ROLE OF LEUKOTRIENE MODIFIERS IN
THE TREATMENT OF ASTHMA

By

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Chair

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ROLE OF LEUKOTRIENE MODIFIERS IN
THE TREATMENT OF ASTHMA

Abstract

By Krzysztof Szygorski, RN, BSN, MS
Washington State University
May 2000

Asthma is the most common respiratory disease encountered by nurse practitioners in clinical practice. There is no cure for asthma and it is not always controlled with existing therapies. Leukotrienes are recognized as the major causing factor in the pathology of asthma. Leukotrienes promote bronchoconstriction, mucus secretion, vascular leak and edema formation. Over the past decade a number of agents, known as leukotriene modifiers or antagonists, have been introduced and approved for the treatment of patients with asthma. Studies demonstrate the effectiveness of leukotriene antagonists in modifying bronchospasm with exercise, pulmonary reaction to aspirin in sensitive patients, and airway response to inhaled antigen. In patients with chronic asthma, leukotriene modifiers improve airflow obstruction, diminish asthma symptoms and decrease use of beta-agonists and inhaled corticosteroids. The goal of this paper is twofold: 1) to assist the nurse practitioner to make appropriate decisions about antileukotriene use; and 2) to delineate criteria used when selecting patients who will benefit from therapy with leukotriene modifiers.
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Introduction

Asthma is the most common respiratory disease encountered by nurse practitioners in clinical practice (Misson, 1999). The disease affects people of all ages, with peaks of onset in childhood and middle age. In 1998, 15 million Americans were affected with this disease. Asthma is the most common chronic disease in children and a major cause of clinic and emergency departments visits (Grant, 1998). Leukotrienes are recognized as major contributory factors in the pathophysiology of asthma. Leukotrienes promote vascular leak and edema formation, bronchial constriction, mucus secretion, eosinophil chemotaxis, and bronchial hyperresponsiveness (Kercsmar, 1999). They play a significant role in the generation and propagation of asthmatic inflammation (Deykin, 1999).

There is no cure for asthma and it is not always well controlled with existing therapies (Dahlen, 1995). Asthma treatment involves the use of inhaled glucocorticoids as anti-inflammatory agents and beta2 agonists or theophylline for acute relief of bronchoconstriction. Over the past decade a number of agents, known as leukotriene modifiers or antagonists, have been introduced and approved for the treatment of patients with asthma (Lazarus, 1999). Leukotriene antagonists modify bronchospasm with exercise, pulmonary reaction to aspirin in sensitive patients, and airway response to inhaled antigen. In patients with chronic asthma, leukotriene modifiers improve airflow obstruction, decrease the need for emergency bronchodilators, and diminish symptoms as well as prevent asthma exacerbations (Busse, 1999).

Unfortunately, there are few data comparing the efficacy of leukotriene modifiers with other preventive anti-inflammatory medications (Kercsmar, 1999). Nurse practitioners face many decisions in prescribing medications. Leukotriene modifiers provide a relatively new
opportunity for asthma control when correctly used. The goal of this literature review is to assist nurse practitioners to make appropriate decisions about leukotriene modifier use and to delineate criteria to select patients who will benefit from therapy with leukotriene modifiers.

**Role of the leukotrienes in the pathogenesis of asthma**

**What are leukotrienes?**

Leukotrienes are lipid mediators derived from arachidonic acid released from membrane phospholipids by the activation of the enzyme phospholipase A2. As presented in Figure 1, arachidonic acid is metabolized to various prostaglandins and thromboxanes by the enzyme cyclo-oxygenase or converted to 5-hydroperoxyeicosatetraenoic acid (5-HPETE) by the enzyme 5-lipoxygenase (5-LO) (Zoidis, 1997). In order to be active, 5-LO must bind to a membrane bound protein known as 5-lipoxygenase activating protein (FLAP). 5-LO and FLAP enzymes may then convert 5-HPETE to leukotriene A4 (LTA4). LTA4 can be converted by different enzymes to either leukotriene B4 (LTB4) or leukotriene C4 (LTC4). LTC4 can form LTD4 and LTE4 in sequential cascade reactions. LTB4 is called noncysteinyl leukotriene, and LTC4, LTD4, and LTE4 are cysteinyl leukotrienes (Spector, 1997). LTB4, LTC4, LTD4 and LTE4 are active leukotrienes. All three cysteinyl leukotrienes (LTC4, LTD4, LTE4) work at the same lung receptors called Cys-LT1 and Cys-LT2 (Dahlen, 1995).

Leukotrienes have been identified in plasma, urine, nasal secretions, sputum, and bronchoalveolar lavage fluid (BALF) from patients with spontaneous exacerbations of asthma and after antigen challenge. Increased LTB4 is found in sputum of patients with cystic fibrosis and in BALF of patients with bronchial asthma and idiopathic pulmonary fibrosis (Smith, 1998).
Figure 1

Formation of leukotrienes and thromboxanes via arachidonic acid breakdown.

STIMULI

CELL MEMBRANE PHOSPHOLIPIDS

PHOSPHOLIPASE A

ARACHIDONIC ACID

CYCLO-OXYGENASE

PROSTAGLANDINS

THROMBOXANE SYNTHASE

THROMBOXANES

5-LO/FLAP

5-LO/FALP

5-HPETE

LTA4

LTA4 HYDROLASE

LTB4

LTC4 SYNTHASE

LTC4

LTD4

LTE4

What factors cause production of leukotrienes?

In order to control asthma symptoms, the practitioner needs to understand the triggers which stimulate leukotriene production. In asthma, several factors can provoke leukotriene synthesis including trauma, infection, inflammation and a presence of an allergen (Spector, 1997). The process of allergens binding to allergen-specific immunoglobulin E (IgE) molecules borne on mast cells allows calcium to enter the cell. An increased intracellular calcium level causes a rapid release of preformed inflammatory mediators and activates the enzyme cytosolic phospholipase A2. Cytosolic phospholipase A2 cleaves arachidonic acid from membrane phospholipids. Arachidonic acid then acts as a substrate for 5-LO and FLAP in the formation of leukotrienes (Spector, 1997)

What cells are capable of leukotrienes production?

When activated, several cell types within the lung are capable of generating the cysteinyl leukotrienes. These cells include mast cells, eosinophils, and macrophages. In addition, several cell types including neutrophils can generate the unstable precursor LTA4. LTA4 can be then converted by endothelial cells, platelets, and eosinophils into the cysteinyl leukotrienes. Furthermore, LTB4 is released from human neutrophils and alveolar macrophages (Dahlen, 1995).

How do the leukotrienes affect airway function in asthma?

As inflammatory mediators, the leukotrienes have a number of physiological effects that cause airway obstruction and hyper-responsiveness. These physiologic effects include increased vascular permeability leading to edema formation, increased mucus production with increased mucociliary transport and contraction of bronchial smooth muscle and infiltration of
inflammatory cells into lung tissues (Zoidis, 1997). Increased vascular permeability leads to airway obstruction when blood, fluids and proteins are exuded into the airways and surrounding tissues. Other inflammatory mediators such as histamine, platelet activating factor, substance P and prostaglandins cause increased vascular permeability also, but the effects of cysteinyll leukotrienes is 400 times more potent than histamine in this regard (Spector, 1997).

Leukotrienes increase mucus production that in combination with extravasated proteins, may form mucus plugs and further decrease airway patency. The obstruction of airways caused by mucus plugs contribute directly to the morbidity and mortality of patients with asthma (Spector, 1997).

LTC4 and LTD4 are 1000 times more potent than histamine in causing bronchoconstriction. Their principal action is the contraction of bronchial smooth muscles. LTE4 is only 100 times more potent than histamine in causing bronchoconstriction but its duration of action lasts longer. Patients with asthma are 100 to 1000 times more responsive to the bronchoconstricting effects of LTC4 and LTD4 than healthy persons. The effects of LTE4 are equivalent in asthma and healthy individuals (Spector, 1997).

Of all leukotrienes, only LTB4 plays an important role in the chemotaxis of inflammatory cells. LTB4 increases neutrophil adhesion to vascular endothelium, enhances neutrophil degranulation and lysosomal enzyme release (Frieri, 1998).

Hyper-responsiveness of asthmatic patients is found to be enhanced by LTD4 and LTE4. Inhalation of LTD4 results in a prolonged period of hyper-responsiveness to inhaled methacholine. The magnitude of this effect is equivalent to that induced by inhaled platelet activating factor, and may last for 14 days. Inhalation of LTE4 prolongs bronchial
responsiveness to histamine that may last up to 1 week (Spector, 1997).

**Role of leukotriene modifiers in the treatment of asthma**

**Leukotriene modifiers approved by Food and Drug Administration**

The family of leukotriene modifiers can be divided into *leukotriene synthesis inhibitors*, which are represented by the 5-LO, and FLAP inhibitors and *cysteinyl-leukotriene receptor antagonists*, represented by CysLT1 and CysLT2 receptor blockers (Zoidis, 1997). Zileuton (trade name; Leutrol, Zyflo) is the only 5-LO inhibitor on United States (U.S.) market, and currently there are no FLAP inhibitors approved by Food and Drug Administration. The CysLT1 receptor antagonist are represented on the market by zafirlukast (trade name; Accolate) and montelukast (trade name; Singulair). Antileukotrienes which target LTB4, BLT and CysLT2 receptor antagonists as well as of LTA4 hydrolase inhibitors, are at preliminary stages of clinical development (Devillier, 1999).

**Pharmacodynamics of antileukotrienes**

Inhibitors of 5-LO directly block this enzyme, thereby preventing the metabolism of arachidonic acid to LTA4 (Zoidis, 1997). Cysteinyl-leukotriene-receptor antagonists block the actions of LTD4, LTC4 and LTE4 on target cells, such as smooth muscle and mucous cells (Zoidis, 1997, Devillier, 1999). Figure 2 may help visualize points at which the leukotriene modifiers work on arachidonic acid cascade.
Leukotriene modifiers: clinical efficacy

Antigen challenge: Leukotriene antagonists such as zafirlukast block approximately 80% of the early asthmatic response (EAR) to inhaled allergens and approximately 50% of the late asthmatic response (LAR) (Barnes, 1995). Nicosia (1999) reported that zafirlukast has been shown to reduce antigen-induced bronchoconstriction in patients with asthma when given orally two hours before challenge. Montelukast is the most advanced member of a family of leukotriene modifiers.
Montelukast has been shown to protect against antigen bronchoprovocation, both during the EAR and the LAR. Of clinical significance is that the protective effect of montelukast lasts longer than that of zafirlukast; thus montelukast can be administered as a single oral dose rather than twice daily like other antileukotrienes (Nicosia, 1999). In another study, participants received oral montelukast 5, 20, 100, or 250 milligrams (mg) 4 hours before inhalation challenge with LTD4. All doses produced at least 85-fold shifts to the right of the LTD4 dose-response curve (Smith, 1998).

**Exercise-and cold air-induced bronchoconstriction:** Most patients with asthma will experience bronchoconstriction with exercise if they achieve a high enough level of exercise and minute ventilation. A similar response occurs following hyperventilation while breathing cold, dry air. Oral zafirlukast (20 mg), given 2 hours before starting an exercise challenge, reduced the maximal fall in FEV1 from 36 to 22% (Smith, 1998). Similar results were observed in patients with asthma who received montelukast 10 mg per day or placebo for 12 weeks. Compared with baseline values, montelukast reduced exercise-induced bronchoconstriction as measured by the area under the curve (-45%), maximum fall in FEV1 (-31%) and the time to recovery (-28%). Importantly, long term treatment did not result in tolerance to the bronchoprotective effect of montelukast (Smith, 1998).

The administration of zileuton 600 mg 4 times daily for 2 days inhibited the exercise-induced bronchoconstriction 41% as compared with placebo. A similar 47% reduction of cold, dry air hyper-apnea-induced bronchoconstriction was reported in asthma patients 3 hours after a single dose of 800 mg of zileuton (Smith, 1998).

**Acute bronchodilation:** There are no data at this time to support using the
antilukotrienes for the acute bronchodilator effects in the emergency treatment of asthma (Johnson, 2000). Barnes (1995) found that leukotriene modifiers improve pulmonary function (improvement of FEV1 by 5-15%) in wheezy asthmatics. The improvement of FEV1 is thought to be a result of the removal of smooth muscle tone caused by presence of leukotrienes.

Smith (1998) reported that zafirlukast (40 mg orally) produced a maximum 8% improvement in the FEV1 3.5 hours after administration in patients with mild-to-moderate asthma. Drazen (1999) found that both CysLT1 receptor agonists (montelukast and zafirlukast) and 5-LO inhibitors (zileuton) improve airway obstruction in 1 to 2 hours. The results of his study suggest that the bronchodilating effect of antileukotrienes is greater in patients with more substantial airway obstruction: the lower the baseline FEV1, the larger the bronchodilation response.

Aspirin-induced asthma: An estimated 5 to 30% of patients with asthma are intolerant of aspirin and other nonsteroidal anti-inflammatory medications. These patients tend to have more severe disease and require treatment with high dosages of inhaled and/or systemic corticosteroids (Smith, 1998). Leukotriene antagonists improve lung function and decrease urine level of LTE4 in aspirin-sensitive asthmatics that can be six times higher than in aspirin tolerant patients with asthma. In patients with aspirin induced asthma, inhibition of the 5-LO pathway is associated with a complete block of the physiological responses to aspirin (Drazen, 1997).

Dahlen (1998) reported that inhaled or oral zileuton led to improvements in pulmonary function and a significant decrease in the use of beta-agonists in aspirin-intolerant asthmatics. The bronchial hyperresponsiveness to histamine was evaluated before and after treatment with
zileuton. There was significant improvement of this measure, possibly indicating a reduction in airway inflammation. Even though a study done by Christie (1991), as reported by Drazen (1999), suggested that not all aspirin-intolerant asthmatics responded to leukotriene modifiers. The report concluded that antileukotrienes should be the drugs of choice for patients with aspirin-induced asthma.

**Chronic asthma:** In order to establish the efficacy of the leuktriene modifiers, it is necessary to use them in the treatment of patients with chronic asthma. Patients who were treated with either beta2-agonists or theophylline, were assigned to three daily dosages of zafirlukast (10, 20, or 40 mg in divided doses) or placebo. The 10, 20, and 40 mg doses of zafirlukast were associated with 7%, 6% and 11% increase in FEV1 values respectively (Busse, 1999). Drazen (1999) reported on a study that compared the potency of antileukotrienes by determining their response to doses of inhaled leukotrienes in patients with chronic-stable asthma. Zafirlukast and montelukast shifted the dose response curve by a factor 100 or more and zileuton inhibited leukotriene synthesis by 70 to 90%. Drazen also found that oral administration of any of these three antileukotrienes to patients with chronic persistent asthma improved airway function, decreased the number of asthma exacerbations and decreased the need for use of beta2-agonists as well as decreased the dose of inhaled corticosteroids required for asthma control.

**Airway inflammation/nocturnal asthma:** Leukotrienes have been found to be primary mediators contributing to nocturnal asthma. Wenzel (1995), reported that there is a rise in the urinary LTE4 level at night in patients with nocturnal asthma. Patients with nocturnal asthma, who received oral montelukast 10 mg daily for 3 days had a 22% decrease in peripheral blood
eosinophils along with improvements in FEV1 (+13%) and daytime symptoms (-16%) (Wenzel, 1998).

Wenzel (1998) provided support for an anti-inflammatory effect of the antileukotrienes by examining the effect of zileuton 600 mg 4 times daily for 1 week on airway inflammation in patients with nocturnal asthma. Zileuton reduced bronchoalveolar lavage fluid LTB4 (-38%) and urinary LTE4 (-76%), decreased peripheral blood and bronchoalveolar lavage eosinophil counts and showed a trend for improving the nocturnal FEV1 (+30%).

Calhoun (1998) found significant decreases in the influx of inflammatory cells at 48 hours postchallenge among patients with asthma treated with zafirlukast (160 mg twice daily) relative to the values obtained from patients receiving only placebo (from 0.03 thousand per milliliter (ml) to 0.13 thousand per ml [p < 0.001]). Eosinophil numbers decreased, from 70.5 thousand per ml to 39.0 thousand per ml (p < 0.05). Furthermore, superoxide release from alveolar macrophages also decreased significantly (p < 0.05).

Efficacy of leukotriene modifiers in comparison with other anti-asthma drugs

Inhaled corticosteroids and antiloukotrienes

In one study zafirlukast 20 mg was compared to inhaled fluticasone 100 ug each given twice daily for 2 weeks to 30 patients with mild-to-moderate disease. Fluticasone produced a larger improvement in histamine-induced airway reactivity and morning peak flow rates than zafirlukast. (Smith, 1998).

Results of Malmstrom’s study (1999) showed inhaled beclomethasone to be significantly more effective in suppressing daytime asthma symptoms than montelukast. Malmstorm reported that inhaled beclomethasone is cheaper and more effective than montelukast and should be used
beclomethasone, "the effect on symptoms has favored inhaled corticosteroids". Both inhaled corticosteroids and leukotriene modifiers produce an improvement in pulmonary function, but the available comparison studies consistently demonstrate a significantly greater impact of inhaled corticosteroids on FEV1 than that seen with the antileukotrienes. At present, Allegra (1999) recommends low-dose inhaled corticosteroids as the reference drugs for the controller therapy of mild persistent asthma, while antileukotrienes may be used as a possible alternative, offering better compliance and minimizing side effects (see Table 1).

In conclusion, direct and indirect comparison of antileukotrienes and inhaled corticosteroids shows that they both have equivalent effect on symptoms and exacerbations but steroids are more effective in terms of respiratory function and number of responders. Leukotiene modifiers are more effective in terms of compliance and causing less side effects (Allegra, 1999).

Table 1
*Inhaled low-dose corticosteroids and antileukotrienes in mild persistent asthma: comparative data*

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<td>Efficacy versus placebo</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Reduction in number of exacerbations</td>
<td>-50%</td>
<td>-50%</td>
</tr>
<tr>
<td>Anti-inflammatory properties</td>
<td>Preliminary data only</td>
<td>Yes</td>
</tr>
<tr>
<td>Long-term effects on airway remodeling</td>
<td>Not known</td>
<td>Yes</td>
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ICS = inhaled corticosteroids. Adapted from Allegra (1999).
but steroids are more effective in terms of respiratory function and number of responders. Leukotriene modifiers are more effective in terms of compliance and causing less side effects (Allegra, 1999).

**Comparison of antileukotrienes and other asthma drugs**

Calhoun (1998) reported no statistically significant differences between zafirlukast and cromolyn in the treatment of patients with mild-to-moderate asthma. The results of a 13-week study comparing zafirlukast 20 mg twice daily to sodium cromoglycate 1.6 mg four times daily in patients with mild-to-moderate asthma demonstrated zafirlukast and sodium cromoglycate to be equally effective (Smith, 1998). However, in another study of 64 patients with more severe asthma (FEV1 < 65% predicted), zafirlukast produced a greater increase in FEV1 compared with sodium cromoglycate or placebo, suggesting that the more severe the asthma, the higher clinical benefit obtained from zafirlukast therapy. Zafirlukast (80 mg twice daily) demonstrated similar improvement in early and late phase reaction to allergen provocation as H1-histamine receptor antagonist loratadine (10 mg twice daily) in allergic asthmatics. The combination of these two drugs was significantly more effective in reducing the area under the FEV1 versus placebo by 75% during the early phase and by 74% during the late phase after allergen challenge (Devillier, 1999).

**Antileukotrienes: safety, side effects and recommended monitoring**

**5-LO inhibitor zileuton:** Antileukotrienes are generally well tolerated, independent of the duration of treatment, and adverse effect rates similar to those of placebo (Allegra, 1999). The most frequent side effects of zileuton are: headache 24.6% (24% placebo), dyspnea 8.2% (2.9% placebo), unspecified pain 7.8% (5.3 % placebo) and nausea 5.5% (3.7% placebo)
Johnson (2000) reported elevations of alanine transaminase (ALT) to greater than 3 times the upper limit of normal occurred in 3.2% of patients taking zileuton in controlled and uncontrolled trials involving more than 5,000 patients. Drazen (1997) identified 3.5% of patients taking zileuton in whom there was a reversible increase in ALT. Except for liver function tests, clinical laboratory results revealed no relevant adverse changes in renal, electrolyte, metabolic, nutritional or endocrine parameters in patients receiving zileuton. The only clinically significant trend on hematology parameters was a greater reduction in eosinophils in patients taking zileuton compared to patients given a placebo. The pattern of liver abnormalities in patients on zileuton therapy is predominantly asymptomatic hepatocellular and with no associated elevation of alkaline phosphatase or bilirubin. Johnson (2000), reported that age greater than 65, chronic alcohol consumption and female gender may increase risk of hepatic dysfunction in persons taking zileuton.

Dube (1999), as well as the Food and Drug Administration, recommend monitoring serum ALT before initiation of zileuton therapy, once a month for the first 3 months, every 2-3 months for the remainder of the first year, and periodically thereafter. Zileuton is contraindicated in patients with active liver disease and should be discontinued if clinical signs or symptoms of hepatic dysfunction (nausea, fatigue, lethargy, pruritis, jaundice, and “flu-like” symptoms) are experienced or ALT levels exceed 5 times upper limit of normal (Johnson, 2000).

Spontaneous resolution of the ALT elevations was observed in 52% of patients who had ALT elevations 3 to 5 times more than upper normal limit and still continued to receive zileuton. All other cases of ALT elevations resolved within a mean of four weeks after cessation of zileuton therapy. Of more than 5,000 patients treated with zileuton in clinical trials, only one
developed symptomatic hepatitis with jaundice, which resolved completely after discontinuing therapy (Dube, 1999).

**Cysteiny1-leukotriene-receptor antagonists:** Accordingly to Allegra (1999), *montelukast* and *zafirlukast* are well tolerated in subjects with mild-to-moderate asthma, independent of the duration of treatment. Neither drug had adverse effects with a greater frequency than placebo (Allegra, 1999). The most frequent side effects caused by zafirlukast are: headache 12.9% (11.7% placebo), infection 3.5% (3.4% placebo), nausea 3.1% (2.0% placebo) and diarrhea 2.8% (2.0% placebo). Side effects associated with montelukast are: headache 18.4% (18.1% placebo), influenza 4.2% (3.9% placebo), abdominal pain 2.9% (2.5% placebo) and cough 2.7% (2.4% placebo) (Johnson, 2000).

Allegra (1999) reported a few incidents of Churg-Strauss syndrome, a rare disease characterized by asthma, eosinophilia and vasculitis in patients treated with zafirlukast or montelukast who had reduced or abandoned their oral steroid treatment. Churg-Strauss syndrome is usually treated with oral steroids. Allegra suggested that the symptoms of Churg-Strauss syndrome were probably unmasked by the reduction in or interruption of the steroid treatment, and indeed no causal relationship has been established between the use of antileukotrienes and this syndrome. Drazen (1999) reported about one case of Churg-Strauss syndrome in 20,000 treatment years, predominantly reported at the beginning of the leukotriene modifiers era in patients with severe persistent asthma receiving zafirlukast. Drazen recommended Churg-Strauss syndrome not be considered a contraindication in the treatment of patients with mild-to-moderate persistent asthma. According to Johnson (2000), Churg-Strauss syndrome has also been reported in patients receiving inhaled corticosteroids who were being...
tapered from systemic steroids. The nurse practitioner should, however, exercise caution when reducing steroid doses as a result of the concurrent use of leukotriene modifiers. It is important to educate patients about reporting myriad symptoms such as rash, fever, malaise and paresthesias which indicate Churg-Strauss syndrome to their nurse practitioner (Johnson, 2000).

Elevations of serum transaminase have been reported very sporadically in patients taking zafirlukast, but the routine monitoring of hepatic enzymes when using zafirlukast or montelukast is not required (Johnson, 2000). In patients receiving the recommended doses of montelukast or zafirlukast, hepatotoxicity has not been noted (Drazen, 1999). Montelukast requires no dose adjustment in patients with hepatitis or cirrhosis (Johnson, 2000). Further, no dose adjustment is required in elderly patients or those with renal insufficiency for any of the three leukotriene modifiers available in the United States (Johnson, 2000).

**Metabolism and drug interaction of leukotriene modifiers**

All three antileukotrienes zileuton, zafirlukast and montelukast, are metabolized by cytochrome P-450. It is recommended to co-administer them carefully with drugs metabolized by the same enzyme (terfenadine, aspirin, erythromycin, theophylline, warfarin, phenotin, phenobarbitone and rifampicin) (Allegra, 1999). Zileuton is oxidatively metabolized by enzymes P-450, CYP1A2, CYP2C9, and CYP3A4. At therapeutic concentrations, zafirlukast inhibits the CYP3A isoenzymes which are crucial in the metabolism of terfenadine, cyclosporine, cisapride and the dihydropyridine calcium channel blockers. In addition, zafirlukast inhibits the isoenzyme CYP2C9, that is involved in metabolism of warfarin, phenytoin, and carbamazepine. Even though montelukast does not inhibit cytochrome P-450 at therapeutic dose, drugs which induce isoenzyme CYP3A4, such as phenotin, phenobarbital, and
rifampin, may decrease montelukast serum level, and subsequent clinical response (Johnson, 2000).

Co-administration of zafirlukast or zileuton with warfarin resulted in a decrease in the clearance of warfarin and a significant increase in prothrombin time requiring adjustment of the anticoagulant dose. Neither montelukast, zafirlukast or zileuton interacted with oral contraceptives. There have been no reported interactions between montelukast or zileuton and oral prednisone or digoxin (Devillier, 1999).

Safety benefit of antileukotrienes over other drugs

In comparison with inhaled corticosteroids and beta-agonists, antileukotriene agents provide an improved safety profile (Johnson, 2000). Regular use of short-acting and/or long-acting inhaled beta2-agonists results in tolerance that reduces their broncho-protective effects against induced bronchoconstrictor stimuli, such as methacholine and exercise (O’Byrne, 1999).

Inhaled corticosteroids remain the most effective treatment for asthma. They are, however, minimally absorbed across the lungs into the systemic circulation causing limited but unwanted effects beyond the lungs. The systemic adverse effects of inhaled corticosteroids limit their use, especially in children. The side effects of inhaled corticosteroids seem to be dose related. At the lower dose oral candidiasis occurs in 5-10% of adults and 1% children with asthma. Dysphonia was found in 30% of patients using inhaled corticosteroids. Doses of inhaled corticosteroids of $\geq 400\mu g/day$ of beclomethasone or budesonide in children can result in changes in growth velocity but do not stunt growth. In adult patients, inhaled corticosteroids may cause changes in bones and adrenal glands resulting in osteoporosis, particularly in postmenopausal women and patients with adrenal insufficiency. The incidence of skin bruising
occurs rarely at doses less than 1000ug/day and increases with age and duration of treatment (O’Byrne, 1999). The National Heart, Lung and Blood Institute Expert Panel on Asthma considers inhaled corticosteroids the preferred anti-inflammatory agents, and it is unlikely that leukotriene modifiers will replace corticosteroid therapy entirely in any group of persons with asthma (Horovitz, 1998).

In conclusion, it is important to remember that inhaled corticosteroids have been utilized for over 20 years with minimal side effects at low doses. Although there are reports of osteoporosis, growth retardation in children, and glaucoma from inhaled corticosteroids, the effects are positively correlated with increasing doses. The practitioner who decides to utilize antileukotrienes in practice must take under consideration that clinical experience with these agents is very limited, and there is no safety information for any longer duration of use greater than 3 years (Wenzel, 1998).

**Patient adherence.**

When making a decision about choosing the appropriate treatment for asthma control the nurse practitioner must consider patient adherence. Are the leukotriene modifiers easier to take than other medications and, if so, more effective? The peak onset of action of leukotriene modifiers is within 24 hours of treatment. In contrast, the effects of inhaled corticosteroids therapy are gradual and take several weeks which can theoretically decrease patient adherence (Lipworth, 1999). Kirsche (2000) found that with inhaled corticosteroids, the best techniques allow only 10% to 30% delivery to the lungs and the rest of the medication is swallowed and undergoes first-pass metabolism in the liver. Campos (1998) presented summaries of international studies reporting that one out of every two patients commits errors in applying the
inhalation technique. Up to 80% of doctors surveyed, exhibited faulty knowledge of the inhalation technique. Campos (1998) suggested that even with the use of spacers or turbuhalers a high percentage of errors continued. In his study 57.6% of patients with mild asthma committed an error while using metered dose inhalers. There was also a very high ratio of errors in correct use of inhalers with spacers (44%) and turbuhalers (40%).

All antileukotrienes available in the United Sates are in the oral form making their administration simple and possibly more effective. A study of 167 patients with stable asthma suggested that oral zafirlukast improved patient’s satisfaction and it was preferred 2:1 over inhaled corticosteroids (Johnson, 2000). An additional advantage of oral antileukotrienes is that they provide systemic bioavailability, and avoid the difficulties of trying to achieve correct inhaler use (Johnson, 2000).

**Indications for antileukotriene therapy**

According to Horovitz (1998), the practitioner may use antileukotriene agents as the first-line therapy in the following patients: (1) those with mild to moderate disease who fail to respond adequately to inhaled corticosteroids; (2) patients with moderate to severe asthma who have systemic side effects from high doses of inhaled corticosteroids or who are at risk for these adverse effects (these patients should be considered for a trial of leukotriene modifiers to determine whether these agents will allow a reduction in the use of corticosteroids); (3) patients with poor adherence to inhaled corticosteroids due to improper technique or physical limitations; (4) patients receiving inhaled corticosteroids who are still poorly controlled and who cannot tolerate theophylline or long-acting bronchodilators. In addition, leukotriene modifiers may be considered in the following circumstances: (1) as a preventive strategy for allergen-,
exercise- or aspirin-induced asthma; (2) as add-on therapy for patients whose asthma is insufficiently controlled with inhaled corticosteroids; (3) to reduce the amount of inhaled or oral corticosteroids needed to control disease in patients with moderate or severe asthma; (4) to provide a steady protection in patients with exercise-induced bronchoconstriction who regularly use inhaled beta-agonists (O'Byrne, 1997). These indications also apply to children age 6 and older with montelukast being approved for use in children as young as 6 years of age and zafirlukast approved for use with children 12 years of age and older. Zileuton is the only antileukotriene whose safety has not been established in pediatric patients younger than 12 years of age (Johnson, 2000).

The choice among the available antileukotriene agents should be based on dosing convenience, cost, drug interaction and tolerability concerns (Johnson, 2000). It is, however, critical for the nurse practitioner to know that because of their slow onset of action, leukotriene modifiers are not indicated for the treatment of acute exacerbations of asthma and must always be prescribed in combination with short-acting inhaled beta2-agonists, to be used as required. During antileukotriene therapy, the practitioner should monitor patients for asthma aggravation and not hesitate to add inhaled or systemic corticosteroids to the treatment regimen if the asthma becomes aggravated (Renzi, 1999). Also, it is important to educate patients to take antileukotrienes (especially zafirlukast) 1 hour before or 2 hours after meals since the presence of food decreases their bioavailability (Allegra, 1999).

The nurse practitioner should remember that antileukotrienes act more rapidly than inhaled corticosteroids, so if no improvement is seen in 14 days, a response is unlikely, and the drug should be discontinued. No indication is apparent for the use of antileukotrienes in
patients with very mild, intermittent asthma, in whom infrequent use of inhaled beta2-agonists provides adequate control of symptoms (O’Byrne, 1997). Antileukotrienes have not been approved for pregnant or lactating patients (Johnson, 2000).

**Pharmacoeconomics**

In 1997, Kupecz reported that the wholesale price of 30 days of treatment with the lowest recommended adult dose (20 mg orally twice per day) of zafirlukast was $52.50. This drug was more costly than the monthly price of inhaled corticosteroids ($29.50-$43.40) but compared favorably with cromolyn ($75.43-90.13), nedocromil ($53.53) and the long acting beta2-agonist salmeterol ($52.76). Table 2 presents the cost of one month supply of leukotriene modifiers in asthma treatment.

Table 2

**Monthly cost of therapy with antileukotrienes**

<table>
<thead>
<tr>
<th></th>
<th>Recommended adult dosage</th>
<th>Number of pills for 30-day supply</th>
<th>Cost for 30-day supply*</th>
</tr>
</thead>
<tbody>
<tr>
<td>zileulton</td>
<td>600mg qid</td>
<td>120</td>
<td>$82.53</td>
</tr>
<tr>
<td>zafirlukast</td>
<td>20mg bid</td>
<td>60</td>
<td>$59.77</td>
</tr>
<tr>
<td>montelukast</td>
<td>10mg qd</td>
<td>30</td>
<td>$57.92</td>
</tr>
</tbody>
</table>

*Based on average wholesale price. Adapted from Johnson (2000).

Pharmaco-economic studies with zafirlukast showed that, compared with placebo,
controlled therapy with antileukotrienes decreased by over 50% both the direct (fewer healthcare contacts, reduced use of concomitant drugs and beta2-agonists) and indirect costs (greater productivity due to reduced absenteeism from work or school), while at the same time improved qualitative parameters of the individual’s well-being. These included number of days without activity limitation (19% increase, p<0.001), number of days free of symptoms (89% increase, p=0.03), number of days without using “as needed” beta2-agonists (89% increase, p=0.001), and the number of episode-free days (98% increase, p=0.003). Costs related to hospital admissions due to asthma exacerbations account for approximately 41% of the overall cost of treating asthma while costs due to clinical visits and days of absence from school/work have been estimated to account for 19% and 33% respectively. In a population of untreated patients, leukotriene modifiers reduced each of these costs by more than 50%, and reduced overall costs of managing asthma by 93% (Allegra, 1999).

Johnson, (2000), agreed that the addition of zafirlukast to the treatment of patients receiving only short-acting beta2-agonists resulted in a significant reduction in health care utilization as compared with placebo. The cost-effectiveness of adding antileukotrienes to inhaled corticosteroids appears clinically important, as a result of fewer exacerbations.

Summary

On the basis of available data, practitioners may consider adding leukotriene modifiers to reduce asthma symptoms and exacerbations, to improve airway function, and to decrease the need for concomitant beta2-agonist and inhaled corticosteroids for patients with asthma. Leukotriene modifiers may be particularly beneficial in patients with aspirin-and exercise-induced asthma, conditions in which leukotrienes are thought to be important mediators.
Practitioners may use these agents as a first-line anti-inflammatory therapy in patients requiring more than simple bronchodilator therapy (Spector, 1997). The positive attributes of the leukotriene modifiers include oral administration, both anti-inflammatory and bronchodilator properties and excellent safety profile in adults and children. The negative attributes associated with antileukotrienes are systemic administration with possible effects on immune function and lower efficacy than inhaled corticosteroids in mild-to-moderate asthma. Leukotriene modifiers should not be used for relief of acute symptoms, since beta-agonists are effective and have a much more rapid onset of action (Smith, 1998). Overall, because of their better compliance and fewer side effects, the leukotriene modifiers are a more practical alternative than current available therapies. For equivalent asthma control, these agents allow the use of lower doses of inhaled and oral steroids, and beta2-agonists. The good compliance resulting from oral administration of leukotriene modifiers may provide better and more sustained adherence to asthma therapy leading to significant improvement in quality of life and further reduction in the cost associated with hospitalizations and absenteeism from work or school (Allegra, 1999). Table 3 summarizes the most important factors nurse practitioners need to consider when making a decision whether to use leukotriene modifiers in the treatment of asthma.
Table 3

**Indication and general profile of leukotriene modifiers**

<table>
<thead>
<tr>
<th>Indications</th>
<th>Zileuton</th>
<th>Zafirlukast</th>
<th>Montelukast</th>
</tr>
</thead>
<tbody>
<tr>
<td>bronchoconstriction</td>
<td>not indicated</td>
<td>indicated</td>
<td>indicated</td>
</tr>
<tr>
<td>exercise-induced as asthma</td>
<td>indicated</td>
<td>indicated</td>
<td>not indicated</td>
</tr>
<tr>
<td>cold-induced asthma</td>
<td>indicated</td>
<td>indicated</td>
<td>not indicated</td>
</tr>
<tr>
<td>aspirin-induced asthma</td>
<td>indicated</td>
<td>not indicated</td>
<td>indicated</td>
</tr>
<tr>
<td>allergic asthma</td>
<td>not indicated</td>
<td>indicated</td>
<td>indicated</td>
</tr>
<tr>
<td>chronic asthma</td>
<td>indicated</td>
<td>indicated</td>
<td>indicated</td>
</tr>
</tbody>
</table>

**Recommended dosages**

- adult
  - Zileuton: 600mg qid
  - Zafirlukast: 20mg bid
  - Montelukast: 10mg qd at hs
- children
  - Zileuton: not indicated in pts<12y.o.
  - Zafirlukast: 10mg minitablet bid (ages 7-11)
  - Montelukast: 5mg chewable tablet qd at hs (ages 6-14)

**Metabolism**

- liver, P-450

**Food interaction**

- no
- yes; take 1 hr before or 2 hrs after meals
- no

**Drug interaction**

- warf, prop, theo, terf
- warf, aspirin, theo, eryth, terf, phenotoin, carbamazepine
- phenobarbitol

**Most frequent adverse reactions**

- headache
dyspepsia, nausea
unspecified pain

- headache
nausea, diarrhea
nausea, diarrhea

- headache, cough
flu-like symptoms
abdominal pain

**Warnings**

- increased liver enzymes
- may be associated with Churg-Strauss sx
- none

**Need for monitoring**

- serum ALT
- none
- none

**Pregnancy category**

- C
- B
- B

**Use in nursing mothers**

- not recommended
- not recommended
- exercise caution

*Adopted from Johnson (2000) and Spector (1997).*
References


