Antileukotriene agents in asthma: The dart that kills the elephant?

Education

Éducation

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Abstract

THE PERSISTENCE OF AIRWAY INFLAMMATION is believed to cause the mechanical changes and symptoms of asthma. After decades of research, a new class of medication has emerged that focuses on leukotrienes, mediators of inflammation. These substances are potent inducers of bronchoconstriction, increased vascular permeability and mucus production, and they potentiate the influx of inflammatory cells in the airways of patients with asthma. In this article the author reviews the development, mechanism of action, and clinical and toxic effects of the leukotriene synthesis inhibitors and receptor antagonists that are entering the North American market. These agents can decrease airway response to antigen, airway hyperresponsiveness and exercise-induced asthma. They are also effective inhibitors of ASA-induced symptoms. Although few published studies are available, the antileukotrienes seem almost as effective in the management of chronic asthma as low-dose inhaled corticosteroids, and their use permits a decrease in the frequency of use or dose of corticosteroids. Further evaluation and clinical experience will determine the position of targeted inhibition of the leukotriene pathway in the treatment of asthma.

Résumé

ON CROIT QUE LA PERSISTANCE DE L'INFLAMMATION des voies respiratoires provoque les changements mécaniques et les symptômes de l'asthme. Après des décennies de recherche, on a produit une nouvelle catégorie de médicaments qui visent avant tout les leukotriènes, médiateurs de l'inflammation. Ces substances sont de puissants inducteurs de la bronchoconstriction, d'une augmentation de la perméabilité vasculaire et de la production de mucus. Elles potentialisent aussi l'influx de cellules inflammatoires dans les voies respiratoires des patients atteints d'asthme. Dans cet article, l'auteur passe en revue la mise au point, le mode d'action et les effets cliniques et toxiques des inhibiteurs de la synthèse et des antagonistes des récepteurs des leukotriènes qui arrivent sur le marché nord-américain. Ces agents peuvent réduire la réaction des voies respiratoires à l'antigène, l'hyperréactivité des voies respiratoires et l'asthme d'effort. Ils sont aussi des inhibiteurs efficaces de la provocation par ASA. Même s'il y a peu d'études publiées disponibles, les antileukotriènes semblent presque aussi efficaces pour le traitement de l'asthme chronique que les corticostéroïdes inhalés à faible dose et leur utilisation permet de réduire l'utilisation ou les doses de corticostéroïdes. Une évaluation et une expérience clinique plus poussées permettront de déterminer où se situe l'inhibition ciblée des voies des leukotriènes dans le traitement de l'asthme.

Asthma is a chronic disease of the airways of the lungs, characterized by reversible obstruction and increased responsiveness to specific stimuli, which consist mostly of allergens, and some nonspecific stimuli, such as cold air, exercise and irritants.[1] A detailed analysis of the clinical, biological and histological characteristics of asthma indicates that it is an inflammatory disease of the airways and that the inflammation can lead to chronic and possibly irreversible changes affecting physiological response to different stimuli.[2] Indeed, it is now clear that even patients with mild, asymptomatic asthma have inflammatory

changes in their airways, characterized by infiltration of the mucosa and epithelium with activated T cells, mast cells and eosinophils.[3]

Because the persistence of inflammation plays such a central role in the symptoms and physiological changes encountered in asthma, it is not surprising that Canadian guidelines for asthma management have selected this aspect of the disease for specific therapeutic intervention.[4] When asthma is not acceptably controlled, as defined in Table 1, anti-inflammatory medication must be given. Systemic corticosteroids have been a mainstay in the treatment of both chronic severe asthma and acute asthmatic exacerbation for many decades. However, the serious side effects that accompany therapeutic doses of systemic steroids led to the introduction of inhaled corticosteroids in the 1970s. These formulations are now recommended as first-line therapy for patients whose asthma is not otherwise acceptably controlled.

Inhaled corticosteroids seem to act by an anti-inflammatory effect in the bronchial mucosa.[5] However, since their introduction, there has been a rise in asthma prevalence, morbidity rate and mortality rate, and many patients still have poorly controlled asthma and a poor quality of life. These trends cannot be explained only by poor compliance with inhalation therapy or poor technique of administration.[6] In addition, not only do inhaled corticosteroids have local side effects (including dysphonia and candidiasis), but they also have systemic effects when employed at moderate to high concentration,[7] and long-term use has been associated with adrenal suppression, disturbed bone metabolism, skin thinning, behavioural changes, alterations in carbohydrate metabolism, and the development of posterior subcapsular and nuclear cataracts.[7,8] These problems have rekindled the search for alternative, well-tolerated, effective pharmacological agents that target airway inflammation.

Table 1: Criteria for asthma control*

Characteristic	Good control	Acceptable control
Daytime symptoms	None	< 3 d/wk
Nighttime symptoms	Does not awake	Awakens < 1 night/wk
Physical activity	Normal	Normal
Exacerbations	None	Mild, infrequent
Absenteeism	None	None
Need for prn β_2-agonist	None†	< 3 doses/wk
FEV_1; FEV_1/FVC	Normal	90% personal best
PEF	Normal	90% personal best
PEF variability	< 10% diurnal variation‡ 5 d/wk	< 15% diurnal variation 5 d/wk

Note: prn = on as-needed basis, FEV_1 = forced expiratory volume in first second; FVC = forced vital capacity, determined by spirometry; PEF = peak expiratory flow, determined with a portable peak flowmeter.
*Reproduced with permission of *Canadian Respiratory Journal* 1996;3:89-100 (ref. 4).
†May use 1 dose/day for prevention of exercise-induced symptoms.
‡Diurnal variation is calculated as [(highest value – lowest value) / highest value] x 100.

The leukotriene pathway

Leukotrienes, prostaglandins and thromboxanes are part of a group of biologically active fatty acids known as eicosanoids.[9] Leukotrienes are not stored in cells but are generated, upon activation of various cell types, by lipoxygenation of the arachidonic acid liberated by phospholipase A_2 in the perinuclear membrane, which separates the nucleus from the cytoplasm. Arachidonic acid is also the substrate of the cyclo-oxygenases, the action of which leads to the formation of prostaglandins and thromboxanes.

Leukotriene synthesis results from the action of 5-lipoxygenase on arachidonic acid[10] (Fig. 1). This enzyme cannot metabolize free arachidonic acid; instead, it must be bound to a membrane-bound protein called 5-lipoxygenase activating protein (FLAP). The interaction of arachidonic acid, FLAP and 5-lipoxygenase leads to the production of the unstable compound 5-hydroxyperoxyeiocosatetraenoic acid (5-HPETE), which is either reduced or converted to leukotriene A_4. Leukotriene A_4 is then converted by a hydrolase to leukotriene B_4 or by a synthase (glutathione-S-transferase) to leukotriene C_4. The leukotrienes are excreted to the extracellular milieu by a carrier-mediated mechanism.

Leukotriene B_4 is produced preferentially by neutrophils and monocytes. Transcellular biosynthesis involving the export of leukotriene A_4 can lead to the production of leukotriene B_4 in erythrocytes, endothelial cells and T lymphocytes. Leukotriene B_4 is a chemotactic agent for neutrophils and causes leukocyte activation. As early as 1940, a substance that caused smooth-muscle contraction was shown to be released by the lungs of antigen-sensitized guinea pigs. This substance was first called slow-reacting substance and later slow-reacting substance of anaphylaxis.[11] It was not until the 1980s that the physiochemical and biochemical properties of this substance were shown to be caused by the cysteinyl leukotrienes C_4, D_4 and E_4.[12] Activated eosinophils and mast cells preferentially make cysteinyl leukotrienes. Monocytes can also produce these substances, and transcellular biosynthesis leads to their production in endothelial cells and platelets.

Leukotrienes in asthma

The airways of patients with asthma are infiltrated with activated eosinophils, mast cells and lymphocytes.[2,3] These cells are probably responsible for the greater return of leukotrienes from bronchial and bronchoalveolar lavage

of patients with asthma than from lavage of normal subjects.[13–15] The leukotriene return does not differ between atopic and nonatopic asthmatic patients,[13] although antigen challenge increases leukotriene return in atopic asthmatic patients only.[14,15]

Leukotrienes in the airways can contribute to the physiological and pathological changes of asthma (Fig. 1). Cysteinyl leukotrienes are several orders of magnitude more potent than acetylcholine and histamine as contractile agonists of human airways.[16] Leukotrienes increase microvascular permeability, modulate the afferent nervous system, stimulate mucus release, slow mucus transport and decrease the activity of human respiratory cilia.[17] In addition, they increase eosinophil influx and smooth-muscle mass after antigen challenge. These effects may all be important in airway hyperresponsiveness, impairment of mucociliary transport, formation of mucus plugs, shedding of epithelial cells, narrowing of the small airways and influx of inflammatory cells.

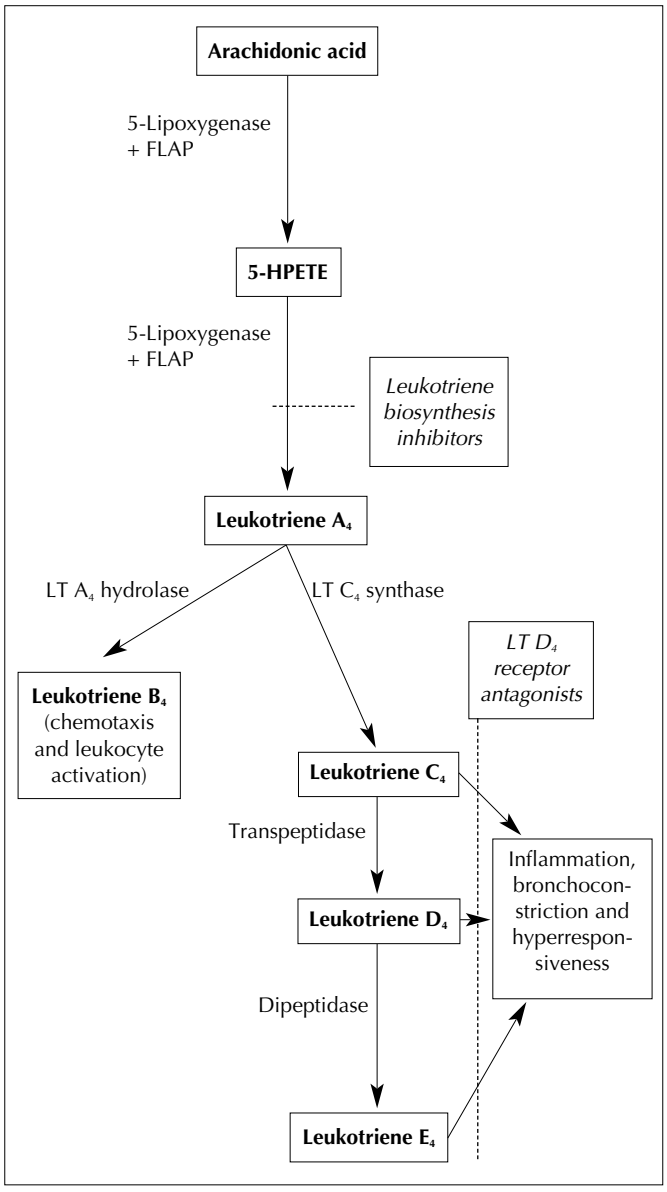

Fig. 1: The leukotriene synthesis pathway. Leukotriene biosynthesis inhibitors act on either 5-lipoxygenase or its activating protein. The leukotriene receptor antagonists target either leukotriene B_4 or D_4; however, because leukotriene B_4 is mostly chemotactic for neutrophils, research on antagonists for this part of the pathway has concentrated on inflammatory diseases other than asthma. FLAP = 5-lipoxygenase activating protein, 5-HPETE = 5-hydroxyperoxy-eiocosatetraenoic acid, LT = leukotriene.

Targets in the leukotriene pathway

Major efforts have been made to inhibit the synthesis of leukotrienes or to block their effects. Researchers have concentrated on 4 points in the leukotriene pathway. The first 2 relate to leukotriene biosynthesis (Fig. 1), and the goal is inhibition of either 5-lipoxygenase or the membrane-bound protein FLAP. The other 2 occur later in the pathway and involve receptor antagonists directed against leukotriene B_4 or D_4. The first antileukotrienes to be developed were disappointing because of a lack of potency and specificity. Because leukotriene B_4 is mostly chemotactic for neutrophils, research on antagonists for this part of the pathway has concentrated on inflammatory diseases other than asthma. Several FLAP inhibitors are under development, as are numerous 5-lipoxygenase inhibitors and leukotriene D_4 antagonists.

The antileukotrienes currently available in the US and Canada — two receptor antagonists for leukotriene D_4 and one 5-lipoxygenase inhibitor — and the receptor antagonist that may appear eventually in Canada are presented in Table 2. All are prescribed as pills to be taken from once a day (montelukast) to 4 times a day (zileuton). All will be approved for adults and elderly patients. Zafirlukast and zileuton have been approved for use in adolescents (those 12 years of age and older) in the United States, and montelukast, a drug that was developed in Canada, is targeted for patients older than 6 years of age.

Antileukotrienes in asthma

At this time, the clinical effectiveness of antileukotrienes seems comparable for all agents, although no study directly comparing efficacy has been performed (Table 3).[18–53]

In atopic asthma, allergen challenge studies are performed to determine whether there are early- or late-phase allergic airway responses. A late-phase response is thought to represent an inflammatory component of airway obstruction. The leukotriene D_4 receptor antagonists inhibit up to 81% of the early airway response and up to 57% of

the late airway response after antigen challenge.[18–20] One of the only differences in effects between the leukotriene D_4 receptor antagonists and zileuton, a 5-lipoxygenase inhibitor, is that the latter has only small effects on the early response and does not inhibit the late response,[21] although it prevents eosinophil infiltration into the airways after antigen challenge.[22] This difference may be attributed to dose, potency or the short half-life of zileuton.

Antileukotriene agents can decrease airway responsiveness to methacholine, allergens or cold air.[23–25] All of the drugs inhibit by up to 50% the drop in forced expiratory volume in the first second (FEV_1) that occurs after exercise.[26–30] An even more dramatic response is found in ASA-sensitive asthmatic patients, in whom the bronchoconstriction and nasal and gastrointestinal symptoms that follow ASA challenge can be almost completely inhibited[34,35] and asthma control improved with a leukotriene D_4 receptor antagonist.[33]

Double-blind, randomized, placebo-controlled studies in patients with mild to moderate asthma have shown that antileukotrienes have a definite therapeutic benefit. In 139 asthmatic patients whose FEV_1 was 40% to 75% of the predicted value, a 4-week course of zileuton led to a 13.4% increase in FEV_1 and a substantial reduction in symptoms and use of β_2-agonists.[40] In 276 asthmatic subjects with similar FEV_1 who received either 10, 20 or 40 mg of zafirlukast or placebo twice a day, the efficacy of the drug in affecting objective and subjective measures was dose dependent.[39] The 40-mg dose was associated with 46% fewer awakenings, 30% less use of albuterol, 27% fewer daytime symptoms and 11% greater FEV_1 than placebo. In another study montelukast or placebo was administered to 29 patients with FEV_1 of 50% to 80% of predicted for 10 ⅓ days.[37] Montelukast was associated with 10.9% greater FEV_1 than placebo on day 1 and 13.4% greater FEV_1 on day 11. Daily use of β_2-agonist, mean daytime symptom scores and nocturnal awakenings were also lower in patients receiving montelukast than in those receiving the placebo. However, there were no important differences in the effect of the antileukotriene between those who were receiving inhaled corticosteroids and those who were not. These results underline the rapidity with which this medication takes effect and its broad applicability in patients with asthma.

Only one study has been performed in children with chronic asthma.[36] In 336 children 6 to 14 years old with FEV_1 between 50% and 85% of predicted, montelukast was associated with better FEV_1, decreased use of β_2-agonist, improved quality of life, better global evaluation by the parents and reduced rate of asthma exacerbations.

Antileukotrienes exert their effects principally by affecting the leukotriene pathway. In addition, these agents have other anti-inflammatory effects, because they also decrease the level of eosinophils in the airways and the blood.[36,41–43] Few studies have compared the effectiveness of antileukotrienes and other medications. The clinical effectiveness of leukotriene D_4 receptor antagonists is reportedly similar to that of low-dose inhaled corticosteroids, although FEV_1 was significantly more improved in the group treated with inhaled corticosteroids.[44–46] Most studies have shown that leukotriene D_4 receptor antagonists permit a decrease in the dosage of inhaled corticosteroids in patients with moderate or severe asthma.[47–50] In 226 adults taking inhaled corticosteroids whose FEV_1 was greater than 70% of the predicted value, 10 mg of montelukast at bedtime permitted tapering of the corticosteroids.[47] Fewer of the treated patients discontinued the study with failed weaning from corticosteroids (16% v. 30% of those receiving placebo), and more of them were tapered off corticosteroids altogether (40% v. 29%). These responses were independent of whether patients

Table 2: Characteristics of antileukotrienes for asthma in phase III clinical trials or launched

Drug*	Compund identification	Status	Age group, yr	Dosage	Cost, US$/mo
Leukotriene D_4 receptor antagonists					
Montelukast (Singulair)	MK-0476 (Merck Frosst)	Launched in Mexico, Canada, US	> 6	10 mg/d or 5 mg/d (6–14 yr)	75.80
Pranlukast (Ultair)	ONO-1078 (SmithKline Beecham)	Launched in Japan; phase III trials in UK, US	Adult	300–450 mg once or twice daily	ND
Zafirlukast (Accolate)	ICI-204219 (Zeneca)	Launched in Canada, US	> 12	20 mg/bid	52.50
5-lipoxygenase inhibitor					
Zileuton (Zyflo)	A-64077 (Abbott)	Launched in US	> 12	600 mg/qid	75.00

Note: ND = not determined.
*Generic name, with trade name in parentheses.

were initially receiving high- or low-dose inhaled corticosteroids. This therapeutic effect may be important because of the potential side effects of high-dose inhalation steroid therapy over prolonged periods.[7,8] The therapeutic effects of antileukotrienes in asthma are reportedly at least comparable to those of cromoglycate, nedocromil and theophylline.[51–53]

Advantages, disadvantages and adverse effects

Over more than 2 decades, many drugs have been introduced for the treatment of asthma but all have been modifications of known classes of anti-asthmatic or anti-allergic medications. The antileukotrienes are a new class of agents that target a specific site in the inflammation cascade. In theory, this should have the advantage of fewer side effects on the immune system. One disadvantage is that some patients do not respond to antileukotrienes, perhaps because leukotrienes are not a major factor in their airway inflammation.

Because these agents are taken by mouth, drug delivery and compliance should be better than for inhaled medications, especially in children, in whom low rates of compliance with inhaled corticosteroids are associated with exacerbation of disease.[54] This advantage may also help to decrease the time needed to educate patients, since physicians would not need to discuss the toxic effects and side effects of inhaled corticosteroids.[55] The approximate cost of the agents available to date in Canada is comparable to that of long-acting inhaled β_2-agonists.

Because there has been at most only 2 years of experience with these medications, it is too soon to know their long-term effects in people with chronic asthma. The antileukotrienes are generally well tolerated, the most common side effect being headache, but this problem seems to occur at the same rate in patients receiving placebo.[37–40] Several antileukotrienes have been withdrawn because of their toxic effects on the liver. Zileuton, for example, caused an increase in alanine aminotransferase activity of 3 times or more in 2% to 5% of patients and can also cause symptomatic hepatitis with jaundice.[56] These adverse effects resolved when the drug was stopped. For this reason and because of drug interactions, it is unlikely that zileuton will be released in Canada.

Among the leukotriene D_4 receptor antagonists, zafirlukast must be taken 1 hour before or 2 hours after meals. This drug is metabolized in the liver and increases serum concentration of warfarin.[57] Because zafirlukast inhibits the cytochrome P-450 isoenzyme CYP3A4, drugs metabolized by this enzyme should be used cautiously in patients receiving zafirlukast. A recent

Table 3: Established effects of antileukotrienes

	Leukotriene D_4 receptor antagonists			5-lipoxygenase inhibitor
Subject of study	Montelukast	Pranlukast	Zafirlukast	Zileuton
Early response	Effective[18]	Effective[19]	Effective[20]	Effective[21]
Late response	Effective[18]	Effective[19]	Effective[20]	Not effective[21,22]
Hyperresponsiveness	ND	Effective (methacholine)[23]	Effective (allergen)[24]	Effective (cold air)[25]
Exercise-induced asthma				
Child	Effective[26]	ND	ND	ND
Adult	Effective[27]	Effective[28]	Effective[29]	Effective[30]
Allergic rhinitis	ND	ND	Effective[31]	Effective[32]
ASA sensitivity (or challenge)	Effective[33]	Effective[34]	ND	Effective[35]
Chronic asthma				
Child	Effective[36]	ND	ND	ND
Adult	Effective[37]	Effective[38]	Effective[39]	Effective[40]
Eosinophil level	Effective[41]	Effective[42]	Effective[43]	Effective[43]
Comparisons				
Inhaled steroids	Similar[44]	Similar[45]	Similar[46]	ND
Steroid wean	Effective[47]	Effective[48]	Effective[49] Not effective[50]	ND
With nedocromil or cromoglycate	ND	Similar[51]	Similar[52]	ND
With theophylline	ND	ND	ND	Similar[53]

Note: ND = Not determined.

report described the Churg Strauss syndrome, a rare form of vasculitis that presents with asthma, cardiomyopathy and neuritis, in patients receiving zafirlukast.[58] This disease has also been described in asthmatic patients receiving other medications. As of Jan. 1, 1998, the incidence of Churg Strauss syndrome in patients treated with zafirlukast was similar to what would be expected in all patients with asthma (56 per million patients).[58] Because all of the confirmed cases occurred in patients who had been weaned from corticosteroids, patients should be weaned from these medications with prudence when they respond to antileukotrienes, and all cases of Churg Strauss syndrome in patients receiving antileukotrienes should be reported.

Pranlukast, another leukotriene D_4 receptor antagonist, is also metabolized by the liver, so the same caution about interactions with medications metabolized in the liver applies. Montelukast has been specifically modified so as not to induce peroxisomal enzymes.[59] When patients are given the recommended doses of this drug, it may not be necessary to monitor or modify other medications metabolized by the liver and administered concomitantly.

Who should receive antileukotrienes?

In most patients the antileukotrienes seem to be as effective in the treatment of chronic asthma as cromoglycate, nedocromil, theophylline and low-dose inhaled corticosteroids. Antileukotrienes decrease the number of inflammatory cells that play a role in the pathogenesis of asthma. In addition, their steroid-sparing effect and the continued clinical improvement that is seen over several weeks suggest that they may also modify the disease process to some extent. Dworski and associates[60] have shown that corticosteroids do not decrease eicosanoids in the lungs of patients with asthma, but if antileukotriene therapy results in lower levels of eicosanoids and hence their effects, there may be beneficial effects on the persistent lung inflammation of asthmatic patients.

Antileukotrienes are not indicated for the treatment of acute exacerbations of asthma and must always be prescribed in combination with short-acting inhaled β_2-agonists, to be used as required. If a patient's asthma becomes aggravated during antileukotriene therapy, the physician must be prepared to add inhaled or systemic corticosteroids to the treatment regimen. Although the 1996 Canadian consensus conference on asthma therapy did not discuss antileukotrienes,[4] these agents represent the first generation of a new type of targeted drug therapy in asthma — a dart that kills certain elephants. Until we determine definitively the characteristics of the patients who will respond to these agents, a short therapeutic trial is recommended. Antileukotrienes should be considered in the following circumstances: in patients with mild to moderate asthma in whom corticosteroids are not the first choice (because of side effects on current medications, poor inhalation technique or poor compliance, or refusal or hesitation to take inhaled corticosteroids even after appropriate education); as a preventive strategy for allergen-, exercise- or ASA-induced asthma; as add-on therapy for patients whose asthma is insufficiently controlled with inhaled corticosteroids; and to reduce the amount of inhaled or oral corticosteroids needed to control disease in patients with moderate or severe asthma. The physician should expect an improvement in approximately 50% of patients. Antileukotrienes generally act rapidly, so if no improvement occurs within 14 days, a response is unlikely, and the drug should be discontinued.

Competing interests: Dr. Renzi has received funding from several pharmaceutical companies to perform phase II and phase III studies related to asthma treatment. He has also given talks and presented continuing medical education events sponsored by pharmaceutical companies. He directs an asthma clinic that receives educational grants from 3 pharmaceutical companies.

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