Leukotriene Inhibitors in the Treatment of Allergy and Asthma

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Leukotriene inhibitors are the first new class of medications for the treatment of persistent asthma that have been approved by the U.S. Food and Drug Administration in more than two decades. They also have been approved for the treatment of allergic rhinitis. Prescriptions of leukotriene inhibitors have outpaced the evidence supporting their use, perhaps because of perceived ease of use compared with other asthma medications. In the treatment of persistent asthma, randomized controlled trials have shown leukotriene inhibitors to be more effective than placebo but less effective than inhaled corticosteroids. The use of leukotriene inhibitors has not consistently shown an inhaled-steroid–sparing effect, a reduction in need for systemic steroid treatment, or a cost savings. For exercise-induced asthma, leukotriene inhibitors are as effective as long-acting beta$_2$-agonist bronchodilators and are superior to placebo; they have not been compared with short-acting bronchodilators. Leukotriene inhibitors are as effective as antihistamines but are less effective than intranasal steroids for the treatment of allergic rhinitis. The use of leukotriene inhibitors in treating atopic dermatitis, aspirin-intolerant asthma, and chronic idiopathic urticaria appears promising but has not been studied thoroughly. Leukotriene inhibitors have minimal side effects and are well tolerated in most populations. (Am Fam Physician 2007;75:65-70. Copyright © 2007 American Academy of Family Physicians.)

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Approximately one third of all prescriptions for maintenance therapy in patients with persistent asthma are for leukotriene inhibitors; however, evidence of their effectiveness compared with other treatments is mixed. The popularity of this class of medications is likely because of convenient dosing, perceived ease of use, and concerns about side effects from long-term use of inhaled corticosteroids.

Leukotrienes

Leukotrienes are synthesized in response to many triggers, including receptor activation, antigen-antibody interaction, physical stimuli such as cold, and any stimulation that increases intercellular calcium.[1] These potent inflammatory mediators promote neutrophil-endothelial interactions, inducing bronchoconstriction and enhancing airway hyperresponsiveness. They also stimulate smooth muscle hypertrophy, mucus hypersecretion, and the influx of eosinophils into airway tissues[2]; therefore, inhibition of leukotrienes potentially plays an important role in the treatment of asthma and other allergic conditions such as allergic rhinitis, atopic dermatitis, and chronic urticaria.

Leukotriene-Inhibiting Drugs

Leukotriene inhibitors are either leukotriene receptor antagonists or leukotriene synthesis inhibitors, which act by blocking 5-lipoxygenase activity. The leukotriene receptor antagonists include zafirlukast (Accolate) and montelukast (Singulair); zileuton (Zyflo) is the only leukotriene synthesis inhibitor *(Table 1)*.

MONTELUKAST

Montelukast is administered orally once daily and is approved for treatment of asthma in patients two years or older. The bioavailability is similar regardless of patient age, and absorption is not affected by food. No drug interactions have been documented. Side effects in adults are similar to those found with placebo; they occurred in less than

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	*Evidence rating*	*References*
Leukotriene inhibitors are effective in the treatment of asthma but are less effective than inhaled corticosteroids.	A	6
Leukotriene inhibitors added to inhaled corticosteroids are less effective than long-acting beta$_2$ agonists added to inhaled corticosteroids in the treatment of asthma.	A	7, 9, 11, 12
Leukotriene inhibitors are alternative treatments in exercise-induced asthma and can be of benefit for children when oral therapy is preferred over inhalers.	B	12, 13, 16-20
Leukotriene inhibitors are effective in the treatment of allergic rhinitis but are less effective than intranasal corticosteroids.	A	27, 28, 30

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, see page 13 or http://www.aafp.org/afpsort.xml.

2 percent of patients six to 14 years of age. Montelukast is classified by the U.S. Food and Drug Administration (FDA) as pregnancy category B.[3]

ZAFIRLUKAST

Zafirlukast is approved for treatment of asthma in patients seven years or older. The most common adverse effects are pharyngitis, headache, rhinitis, and gastritis. Transient reversible increases in liver enzymes and reports of rare but significant liver dysfunction (including liver failure) have prompted recommendations against prescribing this drug to patients with hepatic dysfunction and recommendations to monitor liver enzymes every two to three months. Zafirlukast is FDA pregnancy category B.[4]

ZILEUTON

Zileuton is approved for treatment of chronic asthma in patients 12 years or older. Because it is metabolized by the cytochrome P450 isoenzyme system of the liver, zileuton may affect other drugs metabolized by these enzymes such as warfarin (Coumadin), theophylline, and propranolol (Inderal). Approximately 5 percent of patients receiving zileuton had increases in liver enzymes that resolved with discontinuation.[5] The manufacturer of zileuton recommends monitoring liver enzymes before initiation of treatment, once a month for three months, and once every two to three months thereafter. Other adverse effects of zileuton include dyspepsia, abdominal pain, and nausea. It is FDA pregnancy category C.[5]

TABLE 1
Leukotriene Inhibitors for the Treatment of Allergy and Asthma

Drug	*Age and recommended oral dose*	*Therapeutic issues*	*Approximate monthly cost**
Montelukast (Singulair)	Adults: 10 mg before bed Children six to 14 years: 5 mg before bed Children two to five years: 4 mg before bed	Renal adjustments: none Hepatic adjustments: in mild to moderate disease	$104.40 (4 mg, 5 mg, or 10-mg)
Zafirlukast (Accolate)	Patients older than 11 years: 20 mg twice daily Children seven to 11 years: 10 mg twice daily	Renal adjustments: none Hepatic adjustments: not defined Monitor hepatic enzymes every two to three months Administration with meals decreases bioavailability; take at least one hour before meals or two hours after Inhibits metabolism of warfarin (Coumadin), increasing prothrombin time	$88.10 (10 mg or 20 mg)
Zileuton (Zyflo)	Patients older than 12 years: 600 mg four times daily	Can inhibit metabolism of warfarin, theophylline, and propranolol (Inderal) Monitor hepatic enzymes every two to three months	$273.75 (600 mg)

**—Estimated cost to the pharmacist based on average wholesale prices in Red Book. Montvale, N.J.: Medical Economics Data, 2006. Cost to the patient will be higher, depending on prescription filling fee.*

Leukotriene Inhibitors in the Treatment of Asthma

Many studies have compared leukotriene inhibitors with other asthma treatments. Two Cochrane Reviews evaluated research comparing leukotriene inhibitors with inhaled corticosteroids in the management of recurrent and persistent asthma in children and adults.[6,7] Patients with persistent asthma who received leukotriene inhibitors were 65 percent more likely to experience an exacerbation requiring systemic steroids than patients receiving inhaled corticosteroids. This equates to one out of every 26 patients treated with a leukotriene inhibitor rather than an inhaled corticosteroid experiencing an exacerbation.[6] The addition of leukotriene inhibitors to inhaled corticosteroids did not result in a statistically significant reduction in the need for systemic steroids.[7]

Leukotriene inhibitors also have been evaluated as inhaled-steroid–sparing agents. In these studies, the addition of a leukotriene inhibitor to inhaled corticosteroids did not result in a lower inhaled corticosteroid dose; however, it did result in fewer withdrawals caused by poor control (relative risk = 0.63; 95% confidence interval, 0.42 to 0.95).[7] In contrast, the use of long-acting $beta_2$ agonists in patients treated with inhaled fluticasone (Flovent) 250 mcg can be steroid sparing with the addition of inhaled salmeterol (Serevent), allowing for a 60 percent reduction in fluticasone to 100 mcg while still maintaining overall asthma control.[8]

A recent Cochrane Review summarized the addition of a long-acting $beta_2$ agonist compared with a leukotriene receptor agonist in patients receiving inhaled steroids.[9] This study concluded that in adults with asthma inadequately controlled by low-dose inhaled steroids, the addition of a long-acting $beta_2$ agonist was superior in preventing exacerbations requiring systemic steroids.

One randomized controlled trial (RCT) of 889 patients with incomplete control of asthma symptoms on inhaled budesonide (Rhinocort) found that adding montelukast was clinically equivalent to doubling the dose of budesonide.[10]

As recently as 2002, the National Asthma Education and Prevention Program (NAEPP) and other academic organizations placed leukotriene inhibitors as a third-line add-on agent when intermittent short-acting inhaled $beta_2$ agonists are insufficient; the addition of inhaled corticosteroids was first-line, and long-acting $beta_2$ agonists were second-line agents to short-acting $beta_2$ agonists.[11-13] The NAEPP expert panel report states that leukotriene inhibitors should not be considered a preferred therapy for the treatment of mild persistent asthma but rather an alternative.[13] Leukotriene inhibitors may also be used in combination with inhaled corticosteroids in the treatment of moderate persistent asthma. This recommendation was based on only modest evidence of benefit.[12] The NAEPP expert panel report also included recommendations for managing asthma using the stepwise approach *(Table 2)*.[13]

Leukotriene inhibitors have been shown to have significant benefit over placebo in the prevention of viral-induced asthma exacerbations in children with a history of intermittent asthma. In a study of children two to five years of age with intermittent asthma, montelukast reduced the frequency of upper respiratory infection–induced exacerbation of asthma (number needed to treat [NNT] = 9).[14] No studies have compared leukotriene inhibitors with inhaled corticosteroids for this indication.

Leukotriene inhibitors may have a role in the treatment of acute asthma. High doses of zafirlukast (160 mg) given to patients upon arrival in the emergency department reduced the number of patients who had an extended stay of longer than four hours (NNT = 20). Continuing the drug at a dose of 20 mg twice daily for 28 days also improved outcomes (NNT to prevent one relapse = 20).[15]

Most of these studies have shown that leukotriene inhibitors, when used alone, are more effective than placebo for the treatment of asthma; however, they are less effective than inhaled corticosteroids or long-acting $beta_2$ agonists.[6,7] Two studies of overall treatment costs showed that the combination of salmeterol and fluticasone (Advair Diskus) was more cost-effective than montelukast plus fluticasone.[16,17] It may be reasonable to add leukotriene inhibitor therapy in some situations, such as in children if there is concern about side effects from increasing doses of inhaled corticosteroids. However, leukotriene inhibitors should not be substituted for inhaled corticosteroids when the latter are clinically indicated.

Leukotriene inhibitors have been shown to be more effective than placebo but less effective than inhaled corticosteroids in treating persistent asthma.

EXERCISE-INDUCED ASTHMA

Traditionally, pretreatment with a short-acting $beta_2$ agonist has been used for prevention of exercise-induced asthma. Long-acting $beta_2$ agonists sometimes are used instead to lengthen the duration of protection.[18] Short-acting $beta_2$ agonists provide protection for up to two

hours, whereas long-acting beta$_2$ agonists protect for up to 12 hours. Both montelukast[19] and zafirlukast[20] have shown significant beneficial effects in treatment of exercise-induced bronchospasm when compared with placebo. A single dose of leukotriene inhibitors within one hour before exercise was equal to a long-acting beta$_2$ agonist in preventing exercise-induced asthma.[21]

Notably, over an eight-week study period, the tolerance that some patients developed to long-acting beta$_2$ agonists did not occur in patients receiving leukotriene inhibitors.[22] One review suggests that using leukotriene inhibitors may be preferable to increasing the dose of beta$_2$ agonists.[23] Leukotriene inhibitors can provide a useful alternative in preventing exercise-induced asthma, especially in young children for whom the use of an inhaler may be difficult, or for persons who receive incomplete protection from short-acting beta$_2$ agonists.

TABLE 2
Stepwise Approach for Asthma Management in Infants and Young Children*

Step/Severity	*Symptom occurrence*	*Medications*
Step 1 Mild intermittent	Two or less days per week Two or less nights per month	Short-acting beta$_2$ agonists as needed†
Step 2 Mild persistent	More than two days per week; less than once per day More than two nights per month	Step 1 and low-dose inhaled corticosteroids† *or* inhaled cromoglycate *or* leukotriene modifier *or* theophylline *or* nedocromil (Tilade)
Step 3 Moderate persistent	Daily More than one night per week	Step 1 and low- to medium-dose inhaled corticosteroids and long-acting inhaled beta$_2$ agonists† *or* increased dose inhaled corticosteroid *or* low- to medium-dose inhaled corticosteroid and either a leukotriene modifier or theophylline
Step 4 Severe persistent	Continual or frequent	Step 1 and high-dose inhaled corticosteroid and long-acting inhaled beta$_2$ agonists† and, if needed, systemic corticosteroids

**—Five years or younger.*

†—Preferred treatment.

Adapted from the National Institute of Health. National Asthma Education and Prevention Program. NAEPP expert panel report. Guidelines for the diagnosis and management of asthma—update on selected topics 2002. NIH publication no. 97-4051. Accessed March 23, 2006, at: http://www.nhlbi.nih.gov/guidelines/asthma/execsumm.pdf.

ASPIRIN-INTOLERANT ASTHMA

A double-blind, placebo-controlled RCT of 80 patients has shown that montelukast was more beneficial than placebo in improving forced expiratory volume in one second, improving symptoms, decreasing exacerbations, and providing one more night per week of uninterrupted sleep in patients with aspirin-induced or aspirin-intolerant asthma.[24] Two smaller randomized trials (eight and 40 patients) involving zileuton also support the clinical effectiveness of leukotriene inhibitors in bronchoconstriction induced by aspirin or nonsteroidal anti-inflammatory drugs, as well as for asthma control in patients receiving oral or inhaled steroids.[25,26]

Leukotriene Inhibitors in the Treatment of Allergic Rhinitis

The FDA has approved montelukast for the treatment of allergic rhinitis. Studies show that montelukast was more beneficial than placebo and equally as effective as loratadine (Claritin) for the treatment of seasonal allergic rhinitis. There was only a marginal benefit in adding montelukast to loratadine, and neither montelukast nor loratadine were as effective as intranasal steroids.[27,28] In addition, a recent study comparing montelukast with pseudoephedrine showed equal benefit with no difference in side effects.[29]

A systematic review and meta-analysis compared intranasal steroids, leukotriene inhibitors, and antihistamines in the treatment of allergic rhinitis.[30] Intranasal corticosteroids showed a 12 percent absolute improvement over leukotriene

inhibitors on a weighted mean difference of a composite nasal symptom score. Leukotriene inhibitors were not statistically different from antihistamines for nasal symptoms but were significantly less effective than antihistamines as rated by a score measuring quality of life. Although the combination of leukotriene inhibitors with antihistamines was significantly more effective for nasal symptoms than either alone, this combination was not statistically significant using a score measuring quality of life. There was no statistically significant difference between intranasal corticosteroids and the combination of leukotriene inhibitors plus antihistamines for nasal symptoms, but there was a 3 percent nonsignificant trend supporting intranasal steroid use.[30]

Even if the combination was clinically equivalent to intranasal steroids, the cost of two drugs (leukotriene inhibitor and an antihistamine) would exceed the cost of intranasal steroids alone. Thus, intranasal corticosteroids remain the treatment of choice. The availability of generic second-generation antihistamines argues for the addition of an antihistamine if intranasal steroids do not sufficiently control symptoms.

Leukotriene Inhibitors in the Treatment of Atopic Dermatitis

Experimental data have suggested that leukotrienes may be involved in the pathogenesis of atopic dermatitis. Because the majority of children with atopic dermatitis later develop allergic rhinitis and asthma, it is conceivable that early leukotriene inhibitor use could not only treat atopic dermatitis but also modify the disease course of allergic rhinitis and asthma in children. However, there are only a few small studies of the use of leukotriene inhibitors in the treatment of atopic dermatitis, most of which are either case reports or small randomized crossover trials. Two studies showed small but significant improvements in atopic dermatitis with the use of these agents.[31,32] Another study on the use of either montelukast or zafirlukast in seven patients in a nonrandomized, no-control, add-on usage trial showed that leukotriene inhibitors did not lead to a sustained benefit for extensive atopic dermatitis.[33] The role of leukotriene inhibitors in atopic dermatitis has yet to be defined.

Leukotriene Inhibitors in the Treatment of Chronic Urticaria

Leukotriene inhibitors have been studied as monotherapy or for use in combination with the mainstay of oral antihistamine in the treatment of chronic idiopathic urticaria. One study did show that montelukast was more effective in reducing urticaria activity scores than placebo ($P < .001$) in the treatment of chronic idiopathic urticaria, with a statistically significant decrease in the use of antihistamines as well.[34] Another randomized study comparing the antihistamine desloratadine (Clarinex) with montelukast in treating chronic idiopathic urticaria showed that montelukast was more effective than placebo but less effective than desloratadine.[35] There was no benefit to adding montelukast to desloratadine. This study was limited by a high drop-out rate in the montelukast-only and placebo groups of the study. No leukotriene inhibitors are currently approved for use in chronic urticaria.

Data Sources: The data sources for this review included Medline searches using the key words leukotriene inhibitors, antagonists, receptor blockers and modifiers, asthma, allergic rhinitis, atopic dermatitis, and urticaria.

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