

The Role of Cysteinyl Leukotriene Receptor Antagonists in Asthma Therapy

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As techniques of asthma management have advanced in recent years, a new understanding of the etiology of the disease also has evolved that has implications for treatment. Asthma, even in its milder forms, is now seen primarily as a disease of airway inflammation and as a chronic illness. Cysteinyl leukotriene receptor antagonists (LTRAs), the newest class of therapeutic drugs for treating asthma, possess both anti-inflammatory and bronchodilator properties and may be one of the most promising developments in asthma treatment during the past 2 decades. These drugs join the arsenal of medications already used in asthma management, including inhaled corticosteroids (ICSs), β_2 -agonists, and theophylline. This article will focus on several LTRAs, discussing the results of clinical trials investigating their effectiveness in treating asthma, comparing them to drugs currently used to treat the disease, and suggesting their potential advantage in securing patient adherence to therapy.

OVERVIEW

According to the 1997 Expert Panel Report 2 (EPR-2) from the National Asthma Education and Prevention Program, many cells and cellular elements (in particular, mast cells, eosinophils, T lymphocytes, macrophages, neutrophils, and epithelial cells) play major pathogenic roles in asthma.¹ More specifically, inflammatory cells and their secreted mediators obstruct the airways by spasm of bronchial smooth muscle, hypersecretion of mucus, edema of the bronchial mucosa, infiltration of airway submucosa, and injury and death of mucosal cells with desquamation into the airways.

Leukotrienes (LTs) likewise have a significant role in asthma's inflammatory pathogenesis. Several key characteristics of the asthmatic lung, including bronchoconstriction, microvascular permeability, bronchial hyperresponsiveness, inflammatory cell (eg, eosinophil) accumulation, and mucus hypersecretion, result from LT action.² For example, the release of LTs in lung tissue contributes to sustained bronchoconstriction and may be responsible for maintaining the

increased bronchoconstriction seen in asthma.³ Inhibiting the action of LTs, therefore, may reduce the inflammatory processes, help control symptoms, and prevent future episodes of asthma.⁴

The recently approved LTRA agents block the action of cysteinyl LTs that are released from various inflammatory cells (ie, mast cells, eosinophils, alveolar macrophages, and polymorphonuclear cells) associated with asthma. Although ICSs are still most effective in reducing inflammation in patients with asthma and are recommended by the EPR-2 and the Global Initiatives for Asthma (GINA) guidelines for treatment of all severities of asthma,^{1,5} the EPR-2 guidelines do list LTRAs as an alternative monotherapy to ICSs or chromones for the control of mild, persistent asthma (**Table 1, Step 2**). Moreover, the 1998 revision of the GINA guidelines designates LTRAs as possible therapy for both mild, persistent, and moderate, persistent, asthma.⁵

Data from several clinical trials suggest that the LTRAs may play a role in controlling and preventing asthma symptoms in mild, moderate, and even severe asthma.⁶⁻¹² First of all, LTRAs have been shown to be effective both alone and as add-on treatment to other controller agents (primarily ICSs) in patients with mild-to-moderate asthma.^{6,7,9} Secondly, LTRAs may provide added control to that already provided by ICSs in patients on high doses of ICSs.^{8,12} Thirdly, the additive effect of LTRAs may permit reducing or tapering the necessary ICS dose in patients whose symptoms have been controlled.^{10,11} Additionally, LTRAs may be effective in treating induced forms of asthma (eg, exercise-induced,^{13,14} aspirin-induced,¹⁵ or allergen-induced^{16,17}).

LEUKOTRIENE ANTAGONISTS

Site of Action

Arachidonic acid (after being newly cleared from cell membrane phospholipids by a phospholipase A_2 in activated eosinophils, mast cells, and alveolar macrophages)

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Table 1. Classification of Asthma Severity and Recommended Approach to Therapy

Severity Classification	Clinical Features Prior to Treatment	Lung Function	Therapy
Step 1 Mild intermittent	Symptoms ≤ 2 times/wk Asymptomatic and normal PEF between exacerbations Exacerbations brief (from a few hours to a few days); intensity may vary Nocturnal symptoms ≤ 2 times/m	FEV ₁ or PEF $\geq 80\%$ of the predicted value PEF variability $< 20\%$	No daily medication needed
Step 2 Mild persistent	Symptoms > 2 times/wk, but < 1 time daily Exacerbations may affect activity Nocturnal symptoms > 2 times/m	FEV ₁ or PEF $\geq 80\%$ of the predicted value PEF variability 20% to 30%	Once daily medication: Inhaled corticosteroid (low dose), cromolyn, or nedocromil <i>or</i> Sustained-release theophylline <i>or</i> Leukotriene modifier
Step 3 Moderate persistent	Daily symptoms Daily use of inhaled short-acting β_2 -agonist Exacerbations affect activity Exacerbations ≥ 2 times/wk and may last for days Nocturnal symptoms > 1 time/wk	FEV ₁ or PEF $> 60\%$ but $< 80\%$ of the predicted value PEF variability $> 30\%$	Daily medication(s): Inhaled corticosteroid (medium dose) <i>or</i> Inhaled corticosteroid (low-medium dose) plus inhaled β_2 -agonist, sustained-release theophylline, or long-acting β_2 -agonist tablets <i>If needed:</i> Inhaled corticosteroid (medium-high dose) plus inhaled β_2 -agonist, sustained release theophylline, or long-acting β_2 -agonist tablets
Step 4 Severe persistent	Continual symptoms Limited physical activity Frequent exacerbations Frequent nocturnal symptoms	FEV ₁ or PEF $\leq 60\%$ of the predicted value PEF variability $> 30\%$	Daily medications: Inhaled corticosteroid (high dose) <i>plus</i> Inhaled β_2 -agonist, sustained-release theophylline, or long-acting β_2 -agonist tablets <i>plus</i> Corticosteroid tablets

FEV₁ = forced expiratory volume in 1 second; PEF = peak expiratory flow.

Adapted from National Asthma Education and Prevention Program: *Guidelines for the Diagnosis and Management of Asthma: Expert Panel Report 2*. Bethesda, MD: US Department of Health and Human Services, Public Health Service, National Institutes of Health, National Heart, Lung, and Blood Institute; 1997. Clinical Practice Guidelines, NIH Publication No. 98-4051.

is converted by the enzyme 5-lipoxygenase into leukotriene A₄ (LTA₄) (**Figure 1**).¹⁸ LTA₄ is an unstable intermediate product that is processed into cysteinyl LTs (LTC₄, LTD₄, and LTE₄), which exert their effects extracellularly. A separate pathway produces LTB₄. The

LTRAs inhibit the binding of cysteinyl LTs to (and the activation of) the cysteinyl LT receptor, thereby blocking cysteinyl LT-mediated actions.¹⁹

Although LTs have a potency 1000 times that of histamines for causing bronchoconstriction, LTRAs have

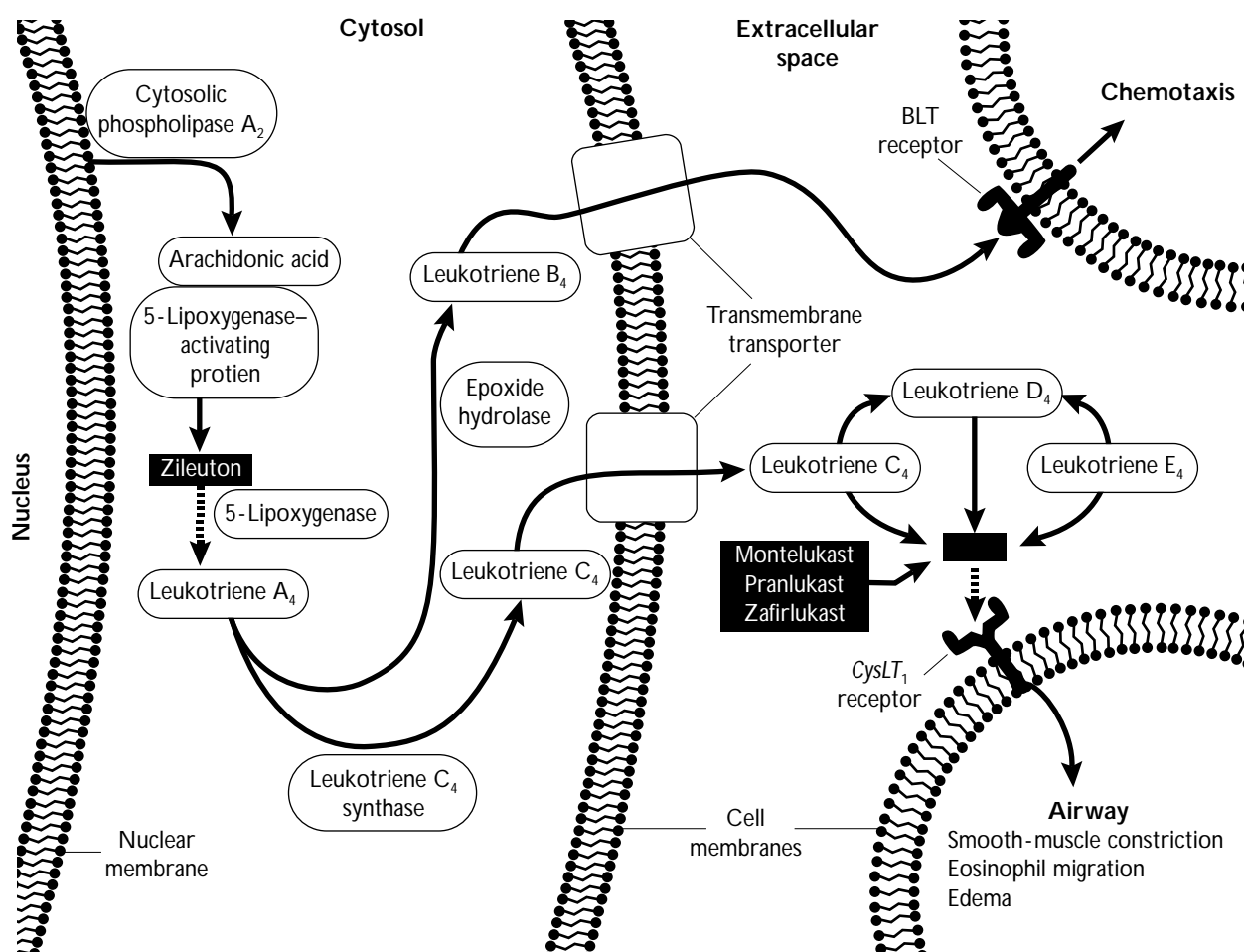


Figure 1. The inflammatory process can be blocked by leukotriene modifiers, corticosteroids, chromones, nonsteroidal anti-inflammatory drugs, and aspirin, all of which interfere with the arachidonic acid cascade at different points in the biosynthesis of inflammatory metabolites. Several of these intervention points provide opportunities to control the inflammatory process in chronic asthma. Enzymes shown: cytosolic phospholipase A_2 , 5-lipoxygenase, leukotriene C_4 synthase, epoxide hydrolase. Products shown: arachidonic acid, leukotrienes A_4 , B_4 , C_4 , D_4 , and E_4 . Essential cofactors shown: 5-lipoxygenase-activating protein. BLT receptor = B leukotriene receptor. Reprinted with permission from Drazen JM, Israel E, O'Byrne PM: Treatment of asthma with drugs modifying the leukotriene pathway. *N Engl J Med* 1999;340:198. Copyright 1999 Massachusetts Medical Society. All rights reserved.

been shown to attenuate this physiologic action substantially.^{20,21} Historically, cysteinyl LTs were referred to as the slow-reacting-substance of anaphylaxis; only later was it understood that cysteinyl LTs could actually promote the airway inflammation, bronchial hyperactivity, and smooth muscle contraction associated with asthma.^{4,22}

Zafirlukast

Zafirlukast, the first LTRA approved by the Food and Drug Administration (FDA), has relieved symptoms of asthma in adult patients with a baseline forced expiratory volume in 1 second (FEV_1) between 40% and 75% of the

predicted value.²³ For patients also using β_2 -agonists on an as-needed basis, zafirlukast caused a dose-dependent reduction in FEV_1 , with patients randomized to the highest dosages showing the greatest benefits. The number of nocturnal awakenings and morning and daytime asthma symptoms were all significantly decreased in patients receiving zafirlukast. A separate study of children age 12 to 17 years produced similar results in terms of asthma relief.²⁴

In a recent placebo-controlled trial involving children age 5 to 11 years, 10 mg of zafirlukast administered twice daily was considered the most effective dosage for

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decreasing dependence on β_2 -agonists and improving pulmonary function as measured by FEV₁, morning and evening peak expiratory flow rates (PEFRs), and peak flow variability.²⁵ Zafirlukast and placebo were similarly well tolerated. These findings suggest that zafirlukast (10 mg twice daily) may be appropriate for the treatment of mild-to-moderate asthma in children.²⁵

Randomized trials have further shown that zafirlukast administered in conjunction with a β -agonist to treat mild-to-moderate asthma is more effective than is a β -agonist alone⁶ and can protect against both exercise-induced²⁶ and allergen-induced^{27,28} bronchoconstriction.

Several trials have reported that use of zafirlukast as an additional therapy can elicit a corticosteroid-sparing effect because the use of an LTRA may preclude the necessity of further increasing the ICS dose to control symptoms in patients already on an ICS regimen.^{10,29} Another study reported that adding zafirlukast (40 or 80 mg twice daily) to a low-dose (336 μ g/day) of beclomethasone was as effective as doubling the beclomethasone dose in relieving asthma symptoms.¹⁰ In a similar trial with patients who were still symptomatic while on moderate (400–500 μ g/day) doses of inhaled beclomethasone, the addition of zafirlukast (20 or 80 mg twice daily) was found to be an effective alternative to doubling the ICS dose in improving asthma symptoms.²⁹ Another study suggested that zafirlukast (20 or 80 mg twice daily) was as effective as a low dose of beclomethasone (200–250 μ g/day) in improving lung function (as measured by FEV₁ and PEFR) and in decreasing dependence on β -agonist use in patients with mild-to-moderate asthma.³⁰

Besides its reported effectiveness in reducing instances of exercise-induced bronchoconstriction,^{26,31} zafirlukast is also being studied as a possible inhibitor of aspirin-induced asthma, an effect already reported for another LTRA.^{15,32}

Zafirlukast requires twice-daily dosing in all patients; the recommended dosage is 20 mg twice daily in adults and children age 12 years and older and 10 mg twice daily in children age 7 to 11 years. Because food reduces its bioavailability, zafirlukast should be taken 1 hour before or 2 hours after meals.³³ Zafirlukast's metabolism is hepatic, so clearance is generally decreased in the elderly and in patients with hepatic impairment.³⁴ Consequently, the elimination half-life of zafirlukast is longer in the elderly and in patients with liver disease than in younger, healthy adults. As an inhibitor of the P-450 cytochrome CYP3A4 system, zafirlukast increases concentrations of other drugs metabolized by this system (eg, warfarin³⁴); theophylline levels also increase after zafirlukast use.³⁵

Montelukast

Montelukast, the most recently approved LTRA, is taken once daily. It has been studied in asthma patients with a baseline FEV₁ between 50% and 85% of the predicted value and has been shown to improve pulmonary function (as measured by FEV₁ and PEFR), decrease dependence on β -agonist use, and ameliorate symptoms in both adults and children (**Figure 2**).^{7,9,36} Other clinical data suggest that the concomitant use of montelukast with ICSs can allow for the gradual reduction of the ICS dose used to control asthma in adults without compromising the efficacy of the ICS therapy.¹¹ Furthermore, montelukast has been shown to attenuate the inflammatory process. Studies have indicated a significant decrease in the blood eosinophil cell levels in both adults and children during the treatment period.^{7,9,36,37} Most recently, montelukast has been shown to reduce sputum eosinophils by 3.7% to 7.5%.³⁷

In children age 6 to 14 years, montelukast taken once daily (in a 5-mg chewable tablet) relieved the symptoms of chronic asthma and significantly improved FEV₁.⁹ Notable reductions in the number of patients with exacerbated asthma and the number of days a patient had asthma exacerbations were observed, as was improvement in parents' global evaluation of their child's symptoms. The principal adverse effects of montelukast (occurring in more than 10% of cases) were upper respiratory infection, headache, asthma, and pharyngitis; however, these effects were similar to those observed in patients receiving placebo.

The FDA recently approved a 4-mg chewable tablet of montelukast to be taken once daily for children age 2 to 5 years. In a 12-week safety study of children in this age group who had a history of physician-diagnosed asthma, the adverse effects of montelukast and placebo were similar to those reported for 6- to 14-year-old children.³⁸ These adverse effects, which had a greater than 10% occurrence rate, most frequently included fever, asthma, upper respiratory infection, and pharyngitis and were seen to occur in patients receiving a placebo at a similar rate. The efficacy of this dose of montelukast (ie, a 4-mg chewable tablet) was further evaluated in the same age group using exploratory endpoints because the children were too young to perform the standard measurements of pulmonary function.³⁶ Montelukast compared favorably to placebo in the following ways: significantly decreasing the number of days with symptoms, the days requiring β -agonist use, and the peripheral blood eosinophil level; increasing the number of days without asthma; and improving the daytime asthma symptoms score, the corticosteroid rescue, and the physicians' global evaluation.

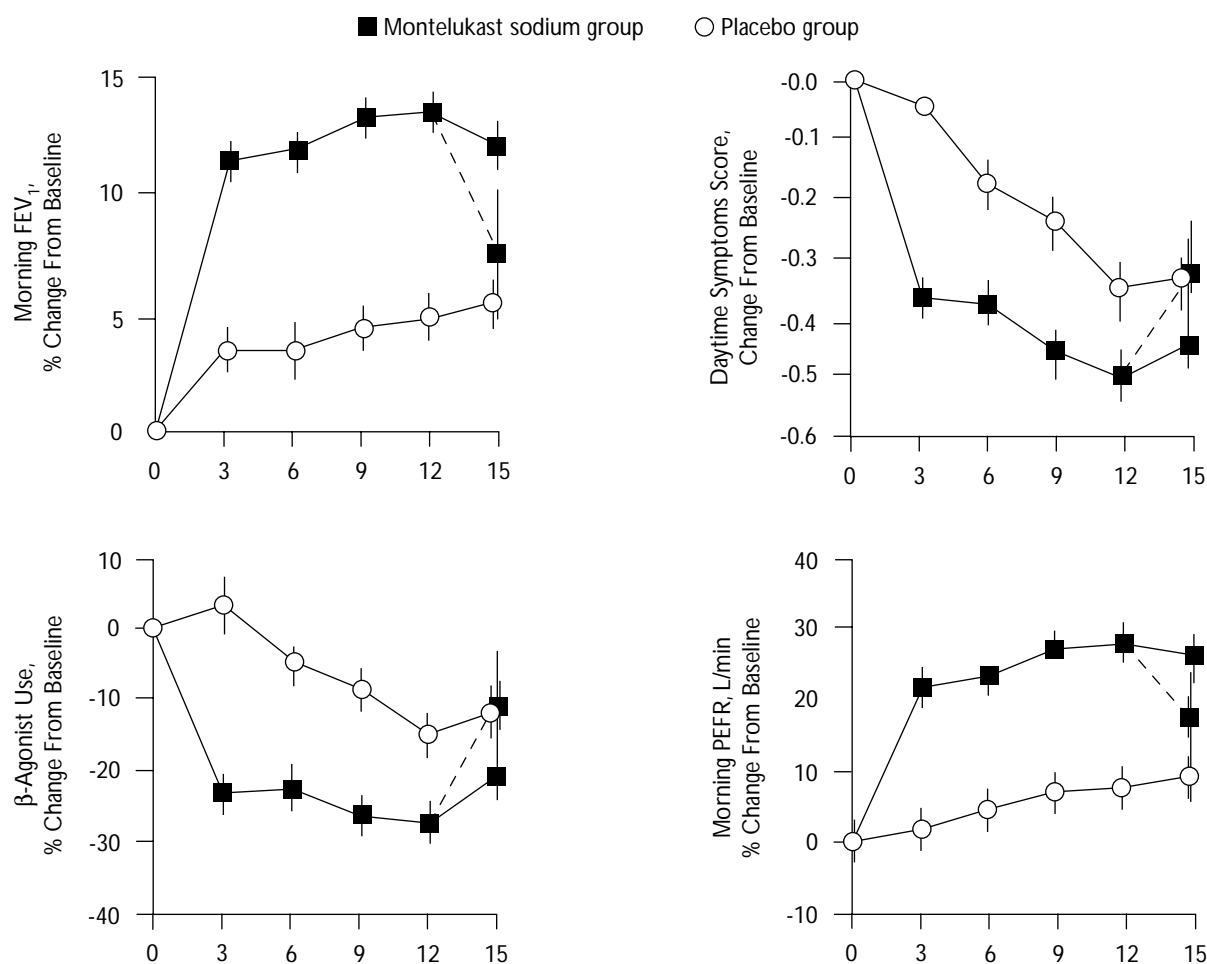


Figure 2. The effect of montelukast sodium and placebo on forced expiratory volume in 1 second (FEV₁), daytime asthma symptoms score, as-needed β -agonist use, and peak expiratory flow rate (PEFR) during the 12-week active treatment period and the 3-week placebo washout period. FEV₁ was measured at every visit; PEFR, daytime asthma symptoms, nocturnal awakenings, and as-needed β -agonist use were recorded daily by the patients. Montelukast, in contrast to placebo, caused significant ($P < 0.001$) improvements in all endpoints. The dashed line represents a patient subgroup switched to placebo in the placebo washout period. The values reported are mean \pm SE. Reprinted with permission from Reiss TF, Chervinsky P, Dockhorn RJ, et al: Montelukast, a once-daily leukotriene receptor antagonist, in the treatment of chronic asthma: a multicenter, randomized, double-blind trial. Montelukast Clinical Research Study Group. *Arch Intern Med* 1998;158:1213-1220.

Other studies have examined the efficacy of montelukast in treating exercise-induced forms of asthma.^{13,39} According to these reported results, montelukast effectively prevented attacks induced by exercise in both adult (Figure 3) and pediatric patients. Both populations receiving montelukast demonstrated an inhibition of postexercise reductions in FEV₁ when compared with groups receiving placebo. Compared with the long-acting inhaled β_2 -agonist salmeterol, montelukast was superior in preventing exercise-induced bronchoconstriction, and its use did not result

in tolerance.⁴⁰ Moreover, over the course of the study, the bronchoprotective effect of montelukast was consistent, whereas that of salmeterol decreased. Montelukast also appears to improve symptoms associated with aspirin-induced¹⁵ and allergen-induced¹⁷ asthma.

Several trials have suggested that montelukast, like zafirlukast, improves pulmonary function and controls asthma symptoms to a degree that is statistically similar to that obtained with a low dose (200 μ g/day) of beclomethasone (although beclomethasone is slightly more efficacious).^{41,42} In a recent randomized,

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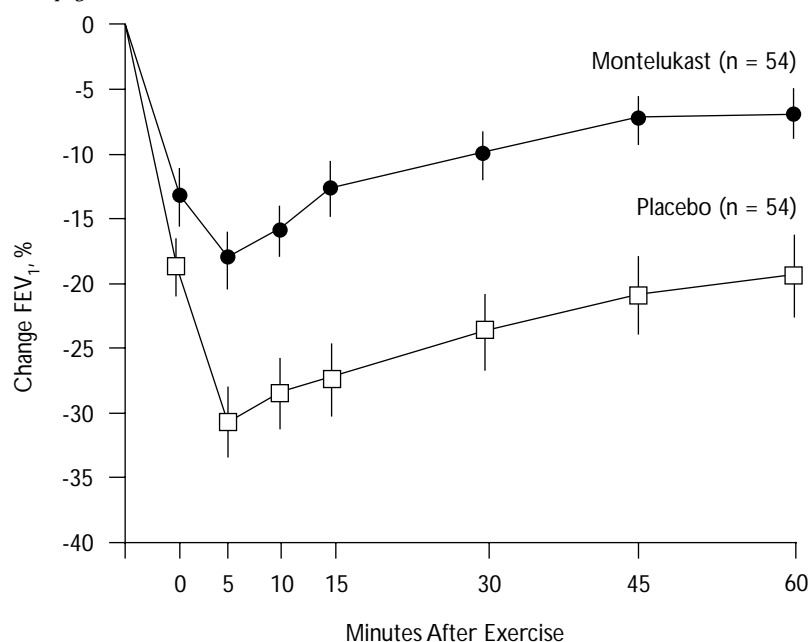


Figure 3. Mean (\pm SE) changes in forced expiratory value in 1 second (FEV₁) after exercise challenge after 12 weeks of treatment with montelukast or placebo. Treatment with montelukast was associated with a significant ($P = 0.002$) reduction in exercise-induced bronchoconstriction. Reprinted with permission from Leff JA, Busse WW, Pearlman D: Montelukast, a leukotriene-receptor antagonist, for the treatment of mild asthma and exercise induced bronchoconstriction. *N Engl J Med* 1998;339:147-152. Copyright 1998 Massachusetts Medical Society. All rights reserved.

double-blind, placebo-controlled study of 895 patients with chronic asthma (FEV₁ 50% to 85% of the predicted value), beclomethasone showed a decrease in the daytime symptoms score of 0.62, whereas montelukast showed a reduction of 0.41 (reduction in placebo, 0.17).⁴¹ Although beclomethasone had a greater mean clinical benefit than montelukast, montelukast had a more rapid onset and greater initial effect during the first week of treatment. For patients who have required moderate-to-high ICS doses for asthma control, montelukast (10 mg administered once daily) can allow for the tapering of ICSs while maintaining symptom control.¹¹

Montelukast is taken orally, once daily; its bioavailability is unaffected by food intake. The recommended daily dose is 10 mg daily for adults, 5 mg daily for children age 6 to 14 years, and 4 mg daily for children age 2 to 5 years. Although metabolized through the P-450 enzyme system, montelukast does not interfere with enzyme functions and thus does not markedly alter the plasma half-life of coadministered drugs, resulting in a profile of no drug interactions.^{43,44}

LEUKOTRIENE INHIBITORS COMPARED WITH OTHER ASTHMA MEDICATIONS

To facilitate asthma management decisions, medications are now classified into 2 major groups: long-term controllers (primarily anti-inflammatory agents directed at maintaining control of persistent asthma) and short-term relievers (directed at acutely relieving symptoms and exacerbations). Long-term controllers include

corticosteroids, cromolyn, nedocromil, long-acting β_2 -agonists, theophylline, the LT synthesis inhibitor zileuton, and LTRAs. Long-acting inhaled β_2 -agonists, which have not exhibited consistent anti-inflammatory effects, should be used as a corticosteroid-sparing or -reducing agent only in conjunction with anti-inflammatory therapy and not as monotherapy.¹ Both montelukast and zafirlukast can be used as first-line asthma controller therapy in patients with mild persistent asthma who experience daytime symptoms 2 or more times per week and nocturnal symptoms more than 2 times per month (Table 1, Step 2).¹

Inhaled Corticosteroids

Early intervention using anti-inflammatory ICSs in patients with mild persistent asthma can diminish irreversible damage to the airways.^{1,45} In light of this fact, ICSs have been introduced at an increasingly earlier stage and higher dose than had been initially established.⁴⁶ Although necessary, this more aggressive use of ICSs does increase the potential for the adverse effects associated with long-term ICS use. Whereas the reported adverse effects associated with ICSs are fewer than those associated with oral corticosteroids, they are worth noting and include adrenal function suppression, osteoporosis, glaucoma, ocular hypertension, and cataracts.⁴⁷⁻⁵¹ These effects are more pronounced when ICSs are administered at high doses and for prolonged periods of time. It should be noted that many of these adverse effects were more likely to occur in older patients and that some of the studies cited used relatively high dosages of ICSs.

The exact nature of the adverse effects of ICSs in children is still controversial, but diminished linear growth and changes in bone metabolism in pediatric patients are concerns that have been raised,⁵² prompting the FDA to include the following wording in the mandated label warning (even without any evidence of hypothalamo-pituitary-adrenal axis suppression): "Orally inhaled steroids may cause a reduction in growth velocity when administered to pediatric patients."⁵³ However, recent studies examining the effect of the ICS budesonide on growth in children have suggested that any growth reduction is temporary and does not affect adult height.^{54,55} The potential growth effects of prolonged treatments in children should be weighed against the availability, cost, and effectiveness of noncorticosteroidal treatment alternatives. To minimize the effects of corticosteroids, each physician should monitor the patient's symptoms and taper use of ICSs to the minimal therapeutic dose with the help of another controller that reduces inflammation.

A promising development reported in several preliminary findings is that a combined therapeutic regimen consisting of ICSs with LTRAs has allowed significant reductions in corticosteroid doses used (compared to the doses needed when corticosteroids only are prescribed), with equivalent control of asthma symptoms.^{10,11,29} As discussed earlier, studies of patients with mild-to-moderate asthma indicate that LTRAs may be an effective alternative to ICSs for those patients who do not respond to the effects of corticosteroids or do not adhere to their corticosteroid therapy.^{29,42}

A small number of patients experiencing symptoms compatible with severe asthma have exhibited a granulomatous eosinophilic vasculitis known as Churg-Strauss Syndrome (CSS). This rare syndrome, which is associated with asthma, is in fact often misdiagnosed simply as asthma. Patients with CSS have very difficult symptoms to manage and most often require either oral or inhaled corticosteroids as treatment. The syndrome most often manifests itself in the setting of corticosteroid reduction prompted by additional controller medication.⁵⁶⁻⁵⁹ Symptoms generally improve when the corticosteroid treatment is reinstated.

CSS has been reported in a very small number of patients using LTRAs; to date, no relationship has been established between CSS and LTRAs.⁵⁷⁻⁵⁹ The most consistent explanation of the association of CSS with LTRAs is that the LTRAs permit a reduction of oral or inhaled corticosteroid use, thereby permitting previously undiagnosed CSS to be unmasked and exhibited.^{58,60} However, because CSS has been documented in asthmatic patients who were treated with zafirlukast, mon-

telukast, and pranlukast,⁵⁷⁻⁵⁹ information about CSS is now included in their respective package inserts.

The appearance of CSS is not limited to patients taking LTRAs but in fact has been documented in corticosteroid-dependent asthmatic patients who exhibited the syndrome when prednisolone was discontinued or tapered.⁶¹ Use of fluticasone, one of the more potent ICSs that has allowed tapering of oral corticosteroid doses, has also been accompanied by manifestations of CSS; a letter has been published indicating that this information about CSS would be added to the package insert of fluticasone (similar to the information added for LTRAs).⁶²

β_2 -Agonists

Long-acting β_2 -agonists, which directly cause bronchodilation, may be employed in conjunction with ICSs, whereas short-acting β_2 -agonists are considered the primary rescue agent when significant acute symptoms develop. Although the LTRAs begin to act within hours, β_2 -agonists begin to act within minutes. Therefore, LTRAs are not indicated for use as reliever or rescue agents with these drugs. Use of either long- or short-acting β_2 -agonists, however, may lead eventually to tolerance and a consequent diminishing of their bronchoprotective effects.⁴⁰ The overuse of reliever therapy, combined with the underuse of controller anti-inflammatory medication, may result in increased asthma morbidity and mortality.⁶³ Thus, β_2 -agonists are generally most effective in therapy intended to alleviate either episodic asthma exacerbations or induced or intermittent symptoms of asthma.

Use of long-term controller agents such as LTRAs in combination with a β_2 -agonist reliever agent represents a promising strategy for managing some kinds of induced asthma (eg, that induced by exercise or allergens). When these agents are used together, the effects are additive, indicating that their mechanisms of action are unique.⁶⁴ Whereas β_2 -agonists work through sympathomimetic effects, LTRAs block the direct bronchoconstrictive actions of LTs; consequently, the combination provides additive effects.

TREATMENT ADHERENCE AND ADDITIONAL CHALLENGES IN ASTHMA MANAGEMENT

The rate of nonadherence to treatment among patients with asthma ranges from 30% to 70%.⁶⁵ This problem is common to all chronic diseases in which successful treatment produces long remission periods. For asthma management, adherence typically requires a patient to be able to correctly administer inhaled medications daily. Effective long-term therapy often

requires self-monitoring of pulmonary function with a peak-flow meter and a working knowledge of what environmental insults, activities, and other causative factors to avoid. In cases involving children and the elderly, effective communication with the caregiver is vital.

Nonadherence to treatment is costly. Approximately \$3 billion of the \$6.2 billion total cost of asthma management incurred in the year 1990 resulted from emergency department visits and hospitalizations (Table 2); many of the patients involved in these situations were repeat presenters.⁶⁶ Although only approximately 5% to 10% of patients with asthma require hospitalization, this relatively small number of patients generate approximately 70% of the total caregiving costs of asthma.⁶⁷ Programs designed to improve self-management have achieved significant savings through reduced hospitalizations and emergency department use.^{67,68} However, greater ease of drug administration and simplification of dosage regimens are key steps to improving adherence and avoiding acute exacerbations.

A study of inhaled medications in children with asthma reported that 71% of patients adhered to therapy with twice daily dosing, 34% with 3-times daily dosing, and 18% with 4-times daily dosing.⁶⁹ Another article stated that more than 90% of the patients studied exaggerated their self-disclosed use of ICSs, which was monitored electronically, and low rates of compliance were associated with the exacerbation of asthma.⁷⁰ In adolescents, once daily dosing with theophylline tablets has been shown to lead to significantly superior adherence versus twice daily administration of ICSs or 4-times daily cromolyn.⁷¹ Adolescents by nature are prone to have adherence problems with inhaled medications for reasons of inconvenience, peer perceptions, and inhaler coordination difficulties.^{72,73} Assessment of inhaler technique showed that 44% of patients could not perform all essential steps of correct inhaler use despite growing awareness of the problem on the part of physicians.⁷⁴ A recent study showed that only 35 (29%) of 122 adolescents could use their inhalers correctly at study entry and, after 4 weeks of treatment and instructions, 14% were still unable to perform all essential steps correctly. The steps that caused these patients the greatest problems were "holding breath for 10 seconds" and "tilting the head back at dosing"; patients also stated a preference for the simplicity of dosing with tablets versus inhalers.⁷⁵

Oral LTRAs taken once or twice daily offer the possibility of superior adherence to therapy and thus more consistent control of inflammation compared with what is offered by inhaled therapies. On the other hand, whereas an oral LTRA taken once or

Table 2. Costs of Asthma in the United States, 1990

Category	Cost* (in millions of dollars)
Direct costs	
Hospital care	
Inpatient	1,559.6
Emergency department	295.0
Outpatient	190.3
Physicians' services	
Inpatient	146.0
Outpatient	347.0
Medications	1,099.7
All direct expenditures	3,637.6
Indirect costs	
School days lost	899.7
Loss of work	
Outside employment	
Men	134.8
Women	211.5
Housekeeping	503.0
Mortality	
Men	390.2
Women	429.1
All indirect costs	2,568.4

*Column may not add up to totals shown, because of rounding.

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twice daily might produce excellent adherence, it would most likely not have as large a magnitude of efficacy as most ICSs, especially at higher ICS doses. Yet the effectiveness of a drug in a real-world setting, as opposed to the setting of a controlled clinical trial, is a function of both adherence and efficacy. Therefore, it is possible that the effectiveness of LTRAs might be comparable to that of ICSs in some patients. Although few studies have investigated this possibility, an extension study of montelukast beyond the 12-week clinical trial showed montelukast to be as effective as low-dose beclomethasone.⁷⁶

CONCLUSIONS

Given the controversies surrounding extended use of long-acting β_2 -agonist drugs, the potential benefits

of additional treatment uses and strategies involving LTRAs seem clear. As a controller therapy, LTRAs appear to have a significant role in reducing asthma not controlled by β_2 -agonists alone in patients who experience symptoms more than twice per week.

The LTRAs montelukast and zafirlukast, which are the first new antiasthma agents produced in more than 2 decades, have the potential to provide major therapeutic benefits in asthma management. That LTRAs can improve symptoms of patients already on ICSs could indicate their ability to inhibit a different part of the inflammation sequelae not efficiently blocked by traditional corticosteroid therapy.^{8,9} Leukotriene modifiers, then, are promising agents for combination treatment strategies and for potential reductions in long-term corticosteroid dosing.

Studies have indicated that LTRAs can provide excellent control and long-term reliability in treating asthma.⁷⁶ In fact, the targeted mechanism of action of LTRAs and the protective role they potentially play in cases of ingestion of aspirin or nonsteroidal anti-inflammatory agents^{15,32} may cause them to become the treatment of choice for aspirin-sensitive patients with asthma. LTRAs also have provided caregivers with a new therapeutic option that is both safe and effective in pediatric patients as young as age 6 years for montelukast and 12 years for zafirlukast. Neither montelukast nor zafirlukast requires clinical monitoring in most patients, and there is no need to monitor serum transaminase enzyme levels as there is for the LT modifier zileuton. Moreover, LTRAs do not become less efficacious when used in long-term treatment, in contrast to salmeterol^{40,77,78} and ICS,^{79,80} both of which lead to the development of tolerance. Finally, the easier once or twice daily dosing requirements of LTRAs may encourage better patient adherence to therapy.

Nevertheless, the challenge in asthma management is not only pharmacologic. In view of the many psychosocial factors of this disease, the effective management of asthma requires a strong individual caregiver-patient relationship. An ongoing team effort involving the physician and the patient or, in the case of pediatric patients, involving physicians, parents, and schools is required. The advent of effective and easily tolerated anti-inflammatory oral agents such as the LTRAs should facilitate achieving these goals in effective asthma management.

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