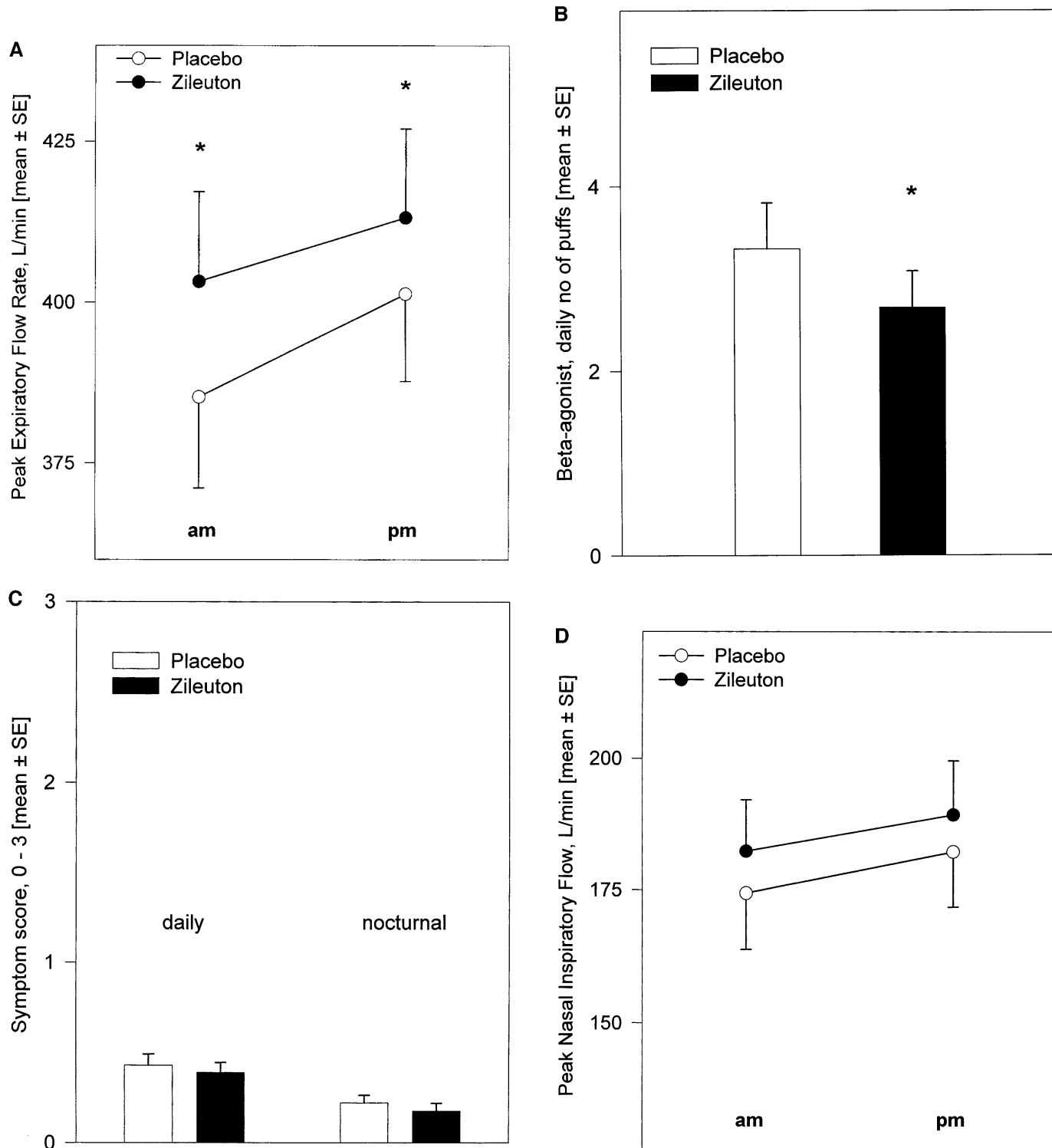


Figure 3. Comparison between treatments of diary card data; each subject's average over the respective 6-wk treatment period is used for the calculations of treatment means. (A) Morning and evening PEFV values were higher during zileuton treatment, corresponding to 18 ($p < 0.001$) and 12 L/min differences from placebo, respectively ($p < 0.01$). (B) Beta-agonist use ($p < 0.05$ versus placebo). (C) Day and nighttime symptom scores ($p = 0.40$ and 0.23 , respectively). (D) Morning and evening PNIFs ($p = 0.13$ and 0.08).

For LTD₄ bronchoprovocations, a protocol was created that permitted approximately half-log increments in the inhaled dose (1 pmol, 3 pmol, 10 pmol, etc., with an upper limit of about 340 nmol = 170 µg) every 10 min. This was achieved by using six solutions of good manufacturing practice (GMP)-grade LTD₄ (Cascade Biochemicals, Reading, UK) in concentrations increasing by tenfold (4.2×10^{-9} M to 4.2×10^{-3} M) and a varying number of breaths from each solution. For histamine bronchoprovocations, two concentrations of histamine (1.6 and 16 mg/ml) were used to create increasing doses every third minute.

Urinary Excretion of LTE₄ and Plasma Zileuton Levels

Urinary excretion of LTE₄ was evaluated before and at the end of each period by collection of 2 to 4 hourly samples during the visit 1 wk before the period and during the visit on the last day of each treatment. The concentration of LTE₄ was determined according to a previously validated semi-automated enzyme immunoassay (20). The average of two or three replicate samples from each subject on each occasion was used in the calculation of group means. Plasma concentrations of zileuton and its inactive but late-appearing metabolite A-66193 were determined by high-performance liquid chromatography (HPLC) as described elsewhere (21). Urine and plasma were kept frozen at -70° C until assay.

Statistical Analysis

For data obtained on visit days, i.e., FEV₁, nasal symptom assessments (VAS), and urinary excretion of LTE₄, changes from baseline values before the treatment period were analyzed using a two-period crossover analysis of variance (ANOVA). For variables from the patient diary cards, i.e., PEF₁, PNIF, beta-agonist usage, and daily assessment of asthma symptoms, no baseline data were collected and the two-period crossover ANOVA model was applied for comparison between treatments. Data from the diary cards were calculated as the average of daily values obtained during the whole 6-wk treatment period. The bronchoprovocations were evaluated using the provocative dose causing a 20% fall in FEV₁ (PD₂₀), with the postdiluent recording as baseline. The PD₂₀ was derived by linear interpolation from the respective base 10 logarithm cumulated dose–response curves. Calculations of geometric mean PD₂₀ values were performed on log-transformed raw data. The histamine challenge data were analyzed by comparing the change from baseline in log histamine PD₂₀, whereas for the lysine–acetylsalicylic acid (ASA) and LTD₄ challenges the PD₂₀ values from each treatment were compared using the two-period crossover ANOVA model. Period and carryover effects were analyzed according to Hills and Armitage (22).

RESULTS

All 40 subjects completed both treatment periods. Their baseline FEV₁ values at the start of the respective treatment period did not differ; 2.53 L (95% confidence interval [CI] 2.28–2.78) for zileuton and 2.51 L (95% CI 2.26–2.76) for the placebo period.

There was an acute improvement in pulmonary function after the first dose of zileuton (Figure 2A). As an overall measure, the maximum increase in FEV₁ during the first 0–4 h was 12.7% (95% CI 9.0–16.4) for zileuton, 6.8% (95% CI 3.7–9.9) for placebo, and the difference between the two treatments was 5.9% (95% CI 1.9–9.9; $p < 0.01$). Likewise, at 4 h post-dose an increase in FEV₁ was seen only on zileuton treated days, the treatment difference being 7.5% (95% CI 3–12; $p < 0.01$). The treatment difference of the change in predosing to postdosing FEV₁ was 0.18 L (95% CI 0.08–0.29; $p < 0.001$) (Figure 2A). The improvement in pulmonary function was maintained over the 6-wk period, as shown both by spirometry recordings at the clinic visits (Figure 2B), and by daily peak flow recordings at home (Figure 3A). Thus, at the end of the 6 wk, FEV₁ was increased by 0.14 L during the zileuton period and the mean difference compared with placebo was 0.19 L (95% CI 0.06–0.31; $p < 0.01$).

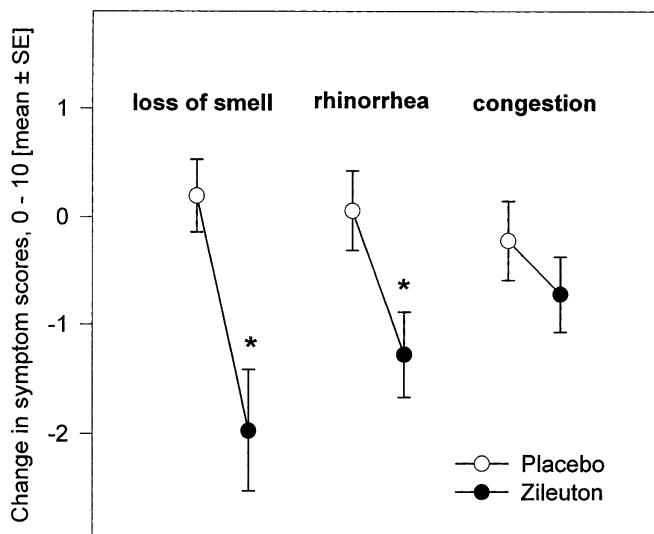


Figure 4. Nasal symptom scores showed a significant reduction in loss of smell and rhinorrhea ($p < 0.01$ and 0.05 , respectively) whereas nasal congestion was unaffected ($p = 0.63$).

Daily use of beta-agonist was significantly lower during treatment with zileuton compared with the placebo treated period, 2.7 versus 3.3 doses respectively (treatment difference 0.64 puffs [95% CI 0.06–1.12]; $p < 0.05$; Figure 3B) whereas there was no statistically significant difference in day and night asthma symptom scores between the two periods (Figure 3C).

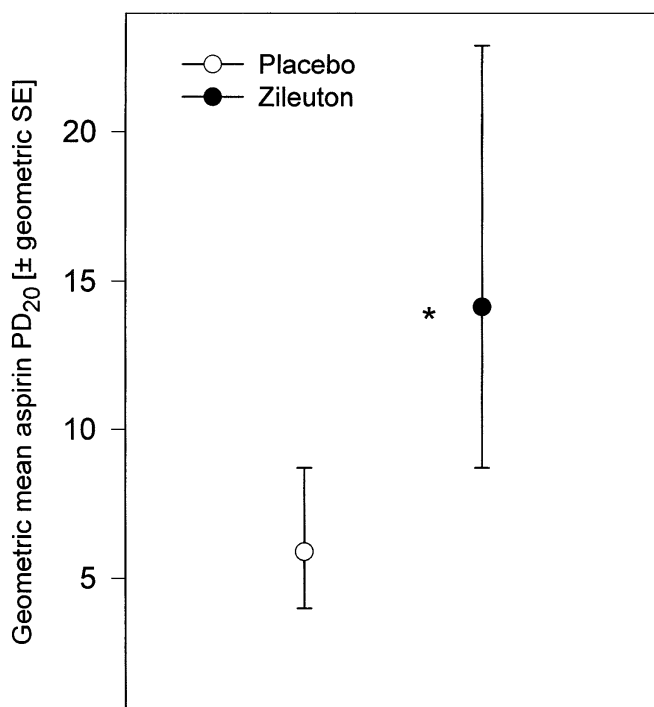


Figure 5. Cumulative bronchoprovocation with lysine–aspirin in 17 Polish subjects after 4 wk of treatment; geometric mean aspirin PD₂₀ (14.1 mg [95% CI 5.0–40]) was significantly higher after zileuton treatment ($p < 0.05$).

Nasal function improved compared with placebo during treatment with zileuton. There was a marked reduction in the VAS scores for loss of smell ($p < 0.01$) and for rhinorrhea ($p < 0.05$, Figure 4). Congestion (Figure 4) and daily measurements of peak nasal inspiratory flow (Figure 3D) showed changes which did not attain statistical significance.

The 17 Polish subjects who underwent cumulative lysine-aspirin bronchoprovocations after 4 wk of treatment, tolerated a significantly higher dose of aspirin during the zileuton treated period (14.1 mg [95% CI 5.0–40]; $p < 0.05$) compared with the placebo period (Figure 5). On the contrary, the geometric mean PD₂₀ for inhaled aspirin was similar after placebo treatment and during the prestudy screening challenge, 5.9 (95% CI 2.6–13.5) and 7.1 mg (95% CI 3.5–14), respectively.

Zileuton did not affect the bronchial reactivity to LTD₄ assessed in 18 Swedish subjects. The geometric mean LTD₄ PD₂₀ was 288 pmol (95% CI 145–575) after 4 wk of placebo treatment and 339 pmol (95% CI 209–550) after 4 wk of zileuton ($p > 0.5$).

Bronchial responsiveness to histamine was reduced during treatment with zileuton. The mean shift in histamine PD₂₀ after the 6-wk treatment was 0.17 ¹⁰log units (95% CI 0.02–0.32) corresponding to 1.5 doubling dose ($p < 0.05$). There was no change in histamine responsiveness during the placebo treatment period (mean shift: 0.01 ¹⁰log units [95% CI –0.14–0.16]).

Zileuton decreased basal urinary excretion of LTE₄ by 36% at the end of the 6-wk treatment period, whereas there was no change in urinary LTE₄ after placebo treatment ($p < 0.01$, Figure 6).

The concentration of zileuton in plasma was 4.5 µg/ml (95% CI 1.2–7.8) on the morning after the last dose of active drug. The metabolite A-66193 was also detectable on the last day of treatment and the mean concentration was 1.5 µg/ml (95% CI 0.6–2.4). There were however no direct correlations between plasma drug levels and the inhibition of urinary LTE₄

excretion, or the effect of zileuton on pulmonary function and other variables (data not shown).

Finally, five subjects had asthma exacerbations during the placebo period and one during the zileuton period. No drug-related side effect occurred during the study. The results were unrelated to the order in which treatments were given.

DISCUSSION

Forty subjects with long-standing asthma, aspirin intolerance, and characteristic chronic nasal symptoms were recruited for the first treatment trial ever conducted in a group of aspirin-intolerant asthmatics. There was no change in pulmonary function during the placebo period, suggesting that the subjects were controlled by treatment according to existing guidelines. However, addition of the leukotriene pathway inhibitor zileuton caused improvements in pulmonary function, involving both acute (Figure 2A) and chronic (Figure 2B) increases in FEV₁. The daily peak flow rates were superior both in the morning and evening compared with placebo (Figure 3A). In fact, on the active treatment, the morning peak flow rates were higher than the evening rates on placebo (Figure 3A). The improvements in pulmonary function were observed despite significantly less daily use of bronchodilator (Figure 3B). The magnitude of the add-on effect of zileuton on pulmonary function varied between 5 and 15% for the variables recorded. The degree of improvement after adding zileuton in our study is, incidentally, similar to the effects reported when the long-acting beta-agonist salmeterol was added to inhaled glucocorticosteroids (23, 24). However, the asthmatics in the studies with salmeterol were on lower doses of glucocorticosteroids, had lower mean baseline pulmonary function, and more asthma symptoms than the group we studied, which makes comparisons difficult.

The view that the patients' asthma was relatively controlled at baseline is supported by the few asthma symptoms reported during the placebo period (mean day and night scores being less than 0.5 on a scale from 0 to 3). Because these individuals had such low asthma symptom scores at baseline, it would be difficult to find a difference between the treatment periods (Figure 3C). Nevertheless, the nasal symptoms of the patients decreased conspicuously (Figure 4). In particular, there was a remarkable return of smell and decrease in rhinorrhea. It has previously been observed that zileuton reduced acute nasal symptoms following challenge with allergen (25) or aspirin (11, 26). This study documented that 5-lipoxygenase inhibition also caused chronic improvement in nasal function. Although aspirin-intolerant asthmatics are especially afflicted by chronic nasal dysfunction, our findings prompt for extended investigations of the effects of 5-lipoxygenase inhibition in other groups of patients with chronic rhinosinusitis.

It has been documented in previous trials in aspirin-tolerant asthmatics that zileuton reduced the number of asthma exacerbations highly significantly (27, 28). There were also fewer asthma exacerbations in our study when the subjects were on zileuton (1 versus 5 on placebo).

There was a small but significant decrease in bronchial hyperresponsiveness to histamine after 6 wk of treatment with zileuton. This occurred even though the majority of the subjects had been treated for many years with moderate to high doses of glucocorticosteroids which are known to attenuate bronchial hyperresponsiveness. In these circumstances, we consider it encouraging that a brief 6-wk treatment period with zileuton produced a detectable further reduction in bronchial hyperresponsiveness. Such an effect is, however, in line

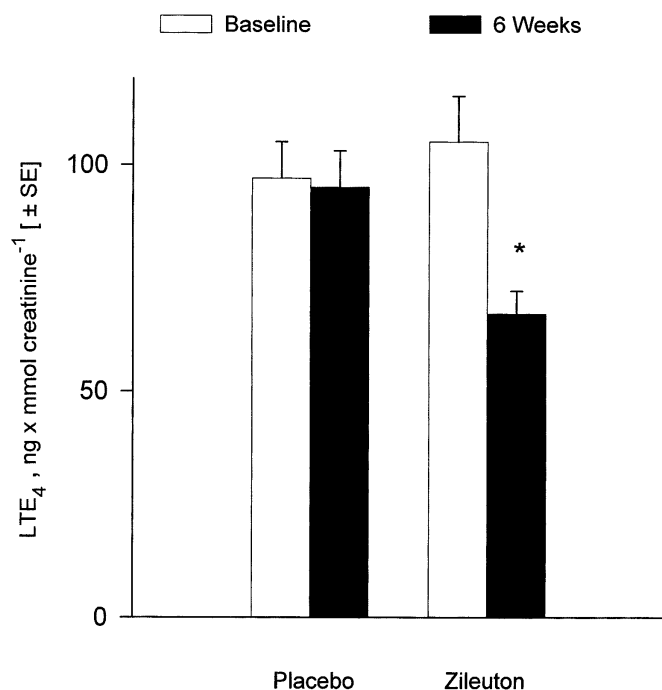


Figure 6. Basal excretion of LTE₄ in the urine was reduced by 36% after 6 wk of treatment with zileuton ($p < 0.01$).

with other indications that leukotrienes contribute to the inflammatory processes that are believed to cause bronchial hyperresponsiveness. For example, inhalation of cysteinyl-leukotrienes increased the number of eosinophilic granulocytes in sputum (6) and in airway mucosa (5) of asthmatics. In the context of this particular study, it is of interest that local segmental bronchial challenge with aspirin induced an activation of eosinophils in the airways of aspirin-intolerant asthmatics (29).

Zileuton inhibited aspirin-induced bronchoconstriction (Figure 5) when tested after 4 wk of treatment. This confirms previous indications (8–12) that leukotrienes mediate a significant component of the airway obstruction evoked by aspirin in aspirin-intolerant asthmatics. Whether or not 5-lipoxygenase inhibition in asthmatics can change airway sensitivity to leukotrienes had previously not been evaluated. It is theoretically conceivable that this might occur as a response at the receptor level to reduced synthesis of the endogenous agonists. However we found no change in bronchial responsiveness to LTD₄ during the treatment with zileuton. Together, the results of the aspirin challenge and the LTD₄ challenge support the specific mode of action of zileuton as 5-lipoxygenase inhibitor (17).

The measurements of urinary LTE₄ indeed documented that zileuton caused significant inhibition of leukotriene synthesis. The plasma levels of zileuton (21) and the degree of inhibition of urinary LTE₄ (11, 27, 30) were in fact almost identical to what has been found in other studies with zileuton. The detection of the metabolite A-66193, which appears 24 h after the first dose and remains constant during multiple dosing (21), supports compliance with therapy during the treatment periods.

The positive treatment effect with zileuton in this group of aspirin-intolerant asthmatics treated with moderate to high doses of glucocorticosteroids may seem surprising in view of the conventional theory that glucocorticosteroids inhibit arachidonic acid liberation, and hence the subsequent formation of leukotrienes and other eicosanoids. However, recent investigations have established that *in vivo* formation of leukotrienes, as well as that of other eicosanoids, is not altered by even high doses of inhaled or oral glucocorticosteroids (31–33). In fact, there are observations suggesting that glucocorticosteroids may increase the synthesis of critical enzymes in the leukotriene pathway (34). This is implicated from our study as well, where the subjects were chronically treated with glucocorticosteroids, but nevertheless excreted LTE₄ into the urine. In fact, the levels of urinary LTE₄ were in the high concentration range previously observed in other studies of aspirin-intolerant asthmatics (8, 13, 14). Recent studies in aspirin-tolerant asthmatics also indicate that addition of antileukotrienes may reduce the need for treatment with high doses of glucocorticosteroids (35), where side effects become an issue.

Considered together, the study has provided the first evidence that leukotrienes play an important role in persistent airway obstruction and chronic nasal symptoms in AIA. This supports the possibility that antileukotrienes may provide a much needed new treatment for AIA. The finding that the addition of zileuton provided an antiasthmatic effect over and above that sustained by chronic treatment with moderate to high doses of glucocorticosteroids has ramifications for the general use of this new class of antiasthmatics.

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