Leukotriene modifiers

Teal S. Hallstrand, MD, MPH\textsuperscript{a,\,*},
William R. Henderson, Jr, MD\textsuperscript{b}

\textsuperscript{a}Division of Pulmonary and Critical Care Medicine, University of Washington, Box 356522, 1959 NE Pacific Street, Seattle, WA 98195-6522, USA
\textsuperscript{b}Division of Allergy and Infectious Diseases, University of Washington, Box 357185, 1959 NE Pacific Street, Seattle, WA 98195-7185

Leukotriene (LT) modifiers represent the first new class of asthma medications to reach US Food and Drug Administration (FDA) approval for the treatment of asthma in the past two decades. The development of leukotriene modifiers was prompted by early studies demonstrating that chemical mediators termed \textit{slow-reacting substance of anaphylaxis} (SRS-A) were important in the pathogenesis of asthma. Components of SRS-A were later identified as cysteinyl LTs. Cysteinyl LTs and LTB\textsubscript{4} are 5-lipoxygenase products formed from arachidonic acid metabolism. There is compelling evidence that LTs play a key role in the pathogenesis of asthma [1]. Drugs have now been developed to inhibit the production and antagonize the effects of LTs, which are now widely used in the management of asthma. The goals of this review are to provide an overview of the role of LTs in the pathogenesis of asthma and to delineate the role of LT modifiers in the management of patients with asthma.

LTs in the pathogenesis of asthma

Asthma is a chronic disease of the airways that leads to variable airflow obstruction. Two basic processes occur in the airways: inflammation and structural changes, which are referred to collectively as airway remodeling. Cellular airway inflammation consists of activated T lymphocytes that secrete cytokines with a type 2 phenotype (Th2), eosinophils, monocytes, and mast cells [2,3]. Airway inflammation is present at the onset of asthma symptoms and persists even in mild asthma [4]. Airway remodeling is
comprised of goblet cell hyperplasia, subepithelial collagen deposition, smooth
muscle hypertrophy and hyperplasia, submucosal gland enlargement, and
bronchial microvascular enlargement and proliferation. Airway remodeling
may or may not be a direct consequence of airway inflammation.

LTs play a key role in perpetuating airway inflammation, lead directly to
airflow obstruction through effects on vascular permeability, mucus produc-
tion, and smooth muscle constriction, and may contribute to airway remod-
eling. LTs are formed from arachidonic acid by the action of 5-lipoxygenase
(5-LO) in the presence of 5-lipoxygenase-activating protein (FLAP) (Fig. 1).
Synthesis of LTs occurs in eosinophils, mast cells, basophils, monocytes,
macrophages, and other airway cells. The cysteiny1 LTs, LTC4, LTD4, and
LTE4 have a cysteinyl residue and bind to G-protein–coupled receptors, the
CysLT receptors. Two CysLT receptors have been identified to date: CysLT1
and CysLT2. The CysLT1 receptor likely mediates most of the pathophysio-
logic effects of LTs in asthma. It is found on airway smooth muscle and on
CD34+ granulocytic precursor cells, eosinophils, monocytes, macrophages,
basophils, and B lymphocytes (Fig. 2) [5]. It may also be expressed on neutro-
phils [6] and mast cells [7]. The CysLT2 receptor is expressed on eosinophils,
lung macrophages, airway smooth muscle, adrenal medulla cells, cardiac
purkinje cells, and brain tissue [8]. Cysteinyl LTs are potent chemoattract-
ants for eosinophils in vivo and in vitro. They mediate airway smooth muscle
constriction, mucus release, and increased vascular permeability. LTB4 does
not have a cysteinyl residue and binds to distinct receptors from the cysteinyl
LTs. The primary action of LTB4 is as a neutrophil chemoattractant.

Drugs developed to inhibit the effects of LTs

Several strategies have been employed to inhibit the effects of LTs in
asthma (Fig. 1). The CysLT1 receptor antagonists, montelukast, pranlukast,
and zafirlukast, block the biological action of leukotrienes C4, D4, and E4.
Only montelukast and zafirlukast are available in the United States. A non-
selective antagonist of CysLT1 and CysLT2 has been developed (BAY
u9773) but is not available clinically. Selective CysLT2 receptor antagonists
have not been developed. The inhibitors of 5-LO (eg, zileuton) and FLAP
(eg, BAY X 1005) block production of both cysteinyl leukotrienes and
LTB4. Zileuton is the only 5-LO inhibitor that has been approved in the
United States. Leukotriene B4 receptor antagonists (eg, CP-105,696 and
LY293111) block experimentally-induced allergic airway inflammation in
animal models but are ineffective in blocking the early or late asthmatic
response in patients with asthma.

Effects of LT modifiers on airway inflammation

LT modifiers block key aspects of the inflammatory cascade in airway
inflammation. The production of Th2 cytokines interleukin 4 and interleukin
Fig. 1. 5-Lipoxygenase and cyclo-oxygenase pathways of arachidonic acid metabolism. 5-LO, 5-lipoxygenase; FLAP, 5-lipoxygenase-activating protein; COX, cyclooxygenase; PG, prostaglandin; TX, thromboxane.
Fig. 2. Expression of a CysLT₁ receptor in human peripheral blood cells. CD34⁺ stem cells express CysLT₁ receptors. Activation of these pluripotent stem cells by cysteinyl LTs and cytokines may lead to their differentiation into mature blood cells. Figueroa et al have demonstrated CysLT₁ receptors on eosinophils, monocyte/macrophages, basophils, and B cells [5]. Other investigators have also observed the CysLT₁ receptor on neutrophils [6] and mast cells [7]. (From Figueroa DJ, Breyer RM, Defoe SK, et al. Expression of the cysteiny leukotriene 1 receptor in normal human lung and peripheral blood leukocytes. Am J Respir Crit Care Med 2001;163:232.)
5 from mite allergen–stimulated peripheral blood mononuclear cells is reduced by pranlukast [9]. Survival of eosinophils, which is prolonged by the cysteiny1 LTs, is reversed in vitro by the administration of either a CysLT₁ receptor antagonist, 5-LO inhibitor, or FLAP inhibitor [10].

Clinical and animal studies demonstrate anti-inflammatory effects of both CysLT₁ receptor antagonists and 5-LO inhibitors. In 14 atopic patients with asthma who developed a late airway response to allergen, there was an increase in cysteiny1 LTs in induced sputum from a baseline of 3.45 ng/ml sputum to 11.95 ng/ml sputum 24 hours after allergen challenge [11]. This increase in LT levels correlated with the increase in induced sputum eosinophils [11]. In a subgroup of patients found to have high LT levels in bronchoalveolar lavage (BAL) fluid, treatment with the 5-LO inhibitor zileuton for 6 weeks lead to a 68% reduction in BAL fluid eosinophils following segmental ragweed allergen challenge compared with those receiving a placebo [12]. In a mouse model of allergic airway inflammation following ovalbumin sensitization, release of cysteiny1 LTs, eosinophils, and mucus into the airways noted after ovalbumin sensitization was inhibited by specific inhibitors of 5-LO and FLAP [13]. In mild to moderate asthma, treatment with pranlukast for 4 weeks led to a reduction in the number of T lymphocytes, mast cells, and EG-2 [ie, secretory form of eosinophil cationic protein (ECP)] positive eosinophils in the bronchial mucosa when compared with a group of patients that received placebo over the same time period [14].

**Effects of LT modifiers on airway remodeling**

Features of airway remodeling such as goblet cell hyperplasia and mucus release, collagen deposition, and airway smooth muscle proliferation may be decreased by treatment with LT modifiers. In Brown Norway rats repeatedly exposed to ovalbumin, there is a threefold increase in airway smooth muscle DNA synthesis following allergen exposure that is significantly attenuated by pretreatment with either the 5-LO inhibitor SB 210661 or pranlukast [15]. In isolated human airway smooth muscle cells, the CysLT₁ receptor antagonists pranlukast and pobilukast reduce enhancement of growth factor-induced DNA synthesis by LTD₄ [16]. Mucus release from the trachea of guinea pigs after allergen exposure is increased after exposure to LTD₄ and significantly decreased by pranlukast and zafirlukast [17]. In BALB/c mice after serial intraperitoneal (days 0 and 14) followed by intranasal (days 14–75) ovalbumin sensitization, many features of airway remodeling develop, including goblet cell hyperplasia, mucus occlusion of the airways, increased airway smooth muscle thickness, and widespread subepithelial collagen deposition in the lung interstitium (Fig. 3) [18]. In this model of airway remodeling, montelukast significantly reduced hyperplasia of airway smooth muscle and goblet cells, mucus plugging, and subepithelial fibrosis (Figs. 4, 5) [18]. The expression of IL-13 mRNA, a profibrotic cytokine
likely involved in the development of chronic airflow obstruction [19], was reduced after montelukast administration (Fig. 6) [18].

**Effects of LT modifiers on bronchoconstriction**

LT modifiers do not have any intrinsic ability to relax smooth muscle. In normal subjects, treatment with a CysLT₁ receptor antagonist fails to cause any bronchodilation [20]; however, the cysteiny l LTs are very potent
mediators of bronchoconstriction, and their antagonism leads to reversal of bronchoconstriction. The bronchodilating effect of zafirlukast is additive to that of a selective B₂-agonist, suggesting that CysLT₁ receptor antagonists and B₂-agonists act at distinct sites [21]. In 51 patients with moderate to severe stable asthma in a three-period crossover study, intravenous (IV) montelukast led to significant bronchodilation at 15 minutes (15.02% IV

Fig. 4. Effect of montelukast on airway inflammation and remodeling in a mouse asthma model. A group of ovalbumin (OVA)-treated mice (see Fig. 3) also were treated with montelukast. Lung tissue from mice treated with montelukast were stained with hematoxylin and eosin to detect eosinophils (A), alcian blue with nuclear fast red counterstaining to detect mucus glycoproteins (B), and Masson’s trichome (C) to assess collagen deposition. The influx of eosinophils into the lung interstitium in the mice treated with OVA alone (not shown) was markedly reduced by montelukast (A). Mucus occlusion of the airways (AW) in OVA-treated mice (see Fig. 3B) was inhibited by montelukast (B). Similarly, collagen deposition (see Fig. 3C) was blocked in OVA-treated mice by the CysLT₁ receptor antagonist (C). (From Henderson WR Jr, Tang LO, Chu SJ, et al. A role for cysteinyl leukotrienes in airway remodeling in a mouse asthma model. Am J Respir Crit Care Med 2002;165:111.)
montelukast, 4.67% oral montelukast, 3.05% placebo) and 1 hour (18.43% IV montelukast, 12.90% oral montelukast, 7.33% placebo) [22].

**Position of LT modifiers in asthma therapy**

Guidelines developed by the National Asthma Education and Prevention Program (NAEPP), most recently in the 1997 Expert Panel Report 2 [23], divide asthma severity into four categories as a framework for the treatment of an individual with asthma. Patients with mild intermittent (step 1)
and mild persistent (step 2) asthma have normal or near-normal resting lung function and intermittent symptoms. In mild intermittent asthma, no long-term preventative medication is deemed necessary. When symptoms occur more frequently, placing the patient in the mild persistent category, the guidelines recommend the use of a long-term preventative agent such as an inhaled corticosteroid. Leukotriene modifiers are considered an alternative to a low-dose inhaled corticosteroid, sustained release theophylline, or a cromone in mild persistent asthma therapy. Patients with moderate (step 3) and severe (step 4) persistent asthma have reduced lung function and frequent symptoms and exacerbations. In moderate to severe asthma, the guidelines recommend inhaled corticosteroids in all patients unless there is a specific contraindication. In these patients, inhaled corticosteroids are

![Graph showing IL-4 and IL-13 levels in OVA, Saline, and Montelukast/OVA treatments.](image)

Fig. 6. Effect of montelukast on lung cytokines in a mouse asthma model. Levels of mRNA for the Th2 cytokines IL-4, IL-5, IL-10, and IL-13 were increased in OVA-treated mice (OVA) compared with saline-treated controls (Saline). Montelukast inhibited mRNA levels of these cytokines in OVA-treated mice. (From Henderson WR Jr, Tang LO, Chu SJ, et al. A role for cysteinyl leukotrienes in airway remodeling in a mouse asthma model. Am J Respir Crit Care Med 2002;165:114.)
often used in combination with a long-acting bronchodilator or sustained release theophylline. Although the 1997 guidelines do not mention LT modifiers in the treatment of moderate to severe asthma, recent clinical studies support the use of LT modifiers in combination with other agents in the management of moderate to severe asthma.

**LT modifiers in the treatment of mild asthma**

Patients with mild asthma who require the use of a quick-relief medication more than twice a week, have nocturnal symptoms more than twice a month, or have increased peak expiratory flow rate (PEFR) variability have persistent asthma that should be treated with a single long-term preventative agent. Mild asthma is an inflammatory disease as indicated by activation of Th2 lymphocytes in the peripheral blood [24] and airway inflammation on bronchial biopsy and bronchoalveolar lavage (BAL) [4]. Data strongly support the use of long-term preventative medications in patients with persistent asthma, particularly inhaled corticosteroids. Because patients with mild asthma have near-normal lung function, other parameters [aside from forced expiratory volume in 1 second (FEV1)] such as symptom and exacerbation frequency, airway hyperresponsiveness, and quality-of-life assessments may be more important in the evaluation of therapies for mild asthma; however, studies that compare LT modifiers with placebo or alternative therapies such as inhaled corticosteroids have been conducted almost exclusively in patients with moderate asthma.

Many well-conducted, randomized, controlled trials establish the effectiveness of LT modifiers in the treatment of persistent asthma compared with placebo. Because a single, long-term preventative medication is recommended in mild persistent asthma, these studies are most pertinent to the treatment of mild asthma. In studies ranging from 3 to 6 months, LT modifiers improve FEV1, reduce the frequency of asthma exacerbations, reduce asthma symptoms and the reliance on short acting B2-agonists, and increase the number of days free of asthma symptoms and quality of life [25–33].

The effect of montelukast was evaluated in a 12-week randomized trial of 681 patients with a mean FEV1 of 67% to 69% of that predicted at the onset (ie, majority of participants with moderate asthma severity); 23% of the patients were receiving inhaled corticosteroids at the time of randomization [33]. After 12 weeks of therapy with montelukast, there was a 13.1% improvement in FEV1 (placebo 4.2%), 24.0 L/min improvement in morning PEFR (placebo 4.6 L/min), and significant reductions in asthma symptoms and the need for short-acting B2-agonist therapy (Fig. 7). Scores on the Asthma Quality-of-Life Questionnaire improved over placebo across all domains in the group that received montelukast. Over the 12 weeks of therapy with montelukast, there were 31% fewer asthma exacerbations and 37% more asthma control days (defined as days without the use of more than 2 puffs of B2-agonist, nocturnal asthma awakening, acute care visit for
asthma, or requirement for a burst of oral corticosteroids). A significant decrease in the number of peripheral blood eosinophils occurred over the 12 weeks, indicating an anti-inflammatory effect of the drug. In a study that examined the effect of montelukast on eosinophilic airway inflammation [34], 40 patients with mild to moderate asthma were treated with montelukast or placebo for 4 weeks and had repeat assessments of the number of eosinophils in induced sputum; a decrease in sputum eosinophils from 7.5% to 3.9% occurred in the group that received montelukast, compared with an increase from 14.5% to 17.9% in the group that received placebo.

The effect of zafirlukast was compared with placebo in a 13-week trial of 762 patients with mild to moderate asthma [30]. Compared with placebo, zafirlukast significantly improved morning FEV$_1$ by 6.3% (3.0% placebo), decreased asthma symptom scores by 26.5% (13.3% placebo), nocturnal awakenings by 19.8% (4.3% placebo), and $B_2$-agonist use by 22.3% (7%...
increase placebo). The rate of asthma exacerbations was reduced from 6.5% in the placebo group to 2.7% in the zafirlukast group. An additional randomized placebo-controlled trial of zafirlukast in 454 patients with moderate to severe asthma showed an improvement in scores of the Asthma Quality-of-Life Questionnaire [32]. Pranlukast, which is not available in the United States, has also shown efficacy in improving FEV₁ and reducing asthma symptoms and exacerbations over 4 weeks of therapy [29]. In studies with montelukast, zafirlukast, and pranlukast, significant improvements in asthma control were noted on the first day of therapy.

The 5-LO inhibitor zileuton, which blocks LT synthesis, was evaluated in a randomized placebo controlled trial of 401 patients with moderate asthma over 13 weeks [27]. There was a significant improvement over placebo in FEV₁ of 15.7% (7.7% placebo) after 13 weeks of treatment with 600 mg four times daily of zileuton. In the group randomized to the placebo, 15.6% had an exacerbation of their asthma requiring systemic corticosteroid treatment, while 6.1% had exacerbation in the group receiving zileuton. Treatment with zileuton also significantly improved health-related quality-of-life. Elevated hepatocellular enzymes (>3 times normal) occurred in 5 of 132 patients randomized to the 600 mg dose of zileuton compared with none of the patients receiving placebo. Because of the need for four times daily dosing and the low incidence of increased liver function tests, use of zileuton in clinical practice in the United States is limited.

A low-dose inhaled corticosteroid (eg, beclomethasone dipropionate 400 µg/day) is generally considered the agent of choice of initial therapy in mild persistent asthma [23]. Large trials comparing a low dose inhaled corticosteroid with an LT modifier in mild asthma have not been published. Multicenter studies have been published that compare the efficacy of monotherapy with an LT modifier with an inhaled corticosteroid in mild to moderate asthma [35–38]. Most studies demonstrate that in moderate asthma, inhaled corticosteroids have a superior effect to LT modifiers on a number of parameters studied, especially lung function.

A large, randomized, controlled trial compared montelukast with inhaled beclomethasone (400 µg/day) over 12 weeks in 895 patients with mild to moderate asthma [35]. The mean FEV₁ of the groups receiving montelukast and beclomethasone was 65% of that predicted (ie, majority of participants with moderate asthma severity) at the onset. The primary endpoint, FEV₁, was increased by 13.1% in the beclomethasone group, 7.4% in the montelukast group, and 0.7% in the placebo group. The median improvement in FEV₁ in the beclomethasone group was 11% (ie, 50% of the recipients improved by at least 11% from baseline); in the group that received montelukast, 42% also had at least an 11% improvement in FEV₁. Inhaled beclomethasone was also superior to montelukast in reducing daytime symptom score (−0.62 beclomethasone, −0.41 montelukast, −0.17 placebo), daily β₂-agonist use (−40% beclomethasone, −24% montelukast, 0% placebo), and the number of nights per week with nocturnal awakenings (−2.4 beclomethasone,
The rate of asthma exacerbations was significantly reduced by both treatments compared with placebo (Fig. 8). Although treatment compliance approached 90% in all groups, 22% of the patients treated with beclomethasone and 34% of the patients treated with montelukast failed to show improvement in FEV$_1$. It is unknown if patients that fail to respond to one agent are likely to respond to the other. An ongoing study though the Childhood Asthma Research and Education Network is designed to determine characteristics of children who do or do not respond to CysLT$_1$ receptor antagonists and inhaled corticosteroids [39].

A small crossover study compared the effect of montelukast with orally inhaled (400 µg/day) and nasally inhaled (200 µg/day) beclomethasone in 12 patients with mild asthma (mean FEV$_1$ 91.2% predicted) [40]. There were no significant differences in FEV$_1$, morning or evening PEFR, asthma symptoms, or rescue inhaler use in the different treatment periods, although the power to detect such differences was low. Seasonal allergic rhinitis symptoms decreased by a greater amount in the beclomethasone group. The PC$_{20}$ for adenosine monophosphate-induced bronchial hyperresponsiveness increased in both groups but was greater in the budesonide group. The amount of exhaled nitric oxide (as a marker of airway inflammation) was

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Fig. 8. Comparison of montelukast, inhaled beclomethasone (200 µg twice daily) and placebo on the time to first asthma attack in patients with mild to moderate asthma. Compared with the placebo group, the montelukast and beclomethasone groups each had significantly more patients without an asthma attack. The proportion of patients without an asthma attack as estimated by a Kaplan-Meier plot. The proportions of patients without an asthma attack were not significantly different between the montelukast and beclomethasone groups. (From Malmstrom K, Rodriguez-Gomez G, Guerra J, et al. Oral montelukast, inhaled beclomethasone, and placebo for chronic asthma. Ann Intern Med 1999;130:493.)
reduced by both treatments, and there were no detectable differences between the treatments. Further study in large groups of patients with mild asthma is necessary to determine the relative efficacy of inhaled corticosteroids and CysLT₁ receptor antagonists in mild asthma.

**LT modifiers in the treatment of moderate to severe asthma**

In moderate to severe asthma, the NAEPP guidelines recommend long-term preventative treatment with an inhaled corticosteroid in all patients, because inhaled corticosteroids are the most reliable way to improve lung function; however, patients with moderate to severe asthma may have abnormalities in lung function that are not fully reversed after initiation of an inhaled corticosteroid. The reasons for this failure to respond to inhaled corticosteroids may be related to poor compliance, the presence of fixed or irreversible airflow obstruction, or different asthma phenotype (e.g., corticosteroid resistant asthma). Escalating the dose of an inhaled corticosteroid may not improve efficacy. Strategies to improve efficacy in moderate to severe asthma have included inhaled corticosteroids in combination with long-acting B₂-agonists, theophylline, or LT modifiers. In the treatment of moderate to severe asthma, each of these strategies is more effective than treatment with an inhaled corticosteroid alone. The primary rationale for using an LT modifier in combination with an inhaled corticosteroid is that LTs are clearly implicated in the pathogenesis of asthma, and corticosteroids (either inhaled at high dose or systemic) do not reduce LT release in the BAL fluid, induced sputum, or urine of asthmatics either at baseline or after an allergen challenge [41–43].

In 79 patients requiring a high dose inhaled corticosteroid (i.e., ≥1500 μg/day of beclomethasone or equivalent), a randomized placebo-controlled study was conducted to determine if the initiation of pranlukast would prevent worsening of asthma during a 50% dose reduction of inhaled corticosteroid [44]. In the group that received placebo, there was a 10.2% decrease in FEV₁ from baseline, whereas the FEV₁ in the group that received pranlukast was unchanged. There was a threefold increase in daytime asthma symptoms, and significant increases in short-acting B₂-agonist use, serum ECP, and exhaled nitric oxide with placebo; no significant change occurred in these parameters in the group that received pranlukast. In a progressive dose reduction study of 226 patients on high-dose inhaled corticosteroids, patients receiving montelukast were able to reduce their dose of inhaled corticosteroid by 47% compared with 30% in the group that received placebo [45]. These studies show that a combination of an LT modifier and inhaled corticosteroid allow the use of a lower dose of inhaled steroid while maintaining good asthma control.

To determine if the addition of a CysLT₁ receptor antagonist improves asthma control in patients incompletely controlled on low-dose inhaled beclomethasone, 642 patients were randomly allocated to receive montelukast
alone, beclomethasone alone, a combination of beclomethasone and montelukast, or placebo for 12 weeks [46]. Compared with the group that continued to receive inhaled beclomethasone alone, the group that received montelukast in addition to the inhaled corticosteroid had a 5.1% improvement in FEV₁ and 25% fewer days with asthma exacerbation (Fig. 9). The group that was randomized to montelukast alone had a 5.3% reduction in FEV₁ compared with baseline while receiving inhaled beclomethasone. There was an additive effect on inflammation, as indicated by a lower peripheral blood eosinophil count, in the group that received montelukast in addition to inhaled beclomethasone [46]. In another study comparing the addition of zafirlukast (80 mg twice daily, which is above the currently approved dose) or placebo in 368 patients that remained symptomatic despite high-dose inhaled corticosteroid (1000 to 4000 μg/day of beclomethasone or equivalent), there was a 9.1% improvement in FEV₁ in the zafirlukast group (4.5% placebo, \( P = 0.01 \)), a 59% reduction in moderate to severe exacerbations, and a 34% reduction in mild exacerbations [47].

**LT modifiers in combination with antihistamine therapy**

The release of LTs into the airway is accompanied by the release of other inflammatory mediators such as prostanoids, histamine, and tryptase during

![Graph showing percent change from baseline for different treatments](https://example.com/graph.png)

Fig. 9. Comparison of montelukast in combination with inhaled beclomethasone with inhaled beclomethasone alone, montelukast alone, and placebo on forced expiratory volume in one second (FEV₁). Patients incompletely controlled on inhaled beclomethasone (200 μg twice daily) were randomly allocated to one of the four treatment groups. The addition of montelukast to beclomethasone significantly improved FEV₁ compared with the group that continued to receive beclomethasone alone. A reduction in FEV₁ occurred in the groups randomized to montelukast alone and placebo. (From Laviolette M, Malmstrom K, Lu S, et al. Montelukast added to inhaled beclomethasone in treatment of asthma. Am J Respir Crit Care Med 1999;160:1865.)
the acute asthmatic response. In an in vitro model of passively sensitized
human bronchus tissue, the combination of the CysLT<sub>1</sub> receptor antagonist
MK-571 and the antihistamine chlorpheniramine produced 87% inhibition
of antihuman IgE antibody-induced contraction compared with 36% for
MK-571 alone and 15% for chlorpheniramine alone [48]. Similarly, a bron-
choprovocation study in patients with asthma showed that the combination
of zafirlukast and the antihistamine loratadine reduced the early and late
airway responses to allergens by 75% and 74% respectively [49]. In contrast,
zafirlukast alone reduced the amount of bronchoconstriction by 62% and
55%, and loratadine alone reduced the amount of bronchoconstriction by
25% and 40% [49].

Recently, the efficacy of CysLT<sub>1</sub> receptor antagonist therapy in combina-
tion with an antihistamine has been evaluated in clinical studies of asthma
and allergic rhinitis. In a randomized, double-blind crossover trial, monte-
lukast alone was compared with the combination of montelukast and lora-
tadine over 2 weeks of treatment in each period [50]. Montelukast alone
improved FEV<sub>1</sub> by 9.7% over placebo; the combination of montelukast and
loratadine improved FEV<sub>1</sub> by 13.9%. Significant improvements in daytime
and nighttime symptom scores and morning and evening PEFR and a
reduction in B<sub>2</sub>-agonist use were noted for combination therapy compared
with montelukast alone [50]. Combination therapy with montelukast and
the antihistamine cetirizine was compared with the combination of inhaled
and intranasal budesonide in a randomized, single-blind, placebo-controlled
crossover study [51]. Significant improvements in PEFR, rescue inhaler use,
asthma symptoms, and daily activity score occurred in both treatment
groups compared with placebo, and there were no detectable differences
between these treatments; however, exhaled nitric oxide was only signifi-
cantly reduced in the budesonide group, and PC<sub>20</sub> for adenosine monophos-
phate was significantly improved only by the combination of montelukast
and cetirizine [51]. Long-term studies are necessary to fully evaluate the effi-
cacy of combination therapy with a CysLT<sub>1</sub> receptor antagonist and anti-
histamine in the treatment of asthma and allergic rhinitis.

**LT modifiers for the prevention of exercise-induced bronchoconstriction**

Exercise-induced bronchoconstriction (EIB) is a common feature of
asthma. Exercise, with its resultant increase in minute ventilation, leads to
drying and cooling of the airways, initiating a cascade of events that leads
to bronchoconstriction. The mechanism of EIB remains controversial; how-
ever, there is evidence to suggest a mast cell–mediated mechanism [52,53].
Measurement of the cysteinyl LT LTE<sub>4</sub> in the urine following exercise has
shown increased amounts of LTE<sub>4</sub> following EIB in some [54–57] but not
all studies [58,59]. In an animal model designed to simulate EIB, hyper-
pnea-induced bronchoconstriction is accompanied by an inflammatory cell
infiltrate and release of cysteinyl LTs into the peripheral airways [60]; however, the best evidence of the role of LTs in the pathogenesis of EIB comes from studies of the effect of CysLT1 receptor antagonists and 5-LO inhibitors on the severity of EIB.

The clinical effectiveness of CysLT1 receptor antagonists for the prevention of EIB is demonstrated by the effect of inhaled zafirlukast (which is not available clinically) given to 9 patients with EIB 30 minutes before exercise [61]. The mean maximal percentage fall in FEV1 after zafirlukast was 14.5%, compared with 30.2% during placebo administration [61]. All patients in the inhaled zafirlukast study had EIB despite treatment with inhaled beclomethasone. These data indicate that CysLT1 receptor antagonists are useful in patients with EIB that persists despite regular treatment with inhaled corticosteroids. Similarly, a single dose of oral zafirlukast (20 mg) 2 hours before exercise reduced the maximum percent reduction in FEV1 from 36.0% during placebo to 21.6% during zafirlukast administration [62].

Both long-acting B2-agonists and CysLT1 receptor antagonists are equally effective at preventing EIB for at least 12 hours after a single dose [63]; however, over 2 weeks of regular dosing with the long-acting B2-agonist salmeterol, there is a reduction of bronchoprotective efficacy of B2-agonists for EIB [64,65]; this effect is not prevented by the coadministration of an inhaled corticosteroid [66]. CysLT1 receptor antagonists provide prolonged protection against EIB without a reduction in efficacy when administered over a prolonged period. In a 12-week, randomized, placebo-controlled trial conducted in 110 patients with mild asthma, montelukast reduced the total amount of EIB (measured by the area under the curve of percent decrease in FEV1 over 60 minutes after exercise) by 47.4% at the end of the dosing interval, 20 to 24 hours after montelukast administration [67]. The efficacy of montelukast was unchanged during continuous therapy at 4, 8, and 12 weeks [67]. Salmeterol and montelukast were compared in two separate 8-week, randomized, placebo-controlled trials of 191 and 197 adults with EIB [68,69]. The results were similar in both trials, demonstrating that efficacy remains unchanged with the CysLT1 receptor antagonist and is reduced with daily dosing of the long-acting B2-agonist. Both salmeterol and montelukast were similarly effective at reducing the severity of EIB after 3 days of therapy; however, the bronchoprotective efficacy of salmeterol decreased at 8 weeks (Fig. 10) [69]. The severity of EIB (determined by the maximum fall in FEV1 following exercise) was reduced by 57.2% in the montelukast group compared with 33.0% in the salmeterol group after 8 weeks of daily dosing [69].

**Role of LT modifiers in aspirin-sensitive asthma**

The syndrome of rhinorhea, nasal polyps, sinusitis, conjunctival edema, and asthma following aspirin ingestion is referred to as *aspirin-induced asthma* (AIA). Intolerance to aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) may occur in as many as 10% to 20% of asthmatics [70].
There is significant interest in the role of LT modifiers in the management of AIA, because patients with this disorder have increased production of cysteinyl LTs, especially in response to oral or inhaled aspirin challenge. The number of mast cells and eosinophils, major sources of cysteinyl LTs, are increased in the airways of individuals with AIA compared with...
aspirin-tolerant asthmatics [71]. The number of cells expressing LTC₄ synthase, the rate-limiting step in the synthesis of the cysteinyl LTs, is four times higher in AIA than in aspirin-tolerant asthma and 19 times greater than in nonasthmatic individuals [72]. A single nucleotide polymorphism in the LTC₄ synthase promoter (A→C255444C) has been described in 39% to 76% of AIA [73,74]; however, this allele also is found in 26% to 44% of aspirin-tolerant asthmatics and approximately 25% of healthy controls [73,74]. Another factor in the development of AIA is the relative underproduction of the anti-inflammatory and bronchodilatory prostaglandin (PG)E₂ that inhibits the release of LTs from inflammatory cells in vitro [75].

Studies support the clinical effectiveness of LT modifiers in bronchoconstriction triggered by aspirin and other NSAIDs. The amount of bronchoconstriction elicited by aspirin can be quantified by determining the dose of lysine-aspirin that is necessary to cause a 20% fall in FEV₁ (ie, PD₂₀ lysine-aspirin). A single dose of montelukast given 1 hour before lysine-aspirin bronchoprovocation caused a median 4.4-fold increase in the dose to evoke a 20% reduction in FEV₁ [76]. Treatment with the 5-LO inhibitor zileuton for 6 to 8 days reduced the mean reduction in FEV₁ following aspirin ingestion in 8 patients with AIA from 18.6% on placebo to 4.4% in active treatment [77]. During treatment with zileuton, the nasal, gastrointestinal, and dermal symptoms following aspirin administration were reduced in some patients with AIA [77].

Because baseline production of cysteinyl LTs is increased in AIA, inhibition of the effect of LTs should lead to a greater degree of bronchodilation than in asthmatics with less LT production. In eight patients with documented AIA, a mean 18% improvement in FEV₁ was observed following administration of montelukast; the magnitude of bronchodilation was associated with the individual response to aspirin challenge [78].

Chronic treatment with a 5-LO inhibitor in AIA improves asthma control. In 40 patients with AIA in whom the majority were receiving inhaled or oral corticosteroids, the 5-LO inhibitor zileuton was added to the patient’s previous medications over 6 weeks in a double-blind crossover study [79]. Despite the lower use of B₂-agonists while on the zileuton treatment arm, there was a 7.5% mean improvement in FEV₁ that was maintained throughout the 6 weeks of the study. Although the study was not adequately powered to evaluate the effect of treatment of the frequency of exacerbations, there was one exacerbation during the treatment period compared with five exacerbations during placebo treatment. Additional benefits were noted in improved nasal congestion and higher nasal inspiratory flow during treatment with the 5-LO inhibitor.

Use of LT modifiers in acute asthma

Acute asthma exacerbations occur in individuals with asthma of all levels of severity. The trigger for acute asthma is often a viral infection, but other
triggers include allergens and cigarette smoke. The inflammatory process that occurs in the airways during acute asthma may differ from that noted during stable conditions. For example, patients presenting to the hospital with severe acute asthma may have prominent neutrophilic airway inflammation and increased production of mucin-like glycoprotein [80,81]. During acute asthma, LTs are elevated in the airways and peripheral blood and then decrease as the exacerbation resolves [82]. Leukotriene modifiers have great potential for use during acute asthma because of their role in reversing LT-mediated bronchoconstriction and in limiting vascular permeability, mucus release, and eosinophil recruitment.

There are currently no published clinical trials using leukotriene modifiers in the management of acute asthma. Therapy for acute asthma generally consists of a selective B2-agonist along with an anticholinergic agent such as ipratropium bromide and systemic corticosteroids to reverse bronchoconstriction and limit the progression of airway inflammation [83]. For LT modifiers to be useful in the treatment of acute asthma, they should provide additional benefits over that already achieved with current therapies. In a pilot phase II study in which 201 patients with acute asthma were randomized to intravenous montelukast or placebo in addition to standard care, there was a significant \((P < 0.01)\) additive improvement in FEV1 at 20, 40, and 60 minutes after montelukast infusion (ie, an approximately 140 ml greater improvement in FEV1 at the 20-minute endpoint) [84].

**Adverse effects of LT modifiers**

The LT modifiers available in the United States are generally well tolerated at the recommended doses. Montelukast and zafirlukast are classified as pregnancy category B, while zileuton is classified as category C based on animal data. Increases in serum alanine aminotransferase occurred in 4.6% of patients receiving zileuton over 1 year compared with 1.1% of patients receiving placebo [85]. Monitoring of hepatic enzymes is required before initiation of zileuton therapy and at periodic intervals while on treatment. Although elevations in liver function tests occurred with increased frequency at higher doses of zafirlukast, at the recommended dose of 20 mg twice a day the frequencies of elevated alanine aminotransferase and aspartate aminotransferase were 1.4% and 0.8%, respectively, and did not differ from placebo [85]. Subsequent case reports in a small number of women have demonstrated severe hepatotoxicity ascribed to drug reactions while on zafirlukast at the recommended dose [86]. Cases of Churg-Strauss syndrome have been reported in patients using CysLT1 receptor antagonists while oral or inhaled corticosteroids were withdrawn; however, a causal link is unlikely [87]. Churg-Strauss syndrome has also been observed when other corticosteroid-sparing agents (eg, fluticasone) have enabled a reduction in systemic doses of corticosteroids for control of severe asthma [88].
Future directions

Additional studies are necessary to fully understand the role of LT modifiers in the treatment of asthma. Large studies are needed to compare LT modifiers with low-dose inhaled corticosteroids in patients with mild asthma. Long-term studies are essential to understand the role of LT modifiers in the prevention of airway remodeling. Studies are needed to identify features of asthma that are associated with a good response to LT modifiers. Extended studies are also necessary to compare combination therapy with an inhaled corticosteroid and LT modifier to other combination therapies, especially with regard to long-term airway function and the frequency of asthma exacerbations. Many unanswered questions remain about the position of LT modifiers in the treatment of acute asthma.

References


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