Asthma is a complex syndrome characterized by variable obstruction to airflow, bronchial hyperresponsiveness, and inflammation. The initiation and propagation of airway inflammation arises from many factors, including mediators generated by resident airway cells and recruited leukocytes. Leukotrienes are biologically active fatty acids derived from the oxidative metabolism of arachidonic acid, an integral component of the cell membrane. A role for leukotrienes in the pathogenesis of asthma has been suggested by their biologic activities, which produce effects that mimic those of clinical asthma, and by the effects of either inhibition of leukotriene production (5-lipoxygenase inhibitors) or antagonism of leukotriene binding to cellular receptors (leukotriene D$_4$-receptor antagonists). The recent U.S. Food and Drug Administration (FDA) approval of a leukotriene-receptor antagonist, zafirlukast (Astra), and a leukotriene synthesis inhibitor, zileuton (Zyflo), provides the first mediator-specific therapy for asthma. This review will consider the biochemistry of the leukotrienes, their biologic role in asthma, and the therapeutic potential of drugs that alter the production or action of leukotrienes, as well as provide guidelines for the use of leukotriene modifiers in patients with asthma.

**LEUKOTRIENE SYNTHESIS AND METABOLISM**

Leukotrienes are formed from arachidonic acid that is released from the cell-membrane phospholipid bilayer by phospholipase A$_2$ (PLA$_2$) (Figures 1 and 2). The liberated arachidonic acid may then be metabolized by one of several major pathways: the cyclooxygenase pathway, to generate prostaglandins, thromboxanes, and prostacyclin; or the 5-lipoxygenase pathway, to generate the cysteinyl leukotrienes C$_4$, D$_4$, and E$_4$ (2). In humans, 5-lipoxygenase is present only in myeloid cells, i.e., monocytes, eosinophils, basophils, alveolar macrophages, and mast cells. The binding of arachidonic acid to 5-lipoxygenase appears to require the presence of an integral nuclear membrane protein, 5-lipoxygenase-activating protein, which serves as a cofactor to "present" arachidonate to the enzyme. A rachidonate is converted first to an unstable intermediate, 5-hydroperoxy-eicosatetraenoic acid (5-HPETE), and then to the unstable epoxide leukotriene A$_4$. Both of these reactions are catalyzed by activated 5-lipoxygenase, which is translocated to the perinuclear membrane (3).

Leukotriene A$_4$ is a pivotal intermediate in leukotriene biosynthesis and is rapidly converted to either leukotriene B$_4$ (by the cytosolic enzyme leukotriene A$_4$ hydrolase) or to leukotriene C$_4$ (through the action of leukotriene C$_4$ synthase in the nuclear membrane) (4). Once formed, leukotriene C$_4$ is actively transported extracellularly, where glutamic acid is removed to form leukotriene D$_4$ (by $\alpha$-glutamyltranspeptidase), followed by the removal of glycine (by dipeptidase) to form leukotriene E$_4$ (2). These compounds are degraded via an oxidative mechanism, but some leukotriene E$_4$ is excreted in the urine (2).

**LEUKOTRIENES AS MEDIATORS OF ASTHMA**

Leukotrienes can impair mucociliary clearance, enhance mucus secretion, chemotactically attract leukocytes to the airways, and facilitate pulmonary vascular permeability to cause edema. Inhaled leukotrienes C$_4$ and D$_4$ are 1,000 times more potent than histamine in causing airflow obstruction in normal subjects, and have a longer duration of action (5). In patients with asthma, the airways are 100 to 1,000 times more sensitive to inhaled leukotrienes D$_4$ and E$_4$ than are the airways of normal subjects. Inhaled leukotrienes C$_4$ and D$_4$ also increase bronchial hyperresponsiveness to pharmacologic agents, such as methacholine or histamine (6). These responses to exogenous leukotrienes parallel clinical features of airflow obstruction in asthma and suggest a biologic role for these compounds in this disease.

In addition, leukotrienes have been identified in plasma, urine, nasal secretions, sputum, and bronchoalveolar lavage fluid (BA LF) from patients with spontaneous exacerbations of asthma and after antigen challenge (7). U rinary leukotriene E$_4$ measurements can be used to monitor production of leukotrienes in response to selected challenges; for example, basal urinary leukotriene E$_4$ excretion is elevated in aspirin-sensitive asthmatic patients, and increases after aspirin challenge (8). In addition, urinary leukotriene E$_4$ excretion increases during acute exacerbations of asthma (9). These findings, although indirect and correlative, provide evidence that cysteinyl leukotrienes may cause a number of features of asthma.

Leukotriene B$_4$ has been implicated in the airway inflammatory response as well. A $\alpha$ a potent proinflammatory mediator, leukotriene B$_4$ is an attractant for neutrophils, which are associated with nocturnal asthma, and it induces T-lymphocyte production of interleukin 5 (IL-5), which has been correlated with eosinophilia in asthma (10). However, in contrast to the cysteinyl leukotrienes, leukotriene B$_4$ has not been closely linked to asthma, and its specific role in this process is not established.

**MECHANISMS OF MODIFICATION OF LEUKOTRIENE ACTION**

Two approaches have been developed to decrease the action of leukotrienes. One is to block leukotriene synthesis by en-
zyme inhibition, and the other is to interfere with the binding of a leukotriene to its receptor (Figure 2).

Inhibitors of leukotriene synthesis block the formation of both the cysteinyl leukotrienes and leukotriene B\(_4\). These inhibitors can be grouped into two types of compounds based on their site of action. Inhibitors of 5-lipoxygenase bind at or near the active site of this enzyme, and prevent the formation of leukotriene A\(_4\); zileuton is a representative 5-lipoxygenase inhibitor (3). A second class of 5-lipoxygenase inhibitors is thought to represent an acute inflammatory response, and provides a model for the inflammatory component of asthma (15). Leukotriene receptor antagonists and inhibitors of 5-lipoxygenase-activating protein reduce both early- and late-phase reactions to inhaled antigen. 5-lipoxygenase inhibitors can be grouped into two types of compounds based on their site of action. Inhibitors of 5-lipoxygenase block the effects of leukotrienes C\(_4\) and E\(_4\). Representative cysteinyl leukotriene-receptor antagonists, either available now or under investigation, include zafirlukast, pranlukast, and montelukast.

A list of drugs that inhibit leukotriene synthesis and action is shown in Table 1.

### Efficacy of Leukotriene Modifiers on Airflow Obstruction

Asthma is unique among chronic inflammatory conditions of the airways in that diverse factors provoke a reaction with similar symptoms and similar pathologic and physiologic changes. As a consequence, experimental models have been developed to study the pathophysiology of asthma in humans, and have proven useful to assess the efficacy of drugs that reduce leukotriene action in asthma. A representative sample of clinical studies with these agents is summarized in Table 2.

### Antigen-induced Asthma

A antigen inhalation in sensitive patients elicits immediate bronchoconstriction secondary to the release of mast-cell mediators, including leukotrienes (15). Airflow obstruction can also occur 6 to 8 h after antigen challenge; this late-phase reaction is thought to represent an acute inflammatory response, and provides a model for the inflammatory component of asthma (15). Leukotriene receptor antagonists and inhibitors of 5-lipoxygenase-activating protein reduce both early- and late-phase reactions to inhaled antigen. 5-lipoxygenase inhibitors have not improved airflow in such studies, but have atten-

### Table 1

Representative Leukotriene Antagonists and Inhibitors

<table>
<thead>
<tr>
<th>Leukotriene D(_4) Receptor Antagonists</th>
<th>5-Lipoxygenase Activating-Protein Antagonists</th>
<th>5-Lipoxygenase Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zafirlukast (LY 171,883)</td>
<td>MK-886</td>
<td>Zileuton (A 64077)*</td>
</tr>
<tr>
<td>MK-571</td>
<td>MK-0591</td>
<td>ZD 2138</td>
</tr>
<tr>
<td>Verlukast (MK-0679)*</td>
<td>MK-0591</td>
<td>ZD 2138</td>
</tr>
<tr>
<td>Montelukast (MK-0476)*</td>
<td>BAY X1005</td>
<td>A-79175</td>
</tr>
<tr>
<td>Zileuton (IC1 204,219)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pobrilukast (SKF 104,353)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pranlukast (ONO 1078)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* FDA-approved.
† Under investigation and development.

### Table 2

Overview of Representative Studies with Leukotriene Antagonists and 5-Lipoxygenase Inhibitors

<table>
<thead>
<tr>
<th>Asthma Model</th>
<th>Drug</th>
<th>Daily Dosage</th>
<th>Study Duration</th>
<th>No. of Patients</th>
<th>Outcome</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise-induced asthma</td>
<td>Zafirlukast</td>
<td>20 mg</td>
<td>Single dose</td>
<td>8</td>
<td>Attenuation of mean FEV(_1) decrease of 22%; Bronchospasm inhibited 41% versus placebo</td>
<td>Finnerty, et al. (18)</td>
</tr>
<tr>
<td></td>
<td>Zileuton</td>
<td>2.4 g</td>
<td>Single dose</td>
<td>24</td>
<td>FEV(_1) drop attenuated 47%</td>
<td>Meltzer, et al. (20)</td>
</tr>
<tr>
<td></td>
<td>Pobrilukast</td>
<td>893 g inhaled</td>
<td>Single dose</td>
<td>6</td>
<td>4.4-fold right shift of dose-response curve in all patients</td>
<td>Christie, et al. (22)</td>
</tr>
<tr>
<td></td>
<td>Verlukast</td>
<td>750 mg</td>
<td>Single dose</td>
<td>8</td>
<td></td>
<td>Dahlén, et al. (23)</td>
</tr>
<tr>
<td></td>
<td>Zileuton</td>
<td>2.4 g</td>
<td>1 wk</td>
<td>8</td>
<td>FEV(_1) unchanged after challenge/nasal, gastrointestinal, dermal symptoms blocked</td>
<td>Israel, et al. (8)</td>
</tr>
<tr>
<td>Aspirin-induced asthma</td>
<td>Zafirlukast</td>
<td>10 mg, 20 mg, 40 mg</td>
<td>6 wk</td>
<td>276</td>
<td>↑ FEV(_1)*, ↓ symptoms, ↓ β-agonist use; Dose dependent improvement noted</td>
<td>Spector, et al. (24)</td>
</tr>
<tr>
<td></td>
<td>Zileuton</td>
<td>2.4 g, 1.6 g, or placebo</td>
<td>4 wk</td>
<td>139</td>
<td>↑ FEV(_1)*, ↑ PEFR†, ↓ symptoms, ↓ β-agonist use</td>
<td>Israel, et al. (29)</td>
</tr>
<tr>
<td></td>
<td>Zileuton</td>
<td>2.4 g, 1.6 g, or placebo</td>
<td>13 wk</td>
<td>401</td>
<td>↑ FEV(_1)*, ↑ quality of life, ↓ asthma exacerbations requiring oral corticosteroids</td>
<td>Israel, et al. (30)</td>
</tr>
</tbody>
</table>

* FEV\(_1\) denotes the forced expiratory volume in 1 s.
† PEFR denotes the peak expiratory flow rate.
uated the influx of eosinophils into the airway— a hallmark of allergic inflammation in asthma.

Zafirlukast inhibits the action of inhaled leukotriene D4 in both asthmatic patients and normal subjects. In double-blind, placebo-controlled trials, zafirlukast significantly attenuated both the early and the late responses to inhaled antigen, and reduced the bronchial hyperresponsiveness to histamine that normally accompanies antigen inhalation (16). In eight atopic asthma patients given a single 40-mg oral dose of zafirlukast, the FEV1 decreased in response to antigen (grass pollen or dust mite) by only 6%, as compared with a 32% decrease in patients given placebo. The late-phase response to antigen was also significantly weaker in patients treated with zafirlukast (13% decrease in FEV1 versus a 28% decrease in subjects given placebo) (16).

Zileuton has also been evaluated for its effects on antigen-induced allergic airway responses, with varied results. When given in a single 800-mg dose 3 h before an inhaled antigen challenge, zileuton did not significantly diminish either early or late airflow obstruction (9). However, urinary leukotriene E4 excretion, a marker of leukotriene production, was reduced by 50%. In another study, BALF obtained 24 h after bronchial challenge with ragweed antigen contained less leukotriene and fewer eosinophils in subjects pretreated with zileuton (2.4 g/d for 8 d) than in those given placebo (17). Overall, eosinophil migration into the airway was inhibited by more than 80% after administration of zileuton. The effect of zileuton on eosinophil recruitment to the lung suggests an ability to alter this component of the inflammatory response to antigen.

With antigen challenge taken as a model for a component of clinical asthma, leukotriene-receptor antagonists and 5-lipoxygenase-activating-protein inhibitors afford significant protection from bronchoconstriction when given before antigen exposure. Although zileuton does not appreciably alter airway obstruction caused by inhaled antigen, it does inhibit inflammatory-cell egress into the airway. These studies suggest that leukotriene modifiers have antiinflammatory activity.

**Exercise-induced Bronchospasm**

Several leukotriene antagonists have been tested in subjects with exercise-induced bronchospasm (18, 19). In eight asthma patients with documented exercise-induced bronchospasm (defined as at least a 25% decrease in FEV1 from baseline after exercise), pretreatment with a single 20-mg dose of zafirlukast 2 h before exercise reduced the mean maximum decrease in FEV1 after exercise to 22%, as compared with a 36% decrease after placebo (18). In several subjects, zafirlukast completely inhibited exercise-induced bronchospasm. Similar protective effects were found with an inhaled formulation of zafirlukast.

In a double-blind, placebo-controlled crossover study, administration of the leukotriene D4 antagonist MK-571 20 min before an exercise challenge significantly reduced bronchoconstriction; the mean maximal decrease in FEV1 was 9%, as compared with a 25% decrease after placebo (19). Furthermore, the mean time to recovery of baseline FEV1 after exercise was shortened to 8 min after MK-571 administration, as compared with 33 min after placebo administration. These studies suggest a role for leukotriene D4 in exercise-induced bronchospasm, as well as revealing the effectiveness of leukotriene antagonists in this condition.

Zileuton has also been evaluated in patients with exercise-induced bronchospasm. Twenty-four asthma patients who had at least a 20% decrease in FEV1 following an exercise challenge received either zileuton (2.4 g/d) or placebo for 2 d prior to exercise (20). Zileuton did not alter baseline pulmonary function in these subjects, but inhibited exercise-induced bronchospasm by an average of 41% as compared with placebo. Furthermore, 5 min after exercise, the zileuton-treated group had a mean FEV1 value that was 86% of their baseline value, as compared with a 74% value in the placebo group (p < 0.01). On the basis of these studies, 5-lipoxygenase inhibitors and leukotriene D4 antagonists appear equally effective in the treatment of patients with exercise-induced bronchospasm.

**Figure 1.** Structure of leukotrienes relevant to asthma. Cysteinyl leukotrienes C4, D4, and E4 are potent mediators that induce smooth-muscle contraction, vascular leakage (or airway edema), mucus secretion, and eosinophil recruitment into the airway. These studies suggest that leukotriene modifiers have antiinflammatory activity.
Aspirin-induced Asthma

Approximately 10% of adult patients with asthma have aspirin-induced asthma, and severe, life-threatening asthma can follow ingestion of aspirin or other nonsteroidal antiinflammatory drugs (NSAIDs) (21). Although the pathophysiology of this condition is unclear, aspirin inhibits the cyclooxygenase pathway and shunts arachidonic acid through the 5-lipoxygenase pathway to produce more leukotriene B$_4$, C$_4$, D$_4$, and E$_4$ (21). Selective bronchial hyperresponsiveness to leukotriene E$_4$ may contribute to the pathophysiology of aspirin-induced asthma (21).

At present, the most effective treatment for aspirin-induced asthma is avoidance of aspirin and NSAIDs. Aspirin desensitization has been successful in some patients, but is not without risk. Two leukotriene D$_4$-receptor antagonists have shown efficacy in patients with aspirin-induced asthma. The inhaled leukotriene D$_4$ antagonist zileuton partly protected five of six sensitive patients after oral aspirin challenge; the decline in FEV$_1$ was reduced by an average of 47% (22). A nontolerant leukotriene D$_4$ antagonist, verlukast, reduced the sensitivity to inhaled lysine-aspirin in sensitive patients by a factor of four, affording some protection from acute bronchospasm; several patients had complete protection from usually provocative doses of aspirin (23).

In a study of eight patients with aspirin-induced asthma treated with zileuton (2.4 g/d for 7 d) or placebo, and given increasing doses of aspirin every 2 h (8), the FEV$_1$ fell by 19% after placebo, whereas zileuton prevented this fall in FEV$_1$. Zileuton also prevented nasal, gastrointestinal, and dermal symptoms, and inhibited aspirin-induced angioedema in three patients.

Together, these results indicate that leukotriene-induced bronchoconstriction is one component of the pathophysiology of aspirin- or analgesic-induced asthma, and that this response can be effectively attenuated by leukotriene modifiers. Moreover, leukotriene modifiers are currently the only medical therapy effective in attenuating aspirin-induced asthma.

Efficacy of Modifiers of Leukotriene Action in Chronic Asthma

Perhaps the most important and clinically relevant studies of the efficacy of the leukotriene modifiers are those involving patients with chronic asthma. Interpretation of these studies is often difficult, owing to restricted patient populations (patients with mild to moderate asthma), the relatively short duration of the trials, and most importantly, the question of the clinical relevance of modest, albeit statistically significant, improvements in airflow. Despite these drawbacks, measurements of clinical importance, such as the patient's daily requirement for β-adrenergic-agonist drug therapy, nocturnal...
asthma symptoms, or the number of exacerbations of asthma requiring systemic corticosteroid treatment can be assessed and compared.

To evaluate the long-term efficacy of zafirlukast, patients with moderate asthma, treated with either a β₂-adrenergic agonist drug or theophylline, were randomly assigned to treatment with either one of three daily dosages of zafirlukast (10, 20, or 40 mg in divided doses) or to placebo for 6 wk (24). The zafirlukast-treated patients improved both subjectively (asthma symptom score) and objectively (FEV₁, number of nocturnal awakenings, and use of β-adrenergic agonist drugs for rescue), and the degree of improvement showed some degree of a dose-dependent response. The 10-, 20-, and 40-mg doses of zafirlukast were associated with 7%, 6%, and 11% increases in FEV₁ values, respectively.

In an examination of the effect of leukotriene modifiers on asthma exacerbations, an important marker of clinical stability, pranlukast was utilized in 79 asthma patients requiring high-dose inhaled beclomethasone (1,500 μg or more) (25). After a 2-wk run-in period, the dose of beclomethasone was halved and patients were randomly assigned to receive pranlukast 450 mg twice daily or placebo for 6 wk. Pulmonary function measures remained unchanged after 6 wk in the pranlukast-treatment group, whereas the FEV₁ decreased by 10.2% from baseline in the placebo group. Daytime asthma symptoms increased 3-fold in the placebo group, as did the use of relief β₂-adrenergic agonists. Asthma symptoms remained unchanged in the pranlukast group, and mean morning and evening peak-flow measurements remained at or above baseline during treatment. Two patients in the placebo group were withdrawn because of asthma exacerbations. Deterioration of asthma control resulting from reductions in high-dose inhaled beclomethasone was curtailed by pranlukast; thus, pranlukast may provide steroid-sparing effects in patients who require high-dose inhaled corticosteroids to control their asthma (25).

In a 3-mo double-blind, placebo trial involving 681 patients, another leukotriene-receptor antagonist, montelukast, administered in a dose of 10 mg daily, produced significant improvements in pulmonary function endpoints as well as a 31% decrease in asthma exacerbation days, and a 37% increase in asthma-free days (26). In patients requiring inhaled corticosteroids (300 to 3,000 μg/d), montelukast at 10 mg daily allowed 40% of montelukast-treated patients to eliminate inhaled steroid use, versus 29% in the placebo group (27). In another study, aspirin-intolerant patients using inhaled and/or oral corticosteroids received 10 mg of montelukast or placebo in a double-blind, parallel-group, 4-wk trial. Those in the montelukast-treatment group had significantly improved peak expiratory flow rates, diminished nocturnal symptoms, and a decrease in β₂-adrenergic agonist use; fewer days with asthma exacerbations were also reported by the montelukast-treated group (28).

The efficacy of zileuton in patients with chronic asthma has been assessed in several large, multicenter trials. In one study, 139 patients with mild to moderate asthma were treated for 4 wk with placebo or zileuton at 1.6 g/d or 2.4 g/d (29). The patients treated with 1.6 g/d had a 10.9% increase and those treated with 2.4 g/d had a 13.4% increase in FEV₁ (Figure 3). Symptom scores and peak expiratory flow measurements also improved in the treatment groups.

In the largest trial of zileuton, 401 patients with mild to moderate asthma were treated for 13 wk (30). The zileuton-treated patients had an increase of 13.4% in FEV₁ at 3 h after the first dose; after 13 wk of treatment, patients treated with 2.4 g/d of zileuton had a mean 15.7% increase in FEV₁ as compared with a 7.7% increase in the placebo group (p = 0.006). The gradual improvement in FEV₁ suggests that zileuton may influence underlying inflammatory processes in patients with chronic asthma. Six percent of the patients in the zileuton-treatment group required oral corticosteroid treatment for exacerbations of asthma during the study, as compared with 15.6% of the patients receiving placebo (p = 0.02). This "steroid-sparing" effect of zileuton was most evident in patients with a baseline FEV₁ of less than 50% predicted. These results suggest that zileuton may stabilize asthma and prevent exacerbations, a therapeutic action often associated with antiinflammatory activity.

In the longest study of zileuton, 373 patients with mild to moderate asthma were given zileuton at 2.4 g/d or 1.6 g/d or placebo over a 6-mo period (31). Improvements in FEV₁ were demonstrated by Day 8, and patients in the 2.4 g/d group continued to have a significant improvement in FEV₁ measures of up to 19% after 120 d. Daytime and nocturnal symptoms decreased in the zileuton-treatment groups, but were significant only in the 2.4 g/d group. Supplemental systemic corticosteroid use for treatment of asthma exacerbations decreased in both zileuton-treatment groups, with the greatest decrease occurring in the 2.4 g/d group. Zileuton at 2.4 g/d was more effective than at 1.6 g/d in alleviating symptoms and asthma exacerbations and improving pulmonary function measures (31).

In another study of the role of leukotrienes in airway inflammation, zileuton was evaluated in patients with nocturnal asthma. In this trial, 12 patients with nocturnal asthma and six normal subjects were randomly assigned within each group to receive zileuton at 2.4 g/d or placebo for 7 d, at which time they underwent bronchoscopy and lavage both at 4:00 p.m. and 4:00 a.m. (7). Following a 1-wk washout period, the protocol...
was repeated in a crossover design, with the placebo-treated patients now receiving zileuton and vice-versa. BALF obtained at 4:00 A.M. from patients with nocturnal asthma had increased leukotriene B₄ and cysteinyl leukotriene concentrations, and high eosinophil counts. Treatment with zileuton decreased leukotriene concentrations and the nocturnal influx of eosinophils, a marker of airway inflammation. In addition, urinary leukotriene E₄ excretion decreased by 75% after zileuton treatment. Zileuton had no statistically significant effect on pulmonary function, a finding probably due to sample size. Nonetheless, these results suggest that leukotrienes may be involved in the pathobiology of nocturnal asthma, and that 5-lipoxygenase inhibitors can inhibit eosinophil recruitment to the airways in patients with nocturnal asthma.

Currently, there is insufficient information to determine whether inhibitors of 5-lipoxygenase-activating protein are effective in patients with chronic asthma. A recently developed 5-lipoxygenase-activating protein antagonist, MK-0591, has been tested in a placebo-controlled trial in 109 patients taking inhaled corticosteroids (beclomethasone or budesonide at an average dose of 800 µg/d) (32). The addition of MK-0591 improved the mean FEV₁ by 7%, with parallel improvements in peak-flow readings and significant reductions in bronchodilator usage.

THERAPEUTIC ROLE OF THE LEUKOTRIENE MODIFIERS IN ASTHMA

Several questions need to be considered when evaluating the clinical effectiveness of the new drugs that reduce leukotriene action in asthma. First, do the drugs alter the underlying disease process? Second, are these new drugs primarily bronchodilators, antiinflammatory drugs, or both? Lastly, how do these drugs compare with existing asthma medications?

At present, it is difficult to translate the improvement in symptoms, the objective changes in airflow (such as in peak expiratory flow rate or FEV₁), and the alterations in ingress of inflammatory cells into airways that have been noted in clinical trials into specific recommendations for clinical practice. A clinically relevant measure of long-term control of asthma is the number of exacerbations that require systemic corticosteroid therapy. Using this criterion as one marker of effectiveness, zileuton decreased exacerbations of asthma by nearly 50% during 13 wk of therapy when compared with use of a placebo (30). Moreover, both zafirlukast and zileuton decrease nocturnal awakenings, β-adrenergic-agonist drug use, and symptoms of asthma. These results suggest that leukotrienes may modify the severity of asthma and possibly those factors that lead to symptoms.

The classification of leukotriene modifiers as either bronchodilators or antiinflammatory drugs is difficult, and it is more correct to classify them for precisely what they do: modify leukotriene activity. This activity may include effects on airflow tone and inflammation. For example, leukotriene modifiers have modest bronchodilator activity; although no leukotriene modifier has actions that match the rapid onset and overall potency of β-adrenergic agonists, the latter may have additive bronchodilator effects when used in combination with leukotriene modifiers (33). Consequently, leukotriene modifiers affect components of airflow obstruction that are distinct from those affected by β-adrenergic agonists, making them useful adjunctive therapy. It is also conceivable that leukotriene modifiers may have a role in the treatment of acute bronchospasm that is refractory to β-adrenergic-agonist therapy. Clinically, a difference between blocking the end-organ response with leukotriene modifiers, such as zafirlukast and pranlukast, and blocking the synthesis of leukotrienes with 5-lipoxygenase inhibitors, such as zileuton, has not been shown. 5-Lipoxygenase is a ubiquitous enzyme, and blocking the biosynthesis of both the cysteinyl leukotrienes and leukotriene B₄ may confer additional benefits; at present, however, those benefits are not established.

One indication of antiinflammatory activity is a gradual increase in FEV₁ values during treatment. Inhaled corticosteroids have such an action. For example, in patients with newly diagnosed mild chronic asthma treated with inhaled budesonide (600 µg twice daily) for 2 yr, the mean FEV₁ value increased by 0.13 L (4%), and morning peak expiratory flow rates increased by 32.8 L/min (7.5%) (34). Inhaled corticosteroids and leukotriene modifiers have been compared in several trials, and early data suggest that the addition of a leukotriene modifier, such as zileuton, may be as effective for asthma control as higher doses of inhaled corticosteroids alone, and that the addition of these compounds may be an alternative to higher doses of inhaled corticosteroids (35). Pranlukast at 300 mg twice daily and 450 mg twice daily has been shown to be comparable to beclomethasone 84 µg four times daily in controlling asthma symptoms, and pranlukast-treated patients have maintained a stable FEV₁ and peak expiratory flow over a 12-wk period (36). A consistent finding in long-term treatment with leukotriene modifiers is a gradual increase in FEV₁. Zileuton, administered over a 13-wk study, increased FEV₁ values to nearly 16% over baseline (30). Moreover, both zileuton and budesonide demonstrate systemic steroid-sparing effects (as evidenced by a marked decrease in oral corticosteroids needed during active medication). Subjects and observation periods in the two studies described here were obviously different, necessitating future comparisons to validate the positioning of the leukotriene inhibitors.

SAFETY OF THE LEUKOTRIENE MODIFIERS

Safety issues with the use of leukotriene modifiers remain to be fully addressed. Long-term safety and efficacy trials are necessary and are ongoing. Most adverse events with these medications have been mild, with headache, dyspepsia, pharyngitis (zafirlukast), macular rash (MK-0591), and reversible elevations in liver transaminase enzyme activities (zileuton) most frequent. Tachyphylaxis has not been reported with the leukotriene modifiers pranlukast and montelukast in exercise studies or long-term chronic asthma studies lasting more than 1 yr (37, 38).

During a 4-wk trial of zileuton, one patient (of 92 treated) had hives and increased serum aminotransferase concentrations after 24 d of treatment with the drug (1.6 g/d) (29). In the 13-wk trial of zileuton (30), five patients of 132 (4%) receiving 2.4 g/d, and three patients of 134 (2%) who were receiving 1.6 g/d, had increases in serum aminotransferase values of at least three times the upper limit of normal. These increases were noted an average of 60 d into treatment, and improved after discontinuation of the drug. None of the 135 patients who received placebo had increased liver enzymes in the study (30). A 6-mo study evaluating zileuton therapy in patients with mild to moderate asthma found that 4% and 5% of those receiving 1.6 g/d or 2.4 g/d, respectively, had liver enzyme elevations in the moderate (3-fold above normal) and severe (more than 8-fold above normal) categories (31). The risk of liver toxicity with zileuton is not fully established, and it is recommended that patients have their liver enzyme activities monitored during therapy. The greatest risk of enzyme elevation appears to occur within the first 3 mo of zileuton treatment. Liver enzymes should be evaluated at the initiation of zileuton therapy.
and monthly thereafter for the first 3 mo, followed by tests every 2 to 3 mo for the remainder of the first year of treatment. Patients should be instructed to report symptoms of liver dysfunction, such as lethargy, nausea, jaundice, right-upper-quadrant pain, or pruritus.

Trials with zafirlukast have revealed that the drug is generally well tolerated. In a 6-wk trial, 206 asthma patients were divided equally into three groups, and received 10, 20, or 40 mg of zafirlukast twice daily (24). The majority of reported adverse events were mild or transient and included headache, nausea, and diarrhea. There were no significant differences in liver enzymes between treatment groups. Four percent of patients treated with 40 mg of zafirlukast twice daily, and 4% of those receiving placebo, experienced slight increases in hepaticaminotransferase levels (specifically gamma-glutamyltransferase). However, one case of symptomatic hepatitis and hyperbilirubinemia was reported in a patient receiving zafirlukast 40 mg daily for 3 months; the patient's liver enzymes returned to normal within 3 mo of zafirlukast discontinuation. A thorough detailed recommendations for liver function tests with zafirlukast therapy have not been described, laboratory studies may be conducted at the initiation of zafirlukast therapy as a baseline, and repeated at appropriate intervals thereafter.

A possible association between zafirlukast and Churg-Strauss syndrome, a rare multisystem allergic granulomatous vasculitis, was proposed after six patients developed this disease while receiving zafirlukast at a time when concomitant doses of oral corticosteroids were being tapered. A causal relationship has not been established between zafirlukast and Churg-Strauss syndrome; however, patients who are decreasing their oral corticosteroid dose while taking zafirlukast should be closely monitored for presenting flulike symptoms such as fevers, myalgia, headaches, and weight loss, since these symptoms may reflect development of the Churg-Strauss syndrome.

**INDICATIONS FOR LEUKOTRIENE MODIFIERS**

Zileuton and zafirlukast, two oral leukotriene modifiers, have been approved for prophylaxis and chronic treatment of asthma in adults and children 12 yr of age and older. Current experience with zileuton and zafirlukast suggests that these drugs may be first-line therapy in the following patients with persistent asthma. (1) Patients with mild to moderate disease who fail to respond adequately to inhaled corticosteroid therapy. (2) Patients with moderate to severe asthma who have systemic side-effects from high doses of inhaled corticosteroids or who are at risk for these adverse effects. These patients should be considered for a trial of leukotriene modifiers to determine whether these agents will allow a reduction in the corticosteroid dose. (3) Patients with poor adherence to a regimen of inhaled corticosteroids because of improper technique or physical limitations. (4) Patients receiving inhaled corticosteroids who are still poorly controlled and who cannot tolerate theophylline or long-acting bronchodilators. There does appear to be a group of patients who respond early (within 2 wk of the beginning of treatment) to leukotriene modifiers with improved peak expiratory flow rates and FEV1 values (36). When these agents are recommended, patients who fit into one of the foregoing categories may benefit from a trial period of zileuton or zafirlukast administration. If the drug appears beneficial after 6 to 8 wk of therapy, a longer treatment period may be indicated, especially for patients receiving oral corticosteroids or high doses of inhaled corticosteroids. Peak expiratory flows monitored at home, along with symptom diaries, are helpful in documenting the efficacy of these agents and indicating the patients who would most benefit from leukotriene modifier therapy.

The updated National Heart, Lung and Blood Institute Expert Panel on Asthma classifies persistent or chronic asthma into four categories, ranging from intermittent (step 1) to severe-persistent (step 4), based on such factors as pulmonary function, symptom frequency, and use of bronchodilators (39). A stepped-care algorithm is provided for the treatment of patients in each category, with each step building upon the drugs used in the previous step. A ntiinflammatory therapy is introduced at step 2 for patients with persistent asthma requiring β-agonist drugs more than three times per week. The Expert Panel classifies the leukotriene inhibitors as "alternatives" to inhaled corticosteroids for the treatment of patients with mild, persistent asthma (step 2) or worse. Inhaled corticosteroids are still regarded as preferred antiinflammatory agents in this protocol, and it is unlikely that leukotriene modifiers would replace corticosteroid therapy entirely in any patient group.

Therapeutic choices in asthma must be based on the overall disease pattern, rather than simply on baseline airway obstruction. Patients with clinically indistinguishable forms of asthma are likely to have biochemically heterogeneous diseases in which different mediators are important pathophysiologically. Further studies of the pathophysiology of asthma (i.e., specific gene activation, cytokine profile, or mediator predominance) may identify subgroups of patients who may derive the greatest benefit from the leukotriene modifiers. Patients with aspirin-sensitive asthma, for example, are ideal candidates for leukotriene-modifier therapy, because no other treatment regimen provides satisfactory results with such a high margin of safety. Although the exact percentages of patients are unknown, a significant number of aspirin-intolerant patients may be able to utilize full-dose aspirin and NSAID therapy for concomitant diseases, such as arthritis, while utilizing leukotriene modifiers for their protective effects on lung function and inhibition of nasal, gastrointestinal, and dermal responses. Similarly, subjects who have exercise-induced bronchospasm that is unresponsive to β-adrenergic-agonist drugs and cromolyn derivatives now have an alternative therapy.

**SUMMARY**

Substantial evidence exists for involvement of the cysteinyl leukotrienes in the pathophysiology of asthma. Once synthesized, leukotrienes exert a number of important pharmacologic actions that contribute to airflow obstruction in asthma: airway smooth-muscle contraction, edema formation, and mucous secretion (2, 3). Not only are exogenously administered leukotrienes capable of reproducing many features of asthma, but there are abundant data demonstrating their in vivo release in episodes of airflow obstruction following laboratory-induced bronchoconstrictor challenges, and supporting a contributory role of leukotrienes in the resting bronchomotor tone of airway smooth muscle (3, 7, 13).

Numerous studies have shown that leukotriene modifiers have protective effects against bronchoprovocative challenges and ease bronchial obstruction in asthma patients (9, 20, 29). Moreover, the beneficial impact of these drugs on asthma may be cumulative, include antiinflammatory effects, and have long-term benefit. The available evidence suggests that blocking leukotriene synthesis or effects on specific receptors will be an effective strategy in asthma treatment. Furthermore, it is possible that combination therapy, using drugs with different sites of action in the leukotriene pathway, might provide additional efficacy, since it is unlikely that either the 5-lipoxy-
genase pathway or the leukotriene D₄ receptor is completely blocked by the currently available respective antagonists. Despite the current information from clinical trials, specific recommendations about the exact role of these compounds in asthma cannot yet be made. Nonetheless, leukotriene modifiers are the first new class of antiasthma drugs to become available in the past 25 yr, and further clinical trials and clinical experience should eventually provide the information needed to determine their role in the treatment of patients with asthma.

References


