Zileuton: clinical implications of 5-Lipoxygenase inhibition in severe airway disease

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Introduction

Asthma is a chronic disease of the airways characterised by heterogeneous inflammation and variable responses to multiple therapies. The goals of asthma pharmacological therapy are to maintain the best possible asthma control while optimising safety and efficacy (1). Despite the availability of controller agents, such as oral corticosteroids (OCS), inhaled steroids (ICS) and long-acting beta-adrenergic receptor agonists (LABAs), there remains an unmet therapeutic need in significant numbers of asthmatics. Recent studies suggest that up to 31% of asthmatics remain uncontrolled despite access to specialty care, the availability of a variety of commercially available therapies and treatment with high doses of inhaled or oral steroids and the fixed-dose combination of a long-acting bronchodilator and an inhaled steroid (2,3). Furthermore, the clinical response to increasing the dose of ICS is variable, suggesting that there is a ‘rule of thirds’ in which one-third of asthmatics have a marked response to steroid therapy, one-third have modest improvement and one-third have minimal improvement (4,5). There is also growing evidence that glucocorticoid-insensitive asthma may have important implications for the pathogenesis of asthma and increased morbidity (6). Multiple reports suggest pathological and inflammatory changes in small airways and alveolar attachments in asthma, particularly severe asthma, and most inhaled medications are unlikely to reach the lung periphery in high amounts, resulting in inadequate drug delivery to the small or distal airways (7,8). Additionally, recent evidence suggests that polymorphisms on the β2-adrenergic receptor are associated with diminished responses to both short and long-acting β2-agonists (9,10).

Leukotrienes are important mediators in asthma pathogenesis (11–16) and 5-Lipoxygenase (5-LO) products have been shown to be increased in all severities of asthma, despite treatment with inhaled and OCS (17–20). Recent reports have suggested that neutrophils may play an important role in asthma, particularly severe and difficult-to-treat populations (8,18,21). Neutrophilic inflammation, which has been shown to be increased in multiple asthma phenotypes, including severe, acute, fatal, sudden-onset, occupational and smoking asthmatics with a corresponding increase in neutrophil numbers and activation states, is resistant to the effects of corticosteroids (18,21,22,24–26). Corticosteroids have been reported to suppress neutrophil apoptosis and...
their use may increase neutrophil numbers (21,27–28). LTB₄, a potent neutrophil chemoattractant, is increased in the bronchoalveolar lavage (BAL) fluid, sputum and tissue of severe asthmatics and the levels remain high despite corticosteroid therapy (8,17,19,22).

The relative insensitivity of the 5-LO pathway to corticosteroid therapy, increased 5-LO products in asthmatic inflammation and increased neutrophilic inflammation support the rationale of zileuton as an additional approach to anti-inflammatory therapy for the treatment of the multiple phenotypes seen in chronic asthma.

5-Lipoxygenase pathway

The 5-LO pathway, which results in the production of leukotrienes, was discovered in the 1970s by Borg eat and Samuelsson (29,30). Leukotrienes play an important role in the clinical course of asthma, the physiological changes seen in asthma and the pathogenesis of the disease (31,32). These biological compounds produce bronchoconstriction and mediate increased microvascular permeability, increased mucus secretion, goblet cell hyperplasia, smooth muscle hypertrophy and inflammatory cellular infiltration (33). Leukotrienes are produced by multiple inflammatory cells, particularly mast cells, basophils, eosinophils, neutrophils and macrophages; all of which have been implicated in asthma. Increased asthma disease severity is associated with increased numbers and activities of neutrophils, eosinophils and mast cells, all rich sources of leukotrienes (13,34–41).

Leukotriene formation by 5-LO

Leukotrienes are generated from arachidonic acid (AA) which must be released from membrane phospholipids upon cellular activation. Cellular activation by immune complexes, bacterial peptides and other stimuli elicit a sequence of events that include cytosolic phospholipase A₂ (cPLA₂) and 5-LO translocation to the nuclear envelope (15). Cytosolic phospholipase A₂ selectively hydrolyses AA from phospholipids from the nuclear envelope, causing a release of AA. Arachidonic acid binds to 5-Lipoxygenase activating protein (FLAP), an arachidonate transfer protein, in the nuclear envelope and the AA–FLAP complex is presented to 5-LO. 5-LO converts AA to 5S-hydroxyperoxy-6E, 8Z,11Z,14Z-eicosatetraenoic acid (5-H₂E₄) which is then converted to 5S-hydroxy-6E,8Z,11Z,14Z-eicosatetraenoic acid (5-HETE) and further converted to 5-oxo-6E,8Z,11Z,14Z-eicosatetraenoic acid (5-oxo-ETE). 5-H₂E₄ can also be converted to the unstable intermediate, leukotriene A₄ (LTA₄). LTA₄ is converted to leukotriene B₄ (LTB₄) by cytosolic LTA₄ hydrolase or to leukotriene C₄ (LTC₄) by perinuclear LTC₄ synthase. LTC₄ undergoes extracellular metabolism to yield leukotriene D₄ (LTD₄) and leukotriene E₄ (LTE₄) (15,42) (Figure 1).

![Figure 1](https://example.com/f1.png) The Arachidonic acid cascade and 5-lipoxygenase. The effects of each key eicosanoid metabolite are described.
Leukotriene B4

Leukotriene B4, one of the major eicosanoids of the 5-LO pathway, is a potent chemoattractant for multiple inflammatory cells, including effector CD8+ T cells (TEFF), eosinophils and neutrophils (17,43). LTB4 is the major 5-LO product of neutrophils, monocytes and alveolar macrophages. LTB4 stimulates leucocyte chemotaxis, chemokinesis and vascular endothelium adherence, delays neutrophil apoptosis and prolongs neutrophil survival. Recent studies in murine models of inflammation have demonstrated that mast cells produce LTB4 following sensitisation and challenge, leading to the migration of CD8+ TEFF cells into the airways, increased interleukin 13 (IL-13) production and enhanced airway reactivity. These events are mediated by the high-affinity LTB4 receptor, BLT1, and are dependent upon the mast cell high affinity immunoglobulin E (IgE) receptor (FCE1R). In humans, BAL fluid levels of LTB4 have been demonstrated to correlate with disease severity and LTB4 levels remain high in the BAL of severe persistent asthmatics despite high-dose oral steroid use (11). A subset of CD8+ TEFF/BLT1+/IL-13+ cells have been identified in BAL fluid of asthmatics, suggesting the therapeutic potential for targeting the LTB4-specific components of the 5-LO pathway that are IgE-independent (44–46).

5-HETE and 5-oxo-ETE

Another major 5-LO product is 5-HETE, which has been recently shown to be an important mediator in asthma. 5-oxo-6,8,11,14-eicosatetraenoic acid is the AA metabolite formed by the oxidation of 5-HETE, and this metabolite is a potent chemoattractant for neutrophils and eosinophils. Among lipid mediators, 5-oxo-ETE is the strongest chemoattractant for eosinophils, with a potency 30 times greater than the chemoattractant properties of the cysteinyl leukotrienes in vitro. The actions of 5-oxo-ETE are mediated by its receptor, OXE, which is highly expressed by eosinophils, neutrophils and monocytes. The impact of inhibiting 5-oxo-ETE and mediating its effects on a variety of cells, particularly eosinophils and neutrophils, is an area of active research in asthmatic inflammation (42).

Cysteinyl leukotrienes

The cysteinyl leukotrienes, LTC4, LTD4 and LTE4, are potent constrictors of airway smooth muscle. Additional cysteinyl leukotriene (cysLT) effects include increased vascular permeability, edema, decreased mucociliary clearance and mucus hypersecretion. The cysLTs are synthesised by mast cells and alveolar macrophages, are potent eosinophil chemotactants as well as autocrine and paracrine mediators of asthmatic inflammation (47). The cysLTs induce physiological effects via two receptors, the cysLT1 and cysLT2 receptors. While most of the effects of leukotrienes with relevance to asthma are mediated by activation of the cysLT1 receptor, the cysLT2 receptor may be a relevant target for treatment in asthma and other inflammatory diseases (47).

Clinical pharmacokinetics and pharmacodynamics of 5-LO inhibition with zileuton

Zileuton, a benzothiophene N-hydroxyurea, was the first oral inhibitor of 5-LO to undergo extensive clinical testing for the treatment of asthma (37). Zileuton has the chemical name (±)-1-(1-Benzoo[b]thien-2-yl)-1-hydroxyurea and the following chemical structure:

Zileuton has the molecular formula C11H12N2O2S and a molecular weight of 236.29 g/mol.

Pharmacokinetics of zileuton

In humans, zileuton is rapidly absorbed after oral administration with a time to maximal concentration (Tmax) of 1.7 ± 0.9 h (mean ± SD) and a mean zileuton peak level (Cmax) of 5.0 ± 2.0 µg/ml for the 600-mg q.i.d. dose (48). After single and multiple doses, the mean area under the curve (AUC) following 600 mg zileuton administration is 19.2 ± 5.6 µgÆh/ml (48). Plasma concentrations of zileuton are proportional to dose, and steady-state levels are predictable from single-dose data, indicating no unusual accumulation of the drug following four times a day dosing. The average apparent oral clearance of zileuton is approximately 1.2 l/kg (48). Zileuton is 93% bound to plasma proteins with albumin as the primary plasma protein binding protein (88% bound) and α1-acid glycoprotein as a more minor binding protein (34% bound) (48). Administration of zileuton with food resulted in a small, but statistically significant, increase (27%) in zileuton Cmax without significant changes in AUC or Tmax. Therefore, zileuton can be administered with or without food (48).
**Zileuton metabolism**

Elimination of zileuton is predominantly via metabolism with a mean terminal half-life of 2.5 h (48). The activity of zileuton is primarily because of the parent drug. Studies with radio-labelled drug in healthy volunteers have demonstrated that 94.5% and 2.2% of the radio-labelled dose is recovered in urine and faeces respectively (48). The major urinary metabolites in humans (approximately 80–90% of the dose) are the zileuton glucuronides (48). The urinary excretion of the inactive N-dehydroxylated metabolite and unchanged zileuton each accounted for < 0.5% of the dose. In *vitro* studies utilising human liver microsomes have shown that zileuton and its N-dehydroxylated metabolite can also be oxidatively metabolised by the cytochrome P45 iso-enzymes CYP1A2, CYP3A and CYP2C9 (37). The pharmacokinetics of zileuton are essentially the same in healthy elderly subjects (> 65 years) (23,39,50), paediatric subjects (8–12 years) (27) as in healthy younger adults and in males compared with females, after adjustments for body weight or body surface area. The pharmacokinetics of zileuton were also similar between healthy volunteers and in patients with either mild-to-moderate asthma or rheumatoid arthritis or subjects with mild, moderate and severe renal insufficiency. In subjects with renal failure who required haemodialysis, pharmacokinetics of zileuton were not altered by haemodialysis. A very small percentage of the administered zileuton dose (< 0.5%) was removed by haemodialysis. Therefore, using dosing adjustment is not necessary in patients with renal dysfunction or in those undergoing haemodialysis (48).

**Pharmacodynamics of zileuton**

Many studies of the effect of zileuton on suppression of 5-LO product formation, including LTB4 and the cysteinyl leukotrienes have been performed. In addition, the specificity of zileuton in inhibiting the products of the 5-LO pathway was assessed by measuring cyclooxygenase products, including thromboxane B2 (TXB2) and prostaglandin D2 (PGD2). Zileuton selectively inhibits the 5-LO enzyme. Multiple studies have demonstrated that zileuton produces little or no inhibition of related enzymes, such as 12-LO, 15-LO and cyclooxygenase, at concentrations of up to 100 μM (51). In an animal model, a 70-mg/kg dose of zileuton failed to significantly inhibit the formation of the cyclooxygenase product TXB2, demonstrating the *in vivo* selectivity of zileuton for leukotriene inhibition. Oral doses of zileuton also inhibited *ex vivo* blood LTB4 biosynthesis in the rat, dog, monkey and sheep. In the dog, an oral dose of 5 mg/kg provided complete inhibition of *ex vivo* leukotriene formation for at least 24 h (51). It is largely suspected that zileuton does not, therefore, shunt AA metabolism, possibly because of an incomplete inhibition of 5-LO and other compensatory mechanisms (40).

The *ex vivo* per cent inhibition of the biosynthesis of LTB4 in whole blood is directly related to plasma concentration of zileuton. After oral administration, peak zileuton plasma levels occur within 2 h after administration and are associated with mean LTB4 inhibition of 98% after the first dose in the zileuton 600 mg group (Figure 2). After 13 weeks of measurement, there is a 92% inhibition 2 h postdosing of 600 mg zileuton (Figure 3). The 50% inhibitory con-
Zileuton: 5-LO pathway inhibition

First-dose LTB$_4$ inhibition (98% inhibition)     Steady–state LTB$_4$ inhibition (92% inhibition)

Figure 3 Peak zileuton plasma levels are associated with mean LTB$_4$ inhibition of 98% at 2 h postdose in the first dose measurement and 92% for the 13 week measurement in chronic persistent asthmatics treated with 600 mg q.i.d. of zileuton ($n = 20$). Zileuton peak plasma levels occurred 2–4 h after administration.

Concentration (IC$_{50}$) for the inhibition of LTB$_4$ in asthma patients treated with zileuton is very similar to that of healthy volunteer subjects; 0.47 and 0.46 mg/ml respectively (Figure 2) (48).

Improvement in the forced expiratory volume in one second (FEV$_1$) in patients treated with zileuton 600 mg was immediate, starting within 0.5 h after first dose. The mean time to achieve maximum per cent improvement in FEV$_1$ was 2–3 h post peak plasma concentration and maximum LTB$_4$ inhibition. The mean peak inhibition of LTB$_4$ in the 600 mg q.i.d. group ($n = 20$) was 98% at peak plasma concentrations. The greatest mean improvements in FEV$_1$ coincided with these plasma levels (Figures 2 and 3) (48,52). The ex vivo inhibition of LTB$_4$ production in whole blood is directly related to the plasma concentration of zileuton (Figure 2) (48).

In a cold air challenge study, ex vivo LTB$_4$ production in whole blood was reduced by 74% ($p \leq 0.001$) following a single 800 mg dose of zileuton. In another study, a single 800 mg of zileuton inhibited LTB$_4$ release in whole blood stimulated with calcium ionophore ex vivo by 92% ($p < 0.01$) (53). Another bronchoprovocation study in aspirin-sensitive asthmatics, zileuton 600 mg q.i.d. for 1 week decreased the baseline urinary LTE$_4$ excretion by 71% ($p < 0.02$) (54). The in vivo activity of zileuton was also examined in 10 patients by measuring LTE$_4$ in urine and BAL fluid following segmental allergen challenge. Urinary LTE$_4$ was reduced by 86% compared with placebo ($p < 0.05$) 4 h postchallenge. BAL LTE$_4$ was similarly reduced by 72% compared with placebo 24 h after challenge (55). In patients with nocturnal asthma, LTB$_4$ and cysteinyl leukotrienes in BAL fluid were significantly reduced by 38.5% and 67%, respectively, after 1 week of zileuton treatment. Nocturnal urinary LTE$_4$ levels were reduced by 76% compared with placebo (57).

The clinical effectiveness of 5-LO inhibition with zileuton therapy was assessed in patients with moderate-to-severe persistent asthma, receiving either zileuton 1.6 or 2.4 g/day over 4 weeks. Urinary LTE$_4$ levels were reduced by 26% and 39%, respectively ($p < 0.01$), while no change was noted in the group receiving placebo (57). In a phase I interaction study conducted in healthy volunteers looking at pharmacokinetic and pharmacodynamic interactions between zileuton and naproxen, zileuton blocked LTB$_4$ without any effect on thromboxane interactions, which had a small trend towards decreasing from baseline after zileuton treatment, while naproxen completely blocked the cyclooxygenase pathway (58). In an antigen challenge study, nasal LTB$_4$ was inhibited by > 90% by a single oral dose of zileuton (800 mg 3 h prior to the challenge) but neither histamine release nor cyclooxygenase product formation was inhibited (53).

Overall, these studies indicate that zileuton is a specific inhibitor of 5-LO, resulting in the suppression of leukotriene production and not the shunting of AA to the cyclooxygenase pathway in humans where this has been studied (48,52,53,58). However, the interactions observed between the cyclooxygenase and 5-LO pathways of AA metabolism are complex. Multiple inflammatory cells produce AA metabolites from both the cyclooxygenase and lipooxygenase pathways and in vitro studies using human lung parenchyma and bronchial tissue and in vivo studies using segmental allergen challenge and BAL have demonstrated that a variety of AA products are synthesised and released during IgE-mediated reactions. Some of these metabolites arise by direct activation of mast cells and others may arise from direct activation of other cells, such as macrophages; theoretically, 5-LO inhibition should not have an effect on the production of cyclooxygenase products if metabolites arise only via these mechanisms. However, some cyclooxygenase products can arise as a result of the effect of 5-LO products on other cells and/or tissues or as a result of the physiologic effects of leukotrienes on airway smooth muscle and mucus glands. In these instances, one could hypothesise that 5-LO inhibition may result in a decrease in the production of cyclooxygenase products (55). Additionally, in cellular, tissue and in vitro models, cyclooxygenase inhibition has been shown to result in an increase or shunting of 5-LO products while other models have shown no effect and in vitro and in vivo data are conflicting (55).
Clinical studies of zileuton

Asthma

The clinical development programme for zileuton included 54 phase II and III studies pursuing five indications. The NDA filed for the use of zileuton for the treatment of chronic asthma included safety and efficacy studies in over 6500 patients of which 3000 were asthmatics. The efficacy evaluation was based on two randomised, placebo-controlled phase III pivotal trials. The 3-month study randomised 401 patients while the 6-month study assessed 373 patients (Figure 4) (57,59).

In multi-centre, placebo-controlled clinical trials, zileuton consistently improved both pulmonary function and asthma symptoms as well as reducing the need for β2-agonists and systemic steroid rescue for acute asthma exacerbations (57,59). The improvement in lung function included both acute bronchodilation (within 1 h) and continued improvement over time (months) (59).

Zileuton was also as effective as theophylline in the management of chronic asthma. In a 3-month, multi-centre, randomised, double-blind, parallel trial, zileuton (600 and 400 mg q.i.d.) was compared with theophylline. Both therapies demonstrated significant improvements in FEV1 within 30 min and sustained protection of pulmonary function over 6 h. Both therapies also improved symptoms and corticosteroid rescue (60). In a randomised, double-blind, multi-centre trial comparing low-dose beclomethasone (400 μg day beclomethasone + 400 or 600 mg zileuton q.i.d.) plus zileuton vs. doubling the dose of beclomethasone (800 μg daily), comparable efficacy was achieved between the two treatment groups with regard to pulmonary function, oral corticosteroid rescue and symptoms during 3 months of therapy (61).

A 12-month, open-label, parallel group surveillance study was conducted to assess the effects of zileuton on clinical efficacy and evaluate liver function elevations when added to usual care in asthma patients. The patients in this trial had baseline FEV1 values of ≥ 35%, aged 16 years and up; 2947 (2458 on zileuton and 489 on usual asthma care alone) patients from 233 centres in the USA entered this trial. Usual care included ICS (57% of patients in the zileuton group, 61% of patients in the usual care alone group), nedocromil (11% zileuton group, 12% usual care alone), inhaled β2-agonists (96% zileuton group, 96% usual care alone) and salmeterol if the dose had been stable for at least 4 weeks before study entry. Endpoints included asthma exacerbations, need for additional asthma therapy, steroid rescue, emergency care, hospitalizations, FEV1 and asthma symptom scores (62). The addition of zileuton to usual care resulted in an improvement of asthma quality of life and significantly reduced the need for steroid rescue and emergency care visits (Figures 5 and 6).

To assess the efficacy of zileuton in more severe asthmatics, patients from the two pivotal phase III trials were stratified by their baseline FEV1 values per the current NHLBI asthma guidelines into mild (n = 13 zileuton; placebo = 12), moderate (n = 126 zileuton; 129 placebo) and severe persistent (n = 110 zileuton;110 placebo) asthma groups (64). Using a post hoc analysis, the mean percent changes in each outcome from baseline to the pre-dosing value on each visit were calculated. Patients whose baseline FEV1 values were ≤ 50% had statistically significant improvements in both daily and nocturnal symptoms and morning trough FEV1 as well as statistically significant reductions in the number of daily β2-agonist puffs and the need for oral corticosteroid rescue (Figure 7). In the group of patients whose baseline
FEV₁ values were < 50%, there were statistically significant improvements in morning trough FEV₁, reductions in the need for oral corticosteroid rescue and a decreased need for rescue β₂-agonists. This analysis suggests an increased efficacy of zileuton in a more severe, difficult-to-treat asthmatic population (64).

Potential mechanisms whereby this population of asthmatics with baseline FEV₁ values ≤ 50% have better outcomes with 5-LO inhibition added to their usual care include a possible neutrophilic inflammatory phenotype with increased LTB₄ and increases in both neutrophil numbers and activation states, a diminished responsiveness to corticosteroids, therapy and delayed neutrophil apoptosis. It is possible that this population of asthmatics may have had comorbidities including aspirin sensitivity with upper Airways inflammation including sinusitis and nasal polyposis. Indeed, multiple reports have suggested that asthmatic inflammation is extremely heterogeneous; smoking asthmatics have increased neutrophilic inflammation and a diminished responsiveness to corticosteroids (49,65–67), which may predispose
this population to have an enhanced response to an agent that modulates the 5-LO pathway.

Asthma provocation studies

In a series of provocation challenges, zileuton significantly reduced airway responses to cold air, exercise, allergen, histamine and aspirin. The efficacy of zileuton in reducing bronchospasm and airway hyper-responsiveness caused by various stimuli was apparent after 1–7 days of treatment, suggesting that 5-LO products play an important role in airways hyper-responsiveness (47,55,68–71). In a randomised, double-blind, placebo-controlled, crossover trial, the effect of a single dose of 800 mg zileuton on bronchoconstriction induced by cold, dry air was examined in 13 asthmatics, aged 18–55 years. All patients had a known cold air-induced 20% drop in FEV\(_1\). After a single dose of zileuton, the amount of cold, dry air needed to reduce the FEV\(_1\) by 10% was increased by 47% (p < 0.002 vs. placebo) along with significant increases of 39% and 26% for PD\(_{15}\) and PD\(_{20}\) respectively (p < 0.005 and 0.02) (40).

In a double-blind, placebo-controlled, crossover exercise challenge model, zileuton administered 600 mg q.i.d. for 2 days prior to exercise in 24 patients with EIA aged 21–45 years allowed for bronchoconstriction that was less severe and shorter in duration compared with placebo. The zileuton-treated group had reductions in exercise-induced bronchospasm (p < 0.01 vs. placebo) and the difference remained significant for 45 min following exercise challenge (72).

In a challenge with aspirin, eight aspirin-sensitive asthmatics (ASA) were challenged with predetermined subthreshold and then threshold doses of aspirin known to elicit a ≥ 15% drop in FEV\(_1\) in a randomised, double-blind, crossover trial. Patients were treated with zileuton 600 mg q.i.d. for 1 week prior to the challenge. Zileuton prevented the decline in FEV\(_1\) in response to aspirin (p < 0.014 vs. placebo) along with a decrease in nasal, gastrointestinal and dermal responses to aspirin. During the challenge, the placebo-treated group had greater than a twofold increase in nasal symptoms (p < 0.006) (54).

Specific phenotypes of asthma

Aspirin-intolerant asthma

Zileuton therapy has been shown to be effective in various clinical phenotypes of asthma. Multiple studies have demonstrated that 5-LO inhibition blunts the effects of aspirin in an aspirin challenge model (41,54).

A study by Dahlen (71) demonstrated that 5-LO inhibition with zileuton added to high doses of inhaled and/or oral steroids in well-controlled aspirin-intolerant asthmatics (FEV\(_1\) approximately 80%) resulted in significant clinical improvements in both the upper and lower airways (Figure 8). A randomised, double-blind, placebo-controlled, crossover trial was performed to study the effects of 5-LO inhibition in a population of patients with known aspirin sensitivity. Aspirin sensitivity was confirmed by an increase in urinary LTE\(_4\) levels following aspirin challenge. Patients were pretreated with zileuton 600 mg q.i.d. or placebo for 6–8 days followed by an aspirin challenge and they were then given the final placebo or zileuton dose. Zileuton treatment prevented the development of upper and lower airways symptoms as well as improvements in the gastrointestinal and

**Figure 8** Zileuton plus conventional therapy improves nasal symptom scores and provides rapid bronchodilatory effects and chronic improvements in lung function in aspirin intolerant asthma (AIA) patients who had zileuton added to their existing asthma therapy. The patients were on high doses of inhaled and/or oral corticosteroid therapy and were considered well-controlled with average FEV\(_1\) values of 80% before the addition of zileuton therapy. (A) Rapid bronchodilatory effect. (B) Sustained improvement in lung function over 6 weeks. (C) Improvement in nasal symptom scores.
dermal symptoms associated with the ingestion of aspirin in this population (54). In another trial, six aspirin intolerant asthmatics were given aspirin challenge doses below the usual provoking dose of 60 mg and then had their doses increased until a respiratory reaction occurred. Pretreatment with zileuton 600 mg q.i.d. was initiated 7 days prior to, and continued during oral aspirin challenges. Patients underwent single-blind oral aspirin challenges with escalating doses of aspirin, every 3 h, according to a standard protocol. While zileuton pretreatment did not inhibit the respiratory reactions, all but one of the zileuton pretreated subjects required a larger dose of aspirin, beyond the baseline provoking doses, to induce a respiratory reaction (73). Placebo-controlled, well-powered trials are needed to confirm these findings.

Nocturnal asthma
In another study by Wenzel, zileuton therapy was studied in a group of nocturnal asthmatics and controls over 7 days. Pulmonary function, methacholine challenge, bronchoscopy leukotriene and thromboxane levels in BAL and urinary LTE4 were collected at 4:00 pm and 4:00 am. BAL fluid LTB4 levels were significantly increased at 4:00 am in the asthmatic group with LTB4 levels correlating significantly with a fall in nocturnal FEV1 (p < 0.0001). Nocturnal asthmatic urinary LTE4 levels were also significantly increased vs. controls. With zileuton therapy after 1 week, there were significant decreases in 4:00 am BAL levels of LTB4 (p = 0.01) and urinary levels of LTE4 (p = 0.01) as well as a trend for improving nocturnal FEV1 (p = 0.086) (56).

Exercise-induced asthma
Two studies have been performed looking at the effect of zileuton on bronchospasm because of exercise. The first, looking at the impact of multiple doses of zileuton 2 days prior to an exercise challenge demonstrated a maximum percent decrement in baseline FEV1 after zileuton treatment of 15.6% vs. 28.1% for the placebo-treated group (p < 0.01) (72). The second study compared single doses of two leukotriene receptor antagonists (LTRAs), montelukast and zafirlukast, a long-acting bronchodilator, salmeterol and zileuton in the attenuation of the effects of exercise-induced bronchospasm. All three had a comparable magnitude of prophylaxis against exercise-induced reductions in FEV1 (74).

Upper airways inflammation

Allergic rhinitis
The 5-LO inhibition with zileuton has been studied in the setting of upper airways inflammation. The effect of zileuton on inhibiting leukotriene production in vivo was examined in nasal lavage fluid following antigen challenge in nine patients with allergic rhinitis. A single 800-mg dose of zileuton suppressed LTB4 production in nasal lavage fluid by 90% immediately following allergen challenge (p < 0.01). 5-HETE synthesis was also reduced by 74% (p < 0.02), while PGD2 and histamine release were not significantly affected (53). In contrast, zileuton did not affect the release of products of the cyclooxygenase TXB2 or 12-LO pathway. These results provide direct evidence for the potential role of 5-LO in the pathogenesis of allergic rhinitis and the attenuation of clinical symptoms (53).

A double-blind, randomised, placebo-controlled crossover trial of 6 weeks of treatment with zileuton 600 mg q.i.d. in aspirin-intolerant asthmatics demonstrated improvements in both the lower and upper airways function and symptoms. Bronchodilatory effects on FEV1 were seen within an hour of dosing of zileuton and there were significant improvements in am and pm peak nasal inspiratory flow (PNIF) and symptoms of anosmia (p < 0.01) and rhinorrhea (71).

In a crossover study of patients with known aspirin sensitivity, zileuton treatment prevented the development of the nasal, pulmonary, gastrointestinal and dermal symptoms associated with the ingestion of aspirin (54).

Chronic nasal polyposis
A recent case series suggested that anosmic patients with chronic nasal polyposis treated with zileuton therapy provides a sustained restoration of smell along with improved quality of life (75). The treatment effects of zileuton and zafirlukast, a cysLT1 receptor antagonist, were assessed in a prospective study of 36 patients with sinonasal polyposis, 77% of whom were on oral steroids. The authors noted that zileuton had a better effect and was able to rescue ‘zafirlukast failures’ with significant improvement in sinus headaches, facial pain and pressure, dental pain, purulent anterior nasal discharge, postnasal drip, nasal congestion and obstruction and olfaction (76).

Sinusitis
In a year-long, open-label surveillance trial comparing zileuton plus usual care vs. usual care alone in 2947 (2458 on zileuton and 489 on usual care), sinusitis was more commonly reported in the usual care group vs. the zileuton plus usual care group (p = 0.001) (62). A recent report suggested that zileuton (600 mg q.i.d.) treatment in an asthmatic with concurrent sinusitis, polyposis and aspirin sensitivity.
provided relief from nasal symptoms (sinus pain, headache and nasal blockage). When treatment was stopped, the patients' symptoms returned, suggesting that the disease process was mediated by 5-LO products and the authors suggested that the inhibition of the 5-LO pathway with zileuton resulted in a regression of the patients' sinusitis and symptoms (77).

These reports suggest that there may be a role for 5-LO inhibition in the treatment and management of sinusitis; double-blind, well-controlled trials are warranted to confirm these initial findings.

Dermatological conditions: atopic dermatitis and urticaria

In a pilot study to examine the role of zileuton in atopic dermatitis, six adult patients received 6 weeks of zileuton therapy, 600 mg q.i.d. Disease dissatisfaction scores decreased from a mean of 8 (out of a possible 10) to 4.4. Pruritis scores showed a trend toward improvement during the study and objective skin erythema scores decreased from a baseline mean of 24 (out of a possible 60) to 14 following zileuton treatment (78).

The clinical efficacy of zileuton in urticaria has been studied. Ellis reported on the need for additional therapy in urticaria patients not responding to antihistamines alone. In this series, one patient was placed on zileuton and showed improvement within 3 h and another patient had improved respiratory status and resolution of urticaria within 24 h of starting zileuton 600 mg q.i.d. (79). Spector (80) reported a case in which a patient with intractable chronic urticaria demonstrated resolution after 4 days of treatment with 600 mg of zileuton q.i.d.

These case reports and pilot study suggest a potential role for 5-LO inhibition in dermatological conditions; larger and more adequately powered, blinded, placebo-controlled trials are warranted to confirm these initial findings.

Chronic obstructive pulmonary disease (COPD)

Chronic obstructive pulmonary disease is characterised by fixed airways obstruction and often associated with neutrophilic inflammation. To examine the effect of 5-LO inhibition in subjects with severe COPD, zileuton 600 mg was administered orally four times a day for 3 months in eight subjects (mean age 66 ± 6 years), with mean FEV$_1$ values of 0.91 ± 0.33 l (29 ± 6% predicted) (81). The primary outcome was exercise capacity measured by the 6-min walk test; secondary outcomes included FEV$_1$, health-related quality of life (HRQL), the St George's Respiratory Questionnaire (SGRQ) and dyspnoea rating. The mean 6-min walk distance increased 244 ft or 24% of baseline (1011 ± 361 to 1255 ± 339 ft, p = 0.007). Changes in the 6-min walk distance correlated strongly with changes in SGRQ total scores (r = -0.73, p < 0.05) and there were significant improvements in the HRQL, suggesting that in patients with severe COPD, zileuton improves exercise capacity and quality of life (81).

These data suggest a potential role for the modulation of the 5-LO pathway; perhaps due to increased neutrophilic component in this population. Placebo-controlled, blinded, randomised trials are warranted to confirm these initial findings.

Approved clinical indications and dosing of zileuton

Zileuton is currently approved by the FDA for the prophylaxis and chronic treatment of asthma in adults and children 12 years of age and older (82). The currently FDA-approved dosing schedule for zileuton is one 600 mg tablet four times a day. For convenience, it may be taken with meals and at bedtime and it is recommended that zileuton be taken regularly, even during symptom-free periods (82).

Dosing frequency

DeBuske (83,84) studied the impact of reducing the dosing and the frequency of the dosing regimen in patients controlled with zileuton q.i.d. dosing. Patients were treated with zileuton q.i.d. for 8 weeks in an open-label phase followed by an 8-week double-blind phase, during which patients received a reduced dose/frequency of zileuton, either 600 (n = 72) or 800 mg (n = 67) t.i.d. During an additional 8-week double-blind phase, the zileuton dose/frequency was further reduced to either 600 (n = 53) or 800 mg (n = 60) b.i.d. Patients had to demonstrate an improvement of at least 10% from baseline FEV$_1$ values to qualify for entry into the t.i.d. phase of this trial, and the entry criteria also stipulated that only β$_2$-agonists were used to treat their asthma. The reduction in dosage did not lead to an increase in acute asthma exacerbations or systemic corticosteroid rescue treatments during the t.i.d. and b.i.d. periods.

The authors suggested that some patients who demonstrate improved pulmonary function following treatment with zileuton 600 mg q.i.d. may be able to maintain a comparable level of improved lung function, symptom control, reduced β$_2$-agonist use and fewer systemic corticosteroid rescue treatments on a lower dose or frequency of zileuton administration (83,84). Importantly, there are no data to support starting patients on zileuton with any dosing regimen other than q.i.d.
Other formulations of zileuton have been developed, including a controlled release b.i.d. tablet formulation and an intravenous formulation (85,86).

The results of a phase I/II clinical trial designed to evaluate safety, tolerability and pharmacokinetics of the intravenous formulation of zileuton with asthma were recently released (85). In this double-blind, placebo-controlled trial, 60 patients were randomised into four escalating dose groups (75, 150, 300 and 600 mg), each receiving one infusion of either zileuton intravenous or placebo. The data suggested that zileuton intravenous was well tolerated at all doses tested with no serious adverse events reported in the trial (85). Further details and information will await peer-reviewed presentations and publication.

A controlled release formulation of zileuton (1200 mg b.i.d.) has been developed and an New Drug Application (NDA) was recently submitted to the FDA for approval. Recently data was released from a 16-week randomised, double-blind, multicentre, placebo-controlled study. A total of 613 patients were randomised into the double-blind dosing period to compare the safety and efficacy of zileuton CR 1200 mg (n = 206) with placebo (n = 203). An arm of the currently approved formulation of zileuton (600 mg q.i.d.) (n = 101) and a zileuton (600 mg q.i.d.) placebo arm (n = 101) were included as a benchmark comparison with previous zileuton (600 mg q.i.d.) efficacy studies. Patients enrolled in the zileuton CR arms had mean FEV₁ values of 58.5%. There was a similar incidence of adverse events in the zileuton CR and placebo groups and the most commonly reported adverse events (≥ 5) were exacerbation of asthma, headache, sinusitis, nausea, nasopharyngitis and pharyngolaryngeal pain. The incidence of elevations in alanine aminotransferase was similar to data reported previously in clinical studies of zileuton (600 mg q.i.d.) (86).

Both of these new formulations are currently in clinical trials.

**Safety**

In placebo-controlled clinical trials, the frequency of liver transaminase (ALT) elevations ≥ 3× upper limit of normal (ULN) was 1.9% for zileuton-treated patients, compared with 0.2% for placebo-treated patients (82). In controlled and uncontrolled trials, one patient developed symptomatic hepatitis with jaundice, which resolved upon discontinuation of therapy. An additional three patients with transaminase elevations developed mild hyperbilirubinemia that was < 3× ULN. There was no evidence of hypersensitivity or other alternative aetiologies for these findings.

In the phase IIIb open-label, long-term safety surveillance study, looking at 2458 patients treated with zileuton in addition to usual care and 489 asthmatics on usual asthma care only, the incidence of liver enzyme increases ≤ 3 or more times ULN occurred in 4.6% of patients in the zileuton group and 1.2% in the usual asthma care group (p < 0.001) (48). These ALT elevations occurred mostly during the first 3 months and there was resolution (to ≤ 2× ULN) in all of the patients with elevations (Figure 5B). Of note, 52% resolved while continuing the drug, having ALT elevations between three and five times ULN, and the remaining 48% resolved (< 2× ULN) upon discontinuation of the drug (mean time of 4 weeks) after cessation of zileuton. Additionally, the monthly risk of an elevation of ALT of 3× ULN in the zileuton-treated group was 2.05% in the first month, decreasing to 1.29% in the second month and to 0.35% in the third month. After the third month, there was no significant difference between the risk of an elevation of ALT 3× ULN for zileuton plus usual care (0.19–0.49%) vs. usual care alone (0.18–0.25%). The magnitude of elevation was independent of the duration of zileuton exposure (48).

Overall, more than 5000 patients have been treated with zileuton in clinical trials. The profile of liver test abnormalities observed strongly suggests a mechanism of liver injury related to a metabolic idiosyncrasy. The mechanisms of idiosyncratic hepatotoxicity are not well understood (87).

Zileuton is contraindicated in patients with active liver disease or transaminase elevations ≥ 3× ULN (82). It is recommended that hepatic transaminases be evaluated at initiation of and during therapy with zileuton (82).

Occurrences of low white blood cell count (≤ 2.8 × 10³/l) were observed in 1.0% of 1678 patients taking zileuton and 0.6% of 1056 patients taking placebo in placebo-controlled studies (85). These findings were transient and the majority of cases returned toward normal or baseline with continued zileuton dosing. All remaining cases returned
toward normal or baseline after discontinuation of zileuton. Similar findings were also noted in a long-term safety surveillance study of 2458 patients treated with zileuton plus usual asthma care vs. 489 patients treated only with usual asthma care for up to 1 year (48,82).

Zileuton is classified as a pregnancy category C (82). There are no adequate and well-controlled studies in pregnant women. Thus, it is recommended that zileuton should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Metabolism and drug interactions**

Zileuton has a rapid oral absorption and a plasma protein binding 93%. The half-life elimination has a mean duration of 2.5 h. There is no effect of age (elderly people, young adults), gender, race and renal insufficiency. Zileuton is metabolised by direct glucuronide conjugation (80–90% of the dose). In vitro studies utilising human liver microsomes have shown that zileuton and its N-dehydroxylated metabolite can also be oxidatively metabolised by the cytochrome P450 isoenzymes CYP1A2, CYP3A and CYP2C9. It is recommended that when taking zileuton, theophylline doses should be reduced by 50% and levels appropriately monitored (48,82). Patients taking propanolol or warfarin should be monitored and the dose adjusted if necessary. Drug–drug interaction studies between zileuton and prednisone and ethinyl estradiol (oral contraceptive) have shown no significant interaction. There is also no significant interaction between zileuton and digoxin, phenytoin, sulfasalazine or naproxen. In a large surveillance study, patients were allowed to continue other asthma medications (ICS, nedocromil, reduced doses of theophylline) as well as other types of drugs including antihypertensives, oral contraceptives and lipid-lowering agents on a case-by-case basis and the safety profile of this study did not differ from the placebo-controlled trials (50,82).

**Conclusion**

In conclusion, the 5-LO pathway results in the formation of leukotrienes, including LTB₄, 5-oxo-ETE and the cysteinyl leukotrienes (LTC₄, LTD₄ and LTE₄). Zileuton is the only commercially and clinically available inhibitor of the 5-LO pathway. In a number of clinical trials, zileuton has been shown to improve airway function and inflammation, asthma symptom control and quality of life in asthmatics. Given the important role that leukotrienes play in airway inflammation, zileuton provides an additional therapeutic option in the chronic management of asthma, particularly severe, difficult-to-treat asthma. In addition, zileuton has shown promise in a number of other conditions, including upper airway inflammatory conditions such as nasal polyps and sinusitis, dermatological disease and COPD. The development of new formulations, including a controlled release tablet formulation for b.i.d. dosing and an intravenous preparation for acute asthma exacerbations may enhance clinical utility and expand therapeutic indications.

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