Leukotriene receptor antagonists and related compounds

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Leukotrienes (LTs), lipid mediators of inflammation, have proved to be important biochemicals involved in the symptoms and physiological changes of asthma. In the past year and a half, the development of three new drugs that modulate the LT pathway has been completed. The first subclass of these drugs, leukotriene receptor antagonists (LTRA) (zafirlukast and montelukast), blocks the interaction of the cysteinyl form of the LTs with the cell type bearing the receptor. The second subclass, the 5-lipoxygenase (5-LO) inhibitors (zileuton) inhibits the 5-LO enzyme, which prevents the formation of both cysteinyl LTs and LTB4. The LT modulators have shown efficacy in inhibiting the physiological changes occurring after allergen, acetylsalicylic acid and exercise challenge in asthmatics. In addition, they have shown efficacy in improving symptoms, beta-agonist use and forced expiratory volume in 1 s (FEV_1) in chronic, 'day-to-day' asthma in patients with mild disease. Comparison studies with low doses of inhaled corticosteroids suggest that LT modulators may have similar effects on symptom scores and beta-agonist use, but have lesser effects on FEV_1. Finally, emerging data suggest that these drugs are beneficial in decreasing the dose of inhaled corticosteroids necessary to control more moderate to severe asthma. While long term studies will be helpful in determining the 'disease modifying' effects of these drugs, data suggest that these drugs are useful in the treatment of a broad range of asthmatic patients.

Key Words: *5-lipoxygenase inhibitors, Inflammation, Inhaled corticosteroids, Leukotriene receptor antagonists*

Antagonistes des récepteurs des leucotriènes et composés associés

RÉSUMÉ : Les leucotriènes (LT), médiateurs lipidiques de l'inflammation, ont prouvé qu'ils sont d'importants agents biochimiques impliqués dans les symptômes et les changements physiologiques de l'asthme. Au cours des dix huit derniers mois, trois nouveaux médicaments qui modulent la voie des leucotriènes ont été mis au point. La première sous-classe de ces médicaments, les antagonistes des récepteurs des leucotriènes (ARLT) (zafirlukast et montélukast), bloquent l'interaction des leucotriènes à groupe cystéinyle avec le type de cellule contenant le récepteur. La deuxième sous-classe, les inhibiteurs de la 5-lipoxygénase (zileuton), inhibent l'enzyme 5-LO, qui prévient la formation à la fois des LT cystéiniques et des LT B4. Les modulateurs des LT ont démontré leur efficacité pour inhiber les changements physiologiques qui surviennent après une épreuve d'effort, un test de provocation à l'aspirine ou aux allergènes chez les asthmatiques. De plus, ils contribuent à l'amélioration des symptômes, à réduire l'utilisation des bêta-agonistes et à augmenter le VEMS chez les patients atteints d'asthme chronique mais léger. Des études comparatives avec des doses faibles de corticostéroïdes en inhalation permettent de croire que les modulateurs des LT ont des effets similaires sur les scores des symptômes et de l'utilisation des bêta-agonistes, mais des effets moindres sur le VEMS. Finalement, des données émergentes permettent de croire que ces médicaments auraient un effet bénéfique concernant la réduction de la dose de corticostéroïdes nécessaire pour maîtriser l'asthme modéré à grave. Des études à long terme seront nécessaires pour déterminer les effets « modificateurs de la maladie » de ces agents, mais les données laissent à penser que ces médicaments sont utiles pour traiter une grande variété de patients asthmatiques.

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Inflammation is a significant contributing factor to the symptoms and physiological changes of asthma. Activation of the arachidonic acid cascade leads to production of lipid mediators known as leukotrienes (LTs), important components of this inflammatory process. In the past 18 months, new drugs have become available that were specifically developed to interfere with that pathway, namely, LT receptor antagonists (LTRAs) and 5-lipoxygenase (5-LO) inhibitors. This is the first time that such 'designer drugs' have become available as a new option to manage chronic asthma.

THE LT PATHWAY

LTs are potent lipid mediators that have long been implicated in the pathogenesis of asthma (Figure 1). They are end-products of the metabolism of arachidonic acid, formed from phospholipids, which are ubiquitous elements of cellular membranes. Arachidonic acid is formed from phospholipids through enzymatic activation of various phospholipases and can then be further metabolized by a variety of pathways. These include the cyclo-oxygenase pathway, which leads to production of prostaglandins and thromboxane (and is inhibited by acetylsalicylic acid (ASA) and other nonsteroidal anti-inflammatory compounds), and the 5-LO pathway, which leads to the production of LTs (1). Activation of 5-LO is thought to require generalized cellular activation and the availability of arachidonic acid as substrate. It is presumed to require interactions with a protein known as 5-LO activating protein, which is thought to channel arachidonic acid to the enzyme 5-LO. 5-LO activation then leads to the production of an intermediate known as LTA4, which can be further metabolized, depending on cell type, to LTB4 or the cysteinyl LTs, LTC4, D4 and E4 (formerly known as slow-reacting substance of anaphylaxis).

LTs are produced almost exclusively by cells of the myeloid lineage. LTB4 is a potent chemoattractant for neutrophils and eosinophils, as well as an activator of neutrophils, which appears to enhance adhesion and migration of the cells through the endothelium (2). Cysteinyl LTs are potent bronchoconstrictors (100 to 1000 times more potent than histamine) that enhance membrane permeability and decrease mucociliary clearance (2). In addition, LTE4 has recently been shown to have chemoattractant properties for eosinophils in the lungs of asthmatics (3). Both cysteinyl LTs and LTB4 have been measured in the airways of asthmatics (4,5). Cysteinyl LTs in humans appear to activate cells predominantly through a single receptor, known as the cystLT1 receptor, although the exact structure of the receptor and whether other receptor types may exist remain elusive (1). LTB4 functions solely through the LTB4 receptor, which was recently cloned (6).

Modulation of LT activity has centered on two components of the pathway (Table 1). Both antagonists of the LT receptor and inhibitors of 5-LO have undergone large scale clinical trials. The chief biological difference between the LTRAs and the 5-LO inhibitors is that LTRAs inhibit the activity of the cysteinyl LTs only, while 5-LO inhibitors block the production of both LTB4 and the cysteinyl LTs, but whether this difference has clinical applications for asthma therapy remains unclear. LTRAs and 5-LO inhibitors have been studied in both laboratory-induced asthma, such as allergen challenge, and in 'day-to- day' or 'chronic' asthma. These agents have largely been studied in mild to moderate asthmatics, but data from more severe patients are emerging as well.

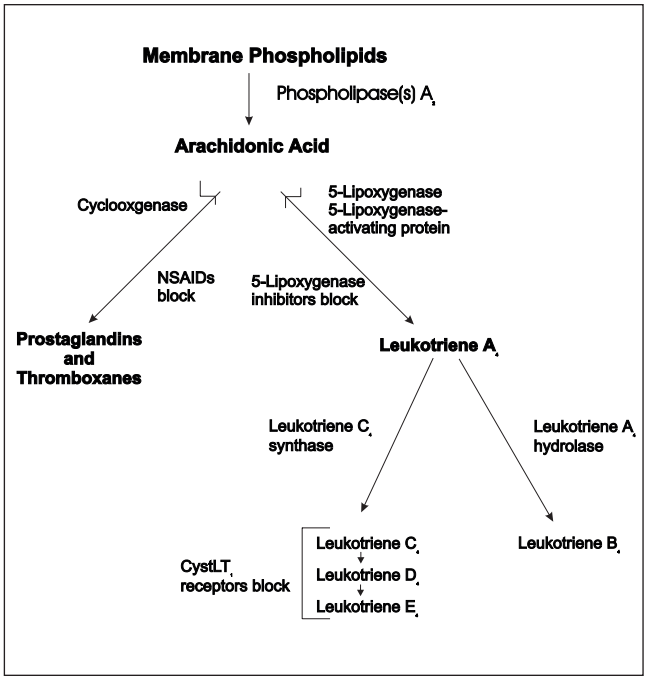

Figure 1) *The arachidonic acid cascade. cystLT Cysteinyl leukotriene receptor; NSAID Nonsteroidal anti-inflammatory drug*

TABLE 1
Leukotriene (LT) antagonists and pathway inhibitors

Receptor antagonists	Pathway inhibitors
Block the actions of cysteinyl LTs	Block the production of LTB4 *and* cysteinyl LTs
zafirlukast (Accolate, Zeneca Pharma Inc)	zileuton (Zyflo, Abbott Pharmaceuticals, USA)
montelukast (Singulair, Merck Frosst Canada Inc)	
pranlukast (Ultair, Onon Ono Pharmaceuticals, Japan)	

EFFICACY IN LABORATORY ASTHMA (CHALLENGE AND BRONCHOSCOPIC STUDIES)

In recent years, LTRAs have been developed that shift the dose response to inhaled LTD4 30- to 100-fold, indicating almost complete blockade of the LT receptor (7). It is not possible to evaluate 5-LO inhibitors in this same way. In addition, LT modulators effectively inhibit allergen- and ASA-induced asthma, with lesser reductions in exercise-induced bronchoconstriction. While the inhibition of the late bronchoconstriction associated with allergen challenge is approximately 50%, the early phase of bronchoconstriction,

which is thought to be predominantly mast cell driven, is almost completely abolished (8,9). In addition to the improvement in obstruction, the LTRA zafirlukast (Accolate, Zeneca Pharma) has demonstrated a small but significant ability to limit the increase in airway reactivity, which normally occurs after allergen exposure.

Bronchoconstriction associated with ASA challenge has also been nearly completely prevented by LTRAs and 5-LO inhibitors, confirming the importance of LTs in the bronchospasm associated with the ASA reaction (10-12). Recently, longer term studies of ASA-sensitive asthmatics support the efficacy of chronic dosing in this population as well (13,14).

The bronchoconstriction associated with exercise appears to be consistently inhibited by LTRAs in the range of 30% to 50%. This inhibition appears to compare favourably to pretreatment with cromolyn (15). A long term study with montelukast (Singulair, Merck Frosst Canada Inc) demonstrated sustained protection against exercise-induced bronchospasm over the 12 weeks of the study, when montelukast was taken 16 to 18 h before exercise (16).

The effect of these drugs on inflammation in the airways has only been partially addressed, and no biopsy studies have yet been reported. However, preliminary work suggests that LTRAs may decrease the inflammatory cell influx into the airways after instillation of allergen and over time. Administration of zafirlukast for one week before instillation of allergen directly into the airways of asthmatics significantly decreased the influx of basophils and lymphocytes into the airways 48 h after allergen exposure compared with placebo. Zafirlukast tended to decrease the numbers of eosinophils migrating into the airways also (17). Montelukast has also demonstrated an effect on sputum eosinophils over time (18).

In a nocturnal asthma model, the 5-LO inhibitor, zileuton (Zyflo, Abbott Pharmaceuticals, USA), was found to decrease urinary and bronchoalveolar lavage fluid (BAL) LT levels, while improving pulmonary function in patients with nocturnal asthma (Figure 2). The improvement in function correlated with the levels of LTB4 in the airways. Additionally, the eosinophils in the BAL and peripheral blood decreased significantly, supporting a cellular-level anti-inflammatory effect (5).

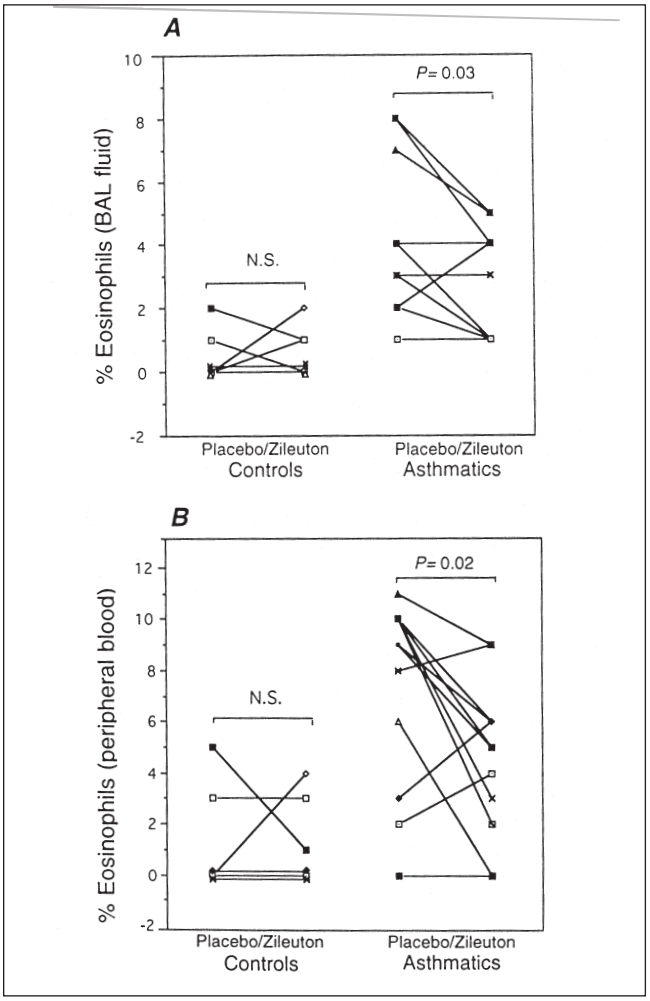

Figure 2) *Zileuton significantly decreased bronchoalveolar lavage (BAL) fluid and peripheral lood eosinophils in nocturnal asthma subjects. NS Not significant*

CHRONIC ASTHMA

Some LT modulators can induce a rapid and significant immediate bronchodilating effect of between 15% and 30% (19). This effect has also been seen with zileuton and high doses of zafirlukast (20,21). These results imply that LTs are always present in the airways of asthmatics and are playing an important role in maintaining baseline asthmatic bronchoconstriction. In addition, concomitant treatment of these individuals with a beta-agonist induces an additive effect on the bronchodilation, suggesting that the two types of compounds are working through different pathways (19).

Several long term, placebo controlled trials have been published in abstract or manuscript form with the LTRAs zafirlukast, pranlukast (Ultair, Onon-Ono Pharma, Japan) and montelukast, and the 5-LO inhibitor zileuton. Although the patients studied had mild asthma as judged by forced expiratory volume in 1 s (FEV_1), medication needs and symptom scores, these compounds have consistently shown both statistical and clinical efficacy in this population (20,22-24). Use of these compounds has led to sustained improvement in FEV_1, symptom scores and beta-agonist use for the duration of the trial compared with placebo. Nocturnal asthma symptoms also appear to be improved by these compounds. Zafirlukast, montelukast and zileuton also significantly decreased the number of occasions on which study subjects needed a steroid burst (24,25).

Studies comparing inhaled corticosteroids with zafirlukast, montelukast and pranlukast have now been carried ou with remarkably similar results. All of these studies suggest that LTRAs are not as effective as low dose beclomethasone in improving FEV_1. Interestingly, however, very few differences are seen between the two types of drugs when evaluating other end-points such as and beta-agonist use (26,27).

Finally, from a clinical efficacy perspective, recent studies with all of the LT-modulating drugs suggest that there are additional benefits to the use of these drugs in patients cur-

rently treated with inhaled corticosteroids. The only study published to date demonstrated that the concomitant use of pranlukast allowed the inhaled corticosteroid dose (1600 µg/day) to be cut to 800 µg/day in moderate asthmatics without compromising asthma control (Figure 3) (28). A similar study was done with montelukast (29). In a somewhat different approach, adding a LT drug (montelukast or zileuton) to low doses of inhaled corticosteroids was better than doubling or maintaining the dose of the inhaled steroids, similar to results of studies with salmeterol and theophylline (30,31).

From a health economic perspective, there are statistically significant improvements in days missed from work and school, as well as significantly decreased rates of asthma exacerbation (23). A recent year-long study has shown that the addition of zileuton to "usual care" (inhaled steroids, theophylline, cromones) appears to reduce the need for steroid bursts, emergency room visits and hospitalizations compared with the "usual care" alone group (32).

These drugs are dosed orally anywhere from one to four times/day. This oral dosing may lead to better compliance with these medications. Zafirlukast is dosed as 20 mg orally bid (without food), montelukast 10 mg every evening (adults) and zileuton 600 mg qid. An eight-week study with montelukast in children recently demonstrated safety and efficacy compared with placebo in children on no or concurrent treatment with inhaled corticosteroids at 5 mg/day (33). The improvement in FEV_1 was in the range seen in the adult studies. All the clinical trials with montelukast were done with bedtime dosing. Nothing is known regarding dosing at other times of the day.

SAFETY

In general, these drugs appear to be well tolerated. Whether some of these drugs have potential liver toxicity is not yet clear, but zileuton has a 3% incidence of elevations in alanine aminotransferase versus placebo (24). Higher doses of zafirlukast (80 mg bid) likely have a similar effect on transaminases. No effect has been seen with montelukast.

There is some suggestion that a tachyphylaxis may occur with some of these compounds, such that higher doses are needed to maintain effective protection against challenges such as exercise (34). However, this effect was not seen with montelukast (16).

Because all of these compounds are metabolized by the liver, the possibility for significant drug interactions with other drugs metabolized by the P450 enzyme system clearly exists, but many such interactions, as could occur with antiepileptic drugs, have not yet been reported. Zafirlukast (and to a smaller extent, zileuton) has considerable interaction with warfarin, such that the dose of warfarin would likely have to be cut by up to 50%. Zileuton is also metabolized via the cytochrome P450 system, and recommendations for concurrent use with theophylline suggest decreasing the dose of theophylline by 50% and then checking the theophylline level. In addition, food appears to interfere with the absorption of zafirlukast, and the drug must be dosed 1 h before or after meals.

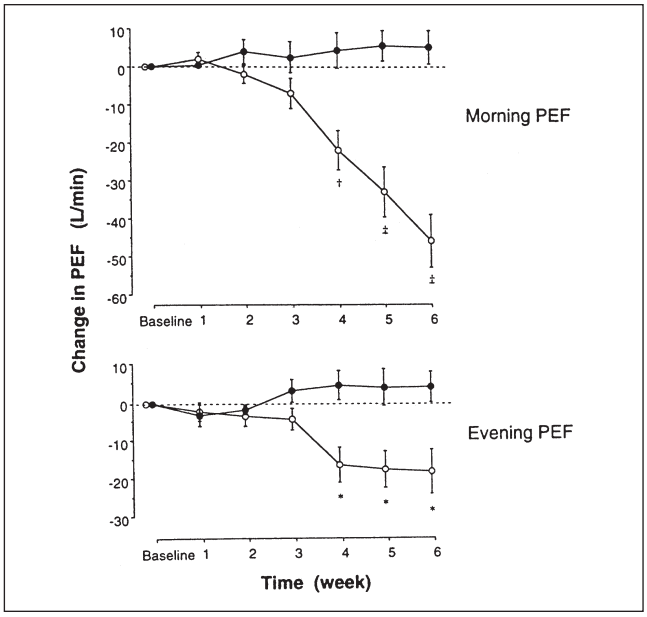

Figure 3) *The leukotriene receptor antagonist pranlukast following a reduction in inhaled steriods was able to prevent reductions in peak flows significantly better than placebo. PEF Peak expiratory flow*

Of perhaps the greatest concern is the possible association of zafirlukast and montelukast with Churg-Strauss syndrome, a rare eosinophilic vasculitis. Recently, eight patients treated with zafirlukast who had previously been on oral steroids were reported to present with Churg-Strauss syndrome. It is currently unclear whether this was a direct causal effect, or whether the Churg-Strauss was there previously and unmasked when the steroids were tapered. More information is needed before conclusions can definitively be drawn, but physicians should seriously consider complaints regarding new rashes or neurological or worsening respiratory symptoms (35). Whether cases will be reported with zileuton is not yet known.

HOW WILL THESE COMPOUNDS BE USED IN THE TREATMENT OF ASTHMA?

As the understanding of the long term efficacy and safety of these LT modulators improves, our ability to place these drugs into treatment guidelines will also improve. The initial evaluation of these drugs by the most recent (1997) National Asthma Education Program guidelines suggest that LT-modulating drugs may be used as an alternative to inhaled corticosteroids in the treatment of mild persistent asthma. Although this is certainly an option, patients with more severe disease may also benefit from add-on therapy to low dose inhaled corticosteroids and/or in more severely obstructed patients as an alternative to theophylline or a long-acting beta-agonist. A distinct advantage of these compounds is the oral dosing which may make compliance and adherence better, especially in the large percentage of patients who do not use their inhaled steroids regularly for any number of reasons. These drugs also promise to be very helpful in the treatment of aspirin-sensitive asthmatics. However, further

clinical experience with the long term disease modifying effects of these drugs is necessary before their final place in asthma treatment is known.

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