Review article

Role of antileukotriene agents in asthma therapy

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Leukotrienes are proinflammatory mediators with special significance in asthma. Released by numerous cell types, particularly after exposure to allergens, leukotrienes cause a potent contraction of bronchial smooth muscle, resulting in reduced airway caliber. Further, they cause plasma to leak from the vessels, resulting in edema, and enhance the secretion of mucus—both events that increase airway obstruction. Thus, leukotrienes have been a target of basic research in asthma. To date, a number of antileukotriene agents have been developed, and three are currently being used in clinical practice in the United States: zafirlukast and montelukast act by antagonizing the leukotriene receptor, and zileuton inhibits leukotriene synthesis. Studies have shown that these agents improve asthma symptoms, pulmonary function, and patient quality of life. Antileukotriene agents have generally been associated with a low incidence of side effects and good tolerability. Currently recommended for mild-to-moderate, persistent asthma, these agents have enabled patients to reduce their use of corticosteroids.

(Key words: asthma, zafirlukast, montelukast, zileuton, leukotrienes, receptor antagonists, synthesis inhibitors)

The recent characterization of the pathophysiology of asthma has led to the development of new modes of therapy:1 In particular, studies of leukotrienes and their role in asthma have prompted great interest in agents that affect leukotriene activity.2-4 This article describes the role of leukotrienes in asthma, the biological effects of antileukotriene agents, and the clinical role of these compounds in patients with asthma.

The most important advance in our understanding of asthma has been a recognition of the major role played by airway inflammation; thus, research has focused on control of inflammatory mechanisms. Important inflammatory events associated with asthma include the recruitment of eosinophils into the airway tissues5 and the activation and degranulation of mast cells.6 Antigens cause mast cells to become activated and degranulate when they bind to antigen-specific receptors on the cell membrane. Degranulating mast cells release a number of inflammatory mediators, including histamine, proteinase acid hydrolases, major basic protein, and eosinophilic cationic protein. Activated mast cells also synthesize and release proinflammatory cytokines, including interleukins, tumor necrosis factor, interferon, and granulocyte-macrophage colony stimulating factor, which promote chemotaxis of neutrophils and eosinophils to the region, enhancing the

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inflammatory response. Other important mediators are formed within activated mast cells from arachidonic acid, an unsaturated fatty acid found in intracellular membranes. Arachidonic acid serves as a precursor for thromboxanes, prostaglandins, and leukotrienes.

**Leukotriene pathway**

In part because of their powerful bronchoconstrictive effects, leukotrienes are now recognized as important mediators of inflammation in asthma. Two essential pharmacologic approaches have been taken in an attempt to reduce the effects of leukotrienes: blockade of leukotriene receptors and interruption of leukotriene biosynthesis.

As mentioned, arachidonic acid is a chemical precursor to the leukotrienes. Arachidonic acid released by intracellular membranes can be metabolized by either of two routes: the cyclooxygenase pathway or the lipoxygenase pathway (Figure 1). The cyclooxygenase pathway gives rise to prostaglandins and thromboxanes, whereas the lipoxygenase pathway produces leukotrienes. The first chemical step in the lipoxygenase pathway involves the enzyme 5-lipoxygenase, which acts with an accessory protein, 5-lipoxygenase activating protein (FLAP), to convert arachidonic acid into an unstable intermediate, 5-hydroperoxyeicosatetraenoic acid (5-HPETE), then to the unstable leukotriene A₄ (LTA₄). From LTA₄, the pathway branches to form either LTC₄, LTD₄, and LTE₄, known collectively as the cysteinylic leukotrienes, or LTB₄. LTC₄ is transported out of the cell and rapidly converted in the circulation to LTD₄, the most potent of the cysteinylic leukotrienes. LTD₄ is further converted to LTE₄, which is approximately 10- to 100-fold less potent than LTD₄. These conversions occur rapidly, resulting in clearance of leukotrienes from the circulation via the kidney.

Most agents that block the synthesis of leukotrienes act by inhibiting 5-lipoxygenase or FLAP activity. Such compounds inhibit the synthesis of LTB₄, as well as the cysteinylic leukotrienes. In con-
Contrast, most leukotriene receptor antagonists block the effects of the cysteinyl leukotrienes at their receptor, CysLT1; hence, they do not affect the activity of LTB4. The relative merits of these two approaches are discussed following a description of the leukotrienes’ role in asthma.

**Role of leukotrienes in asthma**

LTB4 has chemotactic properties and promotes the accumulation and activation of eosinophils, macrophages, and polymorphonuclear leukocytes.15 Although LTB4 is likely to be important in many inflammatory conditions, its role in asthma and its effects on pulmonary function are unclear. Nonetheless, bronchoalveolar lavage studies have shown it to be in the lungs of patients with bronchial asthma.16 LTD4 and LTE4 are the principal ligands of the CysLT1 receptor. Another leukotriene receptor (CysLT2) has been characterized from animal tissues, but its function and whether it is found in human tissues are unclear.17

In experimental animal models, cysteinyl leukotrienes have demonstrated four effects that lead to airflow obstruction in asthma: (1) bronchoconstriction, (2) vascular leakage, (3) increased mucus secretion, and (4) increased cellular infiltration.18-21 Cysteinyl leukotrienes are powerful mediators of bronchoconstriction, being 1000 times more potent than histamine in causing smooth muscle contraction. In studies performed with animal tracheal tissues, picomolar doses caused sustained contraction.19 Effects of leukotriene on the vasculature are also profound. Increased vascular leakage allows inflammatory cells to more easily infiltrate tissues. Plasma leakage causes edema, which can significantly reduce airway caliber. Leukotrienes also cause vascular smooth muscle contraction, resulting in a potent vasoconstrictive response.22 When inhaled by human subjects, cysteinyl leukotrienes induce contraction of bronchial smooth muscle, edema, and mucous secretion—symptoms of asthma.20,21 Leukotrienes also stimulate the release of other mediators that further increase inflammation and airway resistance.

Studies conducted in vitro and in vivo have shown that the production of leukotrienes is increased in patients with asthma and in clinical models of asthma.23 Because LTE4 is excreted unchanged in the urine, urinary levels of this leukotriene are considered to estimate cysteinyl leukotriene production. Urinary LTE4 is elevated in acute asthma and in patients with asthma who are subjected to allergen challenge.24 The same investigators failed to detect an increase in urinary LTE4 after exercise-induced asthma, suggesting that the cysteinyl leukotrienes play a less important role in this clinical entity.25

**Antileukotriene agents in asthma therapy**

Most antileukotriene agents that are developed are administered orally, a factor that is likely to improve patient compliance with therapy compared to inhaled agents.26 Although their ability to inhibit leukotriene activity would suggest an anti-inflammatory effect, antileukotriene agents are not considered to be equivalent to corticosteroids. However, because leukotriene receptors on bronchial smooth muscle directly effect bronchoconstriction and because leukotrienes are clearly involved in the inflammatory response, it is plausible that these new agents combine the beneficial effects of bronchodilating agents and anti-inflammatory agents. The following describes the two strategies that have been employed to reduce leukotriene activity in patients with asthma.

**Cysteinyl leukotriene receptor antagonists**

Three antagonists of the CysLT1 receptor have gained widespread clinical use: zafirlukast (Accolate; Zeneca Pharmaceuticals, Wilmington, Del), montelukast (Singulair; Merck, West Point, Pa), and pranlukast (Ultair; SmithKline Beecham, London). A number of other agents have not yet been approved for marketing, including verlukast, toremilukast, MK0571, SKFI04353, and RG12525. The oral form of zafirlukast was approved for use by the Food and Drug Administration in 1996; montelukast was approved for use in 1998; and pranlukast has been available in Japan for several years. Zafirlukast and montelukast have been shown effective in exercise-induced bronchoconstriction27,28 and in reducing the response to inhaled LTD4.29,30 Although pranlukast is less well studied in the United States, it—like zafirlukast—has been shown to reduce cold-air–31,32 and LTD4-induced bronchoconstriction.33

A six-week, randomized, placebo-controlled trial of zafirlukast in patients with chronic asthma showed that this agent significantly improved several measures of asthma severity, including nocturnal awakenings, albuterol use, and daytime symptoms. In addition, zafirlukast increased FEV1 by an average of 11% (P < 0.05) during the trial.34 This dose-ranging study identified 20 mg twice per day as an effective and safe dosage. Adverse effects reported in the zafirlukast groups were not significantly different in frequency and severity from those reported in the placebo group. The results from this early trial have been confirmed in a recently published 13-week trial in which zafirlukast (20 mg twice per day) resulted in significant decreases in asthma symptoms scores, nighttime awakenings, mornings with asthma, and β-agonist use.35

Zafirlukast had a favorable safety profile in clinical trials and was generally well tolerated by patients. Zafirlukast is metabolized by the cytochrome P-450 enzyme system, and, in rare cases, increased liver enzyme levels may occur. Zafirlukast may affect the clearance of other agents; for example, patients who take warfarin may have prolonged bleeding time that requires dosage adjustments. Monitoring for other drug interactions may also be warranted. Currently, approximately 1 million prescriptions for zafirlukast have been written, providing a large database by which to judge efficacy and safety. Postmarketing reports recently revealed an association between zafirlukast and montelukast use and Churg-Strauss syndrome (CSS), a rare vasculitic syndrome.36,37 However, it has been noted that CSS, although rare, is
independently associated with asthma and may even be clinically diagnosed as asthma. Further, because antileukotriene therapy often permits reductions in corticosteroid therapy, CSS previously hidden by corticosteroid therapy may be “unmasked.” The symptoms of CSS generally improve following reinstitution of corticosteroid therapy.

Montelukast has also been shown safe and efficacious in clinical trials. In a randomized, placebo-controlled, multicenter, parallel-group, dose-ranging study, 343 patients with asthma (FEV1 40% to 80% of predicted) were assigned to 1 of 6 treatment groups: 10-, 100-, or 200-mg doses of montelukast administered once daily in the evening; 10- or 50-mg doses administered twice daily; or placebo. All dosages were associated with significant improvements in pulmonary function tests, β2-adrenergic agonist use, and quality-of-life scores. Adverse events were no different between groups and were not dose-related. Zafirlukast has also been shown to have beneficial effects in children with asthma, and use in children aged 7 to 11 years has recently been approved by the FDA. Additional studies are under way for children under 7 years of age.

Antileukotriene agents are intended for use as chronic therapy in patients with mild-to-moderate asthma. Figure 2. Zafirlukast (solid circles) effects a rapid increase in FEV1 in patients with mild-to-moderate asthma, compared to placebo (hollow circles). Four hours after the administration of zafirlukast, patients were given nebulized salbutamol. The increase in FEV1 demonstrates that the improvements associated with leukotriene receptor antagonists are additive with those of β2-adrenergic agonists.
with asthma. In contrast to the synthesis inhibitors, leukotriene receptor antagonists may be expected to have an acute effect during asthma exacerbations, because leukotrienes directly mediate bronchial smooth muscle contraction and are in higher concentrations in the lungs of patients with asthma than in clinically normal subjects. This bronchodilatory effect is additive with that of β₂-adrenergic agonists (Figure 2), not unexpectedly because of the different mechanisms of bronchodilation involved.

**Leukotriene synthesis inhibitors**

A number of agents that inhibit or reduce the synthesis of leukotrienes have been developed and evaluated. The agent in this class that has been studied most is zileuton (Zyflo; Abbott Laboratories, Abbott Park, Ill), which received FDA approval for treatment of asthma in 1996. Zileuton inhibits 5-lipoxygenase and has been shown to reduce plasma levels of leukotrienes in patients with asthma. In a study of zileuton's anti-inflammatory effects, patients with allergies underwent allergen challenge within a single lung segment. Bronchoalveolar lavage fluid was collected 24 hours later. Leukotriene concentration in bronchoalveolar lavage fluid was reduced by 86% in patients receiving zileuton, which correlated with a significant decrease in the number of eosinophils. Zileuton has been shown to inhibit exercise-induced bronchoconstriction and cold-air–induced bronchoconstriction. A randomized, placebo-controlled trial of patients with mild-to-moderate asthma showed that zileuton (2.4 g/day) improved the forced expiratory volume in 1 second (FEV₁) by an average of 13.4% (P = 0.02), an effect comparable to that associated with theophylline and inhaled steroid therapy. In addition, as-needed use of inhaled β₂-adrenergic agonists, as well as the use of corticosteroids, declined among patients in whom zileuton was administered.

Approval of zileuton, however, was delayed because of concerns regarding liver toxicity. Current labeling recommends liver function tests before starting treatment and periodically thereafter, especially during the first 2 months. Other adverse effects of zileuton were similar across the treatment and placebo groups, except for dyspepsia, which was reported significantly more often in the zileuton group. Zileuton is orally active, and the recommended dosage is 600 mg four times per day. Patients should be monitored for possible drug interactions, and concomitant dosages of warfarin and theophylline may need to be adjusted. As with other drugs that affect the leukotriene system, zileuton is intended for long-term treatment of asthma and is probably of little benefit in acute exacerbations.

Another group of leukotriene biosynthesis inhibitors affect FLAP activity; they include MK886, MK0591, and Bay-X-1005. A number of these agents are under investigation and appear promising in preclinical studies.

**Antileukotriene agents in the daily management of asthma**

Guidelines from the National Heart, Lung, and Blood Institute (NHLBI) published in 1997 advise that asthma should be viewed as a treatable condition and that individuals with asthma should be able to lead nearly normal lives. Patients with asthma should be able to sleep uninterrupted and wake with a clear chest; they should not require hospital and emergency department visits and should be free of side effects from medication. Respiratory function should be normal, allowing patients to exercise, play, and attend work or school. In addition, early aggressive intervention with anti-inflammatory drugs is believed to prevent the irreversible basement membrane thickening (remodeling) associated with chronic asthma. Quality-of-life tests have been developed, allowing clinicians to assess the effects of asthma therapy on their patients’ well-being.

The NHLBI guidelines recommend that antileukotriene agents may be used in patients with mild-to-moderate persistent asthma as a long-term alternative to inhaled corticosteroids, cromolyn, nedocromil, or theophylline therapy. In practical clinical use, these agents may be used in patients who cannot use corticosteroids or who are corticosteroid-resistant; they may also be used in an attempt to reduce the corticosteroid dose in patients with severe asthma. Because antileukotriene agents appear to have efficacy in rhinitis and sinusitis, they may be used in patients with both asthma and upper airway inflammatory disease.

The lowering of corticosteroid doses is an important goal of clinical practice because of their many adverse side effects. Patients with the most severe forms of asthma may require high-dose corticosteroids, which are known to have adverse side effects, some of which may be serious. However, these events are much less likely to occur at the lower doses used with inhaled corticosteroids. Nonetheless, hoarseness, sore throat, oral candidiasis, cataracts, and poor growth in children may occur with inhaled corticosteroid therapy.

**The Food and Drug Administration** has recently required a class-labeling modification that warns of the effects of inhaled corticosteroids on growth in children.

Another important drawback to corticosteroid therapy is patient misperception of the requirement for daily dosing. One reason for this is the failure of these agents to provide the rapid relief that patients are accustomed to with β₂-adrenergic agonist inhalers. Additionally, some patients perceive corticosteroids as being too dangerous for daily use. Even the occasional failure to comply is important, because full corticosteroid efficacy is dependent on uninterrupted use.

Because of these issues, there is a strong clinical need for new efficacious antiasthma agents with improved compliance. Recent studies suggest that antileukotriene agents may help to fulfill this role by reducing or curtailing the need for inhaled corticosteroids, while maintaining normal respiratory function.

Subjective assessments of antileukotriene agents have supplemented and confirmed the results of objective studies, such as those that utilize spirometry as an outcome measure. Some patients enrolled in the 13-week study of zafirlukast use were administered the Asthma Quality of Life Questionnaire, revealing...
significant improvements in the activity limitations, symptoms, emotional function, and exposure to environmental stimuli domains of the questionnaire, as well as in the overall quality-of-life score, compared to placebo. The leukotriene receptor antagonist, pranlukast, has also been shown to improve patient quality of life in a 12-week trial through use of the McMaster University Asthma Quality of Life Questionnaire. Zileuton has also been associated with improved health-related quality of life scores in a 14-week trial that compared zileuton with placebo and theophylline. These studies indicate that patients perceive and appreciate the beneficial effects conferred by antileukotriene agents.

Patients have variable responses to antileukotriene agents and, to date, there is no effective method of determining which patients will accrue the greatest benefit from them. The relative safety of antileukotriene agents suggests that they may be tried as an add-on agent in a variety of patient subgroups. In particular, these include aspirin-sensitive patients and those with allergen-, exercise-, or cold-air–induced bronchoconstriction. Anecdotally, we have found good responses in adolescent athletes who prefer oral medication to inhaled drugs. Zafirlukast has been shown to inhibit 80% of the early response to inhaled allergens and 50% of the late response; therefore, it is reasonable to expect that patients with allergic rhinitis will respond well to this agent, particularly because both asthma and rhinitis symptoms should be improved. It has been suggested that antileukotriene agents should be of particular benefit in aspirin-sensitive patients with asthma. Finally, the anti-inflammatory effects of antileukotriene agents suggest that these agents may have efficacy in a variety of other inflammatory conditions, such as urticaria, inflammatory bowel disease, psoriasis, gout, uveitis, rheumatoid arthritis, and systemic lupus erythematosus; however, these potential benefits need to be assessed in clinical trials.

Because of the proven efficacy and safety of antileukotriene agents, we recommend that patients with mild or moderate persistent asthma be given an antileukotriene agent for a trial period of 6 weeks. Patients with more severe persistent asthma may also warrant a similar trial period of an antileukotriene agent, probably as an add-on agent that may help to reduce corticosteroid therapy. In addition, patients with a variety of asthma-related conditions, including cold-, exercise-, allergen-, and aspirin-induced bronchoconstriction, may be given trials with these new agents.

**Summary**

Antileukotriene agents are the first form of targeted asthma therapy to become available. Studies have shown that they are effective and safe in patients with a range of asthma severities, as well as in those with bronchoconstriction induced by various environmental factors. Antileukotriene agents are currently included in NHLBI guidelines as alternatives to anti-inflammatory therapy in patients with mild persistent asthma; however, they are likely to be useful in other groups of patients, particularly as a corticosteroid-sparing strategy in those with more severe disease.

**References**


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