Zileuton for the Prophylaxis and Chronic Treatment of Asthma

a report by
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Zileuton is the only commercially available leukotriene synthesis inhibitor approved for the prophylaxis and treatment of chronic asthma in adults and adolescents aged 12 years and above. According to the updated and comprehensive 2007 Expert Panel Report 3 (EPR3): Guidelines for the Diagnosis and Management of Asthma, zileuton is an alternative therapeutic option to be added to inhaled corticosteroids (ICS) to enhance asthma control for patients who remain uncontrolled despite using recommended therapy.[1] This article will examine the role of zileuton in asthma management in relation to asthma control as an unmet patient need.

Uncontrolled Asthma Remains an Unmet Need

Despite almost 20 years of global and national guidelines for managing asthma, and despite scientific contributions to understanding its pathogenesis, the burden of this disease remains high.[1] Asthma continues to be associated with mortality, morbidity, and substantial costs to the healthcare system, as well as to the patient. The asthma burden may be higher than estimated as patients, care-givers, and healthcare professionals have been found to overestimate asthma control. The result is that many patients are undertreated, increasing their risk for unwanted symptoms and use of healthcare services, and lowering their ability to participate fully in daily activities.[2]

It was estimated in 2005 that 32.6 million persons—representing more than 11% of the US population—had been diagnosed with asthma during their lifetime. Of those, 22.2 million or almost 8% of the US population had a current diagnosis of asthma, and approximately 55% (12.2 million) suffered an asthma exacerbation during that year. According to national statistics, asthma accounts for 1.8 million emergency department visits annually and almost 500,000 hospitalizations. Eleven people die from asthma every day.[3]

The comprehensive update to the National Heart, Lung, and Blood Institute (NHLBI) Guidelines for Diagnosing and Managing Asthma, the EPR3, released in 2007, places the primary goal for treating asthma on control. This is in contrast to earlier Guidelines that focused on reducing asthma severity.[1] In the EPR3, asthma control is defined according to reductions in two domains: impairment and risk (see *Table 1*). Impairment refers to the frequency and intensity of symptoms and how those symptoms influence the patient's daily life. The goal in reducing impairment thus focuses on reducing asthma symptoms and, ideally, preventing symptoms. Meeting this goal also means that the patient will need little or no rescue medications (for breakthrough symptoms), will have no nocturnal or early morning awakenings due to symptoms, will demonstrate no deficit in pulmonary function, and will be able to lead a normal life, carrying on all activities desired.[1] Risk refers to the potential for negative outcomes, which include symptom exacerbations and associated urgent care (i.e. unscheduled office visits, emergency department visits, hospitalizations), as well as any adverse events associated with treatment.[1]

According to the EPR3, patients who have more than one exacerbation of symptoms a year requiring a short course of oral corticosteroids (OCS) are considered not well controlled.[1] Between May 2006 and May 2007 almost 1.7 million asthma patients received at least one prescription for OCS. This represented the largest single reason for OCS use in the US.[4] What should the physician do when the patient's asthma remains uncontrolled despite optimal therapy? The EPR3 presents a revised step-care approach to therapy, with six steps, each accounting for a progressive drop in asthma control. *Figure 1* shows the medications recommended for use to increase asthma control when a step-up is needed.[1]

According to the updated step-care regimen, zileuton is recommended as an add-on therapy to ICS in both steps 3 and 4: in step 3 it is added to low-dose ICS, the combination providing an alternative to medium-dose ICS; in step 4 it is added to medium-dose ICS, with the combination providing an alternative to medium-dose ICS plus long-acting bronchodilator.[1]

Uncontrolled asthma is not unusual even when patients are using recommended therapy. An analysis of a web-based survey administered to patients with asthma for at least one year who were using multiple controller medications showed that 55% of the 1,812 respondents had uncontrolled asthma as defined by the Asthma Control Test, a self-administered questionnaire.[5]

The reasons for uncontrolled asthma are varied and may reflect genetic heterogeneity and/or different underlying physiological mechanisms that affect how the disease is expressed and how the individual patient responds to specific classes of medication. The variable response of some patients to ICS is well documented, although not clearly understood.[6–9] Additionally, recent evidence suggests that polymorphisms on the β_2-adrenergic receptor are associated with diminished responses to both short- and long-acting β_2-agonists.[10] Finally, multiple asthmatic phenotypes, such as smoking asthmatics, nocturnal asthma, occupational asthma, and exercise-induced bronchospasm, along with a variety of comorbid conditions such as obesity and upper-airway inflammation, influence the variable response to asthma medications.[1] Therefore, targeting multiple inflammatory pathways therapeutically enhances asthma control for many patients.

Table 1: Goals for Improving Asthma Control by Targeting the Domains of Risk and Impairment[1]

Reduction in Impairment	Reduction in Risk
Minimal (ideally no) troublesome symptoms	Minimal (ideally no) symptom exacerbations
No rescue medications needed	No urgent care (unscheduled office visits,
No night-time awakenings due to symptoms	emergency department visits, hospitalizations)
(Near) normal pulmonary function	Minimal (ideally no) adverse events
Normal daily activities	from pharmacotherapy

Figure 1: Step Approach to Asthma Control[1]

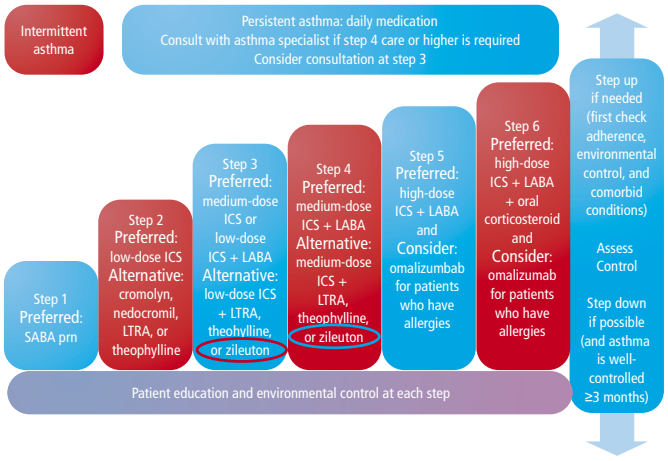
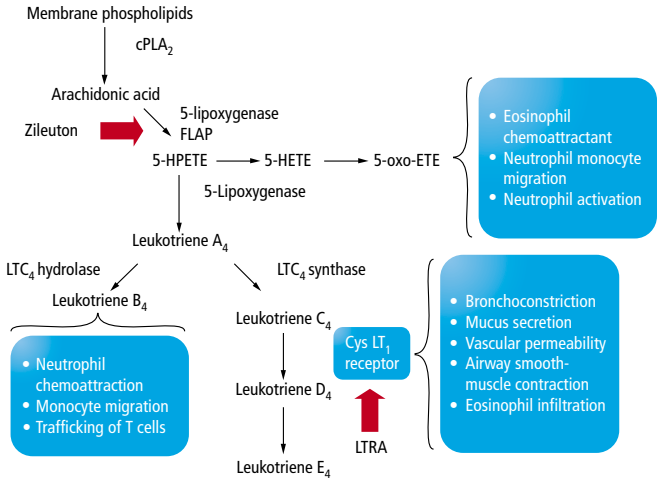


Figure 2: Targeting Leukotrienes in the 5-lipoxygenase Pathway[5]



Arachidonic acid cleaved from membranes by phospholipase A_2 is subsequently metabolized through the 5-lipoxygenase (5-LO) pathway. The initial steps, metabolized by 5-LO, convert arachidonic acid to the unstable intermediary, LTA_4, which is then converted to LTB_4 by LTA_4 hydrolase or to LTC_4 through LTC_4 synthase. The cleavage of LTC_4 creates LTD_4 and LTE_4. 5-LO activates all of the leukotriene receptors (BLT1, BLT2, OXE, $cysLT_1$, $CysLT_2$), thereby contributing to bronchospasm, increased mucus production, increased vascular permeability, and inflammatory cell chemoattraction and chemotaxis. Additionally, the 5-LO intermediary, 5-HpETE, can undergo transformation to 5-oxo-ETE, a potent eosinophil chemoattractant. The 5-LO pathway is activated in many diseases and inflammatory responses may not be completely resolved by glucocorticoids.[5]

Targeting Leukotrienes to Enhance Asthma Control

Leukotrienes are potent lipid mediators synthesized from arachidonic acid, which is cleaved from membrane phospholipids (see *Figure 2*).[5] Leukotrienes are produced by multiple inflammatory cells, particularly mast cells, basophils, eosinophils, neutrophils, and macrophages, all of which have been implicated in asthma pathogenesis. Leukotrienes of interest in asthma include:

- the cysteinyl leukotrienes, $LTC_4/D_4/E_4$, which are involved in bronchoconstriction, mucus secretion, vascular permeability, airway smooth-muscle contraction, and eosinophil infiltration;[5]
- LTB_4, an extremely potent chemoattractant for inflammatory cells (e.g. T-effector cells, eosinophils, neutrophils) and the major 5-lipoxygenase (5-LO) product of neutrophils, monocytes, and alveolar macrophages, which stimulates leukocyte chemotaxis, chemokinesis, and vascular endothelium adherence, delays neutrophil apoptosis, and prolongs neutrophil survival;[11,12] and
- 5-oxo-6,8,11,14-eicosatetraenoic acid (5-oxo-ETE), a chemoattractant for eosinophils that is over 30 times more potent than the cysteinyl leukotrienes; 5-oxo-ETE induces migration of eosinophils and prolongs their survival, activates neutrophils and stimulates neutrophil degranulation, and induces potent basophil migratory responses.[13]

Leukotrienes Are Associated with Uncontrolled Asthma

Leukotrienes are important mediators in asthma pathogenesis, and 5-LO products have been shown to be increased in all levels of asthma severity, despite treatment with ICS and OCS.[5,7,14–16] Multiple studies have demonstrated increases in the 5-LO products 5-HETE, LTB_4, and the cysteinyl leukotrienes, despite corticosteroid treatment; additionally, OCS have not been shown to reduce urinary LTE_4 levels, thought to be a marker of whole-body leukotriene production.[14–16]

There is a strong association between increased leukotriene levels and asthma exacerbations, evidenced by heightened cysteinyl leukotriene production and measurable increases in urinary LTE_4 levels.[17,18] Asthma is a heterogeneous disease, and interest exists in how differences in underlying disease pathology might affect response to treatment. Data exist implicating increased leukotriene levels (measured by urinary LTE_4), an elevated neutrophil:eosinophil ratio, and decreased atopy in some patients who do not show optimal responses to corticosteroids.[6,7]

Related to this, evidence suggests that neutrophilic inflammation may be increased in uncontrolled asthma; an association between neutrophilic inflammation and airflow limitation was recently reported.[19,20] These findings support the concept that non-eosinophilic asthma represents a distinct phenotype with a different epidemiology, underlying pathology, and clinical presentation that includes multiple severe exacerbations and variable responses to corticosteroid therapy. The latter probably reflects the poor response of neutrophilic inflammatory processes to corticosteroids.[21] Indeed, corticosteroids have been shown to prolong neutrophil survival by inhibiting neutrophil apoptosis.[22]

For these patients, pharmacologically targeting 5-LO and subsequent leukotriene production may provide a therapeutic option to enhance asthma control.[1,5] As shown in *Figure 2*, the activity of leukotrienes can be targeted in two ways: first, by blocking the 5-LO enzyme, disrupting synthesis of the cysteinyl and non-cysteinyl leukotrienes using a leukotriene synthesis inhibitor (also referred to as a 5-LO pathway inhibitor) such as zileuton; and second, by antagonizing the $cysLT_1$ receptor to block the action of the cysteinyl leukotrienes with a leukotriene receptor antagonist (LTRA) such as montelukast or zafirlukast.[1,5]

Zileuton

Zileuton is the only US Food and Drug Administration (FDA)-approved leukotriene synthesis inhibitor currently available for the treatment of asthma in the US. Zileuton inhibits 5-LO, thereby blocking the formation of the cysteinyl leukotrienes (LTC_4, LTD_4, LTE_4) and the non-cysteinyl leukotrienes (LTB_4, 5-oxo-ETE; see *Figure 2*). Thus, zileuton is capable of affecting multiple inflammatory mechanisms, including neutrophilic and eosinophilic activity.[1,5]

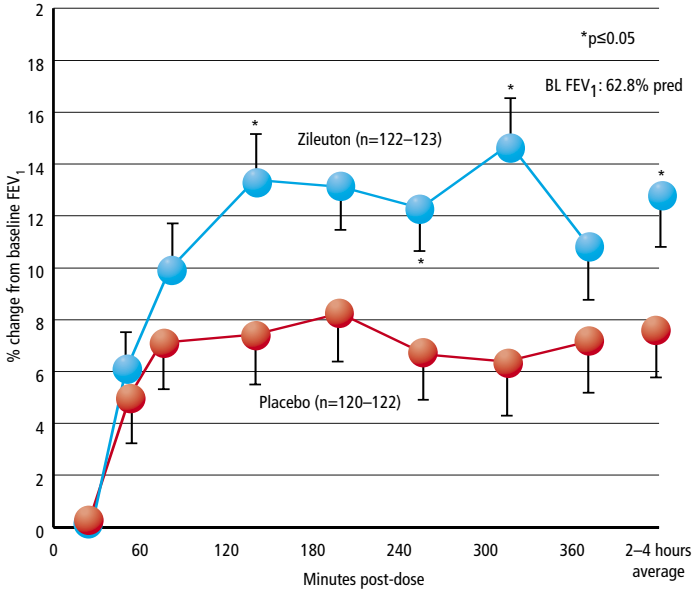
Zileuton given as immediate-release (IR) tablets at a dosage of 600mg four times a day (QID) has been used clinically for more than 10 years; it is now available as a controlled-release (CR) formulation for twice-daily dosing (2x600mg BID) for the prophylaxis and chronic treatment of asthma in adults and adolescents 12 years of age and above. It has been shown to be safe and effective for the treatment of chronic, stable asthma. Clinical studies have demonstrated significant improvements in lung function, daytime and night-time asthma symptoms (including nocturnal awakenings), and need for rescue medications (OCS use and rescue β_2-agonists).[23,24]

Improved asthma control was reported in a six-month study of zileuton IR in 365 patients 18–62 years of age with moderate to severe asthma (mean baseline forced expiratory volume in one second [FEV_1] 62.8% predicted).[23] Patients treated with 600mg zileuton IR QID demonstrated a rapid bronchodilatory effect, with significant increases in FEV_1 from the first dose (see *Figure 3*) through the 176 days of treatment, with no demonstrated tolerance. The mean increase in FEV_1 over the six-month treatment period was 15% for patients treated with 600mg zileuton IR and 7% for placebo-treated patients (p=0.004), an indication of chronic improvement and protection in lung function.[23] A subgroup analysis showed that the most pronounced effects were evident in patients whose baseline FEV_1 was less than 50% predicted: for these patients the mean increase in FEV_1 over the course of the study was 38% (p=0.005).[23]

Significant reductions in both daytime and night-time asthma symptoms were also observed throughout the six-month period (shown for night-time asthma symptoms; see *Figure 4*).[23] Patients treated with zileuton also had fewer asthma exacerbations (defined as worsening symptoms concomitant with a 33% increase in bronchodilator use, a 20% decrease in FEV_1 from the previous visit, or a 25% decrease in morning peak expiratory flow rate [PEFR]). The need for supplemental OCS to treat exacerbations of asthma was over 20% in the placebo group compared with less than 10% for zileuton IR (p<0.001).[23]

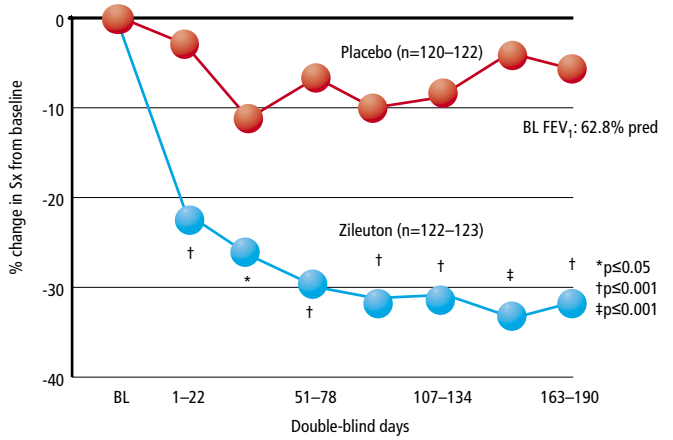
These findings confirm similar results reported for a 13-week placebo-controlled study of zileuton IR in 401 asthma patients.[25] Within 180 minutes of receiving the initial dose, patients treated with 600mg zileuton IR recorded a mean 13.4% increase in FEV_1 compared with a 7.5% increase in the placebo group (p=0.03).[25] Over the course of the 13-week treatment period, the mean changes in FEV_1 were 15.7 and 7.7% for the zileuton IR and placebo groups, respectively (p=0.006). In this study, patients treated with 600mg zileuton IR had significantly more symptom-free days (14.7 versus 8.5; p=0.01) and symptom-free nights (39.5 versus 29.0; p=0.009), and fewer required supplemental OCS for asthma exacerbations (6.1 versus 15.6%; p=0.02).[25]

Figure 3: Improvement in Forced Expiratory Volume in One Second with Zileuton Immediate-release 600mg QID—First-dose Effect



A total of 365 patients (18–62 years of age) with asthma were enrolled in this study, which looked at the effects of zileuton immediate-release (IR) 600mg four times a day (QID) (n=122–123) compared with zileuton IR 400mg QID (n=119–120) and placebo (n=120–122). Only the data for the indicated dose of 600mg QID (IR formulation) are shown.[23]

Figure 4: Reductions in Nocturnal Asthma Symptoms with Zileuton Immediate-release 600mg QID



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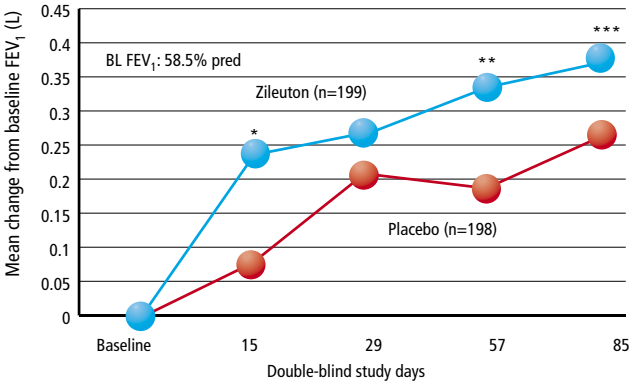
A three-month study of zileuton CR extends these results, showing similar improvements in asthma control with a twice-daily formulation.[24] This study included 591 patients aged 12 years and above (mean age 33.3–35.3 years) who were diagnosed with persistent asthma and who had been treated only with short-acting bronchodilators prior to the study. The mean % predicted FEV_1 at baseline was 58.5%. The patients were randomized to 12 weeks of treatment with 1,200mg zileuton CR BID administered within one hour of morning and evening meals (n=199) or matching placebo (n=198). IR control groups were included: 600mg zileuton IR QID (n=97) and IR placebo (n=97).[24]

Figure 5: Improvement in Forced Expiratory Volume in One Second with Zileuton Continuous-release 1,200mg BID—Chronic Trough Effect[24]



*p≤0.001, zileuton CR versus placebo CR
**p≤0.01, zileuton CR versus placebo CR
***p≤0.05, zileuton CR versus placebo CR

At trial end, patients treated with zileuton CR showed a 21% increase in FEV_1 relative to baseline; patients on placebo had a mean 12% increase over baseline (see *Figure 5*). The difference was statistically significant (p=0.02). The improvement in FEV_1 was evident despite a 15.1% reduction in daily use of beta-agonists in the zileuton CR group; the placebo group showed a 2.3% reduction (p=0.009). Enhanced asthma control was also evident by fewer symptom exacerbations reported by patients treated with zileuton CR.[24] In the zileuton CR study, all treatments were well tolerated with no statistically significant between-treatment differences. The safety profile of zileuton CR was similar to that reported in studies for zileuton IR.[24]

Zileuton is generally well tolerated, but a small number of patients have experienced elevations in alanine aminotransferase (ALT) and bilirubin levels using the IR formulation. A six-month placebo-controlled safety study looked at the CR formulation (1,200mg BID) added to the usual care of patients with moderate asthma. A total of 926 patients were included: 619 received zileuton CR and 307 received placebo.[26] The primary safety variable was an ALT elevation of three times or more than the upper limit of normal (>3xULN), which was observed in 1.8% of patients treated with zileuton CR compared with 0.7% of the placebo-treated patients. The majority of elevations were reported within the first three months of treatment and resolved (to <2xULN) within 21 days after discontinuation. The hepatic function enzyme elevations attributed to zileuton CR did not result in any serious adverse events, such as jaundice or chronic liver disease, in this study.[26]

Summary

In summary, despite advances in knowledge and updates to guidelines for treatment, asthma control remains an unmet goal for many patients and their physicians. Some patients with persistent asthma continue to have symptoms despite recommended treatment (i.e. ICS with or without the addition of a long-acting bronchodilator). Medications targeting 5-LO and its products (the cysteinyl leukotrienes, LTB_4, 5-oxo-ETE) provide another option for control.

The clinical benefits of 5-LO inhibition in asthma patients who remain symptomatic despite recommended therapy have been demonstrated with zileuton, the only FDA-approved leukotriene synthesis inhibitor currently available. The data show enhanced asthma control with zileuton, as evidenced by acute and chronic improvements in lung function, reductions in daytime and night-time symptoms, decreased asthma exacerbations, and less use of rescue medications. Thus, as demonstrated with zileuton, leukotriene synthesis inhibition may be an important pharmacological strategy to enhance and optimize asthma control in these patients. Current NAEPP asthma management guidelines recommend zileuton as an alternative additional therapy in steps 3 and 4—an option that can be added to ICS when patients remain symptomatic. ■

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