Treatment of Asthma with Drugs Modifying the Leukotriene Pathway

Review Articles

Drug Therapy

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TREATMENT OF ASTHMA WITH DRUGS MODIFYING THE LEUKOTRIENE PATHWAY

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IN 1979 and 1980, the chemical structures of the material previously known as slow-reacting substance of anaphylaxis were elucidated as 5(S)-hydroxy-6(R)-glutathionyl-7,9-*trans*-11,14-*cis*-eicosatetraenoic acid[1] and its cysteinyl-glycyl and cysteinyl congener (also known as leukotrienes C_4, D_4, and E_4, respectively). These molecules were so named because the parent molecule was originally isolated from leukocytes, and its carbon backbone contained three double bonds in series, which constitutes a triene. This structural information provided the key to the oxidative pathway of lipid metabolism known as the 5-lipoxygenase pathway.

One of the chief reasons for the interest in slow-reacting substance of anaphylaxis was its ability to stimulate smooth-muscle contraction.[2] However, the main reason for interest among respiratory physicians and scientists was the observation that slow-reacting substance of anaphylaxis stimulated airway smooth muscle by a nonhistaminergic mechanism. After its structure had been elucidated, it proved to be a potent stimulator of smooth muscle in animal and human tissues in vitro and in vivo.[3-5] For example, in normal subjects inhalation of leukotriene D_4 results in the same degree of airway obstruction as inhalation of solutions of histamine or methacholine that are 10,000 times as concentrated.[6-9]

In addition to their potent bronchoconstrictor properties, leukotrienes and other products of the 5-lipoxygenase pathway induce pathophysiologic responses similar to those associated with asthma. Specifically, 5-lipoxygenase products can cause tissue edema[10,11] and migration of eosinophils[12,13] and can stimulate airway secretions.[14,15] The leukotrienes also stimulate cell cycling and proliferation of both smooth muscle and various hematopoietic cells[16-19]; these observations provide further evidence of a potential role of leukotriene modifiers in altering the biology of the airway wall in asthma. Since all these responses contribute to asthma, the pharmaceutical industry initiated research programs to identify substances that could inhibit the action or synthesis of the leukotrienes. By early 1998, three chemically distinct cysteinyl leukotriene-receptor antagonists and an inhibitor of leukotriene synthesis were available by prescription in more than a dozen countries (Table 1). In this article, we will review the biochemistry of the cysteinyl leukotrienes and the drugs that decrease the production or action of leukotrienes, with special attention to the effect of these drugs on laboratory-induced and chronic stable asthma.

THE 5-LIPOXYGENASE PATHWAY

Arachidonic acid is the precursor fatty acid that is transformed into the leukotrienes by way of the 5-lipoxygenase pathway (Fig. 1).[20-22] It becomes available in the intracellular microenvironment when one of the various forms of phospholipase A_2 cleaves it from cell-membrane phospholipids.[23,24] The arachidonic acid so released is presented to 5-lipoxygenase by an integral nuclear-membrane protein known as the 5-lipoxygenase–activating protein.[25,26] The biosynthesis of the leukotrienes then proceeds as a result of the sequential catalytic action of 5-lipoxygenase on arachidonic acid, which first yields 5-hydroperoxyeicosatetraenoic acid and then, through the action of 5-lipoxygenase on 5-hydroperoxyeicosatetraenoic acid, leukotriene A_4 (5,6-oxido-7,9-*trans*-11,14-*cis*-eicosatetraenoic acid). Zileuton inhibits the catalytic conversion of 5-lipoxygenase.[27]

Leukotriene A_4 is unstable and is quickly converted to leukotriene C_4 or leukotriene B_4.[28,29] In three cell types associated with asthma — eosinophils, mast cells, and alveolar macrophages — leukotriene A_4 is converted to leukotriene C_4 by the addition of glutathione at the C-6 position of leukotriene A_4, a reaction catalyzed by leukotriene C_4 synthase. Leukotriene C_4 is then exported to the extracellular space through a specific transmembrane transporter.[30,31] In the extracellular space, the glutamic acid moiety is cleaved from leukotriene C_4 to form leukotriene D_4, which in turn is cleaved by extracellular dipeptidases to form the 6-cysteinyl analogue of leukotriene C_4,

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Table 1. Drugs That Act on the 5-Lipoxygenase Pathway.*

Drug Class and Name	Trade Name	Recommended Oral Dose	Other Information
Leukotriene-receptor antagonist†			
Montelukast	Singulair	10 mg each night in adults; 5 mg each night in children (6–12 yr)	Pediatric dose is a chewable tablet.
Pranlukast‡	Onon, Ultair	225 mg twice daily	
Zafirlukast	Accolate	20 mg twice daily	Take 1 hr before or 2 hr after eating.
5-Lipoxygenase inhibitor			
Zileuton§	Zyflo	600 mg 4 times daily	Measure serum alanine aminotransferase before treatment, every month for 3 months, and periodically thereafter.

*These drugs are currently available by prescription in multiple countries worldwide, except as noted.

†Tomelukast (LY 171883) was the first leukotriene-receptor antagonist to undergo clinical trials for treatment of chronic stable asthma. Because it is no longer under development, it is not considered in this review.

‡Pranlukast is available only in Japan.

§Zileuton is available only in the United States.

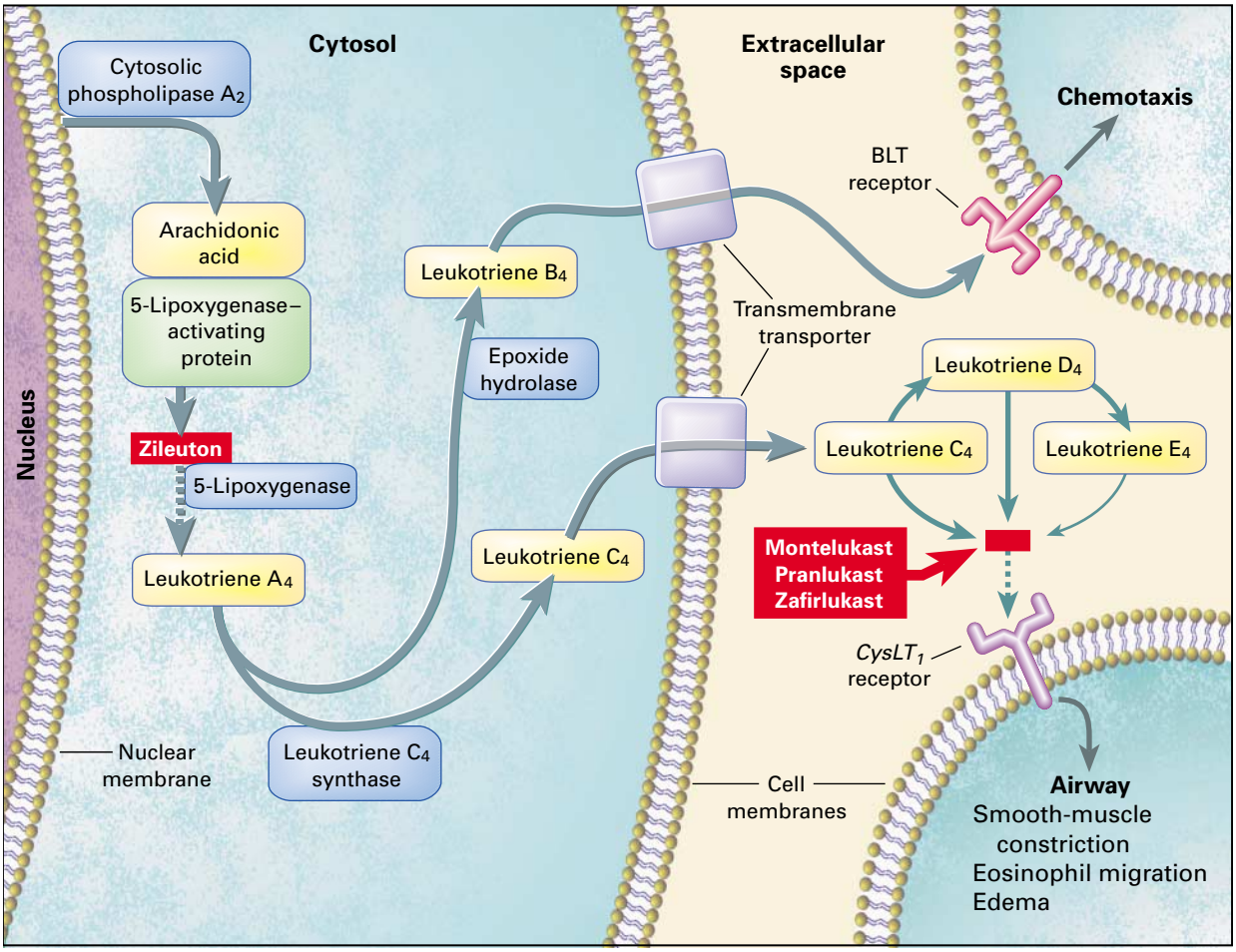

Figure 1. Biochemical Pathways of the Formation and Action of the Leukotrienes and Sites of Action of Leukotriene-Modifying Drugs.

Enzymes are shown in blue, products in yellow, essential cofactor in green, and drugs in red. Although the synthesis of leukotrienes B_4 and C_4 probably takes place in close proximity to the nuclear membrane, for clarity they are shown throughout the cytosol. BLT denotes the B leukotriene receptor. An individual cell may produce the cysteinyl leukotrienes, leukotriene B_4, or in rare cases both.

known as leukotriene E_4. Because leukotriene C_4, leukotriene D_4, and leukotriene E_4 all contain the amino acid cysteine, they are collectively referred to as cysteinyl leukotrienes. The cysteinyl leukotrienes are degraded rapidly in the extracellular space and the liver to inactive products.[32-34] In neutrophils, leukotriene A_4 is converted to leukotriene B_4, which is a dihydroxy as opposed to a cysteinyl leukotriene, by the action of leukotriene A_4 epoxide hydrolase.[29,35,36] Leukotriene B_4 is degraded by multiple pathways, including cytochrome P-450 (CYP4F4, CYP4F5)[37] and 12-hydroxyeicosanoid dehydrogenase,[38] in multiple tissues.

LEUKOTRIENE RECEPTORS

The leukotrienes exert their biologic actions by binding to and activating specific receptors. Two subtypes of the receptor for cysteinyl leukotrienes, *CysLT*$_1$ and *CysLT*$_2$, have been identified pharmacologically, but their molecular structures are not known.[39] The receptor for the noncysteinyl leukotriene, leukotriene B_4, is a seven-transmembrane–spanning receptor known as the B leukotriene receptor (BLT).[40]

Most of the actions of the cysteinyl leukotrienes are mediated by the *CysLT*$_1$ receptor.[22,41,42] These actions include the contraction of human airway smooth muscle, chemotaxis, and increased vascular permeability.[3,14,43,44] In human lung tissue in vitro, leukotriene C_4 and leukotriene D_4 have an equal capacity to stimulate smooth-muscle constriction by acting on *CysLT*$_1$ receptors; the potency of leukotriene E_4 is lower by a factor of 10.[45-48] Since the original description of an antagonist of the action of slow-reacting substance of anaphylaxis,[49] more than a dozen chemically distinct, specific, and selective antagonist drugs that block the binding of leukotrienes to *CysLT*$_1$ receptors have been identified. This class of molecules has been given the generic suffix -lukast; three of them have proved to be effective treatments for asthma (Table 1).

In humans the *CysLT*$_2$ receptor mediates constriction of pulmonary vascular smooth muscle, although this action is less well defined than those mediated by the *CysLT*$_1$ receptor. The BLT receptor predominantly mediates chemotaxis.[40]

PREVENTION OF INDUCED ASTHMA

Leukotrienes are produced during asthmatic reactions by cells involved in the pathogenesis of asthma. However, the most convincing evidence of a causative role of leukotrienes in asthma comes from studies of the effectiveness against asthma of drugs that inhibit the action or formation of leukotrienes. Studies suggesting that these drugs may improve rhinitis[50,51] will not be considered in this review, although such an effect may be an added benefit for patients with asthma.

Studies have shown that leukotriene modifiers are effective in preventing many types of specifically provoked asthmatic responses.[52-63] Some of these studies are reviewed here.

Allergen-Induced Asthma

The inhalation of an allergen by a patient with allergic asthma has several consequences. The first consequence is an acute bronchoconstrictor response that develops within 15 minutes and usually resolves within 2 hours (the allergen-induced early asthmatic response). In 30 to 70 percent of patients, a second period of bronchoconstriction — the late asthmatic response — occurs, beginning 3 to 4 hours after inhalation and lasting up to 24 hours.[64] The late asthmatic response is associated with an increase in airway inflammatory cells (predominantly eosinophils, mast cells, and lymphocytes)[65] and with airway hyperresponsiveness to a variety of inhaled agents; the hyperresponsiveness can last from days to weeks.[66]

Two types of data indicate that the cysteinyl leukotrienes have an important role in the pathogenesis of these allergen-induced responses. First, urinary excretion of leukotriene E_4 increases after the early asthmatic response. Second, several antileukotriene drugs, including the *CysLT*$_1$-receptor antagonists zafirlukast[54] and MK-571[67] and the biosynthesis inhibitors MK-886,[68] MK-591,[69] and BAYx1005,[55] significantly reduce bronchoconstriction during the early asthmatic response and partially attenuate it during the early hours of the late asthmatic response (Fig. 2). These results indicate that cysteinyl leukotrienes mediate much of the bronchoconstriction during the early response and partially mediate bronchoconstriction during the late asthmatic response. Pretreatment with a combination of an antihistamine and a leukotriene modifier virtually eliminates the early and late allergen responses[70]; this observation indicates that histamine and the leukotrienes are the major physiologic mediators of these responses. In a study in which a selective antagonist of leukotriene B_4, which has no effects on the *CysLT*$_1$ receptor, was given to patients before allergen challenge, the cellular infiltrate associated with the early asthmatic response was diminished, but there was no effect on the physiologic response.[71]

Cysteinyl-leukotriene antagonists have not, however, proved effective in inhibiting allergen-induced airway hyperresponsiveness, measured 24 hours after administration of allergen. In several small studies, the biosynthesis inhibitors MK-591,[69] MK-886,[68] and BAYx1005[55] did not inhibit allergen-induced bronchial hyperresponsiveness in the late-phase response.

Cysteinyl leukotrienes have a causative role in allergen-induced airway inflammation. Inhaled cysteinyl leukotrienes selectively increase the number of eosinophils in the airways of patients with asthma.[12,72] Treatment with the leukotriene-receptor antagonist zafirlukast or the 5-lipoxygenase inhibitor zileuton reduced the number of inflammatory cells recovered in bronchoalveolar-lavage fluid from patients with the late asthmatic response after bronchopulmonary segmental allergen challenge.[73,74]

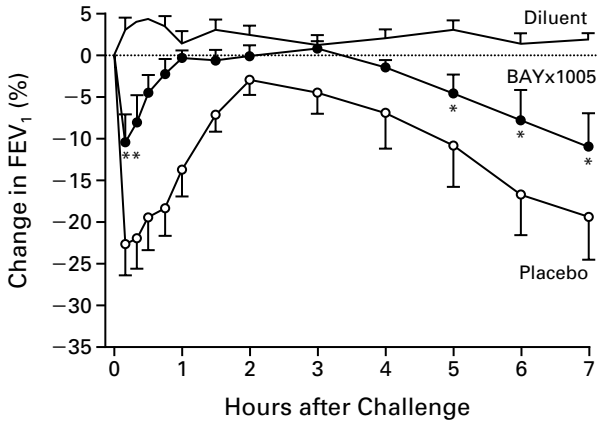

Figure 2. Mean (±SE) Percent Change in Forced Expiratory Volume in One Second (FEV_1) from Base Line in 10 Patients with Asthma after Inhalation of Diluent and during the Early and Late Asthmatic Responses to Allergen Inhalation after Pretreatment with the *CysLT*$_1$-Receptor Antagonist BAYx1005 and Placebo.

BAYx1005 significantly attenuated both early and late responses; the asterisk indicates $P<0.05$, and the double asterisk $P<0.001$. Reproduced from Hamilton et al.,[55] with the permission of the publisher.

Exercise and Cold-Air Hyperventilation

Exercise stimulates bronchoconstriction in 70 to 80 percent of patients with asthma.[75] In contrast to inhaled allergens, exercise infrequently causes late asthmatic responses[76] and does not appear to cause nonspecific airway hyperresponsiveness or airway inflammation. Cysteinyl leukotrienes have been recovered from urine during exercise-induced bronchospasm in some studies[77,78] but not others.[79] The *CysLT*$_1$-receptor antagonists MK-571,[80] zafirlukast,[56] and cinalukast[57] inhibit the maximal bronchoconstrictor response after exercise by 50 to 80 percent, an effect that supports an important role of the cysteinyl leukotrienes in exercise-induced airway obstruction. In addition, when these drugs are given before exercise, they greatly shorten the time to recovery of normal lung function. In some patients with asthma, these drugs completely inhibit the response, but in others they afford less protection. Treatment with the 5-lipoxygenase inhibitor zileuton had similar effects in patients in whom bronchoconstriction was induced by either cold-air hyperventilation[59] or exercise.[58] These studies indicate that cooling and drying of the airways together promote the generation of leukotrienes, which results in bronchoconstriction. However, the degree of protection achieved with leukotriene modifiers varies among patients; administration of a *CysLT*$_1$-receptor antagonist affords complete protection in some, but very little in others.[56]

Aspirin-Induced Asthma

In 3 to 8 percent of patients with asthma, ingestion of aspirin or other nonsteroidal antiinflammatory drugs causes profound, sometimes life-threatening, bronchoconstriction as well as naso-ocular, dermal, and gastrointestinal responses.[81] These patients have an increase in leukotriene C_4 synthase activity,[82] perhaps as a result of a mutation in the promoter region of the leukotriene C_4 synthase gene.[83] Many of these patients have elevated levels of urinary cysteinyl leukotriene excretion, even in the absence of exposure to aspirin,[84] and urinary leukotriene excretion increases further after aspirin challenge.[85,86] Pretreatment with the *CysLT*$_1$-receptor antagonist pobilukast edamine (SK&F 104353-Q)[60] or MK-679[61] prevented the bronchoconstrictor response after the inhalation of lysine aspirin (a water-soluble form of aspirin); pretreatment with the 5-lipoxygenase inhibitor ZD2138[62] inhibited the bronchoconstriction that occurred after oral administration of aspirin, and pretreatment with the 5-lipoxygenase inhibitor zileuton prevented all physiologic responses after oral administration of aspirin.[63] Furthermore, the *CysLT*$_1$-receptor antagonist MK-679 improved lung function in aspirin-sensitive patients with asthma in the absence of aspirin challenge.[87] These results indicate that leukotriene modifiers are the treatment of choice for patients with aspirin-induced asthma.

TREATMENT OF CHRONIC PERSISTENT ASTHMA

The literature contains many reports of clinical trials lasting from 10 days to 6 months that used five different drugs that inhibit the production or action of leukotrienes in patients with chronic persistent asthma.[88-97] Patients with chronic persistent asthma have symptoms of asthma often, especially at night, and have more than 20 percent variation in their peak expiratory flow between evening and morning; their lung function may or may not be abnormal.[98,99] Such patients have been studied in trials of three chemically distinct *CysLT*$_1$-receptor antagonists and one inhibitor of leukotriene synthesis (Table 1). The potency of the receptor antagonists was compared by determining the response to doses of inhaled leukotrienes induced by the antagonist. At the clinically recommended doses, pranlukast shifted the leukotriene D_4 dose–response curve by a factor of more than 25, whereas zafirlukast and montelukast shifted the curve by a factor of 100 or more. Zileuton inhibits its leukotriene synthesis by inhibiting 5-lipoxygenase; clinical doses of zileuton reduce the synthesis of leukotrienes by 70 to 90 percent.[59] Oral administration of any of these drugs to patients with chronic persistent asthma improves airway function, decreases the need for rescue treatment with β-adrenergic agonists, relieves the symptoms of asthma, decreases the frequency of exacerbations of asthma requiring oral glucocorticoid therapy, and decreases the dose of inhaled glucocorticoid required to maintain control of asthma, thus exerting a glucocorticoid-sparing effect.

Short-Term Bronchodilator Effects

Leukotriene modifiers improve airway function rapidly; oral administration of either *CysLT*$_1$-receptor antagonists or 5-lipoxygenase inhibitors results in improvement in airway function within one to three hours.[88,90,91,93,100] In patients with chronic persistent asthma who have airway obstruction at base line and known responsiveness to β-adrenergic–agonist bronchodilators, the magnitude of the improvement in the forced expiratory volume in one second (FEV_1) varies from 8 to 20 percent. The time courses for improvement are similar whether *CysLT*$_1$-receptor antagonists or leukotriene-synthesis inhibitors are administered, indicating that a portion of the airway obstruction in these patients is mediated by ongoing leukotriene production. The bronchodilator effect is greater in patients with more substantial degrees of airway obstruction, and its magnitude is about half that of the response to β-adrenergic agonists. The bronchodilator effects of leukotriene modifiers and β-adrenergic agonists are partially additive. The additive effects suggest that the two types of drugs have different mechanisms of bronchial relaxation and therefore that administration of both may be indicated, for example, in the treatment of patients with asthmatic bronchoconstriction.

Improvement in Airway Function in Chronic Persistent Asthma

Studies lasting for four or more weeks demonstrate that the improvement in airway function in patients with chronic persistent asthma who are treated with leukotriene modifiers persists during prolonged therapy.[93] The magnitude of the improvement in FEV_1 ranges from 9 to 23 percent, depending on the drug studied and on whether the effect is measured at its peak or just before the next dose (Table 2). The effect on FEV_1 is greater in patients with more severe airway obstruction. In one study of the *CysLT*$_1$-receptor antagonist zafirlukast, patients with an FEV_1 value that was more than 80 percent of the predicted value had an increase in FEV_1 of 40 ml, as compared with an increase of 800 ml in patients with an FEV_1 value that was less than 45 percent of the predicted value.[89] Peak expiratory flow rates measured by patients at home also increase by 6 to 10 percent above base line in response to leukotriene-modifier therapy. Most of the improvement in airway function usually occurs within two to four weeks after the initiation of treatment with the drug.

TABLE 2. STUDIES OF LEUKOTRIENE MODIFIERS IN PATIENTS WITH CHRONIC PERSISTENT ASTHMA.*

VARIABLE	ZAFIRLUKAST (SPECTOR ET AL.[89])	MONTELUKAST (REISS ET AL.[94])	PRANLUKAST (BARNES AND PUJET[88])	ZILEUTON (LIU ET AL.[93])
No. of patients	70	408	45	122
Length of study	6 wk	12 wk	4 wk	6 mo
Oral dose	40 mg twice daily†	10 mg daily	337.5 mg twice daily	600 mg 4 times daily
Base-line FEV_1 — % of predicted value	66	67	66	62
Improvement in trough or random FEV_1‡				
Liters	0.23	0.32	~0.31	0.34
Percent	11 (13–14)	13	~11.5§	15 (18)
Improvement in peak FEV_1 — %¶	—	13	—	20 (23)‖
Reduction in β-adrenergic–agonist use — %	31	27	NC	(30)
Improvement in morning PEFR — %	6	6.1	~5	7.1 (8.5)
Treatment failure or glucocorticoid rescue therapy, treatment vs. placebo — %**	2 vs. 10	6.9 vs. 9.6‖	—	8.3 vs. 21.5
Decrease in symptoms (day, night) — %	28, 46	20, —	NC, 28	36, 33

*Values after treatment are compared with pretreatment values. Only data from double-blind, randomized, placebo-controlled studies are included. Although additional studies with each drug have been reported, the studies chosen for inclusion are representative. The number of patients who received active treatment at the dose indicated is given. All values are significantly different from those for placebo unless otherwise indicated. Values not in parentheses represent means over the study period or end-point analyses. Values in parentheses represent maximal effects among the observation intervals reported in the study. Some values have been derived from data in figures and tables. FEV_1 denotes forced expiratory volume in one second, NC no significant change, and PEFR peak expiratory flow rate. Dashes indicate that no data were available.

†The dose of zafirlukast was twice the currently recommended dose.

‡Trough values are values obtained immediately before the next dose. For random values, the time of FEV_1 measurement was not specified.

§The dose was 225 mg.

¶Peak values were recorded at or near the time of the expected peak plasma concentration or peak effects of the drug.

‖There was no significant difference from the value with placebo.

**Treatment failures are given for zafirlukast and glucocorticoid rescue therapy for montelukast and zileuton.

Use of β-Adrenergic Agonists and Symptom Scores

The requirement for rescue therapy with β-adrenergic–agonist drugs reflects the frequency and extent of episodes of bronchoconstriction in patients with asthma. Therapy with most leukotriene modifiers decreases the need for rescue therapy with β-adrenergic agonists by about one third (Table 2); the magnitude of the effect is similar for daytime and nighttime symptoms of asthma.

Requirement for Glucocorticoid Therapy and Markers of Inflammation

The long-term studies mentioned above evaluated the effectiveness of leukotriene modifiers in exacerbations of asthma and the need for glucocorticoid rescue treatment. Treatment with zafirlukast for six weeks reduced the proportion of treatment failures (patients requiring additional therapy) from 10 to 2 percent ($P \leq 0.02$).[89] In two studies of 600 mg of zileuton given four times a day,[92,93] the number of patients who required oral glucocorticoid treatment for exacerbations of asthma was reduced by more than 60 percent ($P=0.02$ and $P=0.05$). As might be expected, the majority of the exacerbations occurred in patients with more severe asthma, in whom the incidence of exacerbations was reduced by 80 percent (Fig. 3).[92] A six-month trial with zileuton reduced the number of episodes of asthma for which glucocorticoid therapy was required and also reduced peripheral eosinophil counts by more than 20 percent.[93]

In patients who were using inhaled glucocorticoids before the study (average dose, 1900 μg of inhaled beclomethasone dipropionate per day), treatment with pranlukast, as compared with placebo, allowed a 50 percent reduction in the inhaled dose of glucocorticoid without loss of asthma control.[101] Furthermore, the patients who received placebo had not only a loss of asthma control but also a rise in the serum eosinophil cationic protein concentration and in exhaled nitric oxide, which are indirect markers of inflammation.

Leukotriene Modifiers as Compared with Other Antiasthma Drugs

Although leukotriene modifiers decrease the need for oral glucocorticoid rescue therapy and permit the reduction of inhaled glucocorticoid doses, their effects have not been directly compared with those of inhaled glucocorticoids in published reports. The data that are available indicate that the magnitude of the improvement in FEV_1 in response to inhaled glucocorticoids exceeds that in response to antileukotrienes in patients with mild-to-moderate persistent asthma.[102]

Inhaled glucocorticoids reduce airway responsiveness to methacholine, which is believed to be an index of nonspecific airway reactivity. No studies of the effect of leukotriene modifiers on methacholine responsiveness have been reported. However, administration of zileuton decreased responsiveness to cold air far beyond the time of its known pharmacologic effects on leukotriene production,[103] an observation that suggests an effect of leukotriene modifiers on nonspecific airway responsiveness.

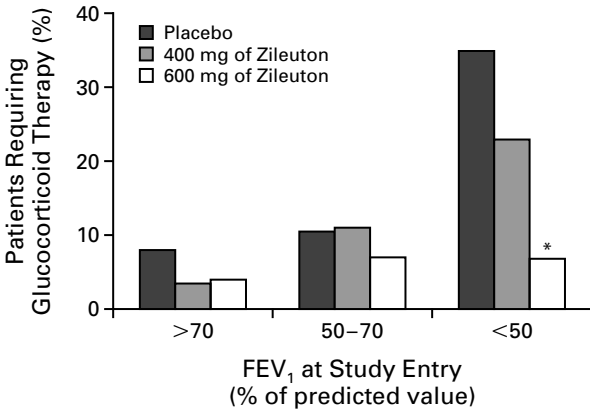

Figure 3. Percentage of Patients with Chronic Persistent Asthma Who Required Oral Glucocorticoid Treatment for Exacerbations of Asthma during 13 Weeks of Treatment with 600 mg or 400 mg of Zileuton or Placebo Four Times Daily.

Groups were stratified according to the forced expiratory volume in one second (FEV_1) as a percentage of the predicted value at study entry. FEV_1 was greater than 70 percent of the predicted value in 111 patients, 50 to 70 percent in 187 patients, and less than 50 percent in 103 patients. The asterisk indicates $P<0.05$ for the comparison with placebo. Reproduced from Israel et al.,[92] with the permission of the publisher.

Zileuton was compared with twice-daily theophylline[104] in a three-month study in which theophylline doses were adjusted according to plasma drug concentrations. The two drugs resulted in similar increases in FEV_1; in the first two months, theophylline resulted in somewhat greater symptomatic improvement than zileuton.

Safety

In six-month trials of zafirlukast, nonrespiratory symptoms or laboratory abnormalities did not occur with greater frequency in the treatment groups than in the placebo groups. However, post-marketing surveillance indicates that doses higher than the recommended dose of 20 mg twice daily can cause elevations in serum aminotransferase concentrations. An idiosyncratic syndrome similar to the Churg–Strauss syndrome, with marked circulating eosinophilia, cardiac failure, and associated eosinophilic vasculitis, has been reported in a few patients treated with zafirlukast[105] or montelukast (post-marketing informational letter). Almost all these patients had been receiving high-dose inhaled or oral glucocorticoids and were able to reduce the dose as a consequence of the effects of the leukotriene antagonists.

It is unclear whether the increased reports of this rare syndrome are due to increased case finding among patients with asthma receiving a new drug or whether the syndrome is the result of a reduction in the glucocorticoid dose or an idiosyncratic effect of leukotriene antagonists or leukotriene modifiers in general. Regardless of its cause, the syndrome is rare, with an apparent incidence of less than 1 case per 15,000 to 20,000 patient-years of treatment.

In the more than two years since pranlukast was introduced in Japan, there have been no reports of unexpected adverse clinical or laboratory events. In phase 1–3 trials of montelukast, the montelukast and placebo groups had similar rates of adverse events and abnormal laboratory values.

Asymptomatic elevations in serum alanine aminotransferase concentrations (by a factor of 3 or more) occurred in 4.6 percent of patients receiving 600 mg of zileuton four times a day, as compared with 1.6 percent of patients receiving placebo.[106] Most of the high values occurred during the first three months of therapy, and they resolved with either continued therapy or discontinuation of treatment. Serum alanine aminotransferase concentrations should be measured when zileuton therapy is initiated, monthly for three months, and periodically thereafter.

Routine Therapy with Drugs That Act on the 5-Lipoxygenase Pathway in Clinical Asthma

Zileuton has broader actions than the *CysLT*$_1$-receptor antagonists in that it inhibits the formation of the cysteinyl leukotrienes, hydroxyeicosatetraenoic acid, and leukotriene B_4, whereas the receptor antagonists only block the action of the cysteinyl leukotrienes. However, there are no published studies comparing the two classes of drugs. At this time, therefore, we can make recommendations only about the use of leukotriene modifiers as a group for the treatment of patients with asthma.

Over the past decade, several organizations have promulgated guidelines for the diagnosis and treatment of asthma.[95,107,108] Because drugs with activity in the 5-lipoxygenase pathway are new and experience with them is largely limited to clinical trials, their role in the treatment of asthma is still in flux. Nevertheless, we think that a number of conclusions can be drawn from the available data.

There are two conditions in which leukotriene modifiers may have particular advantages over other drugs. The first is exercise-induced asthma. The long-lasting effect without the development of tolerance produced by these drugs,[109] as compared with a long-acting β-adrenergic agonist, may be of value for children who want to exercise at school without having to use an intermediate-acting inhaled β-adrenergic agonist, or for adults whose jobs require exercise under atmospheric conditions likely to induce an asthmatic episode.

The second condition is aspirin-induced asthma. Virtually all the physiologic effects of aspirin-induced asthma are due to cysteinyl leukotrienes,[63] and reactions to threshold doses of aspirin can be prevented by inhibition of 5-lipoxygenase. Although we do not recommend administering aspirin to aspirin-sensitive patients, even if they are pretreated with a leukotriene modifier, it is clear that the chronic asthma associated with this syndrome can be substantially improved by long-term treatment with a leukotriene modifier.[87]

CONCLUSIONS

The leukotriene modifiers are the first new drugs for the treatment of asthma to be introduced in more than 20 years, and their exact role remains to be determined. Despite their novelty, however, there are data to support their use in patients with persistent asthma, whether it is mild, moderate, or severe. In patients with mild-to-moderate chronic persistent asthma, leukotriene modifiers improve lung function, decrease the need for β-adrenergic agonists, and result in fewer symptoms of asthma, especially at night. Although inhaled glucocorticoid therapy is more effective with respect to the improvement of lung function,[102] the additional improvement resulting from treatment with inhaled glucocorticoids may be offset by the better compliance achieved with oral treatment.[110] Thus, in our opinion, patients with mild persistent asthma and their physicians can now choose between inhaled glucocorticoids and leukotriene modifiers as first-line therapy. The basis of the choice is the superior efficacy of inhaled glucocorticoids versus the expected superior compliance associated with leukotriene modifiers.

The data reviewed here are inadequate to support a recommendation that patients with moderate-to-severe persistent asthma should be treated with leukotriene-modifier drugs alone, but they provide reason to believe that the addition of a leukotriene modifier to a multifaceted asthma-treatment program will have a salutary effect. In patients with moderate-to-severe chronic persistent asthma, leukotriene-modifier therapy can be combined with inhaled glucocorticoids to maintain control of asthma with lower doses of inhaled glucocorticoids, or it can be added to an existing regimen to achieve better control of asthma. Finally, because the leukotriene modifiers are the first treatment for asthma to result from a search for an inhibitor of a specific biologic process, these new drugs should teach us much about the pathobiology of asthma while providing orally available, safe, and effective therapy.

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