Drug Safety 1998 Sep; 19 (3): 205-218
0114-5916/98/0009-0205/$07.00/0

A Risk-Benefit Assessment of Antileukotrienes in Asthma

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Contents

Abstract

The antileukotriene drugs are the first new therapeutic agents approved for the treatment of asthma in more than 20 years. The currently available compounds are orally active and either prevent the cysteinyl leukotrienes from binding to and activating the cysLT-1 receptor in the lung (leukotriene receptor antagonists) or inhibit leukotriene synthesis (leukotriene synthesis inhibitors).

Studies performed in individuals without asthma and patients with asthma reveal that antileukotrienes prevent the bronchoconstriction produced by exercise, cold-air, allergen, aspirin (acetylsalicylic acid) and sulphur dioxide. Except for the setting of aspirin sensitivity where the antileukotrienes are nearly uniformly effective, individual responses to them are variable with complete protection in some, no protection in others and a modest degree of protection in the majority.

The antileukotrienes bronchodilate the airways of patients with baseline bronchoconstriction, although usually not as well as β-agonists. When given for weeks to months they rapidly improve pulmonary function and symptoms in patients with mild-to-moderate asthma, and probably in patients with more severe asthma as well, and these improvements persist for the duration of treatment. Here too, their beneficial effects are variable and not predictable based on clinical criteria. Recent studies suggest they can reduce asthma-induced airway inflammation and

are equal or more effective than sodium cromoglycate, but equal or less effective than low-to-moderate dosages of inhaled corticosteroids. Initial experience with the antileukotrienes reveals limited toxicity and what appears to be a favourable therapeutic-to-toxic ratio. However, exposure of more patients with differing characteristics for longer periods of time is needed to substantiate this initial impression. The exact role of the antileukotrienes in the treatment of asthma remains to be determined, as does the relative potency of the various agents.

Asthma is a chronic inflammatory disease of the airways. Asthma is characterised by recurrent episodes of wheezing, breathlessness, chest tightness and cough, variable airflow obstruction, often reversible either spontaneously or with treatment and bronchial hyperresponsiveness.[1] The airways of patients with asthma contain lymphocytes, eosinophils, mast cells, neutrophils and alveolar macrophages, as well as multiple cell products including histamine, prostanoids, leukotrienes, platelet activating factor and a variety of cytokines such as tumour necrosis factor α, interleukin (IL) -3, IL-4, IL-5, IL-10 and granulocyte-macrophage colony stimulating factor.[2] Among these cell products, the cysteinyl leukotrienes have been recognised as contributing to the pathogenesis of asthma. Their synthesis is illustrated in figure 1. The elucidation of this pathway and its importance is the result of *in vitro* and animal studies, in addition to human studies. These studies have demonstrated that inhaled leukotrienes can reproduce the key features of asthma (e.g. bronchoconstriction, increased airway reactivity, an inflammatory cell influx in the airways and mucus hypersecretion). They have also shown that the newly developed antileukotriene drugs are effective in the treatment of asthma (reviewed in Smith[3] and in section 1 of this review).

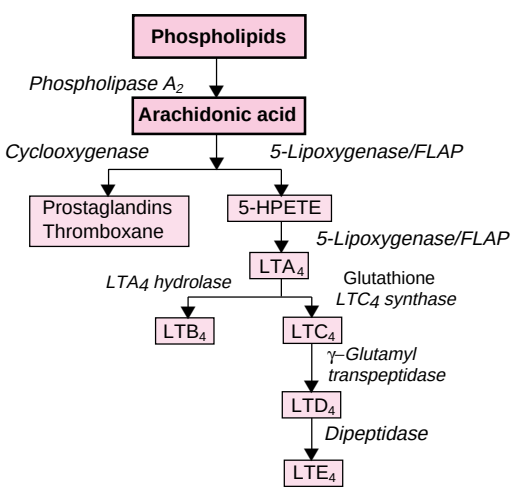

Fig.1. Pathway of arachidonic acid metabolism leading to leukotrienes.
FLAP = 5-lipoxygenase activating protein; **5-HPETE** = 5-hydroperoxyeicosatetraenoic acid; **LT** = leukotriene.

As the first truly new class of therapeutic agents for the treatment of asthma in more than 2 decades, it is important to review the benefits of antileukotrienes as well as their risks. This article reviews the available information on the leukotriene receptor antagonists (drugs that block the cysLT-1 receptor) and the leukotriene synthesis inhibitors (table I). Studies demonstrating the effectiveness of the antileukotrienes in various challenge protocols are reviewed, followed by trials of the leukotriene receptor antagonists and the leukotriene synthesis inhibitors for the long term treatment of asthma. Information about toxicity and pharmacokinetics is also presented, followed by an attempt to define the position of these new drugs in the treatment of asthma. Since new information about these drugs is appearing rapidly, further insights into their place in asthma pharmacotherapy should be forthcoming. As with any new, rapidly expanding field, some of the most recent information has been presented only in abstract form. These data must be considered preliminary and interpreted cautiously.

1. Challenge Studies Using the Antileukotrienes

Several antileukotrienes have been tested for their ability to prevent the bronchoconstrictor re-

Table I. Leukotriene receptor antagonists and leukotriene synthesis inhibitors

Leukotriene receptor antagonists	Leukotriene synthesis inhibitors
Zafirlukast	Zileuton
Pranlukast	MK-886
Montelukast	Bay x1005
Cinalukast	ZD 2138
RG 12525	
BAY x 7195	

sponse to a variety of stimuli. These studies have provided support for the involvement of the cysteinyl leukotrienes in the asthmatic response and a rationale for testing their effectiveness in the treatment of chronic asthma.

1.1 Leukotriene D_4 Challenges

Studies with zafirlukast (ICI 204219) by Smith and colleagues[4-6] in patients with and without asthma revealed that this orally available leukotriene receptor antagonist could shift the leukotriene (LT) D_4 dose-response curve to the right at least 100-fold. In the initial challenge study, zafirlukast 40mg was administered to individuals without asthma 2, 12 or 24 hours before they underwent a LTD_4 bronchial challenge in which increasing concentrations of LTD_4 were inhaled at 10-minute intervals and specific airway conductance was measured 2 to 3 minutes later.[4] Two hours after taking the drug, the LTD_4 dose-response curve was shifted to the right 117-fold. At 12 and 24 hours there were smaller, but significant, 9- and 5-fold shifts to the right. In studies using patients with asthma, single doses of zafirlukast ranging from 2 to 100mg were given 12 hours before inhaling the LTD_4.[5,6] The forced expiratory volume in 1 second (FEV_1) was measured after each inhalation of LTD_4 to determine the concentration of LTD_4 required to reduce the FEV_1 by 20% [provocation concentration $(PC)_{20}$ FEV_1]. In both studies increasing doses of zafirlukast produced increasing protection, with the 10 to 40mg doses producing 10- to 20-fold shifts to the right in the dose-response curve (similar to that seen in the individuals without asthma 12 hours after administration) and the 100mg dose producing nearly a 100-fold shift to the right.

Two other leukotriene receptor antagonists, pranlukast and montelukast, are also potent inhibitors of LTD_4-induced bronchoconstriction.[7-9] When oral pranlukast 450mg twice daily was given to individuals without asthma for 5 days, there was an average 10-fold shift to the right in the LTD_4 dose-response curve 3.5 hours after receiving the first dose and a 26-fold and 7-fold shift to the right on the fifth day, 3.5 and 9.5 hours after the patients received the last dose of the drug.[7] A study in individuals with asthma examined the effect of intravenous pranlukast, given first as a loading dose over 30 minutes and then as a continuous intravenous infusion for 2 additional hours, on LTD_4-induced bronchoconstriction.[8] Bronchoprovocation testing with LTD_4 was started during the pranlukast infusion. The highest dose of the drug (60mg) produced a 100-fold shift to the right in the LTD_4 dose-response curve. The 30 and 10mg doses produced 28- and 13-fold shifts to the right, respectively. Montelukast also inhibits LTD_4-induced bronchoconstriction in patients with asthma.[9] Study participants received oral montelukast 5, 20, 100 or 250mg 4 hours before inhalation challenge with LTD_4. All doses produced at least 85-fold shifts to the right of the LTD_4 dose-response curve (range 85- to 181-fold for the lowest to the highest doses). When the 40 and 200mg doses were given 20 hours before the LTD_4 challenge, the median shifts were at least 56- and 70-fold, respectively.

1.2 Exercise and Cold-Air Challenges

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. Manning and colleagues[10] reported that pretreatment with the leukotriene receptor antagonist MK-571, given intravenously, inhibited exercise-induced bronchoconstriction. The maximal decrease in FEV_1 was reduced from 25 to 9%, while the time to recovery was reduced from 33 minutes to 8 minutes. Similar

results have been reported with zafirlukast. When oral zafirlukast 20mg was taken 2 hours before starting the exercise challenge, the maximal fall in FEV_1 was reduced from 36 to 22%.[11] There was a larger reduction in the area under the FEV_1 versus time curve and, as with MK-571, the duration of exercise-induced bronchoconstriction was reduced. When given by the inhaled route, zafirlukast also reduced exercise-induced bronchoconstriction, decreasing the maximal fall in FEV_1, the area under the curve and the time to recovery.[12] In these studies the inhibitory effect of zafirlukast was nearly complete in some individuals, partial in others and nonexistent in the remaining study participants. This variable effectiveness has been confirmed in other studies with the antileukotrienes, including challenge studies and clinical trials. Zafirlukast can also protect against cold-air hyperpnoea-induced bronchoconstriction.[13-15]

Similar observations have been made with the leukotriene receptor antagonists pranlukast and montelukast.[16,17] Oral pranlukast 450mg twice daily was given for 14 days to patients with exercise-induced bronchoconstriction.[16] Exercise challenge was performed before and at the end of the treatment period. Pranlukast reduced the maximal fall in FEV_1 from 55% before treatment to 30% after treatment. In a separate study, patients with exercise-induced bronchoconstriction received single doses of montelukast (0.4, 2, 10 or 50mg) or placebo 24 hours apart, followed by exercise challenges 20 to 24 hours and 32 to 36 hours after the patients had received the second dose.[17] Compared with placebo, montelukast produced a dose-dependent inhibition at 20 to 24 hours. The 2 highest doses, however, had a similar effect. The inhibition, measured by the area under the FEV_1 versus time curve, was approximately 25%. Less time was needed to recover from the exercise-induced bronchoconstriction. Protection was lost 32 to 36 hours after taking the drug. This is consistent with its expected half-life. In another study, patients with asthma received montelukast 10 mg/day or placebo for 12 weeks.[18] Compared with baseline vaules, montelukast reduced exercise-induced bronchoconstriction as measured by the area under the curve (–45%), maximum fall in FEV_1 (–31%) and time to recovery (–28%). Long term treatment did not result in tolerance to the bronchoprotective effect of montelukast.

Zileuton, a leukotriene synthesis inhibitor, also inhibits exercise and cold-air-induced bronchoconstriction.[19,20] Meltzer et al.[19] reported that the administration of zileuton 600mg 4 times daily for 2 days, inhibited the exercise-induced bronchoconstriction 41% as compared with placebo. Israel and colleagues[20] reported a similar 47% reduction of cold, dry air hyperpnoea-induced bronchoconstriction 3 hours after a single dose of zileuton 800mg. In this study, calcium ionophore-induced *ex vivo* LTB_4 synthesis in whole blood decreased 74% in the zileuton treated patients. Fischer et al.[21] examined the effect of prolonged treatment (13 weeks) with zileuton (400 or 600mg 4 times daily) on airway reactivity to cold, dry air hyperventilation. They found that patients challenged 1 to 10 days after receiving the last dose of zileuton, when zileuton concentrations and *ex vivo* LTB_4 production had returned to pretreatment values, demonstrated nearly a 50% reduction in the bronchoconstrictor response.

These studies indicate that the leukotrienes contribute to exercise- and cold-air-induced bronchoconstriction in the majority of patients with asthma and in some patients they play a predominant role. However, the leukotrienes do not appear to fully account for the bronchoconstriction in most patients.

1.3 Allergen Challenges

Inhalation challenge with an allergen (antigen) is a frequently used model system to assess the potential role of a mediator in asthma. Studies performed with the newer, more potent antileukotrienes in patients with asthma have demonstrated their effectiveness in reducing both the early- and the late-phase response to allergens. Rasmussen and colleagues[22] reported that the leukotriene receptor antagonist MK-571 450mg given intravenously to patients with asthma reduced the early-

and late-phase response to a fixed amount of antigen by 88 and 63%, respectively. Pretreatment with a single dose of zafirlukast 40mg 2 hours before antigen challenge nearly complete ablated the early response and produced an 87% inhibition of the late response in atopic individuals without asthma.[23] In the studies by Findlay et al.[24] and Dahlen et al.[25] antigen was inhaled until at least a 20% reduction in the FEV_1 was achieved. In both studies, patients pretreated with zafirlukast given orally required more antigen than those pretreated with placebo to produce a 20% fall in the FEV_1. O'Shaughnessy and colleagues[26] demonstrated that zafirlukast given by the inhaled route inhibited the early-phase response by 68%, but the late-phase response was reduced by a smaller, not significant 24%. Nathan et al.[27] found that inhaled zafirlukast also inhibited the immediate response to antigen.

Studies also have been performed with other leukotriene receptor antagonists. Taniguchi and colleagues[28] demonstrated that pranlukast 150mg given every 12 hours for 1 week, reduced the early phase response to allergen inhalation. Hamilton and colleagues[29] found that pranlukast 450mg twice daily given for 5 days to patients with mild asthma produced a 48% reduction in the early response, a 31% decrease in the late response and a 78% decrease in allergen-induced airway hyperreactivity. Montelukast also inhibited allergen-induced bronchoconstriction in patients with mild asthma.[30] Montelukast 10mg given 36 hours and 12 hours before allergen challenge reduced the early response by 75% and the late response by 57%.

Zileuton also appears to inhibit allergen-induced bronchoconstriction in patients with asthma. Hui et al.[31] found that a single dose of zileuton 800mg given 3 hours before aerosol antigen challenge reduced the initial decrease in the FEV_1 by nearly 25%. Zileuton had no effect on the late-phase response. The larger effect on the early response, which did not quite reach statistical significance, is consistent with the short half-life of this drug.

As is the case for exercise-induced bronchoconstriction, although the cysteinyl leukotrienes contribute to both the early and late allergen response in a majority of patients with asthma, they do not fully account for the bronchoconstriction in most patients and they may play only a minor role in some.

1.4 Aspirin (Acetylsalicylic Acid) Challenges

A estimated 5 to 30% of patients with asthma are intolerant of aspirin (acetylsalicylic acid) 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. Early anecdotal reports of excellent clinical benefits in patients with a history of aspirin intolerance treated with leukotriene receptor antagonists and synthesis inhibitors, led to studies specifically exploring the role of leukotrienes and the effectiveness of the antileukotrienes in this setting.

Christie and colleagues[32] reported that the prior inhalation of the leukotriene receptor antagonist pobilukast (SK&F 104353) inhibited the bronchoconstriction produced by ingestion of aspirin by nearly 50% in patients with aspirin-sensitive asthma. Dahlen et al.[33] examined the effectiveness of the oral leukotriene receptor antagonist verlukast (MK-0679) in preventing inhaled lysine-aspirin-induced bronchoconstriction in patients with aspirin-sensitive asthma. Pretreatment with verlukast produced a minimum 4.4-fold shift to the right of the lysine-aspirin dose-response curve. In another study, dipyrone (cyclo-oxygenase inhibitor)-induced bronchoconstriction was markedly attenuated by pretreatment with pranlukast.[34] Israel and colleagues[35] also reported that the leukotriene synthesis inhibitor zileuton could nearly completely prevent aspirin-induced bronchoconstriction in aspirin-sensitive individuals with asthma.

In addition to blocking aspirin-induced bronchoconstriction, there is increasing evidence that the leukotriene receptor antagonists have beneficial clinical effects in this patient population. Dahlen et al.[36] reported that verlukast produced

acute bronchodilation in patients with asthma and aspirin sensitivity. The baseline FEV_1 increased 18% (range 5 to 34%). The degree of improvement correlated with the severity of the asthma and the degree of aspirin sensitivity. Kuna and colleagues[37] found that montelukast 10 mg/day given at bedtime for 4 weeks improved asthma control in a group of aspirin-intolerant individuals with asthma whose asthma was incompletely controlled with corticosteroids. The FEV_1 and peak expiratory flow rate (PEFR) increased while symptoms and β-agonist use decreased. Similar results have been reported with the leukotriene synthesis inhibitor zileuton by Dahlen and colleagues.[38] In this crossover study, 40 patients with well-documented, stable aspirin-intolerant asthma, nearly all of whom required medium-to-high dosages of inhaled or oral corticosteroids, were treated with zileuton 600mg 4 times daily or placebo for 4 weeks. Compared with placebo, zileuton improved pulmonary function both in the short term and in the long term (FEV_1 increased 8%), despite lower rescue bronchodilator use, reduced bronchial reactivity to histamine and reduced nasal dysfunction (less rhinorrhoea, improved sense of smell).

The results of these studies provide strong support for using antileukotrienes to treat individuals who have asthma and are aspirin sensitive. In fact, although Christie et al.[32] noted that not all aspirin-intolerant patients respond to them, the available data favour the use of antileukotrienes as first-line therapy in this patient population.

1.5 Other Challenges

There is relatively limited information on the effectiveness of the antileukotrienes against other bronchoconstrictor stimuli in patients with asthma. In a double-blind placebo-controlled crossover study, a single dose of zafirlukast 20mg inhibited the bronchoconstrictor response to sulphur dioxide.[39] Protection was found at both 2 and 10 hours after treatment, but it was greater at 2 hours. Also, a relationship was found between zafirlukast plasma concentrations and its protective effect at the 10 hour time.

2. Bronchodilator Effect of the Antileukotrienes

The antileukotrienes can bronchodilate asthmatic airways and the extent of bronchodilation achieved parallels their pharmacokinetic profile. Hui and Barnes[40] studied patients with mild-to-moderate asthma and baseline airflow obstruction (median FEV_1 71% of predicted). The patients received oral zafirlukast 40mg or placebo and the FEV_1 was measured every 30 minutes for 4 hours. Zafirlukast produced a maximum 8% improvement in the FEV_1 at 3.5 hours. Gaddy et al.[41] reported the bronchodilator effect of intravenous MK-571 (total dosage 776mg given over 6 hours), a leukotriene receptor antagonist, in patients with more severe airflow obstruction (mean FEV_1 63% of predicted). The FEV_1 increased by 22% at the time of the first measurement (20 minutes) and the increase persisted over the entire infusion period. In addition, a relationship was found between the baseline FEV_1 and the magnitude of the bronchodilation induced: the lower the baseline FEV_1, the larger the bronchodilator response. In a subsequent study, MK-571 (125 or 500mg) was administered by bolus infusion to patients with asthma and a mean FEV_1 61% of predicted.[42] Bronchodilation occurred within 15 minutes of administering the 500mg dosage and it persisted for the 8 hour study period. The increase in FEV_1 averaged 16 and 8% after the high and low dosage, respectively and it paralleled the plasma concentrations of the drug. Similar acute bronchodilator effects have been reported with other leukotriene receptor antagonists including RG 12525[43] and montelukast,[44] as well as the leukotriene synthesis inhibitor zileuton.[45] These results suggest that the cysteinyl leukotrienes contribute to the increased bronchomotor tone in at least some patients with asthma. However, there are no data at this time to support using the antileukotrienes for their acute bronchodilator effects in the emergency treatment of asthma.

3. Clinical Response to the Antileukotrienes

Several large multicentre trials have been performed with the antileukotrienes. The ones published as full articles at the time of writing are listed in table II.[45-51] The first report with the leukotriene receptor antagonist zafirlukast was published in 1994.[46] This was a 6-week, double-blind, placebo-controlled, dosage-ranging study in patients with mild-to-moderate asthma receiving only inhaled β_2-agonists. The mean age of the patients was 36 years and the mean duration of asthma was 20 years. None of the patients was taking inhaled or systemic corticosteroids. Compared with baseline, after 6 weeks of treatment the patients receiving the highest dosage of zafirlukast (20mg twice daily) had an 11% increase in the FEV_1 and decreases in night-time awakenings (–46%), daytime asthma symptoms (–27%) and rescue medication use (–31%). A correlation was found between the dosage of the drug or the trough plasma concentration and the increase in the FEV_1.

A 13-week, placebo-controlled, parallel group study compared zafirlukast 20mg twice daily and placebo in patients between 12 and 70 years of age.[47] These patients differed from those in the 6-week study in that they had substantially milder disease with a mean FEV_1 77% of the predicted value. Because of the higher baseline FEV_1 one would have expected a smaller improvement in the FEV_1 than in the 6-week study and this was found. The FEV_1 increased 6% and the morning PEFR increased 7%. The absolute increase and the difference from the placebo group were both significant. Compared with baseline, zafirlukast also decreased daytime asthma symptoms scores (–27%), night-time awakenings (–20%), mornings with asthma (–29%) and β-agonist use (–22%). These improvements occurred within 2 days.

In a separate report, patients with mild-to-moderate asthma (mean FEV_1 74% of predicted in the zafirlukast group and 84% in the placebo group), who were symptomatic and using only a β-agonist, were treated with zafirlukast 20mg or placebo twice daily for 13 weeks.[52] Compaered with baseline, the patients receiving zafirlukast had more days without symptoms (–89%), more days without use of β-agonists (–89%) and more days without episodes of asthma (–98%). In addition, there were fewer healthcare contacts (–55%) and fewer days absent from work or school (–55%).

Two multicentre placebo-controlled trials have examined the safety and tolerability of the leukotriene receptor antagonist pranlukast.[48,53] The study done in Europe used 2 dosages of pranlukast, 225 or 337.5mg, administered twice daily for 4 weeks to patients with mild-to-moderate asthma (mean FEV_1 67% of predicted), 60 to 70% of whom were taking inhaled corticosteroids.[48] The study was not specifically designed to assess effi-

Table II. Clinical trials with the antileukotrienes[a]

Reference	Drug	FEV_1 (% predicted)	FEV_1 (% change)	Nocturnal symptoms (% change)	Symptom score (% change)	β-Agonist use (% change)
Leukotriene receptor antagonists						
Spector et al.[46]	Zafirlukast	61	+11	–46	–27	–31
Fish et al.[47]	Zafirlukast	77	+6	–20	–27	–22
Barnes et al.[48]	Pranlukast	67	+8	–25	–25	–10
Reiss et al.[49]	Montelukast	68	+14	–19	–13	–19
Leukotriene synthesis inhibitors						
Israel et al.[45]	Zileuton	58	+13	ND	–37	–24
Israel et al.[50]	Zileuton	62	+16	–33	–28	–26
Liu et al.[51]	Zileuton	62	+15	–32	–35	–30

a All trials were at least 4 weeks in duration except for the montelukast[49] study which was 10 days.

FEV_1 = forced expiratory volume in 1 second; **ND** = not determined.

cacy, yet the patients receiving pranlukast had an 8 to 10% increase in the FEV_1 and a reduction in summary symptom score (–25%), night-time asthma score (–25%) and β-agonist use (–10%). The other study was performed in the US and used dosages of 337.5 and 450mg given twice daily.[53] Although it too was not powered to assess efficacy, there were improvements in the FEV_1, symptoms and β-agonist use.

Two studies in adults and one in children have reported the effects of long term treatment with montelukast.[49,54,55] In one study, adult patients with mild-to-moderate asthma (mean FEV_1 68% of predicted), approximately 50% of whom were being treated with inhaled corticosteroids, were given montelukast, 200mg 3 times daily, for 10 days.[54] Patients experienced a 12 to 16% improvement in the FEV_1, as well as significant reductions in β-agonist use, daytime symptoms scores and nocturnal awakenings. A second study examined the effects of montelukast 10mg daily over a 3-month period in patients with mild-to-moderate disease.[49] Significant improvements in quality of life, airflow obstruction, asthma exacerbation days (–31%) and asthma-free days (+37%) were reported. Finally, children aged 6 to 14 years with mild-to-moderate disease, 40% of whom were receiving inhaled corticosteroids, were given montelukast 5mg once daily for 2 months.[55] The montelukast-treated group had a 9% increase in FEV_1, as well as a reduction in daily β-agonist use (–12%), peripheral blood eosinophil count, symptoms and asthma exacerbation rate.

There are several published trials with the leukotriene synthesis inhibitor zileuton. The first was a double-blind, placebo-controlled study in which patients with mild-to-moderate asthma were given either placebo or zileuton 400 or 600mg 4 times daily for 4 weeks.[45] As noted above, zileuton had an acute bronchodilator effect. Two hours after its ingestion, the time of peak plasma concentrations, patients receiving the 600mg dosage had an increase in the FEV_1 of nearly 15%. With long term therapy, the FEV_1 increased by 13% and there were reductions in β_2-agonist use (–24%) and daily symptoms (–37%). Subsequent 13-week[50] and 6-month[51] studies confirmed these findings (table II) and also demonstrated improvements in quality of life.

Few studies have directly compared the antileukotrienes with other drugs approved for the treatment of chronic asthma. Nathan and colleagues[56] reported the results of a 13-week study comparing zafirlukast 20mg twice daily to sodium cromoglycate 1.6mg four times daily in patients with mild-to-moderate disease. Zafirlukast and sodium cromoglycate were equally effective and both were more effective than placebo. A subgroup analysis indicated that zafirlukast was more effective in the patients with more severe disease. Zafirlukast has also been compared with low dosages of inhaled corticosteroids.[57,58] In one study, patients with mild asthma receiving only as needed β-agonists were treated with either zafirlukast 20 or 80mg or inhaled beclomethasone 200 to 250μg twice daily for 6 weeks.[57] Both drugs produced beneficial effects and were well tolerated, but the patients receiving inhaled beclomethasone appeared to do better. A crossover study compared zafirlukast 20mg to inhaled fluticasone 100μg each given twice daily for 2 weeks to 30 patients with mild-to-moderate disease.[58] Fluticasone produced a larger improvement in histamine-induced airway reactivity and morning peak flow rates.

Two placebo-controlled 12-week trials have compared oral pranlukast to either inhaled nedocromil or beclomethasone.[59,60] In patients with mild-to-moderate asthma given pranlukast 150, 300 or 450mg twice daily or nedocromil 3.5mg 4 times daily, nedocromil did not improve the FEV_1 at any time, while the highest dosage of pranlukast produced a 320ml increase in the FEV_1 (compared to a 60ml increase in the placebo group).[59] Pranlukast also improved symptoms and reduced the need for rescue medication. In another study, patients received either pranlukast 300 or 450mg twice daily or beclomethasone 84μg 4 times daily.[60] All active treatment groups had statistically significant improvements in the FEV_1, PEFR, symptom scores and the need for rescue medications.

Apparently, there were no differences between the pranlukast and beclomethasone treatments.

Many of the previously described studies evaluated patients with mild-to-moderate asthma, most of whom were not taking corticosteroids. The effectiveness of the antileukotrienes in patients with more severe disease has been demonstrated in several recent reports. In one study, pranlukast 450mg or placebo was given twice daily for 6 weeks to patients who required high dosages (≥1500 μg/day) of inhaled corticosteroids.[61] After a run-in period of 2 weeks to assess stability, the corticosteroid dosage was reduced by 50%. The patients receiving placebo experienced a deterioration in asthma control including a 10% decrease in the FEV_1 and morning PEFR along with an increase in symptoms. In contrast, pulmonary function remained stable and symptoms well-controlled in the patients treated with pranlukast. Virchow and colleagues[62] examined the effect of adding oral zafirlukast to the treatment regimens of patients who were symptomatic despite treatment with high dosages of inhaled corticosteroids (mean dosage 1600μg of beclomethasone or equivalent). Zafirlukast produced a significant improvement in PEFR along with better asthma control over the 6 week treatment period. As noted earlier, the addition of zileuton to corticosteroids in patients with aspirin-sensitive asthma resulted in substantial clinical benefits.[38]

Additional support for the antileukotrienes comes from studies examining their ability to reduce airway inflammation. Zhang et al.[63] reported that patients with asthma who received oral montelukast 10mg daily for 3 months had a 22% decrease in peripheral blood eosinophils along with improvements in the FEV_1 (+13%) and daytime symptoms (–16%). A reduction in the number of peripheral blood eosinophils was seen in children after being treated with montelukast for 2 months.[55] The effect of montelukast 10mg on sputum eosinophilia over a 4 week period in patients with a baseline FEV_1 65 to 85% of predicted has been reported.[64] All patients had at least 5% eosinophils in their sputum. The montelukast-treated group had nearly a 50% reduction in the percentage of eosinophils, while the placebo-treated group had a slight increase. Montelukast also improved symptoms and pulmonary function and reduced β-agonist use. Calhoun et al.[65] used a crossover design to examine the effect of zafirlukast, 160mg twice daily for 7 days, on the inflammatory cell influx immediately and 48 hours after segmental allergen challenge in patients with mild asthma. Zafirlukast attenuated the influx of basophils and lymphocytes and it reduced spontaneous superoxide release from alveolar macrophages, findings consistent with an anti-inflammatory effect of the drug. Wenzel and colleagues[66] also provided support for an anti-inflammatory effect of the antileukotrienes by examining the effect of zileuton 600mg 4 times daily for 1 week on airway inflammation in patients with nocturnal asthma. Zileuton reduced bronchoalveolar lavage (BAL) fluid LTB_4 (–38%) and urinary LTE_4 (–76%), decreased peripheral blood and BAL eosinophil counts and showed a trend for improving the nocturnal FEV_1 (+30%).

Based on these studies it is possible to conclude that long term administration of the current generation of antileukotrienes to symptomatic patients with mild-to-moderate asthma, who have a mean FEV_1 of 60 to 70% of predicted and are receiving treatment with a β-agonist alone, on average results in a 10 to 15% increase in the FEV_1 and PEFR and a 25 to 50% decrease in nocturnal awakenings, symptom scores, β-agonist use and asthma exacerbations. Patients who are symptomatic but have less severe pulmonary function abnormalities, as expected, have a smaller improvement in the FEV_1 and some of the other measures. However, they too obtain substantial clinical benefit which may be comparable to or slightly less than that seen with low-to-moderate dosages of inhaled corticosteroids. In patients with more severe disease already receiving inhaled corticosteroids, systemic corticosteroids or both, the antileukotrienes appear to provide additional benefit, at least in some individuals. Further, the antileukotrienes appear to be as effective in patients receiving as in those not re-

ceiving corticosteroids. This conclusion is consistent with *in vitro* studies demonstrating that corticosteroids have a limited ability to inhibit the production of mast cell mediators, including the cysteinyl leukotrienes,[67] and a recent report that corticosteroids increase 5-lipoxygenase (5-LO) and 5-LO activating protein mRNA and protein in a monocyte-like cell line.[68]

4. Toxicity

As there has been relatively limited experience with the antileukotrienes, their toxicity may not be fully defined. Initial results with zafirlukast using dosages from 0.4 to 160 mg/day in controlled clinical trials for up to 20 weeks and continuing for up to 2 years in open label trial extensions, reveal an adverse effect profile similar to that seen in placebo-treated patients.[69] A slight increase in gastrointestinal adverse effects was seen, although the incidence was low (3.3 *vs* 2.1% in the placebo group). An apparent increase was also seen in infections, mainly respiratory, in elderly study participants, but did not result in withdrawal. Liver function abnormalities were no greater than those seen in placebo-treated patients with dosages up to 40mg twice daily (twice the recommended dosage in the US). However, it is possible that higher dosages (e.g. 80mg twice daily) may produce some liver toxicity.

The manufacturer has provided unpublished information for montelukast.[70] Adverse events reported in controlled, clinical trials with the 10 mg/day dosage have been the same as those seen in placebo-treated patients. More limited data are available for both zafirlukast and montelukast in children, but the adverse effect profile appears to be the same as in adults.

The leukotriene synthesis inhibitor zileuton can produce liver toxicity which is manifested as an increase in serum transaminase levels. In data reported by the manufacturer,[71] liver function test abnormalities occurred about 2 to 4 times as often as in placebo-treated patients (2 to 5% incidence in zileuton-treated patients). It is recommended that patients receiving zileuton have liver function tests performed before starting therapy, monthly for the first 3 months, every 2 to 3 months for the remainder of the first year and periodically thereafter. Such monitoring is not required when using zafirlukast.

There have been anecdotal reports of patients receiving zafirlukast who developed a systemic vasculitis consistent with the Churg-Strauss syndrome.[72] These individuals had required oral corticosteroids to control their asthma. The effectiveness of zafirlukast enabled the dosage of oral corticosteroid to be reduced or discontinued and shortly thereafter vasculitis was diagnosed. It is unclear whether these cases represent direct toxicity of the drug or are the result of reducing or eliminating the corticosteroid dosage, especially since the Churg-Strauss syndrome occurs only in patients with asthma. These cases have only occurred in patients with severe asthma.

5. Effects of Disease on Antileukotriene Metabolism and Excretion

Data presented in zafirlukast prescribing information from the manufacturer indicate that its metabolism is the same in patients with asthma and normal volunteers.[73] Advanced age increases the area under the curve (plasma concentration versus time) and the maximum serum concentration of the drug. Clearance is reduced in patients with hepatic impairment such that patients with stable alcoholic cirrhosis have a 50 to 60% increase in the area under the curve and the maximum serum concentration. Renal disease appears to have no effect on zafirlukast metabolism and clearance. Information is not currently available on the effect of age or other diseases on pranlukast or montelukast metabolism and excretion.

Age and renal impairment do not influence the metabolism of zileuton. As a result, dosage reductions are not required for elderly patients and patients with renal failure, even those on haemodialysis.[74] Clearance is reduced in patients with mild-to-moderate hepatic impairment and reductions in dosage may be necessary.[75] The use of

zileuton is contraindicated in patients with active liver disease.

6. Drug-Drug Interactions

Zafirlukast is metabolised by the cytochrome P450 (CYP) isoenzyme CYP2C9.[76] In an *in vitro* system, concentrations of zafirlukast approaching clinically relevant plasma concentrations inhibited the isoenzymes CYP2C9 and CYP3A.[77] Therefore, one would anticipate drug-drug interactions between zafirlukast and other drugs metabolised by these enzymes. For example, coadministration of zafirlukast and warfarin reduces warfarin metabolism and increases the prothrombin time.[78] Close monitoring of the prothrombin time and adjustment of the warfarin dosage are therefore recommended if these 2 drugs are coadministered. In contrast, zafirlukast has no effect on terfenadine metabolism or the QTc interval, while terfenadine increases zafirlukast metabolism thereby decreasing the area under the curve and its maximum plasma concentration.[79,80] Coadministration with theophylline and erythromycin have been reported to reduce plasma zafirlukast concentrations by 30 to 40%, while aspirin increases zafirlukast concentrations by 45%. Zafirlukast does not appear to reduce the effectiveness of oral contraceptives.

There is less published information available for the other leukotriene receptor antagonists. According to information provided by the manufacturer, montelukast is not metabolised by the CYP system and significant drug interactions have not been identified. Pharmacokinetic studies have been performed and have failed to demonstrate 'clinically important effects' of montelukast on the metabolism of theophylline, warfarin, digoxin, terfenadine, prednisone, prednisolone and oral contraceptives. Information is not available on whether other drugs can alter montelukast pharmacokinetics and clinical efficacy.

Zileuton is metabolised by CYP enzymes including CYP2C9, CYP1A2 and CYP3A.[81] Therefore, it is not surprising that zileuton can influence the metabolism of a number of drugs. For example, zileuton reduces warfarin clearance and increases the prothrombin time.[82] It also reduces theophylline clearance and increases serum theophylline concentration.[83] Yet, zileuton has no apparent effect on digoxin, phenytoin, naprosyn or prednisone metabolism. Prednisone may have a small, but probably clinically insignificant, effect on zileuton metabolism.[84]

Although there is a substantial and rapidly growing experience with these new antileukotrienes, additional studies and more experience are needed. Potential drug interactions and the effects of various disease states as well as age should be considered when prescribing them.

7. Food Interactions

Because food high in protein or fat reduces the absorption of zafirlukast, the agent should be taken 1 hour before or 2 hours after a meal. Food interactions appear to be clinically unimportant with zileuton and they have not been reported with montelukast.

8. Place in Asthma Treatment

In whom and when should these new antileukotrienes be used? Presently, there are no universally agreed upon recommendations. Any recommendations must be based on disease characteristics such as asthma severity, other drugs available and their potential toxicities, concomitant diseases and their treatment and current information about the antileukotrienes including positive and negative attributes. The positive attributes of the antileukotrienes include oral administration, once or twice daily administration (currently for the leukotriene receptor antagonists), both bronchodilator and anti-inflammatory properties and an excellent safety profile in adults and children (at least based on initial experience). Their 'negative' attributes are few but include concern about systemic administration with possible effects on immune function and an efficacy somewhat lower than inhaled corticosteroids (based on rather limited data with the current generation of compounds) in patients with mild-to-moderate disease.

Except for patients with aspirin-sensitive asthma who generally respond well to the antileukotrienes, it is not possible to identify the patients most likely to benefit from these agents. In all clinical trials, including challenge studies and long term efficacy studies and recent experience in the clinic with zafirlukast and zileuton, the response to the antileukotrienes has been variable. Some patients have experienced dramatic beneficial effects and others have not improved at all. The majority of patients have experienced a modest benefit. Although most of the large clinical studies already published were performed in patients with mild-to-moderate disease not receiving corticosteroids, the antileukotrienes have been used successfully in patients with more severe disease. In fact, the data presented earlier suggesting that corticosteroids do not down-regulate leukotriene synthesis (any decrease appears to result from fewer inflammatory cells in the airways), supports the notion that the antileukotrienes can complement the beneficial effects of corticosteroids.

Recent studies have begun to provide a genetic basis for the variable response to the antileukotriene drugs. In and colleagues[85] have reported that certain polymorphisms of the 5-LO gene are associated with reduced 5-LO function. This may result in reduced leukotriene synthesis and decreased responsiveness to the therapeutic effects of the antileukotrienes. On the other hand, it has been also been reported that patients with aspirin-intolerant asthma, a group known to respond rather well to the antileukotrienes, have striking overexpression of LTC_4 synthase in their bronchial mucosa[86] and this overexpression is linked to a polymorphism of the LTC_4 synthase gene promoter.[87]

Since antileukotrienes are effective when administered orally, improve pulmonary function and reduce symptoms in patients with a wide range of asthma severity and appear to have limited toxicity, one can consider using them in patients with all degrees of asthma severity. It is not possible to predict who will respond favourably and a trial and error approach must be taken, an approach typical of most new therapies in medicine. In the future, genetic testing may identify the patients whose asthma will and will not respond with a high degree of certainty. As additional research in this area and others (e.g. effect of combining antileukotrienes with antihistamines or long-acting β-agonists) is performed and experience is gained with the antileukotrienes, more specific recommendations for their use will be forthcoming.

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