

Review article

Leukotrienes as therapeutic target in asthma

Pauwels RA, Joos GF, Kips JC. Leukotrienes as therapeutic target in asthma.

Allergy 1995; 50: 615-622. © Munksgaard 1995.

R. A. Pauwels, G. F. Joos, J. C. Kips

Prof. Romain Pauwels
Department of Respiratory Diseases
University Hospital
De Pintelaan 185
B9000 Ghent
Belgium

Accepted for publication 25 November 1994

Asthma is a disorder of the intrathoracic airways characterized by variable airflow obstruction and airway hyperresponsiveness to a variety of stimuli. The pathology of asthma is characterized by the presence of airway inflammation in which many cells such as eosinophils, mast cells and T lymphocytes play a role. The activated cells release various pro-inflammatory and inflammatory mediators, whose individual role is largely unknown. The contribution of an individual mediator or molecule in complex diseases such as asthma can only be accepted if the mediator causes pathological or physiopathological alterations that are comparable with the changes observed in the disease, if the presence of the mediator can be demonstrated in affected tissue, and finally if a selective synthesis inhibitor or receptor antagonist modifies the disease. The aim of this paper is to review the evidence that leukotrienes play a role in the pathogenesis of asthma, especially in the light of the results of clinical therapeutic studies with 5-lipoxygenase-inhibitors (5LO-inhibitors), 5-lipoxygenase-activating-protein-inhibitors (FLAP-inhibitors), and LTD₄-receptor-antagonists (LT-antagonists).

Origin of leukotrienes in asthma

Synthetic pathways

Leukotrienes are generated by lipoxygenation of arachidonic acid (57). They are not stored in cells but are newly formed upon activation of various cell types. The release of arachidonic acid from cell membrane phospholipids is the result of activation of phospholipase A₂ or C by cell stimulation. Phos-

pholipase A₂ cleaves arachidonic acid from the phospholipids in the cell membrane. Phospholipase C cleaves membrane phospholipids into a phosphorylated base and diacylglycerol. Diacylglycerol is then cleaved into monoacylglycerol and arachidonic acid by diglyceride lipase. Arachidonic acid forms the substrate of different enzymes such as cyclooxygenases, lipoxygenases and monooxygenases (25). Leukotriene synthesis results from the action of the 5-lipoxygenase enzyme on arachidonic acid (21) (Fig. 1). However, the 5-lipoxygenase enzyme (5LO) is by itself incapable of metabolizing free arachidonic acid. The arachidonic acid must be bound to a membrane-bound protein called the 5-lipoxygenase-activating-protein (FLAP). FLAP has a lipid substrate binding domain and belongs to the same family of proteins as the leukotriene C₄ synthetase. The interaction of arachidonic acid, FLAP, and 5LO generates the unstable intermediate 5-HPETE (5-hydroperoxy-eicosatetraenoic acid), which is either reduced to 5-HETE or converted to leukotriene A₄ (LTA₄). LTA₄ is processed either by the LTA₄-hydrolase to leukotriene B₄ (LTB₄) or by the LTC₄ synthase (glutathione-S-transferase) to leukotriene C₄. LTB₄ has the basic eicosanoid structure, while LTC₄ is composed of an eicosanoid linked to the tripeptide glutathione. LTC₄ is cleaved by gamma-glutamyl transpeptidase to LTD₄, which is cleaved by a dipeptidase to LTE₄. LTC₄, LTD₄, and LTE₄ are collectively designated as sulfidopeptide-leukotrienes or cysteinyl leukotrienes. The leukotrienes are secreted to the extracellular milieu via a carrier-mediated mechanism.

LEUKOTRIENE SYNTHESIS

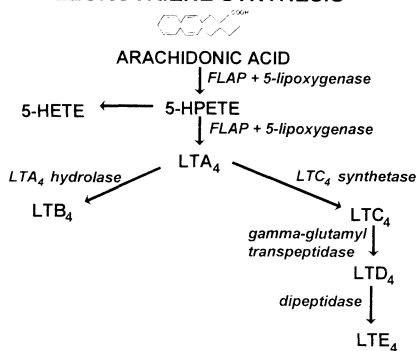


Fig. 1. Schematic representation of pathway of leukotriene synthesis.

Cellular origin

The selective expression of enzymes of the synthetic pathway is responsible for the preferential synthesis of some leukotrienes by different cell types (Fig. 2). Monocytes and macrophages have the capacity to synthesize both LTB_4 and LTC_4 . Neutrophils preferentially make LTB_4 , while activated eosinophils and mast cells preferentially generate LTC_4 . LTA_4 can be produced and exported by a great number of different cell types and subsequently metabolized in other cell types (43). This transcellular synthesis leads to the generation of LTB_4 by erythrocytes, endothelial cells, and T lymphocytes and the generation of LTC_4 by endothelial cells and platelets.

Leukotriene synthesis in asthma

Many studies have shown that the airway mucosa and submucosa of patients with asthma are infil-

Cells	LTB_4	LTC_4
Neutrophils	+	
Monocytes	+	+
Eosinophils		+
Mast cells		+
TRANSCELLULAR BIOSYNTHESIS		
Erythrocytes	+	
Endothelial cells	+	+
T lymphocytes	+	
Platelets		+

Fig. 2. Cellular origin of leukotrienes in man.

trated by activated eosinophils, neutrophils, mast cells, monocytes, and T lymphocytes. Constitutional cells such as epithelial cells, endothelial cells, and fibroblasts are equally activated. Therefore eosinophils, neutrophils, mast cells, monocytes, T lymphocytes, endothelial cells, and platelets can generate leukotrienes in the airways of asthmatic patients.

Several studies have now directly or indirectly demonstrated the secretion of leukotrienes in the airways of asthmatics. Lam et al. (41) measured leukotriene concentrations in the bronchial lavage fluid of 17 asthmatic (seven atopic and 10 nonatopic) and nine healthy subjects. LTE_4 was detected in the lavage fluid of 15 of the 17 asthmatic patients and in none of the healthy subjects. The mean concentration in the asthmatics was 2.2 ng/ml. The bronchial lavage fluid concentration of LTE_4 was not different between atopic and nonatopic asthmatics. There was no correlation between the LTE_4 concentration and the baseline FEV_1 in these subjects. LTD_4 was detected in the bronchial lavage fluid of two of the asthmatic and none of the healthy subjects. 20-OH- LTB_4 was found in 12 of the asthmatic subjects and in none of the healthy subjects. The mean 20-OH- LTB_4 concentration in the lavage fluid of the asthmatics was 1.4 ng/ml. No correlation was found between 20-OH- LTB_4 or LTE_4 concentration and the percentage or number of macrophages, epithelial cells, eosinophils, or neutrophils in the bronchial lavage fluid.

Wardlaw et al. (70) were able to demonstrate increased concentrations of LTC_4 and LTB_4 in the bronchoalveolar lavage (BAL) fluid of patients with symptomatic asthma, compared with nonasthmatic control or hay fever subjects. The LTB_4 and LTC_4 concentrations in asymptomatic asthmatics were not different from the control subjects.

Local endobronchial allergen challenge is to some extent an artificial situation because the allergen concentration that is applied locally is probably far higher than the naturally occurring endobronchial allergen concentration. Using this endobronchial challenge method, Wenzel et al. (72) demonstrated a significant increase in endobronchial LTC_4 concentration 5 min after local endobronchial allergen challenge in atopic asthmatics. The atopic nonasthmatic patients had also some, but smaller, increase in LTC_4 concentration. LTC_4 was not detectable in control and in nonatopic asthmatics.

Challenge with inhaled aspirin in aspirin-sensitive asthmatics caused an increase in LTE_4 concentration in BAL fluid; did not affect the concentrations of 5-HETE, 12-HETE, and 15-HETE; and decreased the production of cyclooxygenase products in the airways (59).

Besides the direct demonstration of the presence of leukotrienes in airway fluid, the measurement of

urinary excretion of LTE_4 has been used as a method to demonstrate the *in vivo* synthesis of LTC_4 . Indeed, synthesized and secreted LTC_4 is rapidly metabolized to LTD_4 and LTE_4 . In normal subjects, 4–13% of the intravenously administered LTC_4 is recovered in the urine as intact LTE_4 . The inhalation of bronchoconstricting doses of LTC_4 or LTE_4 was shown to increase urinary LTE_4 excretion in a dose-dependent fashion (10). The urinary excretion of LTE_4 might therefore be used as a parameter of LTC_4 synthesis. Taylor et al. (66) observed an increase in urinary LTE_4 excretion during the 3 h following an inhalational allergen challenge in allergic asthmatics. Urinary LTE_4 excretion was also significantly higher in subjects with acute severe asthma compared to normal controls or subjects with stable asthma or allergic rhinitis but a substantial overlap between the different groups was noted. Both Manning et al. (45) and Sladek et al. (58) confirmed the increase in urinary LTE_4 excretion in the first 3 h following allergen inhalation in allergic asthmatics but could not find such an increase during the late asthmatic reaction following allergen challenge.

The data on urinary LTE_4 excretion during and following exercise-induced asthma are more equivocal. Smith et al. (60) and Taylor et al. (68) observed no significant increase in LTE_4 excretion during the 3 h following exercise challenge, but, in a larger study, Kikawa et al. (35) found a significantly increased urinary LTE_4 excretion during the first 2 h following exercise in children with exercise-induced asthma and not in healthy children performing the same exercise. These investigators also noted a significant correlation between the LTE_4 excretion after exercise and the degree of exercise-induced bronchoconstriction.

Both Kumlin et al. (39) and Christie et al. (9) found that the baseline urinary excretion of LTE_4 is increased in aspirin-sensitive asthmatics and that inhalational challenge with lysine-aspirin in these subjects causes a further increase of the urinary LTE_4 excretion. Challenge with oral aspirin has also been shown to increase the urinary excretion of LTE_4 in aspirin-sensitive asthmatics (38).

Summarizing the current evidence of the presence of leukotrienes in asthma, we may conclude that different studies have shown that increased concentrations of LTB_4 , LTC_4 , and LTE_4 are present in the airways of asthmatic subjects. Challenge with allergen, exercise, or aspirin in sensitive subjects causes an increased synthesis of the sulfidopeptide-leukotrienes. Acute severe asthma and aspirin-sensitive asthma are associated with an increased LT-synthesis.

Pathophysiological effects of leukotrienes relevant to asthma

Leukotrienes have been shown to cause bronchoconstriction, increased vascular permeability, and mucus hypersecretion (15). These effects may certainly be relevant to the role of leukotrienes in asthma. Less well established are the effects of leukotrienes on airway responsiveness and on cellular infiltration in the cell wall.

Leukotrienes have been shown *in vitro* to be potent constrictors of airway smooth muscle (4, 16). LTC_4 and LTD_4 are 1000-fold more potent than histamine in contracting human airway smooth muscle. The same order of potency difference is observed *in vivo* in the bronchoconstrictory effect of inhaled LTC_4 or LTD_4 vs histamine in healthy subjects (1, 3, 18, 61). The potency difference as bronchoconstrictors *in vivo* between these leukotrienes and histamine is much less in asthmatic subjects. This observation might be regarded as evidence for the *in vivo* secretion of leukotrienes in asthma leading to a certain degree of tachyphylaxis.

The onset of the bronchoconstrictor response to inhaled LTC_4 is later than the response to inhaled LTD_4 . This difference in onset of action can be explained by the fact that there is only one type of sulfidopeptide leukotriene-receptor in human airways, the LTD_4 -receptor, and that the inhaled LTC_4 must first be metabolized to LTD_4 before it can cause bronchoconstriction. LTE_4 is a less potent bronchoconstrictor than LTC_4 or LTD_4 *in vitro* and *in vivo* in healthy subjects. However, in asthma and especially in aspirin-sensitive asthmatics, there appears to be a relative hyperresponsiveness to inhaled LTE_4 compared to LTC_4 and LTD_4 (2).

The sulfidopeptide-leukotrienes have been shown to increase the microvascular permeability by opening endothelial gaps in the postcapillary venules (53). They can thus contribute to plasma extravasation and tissue edema. Sulfidopeptide-leukotrienes are also potent mucus secretagogues, both *in vitro* and *in vivo* (48).

There have been suggestions that the inhalation of LTD_4 by healthy subjects and the inhalation of LTE_4 by asthmatics causes an increase in airway responsiveness to histamine (2, 34). The effects on histamine responsiveness are rather limited, and the pathophysiological relevance of these findings is still unclear.

Although LTB_4 is a potent chemoattractant for neutrophils and far less for eosinophils, its role in asthma is not clear. Laitinen et al. (40) demonstrated in a small number of asthmatic subjects that the inhalation of LTE_4 elicited an increase in the number of eosinophils and neutrophils in the lamina propria of the airways 4 h after inhalation. These find-

ings in asthmatics are supported by animal data on the granulocyte chemotactic activity of inhaled sulfidopeptide-leukotrienes (5).

Activity of leukotriene receptor-antagonists or synthesis inhibitors in asthma

The ultimate test of the role of leukotrienes in asthma is the effect of specific receptor-antagonists or synthesis inhibitors on the disease. Many potent molecules have become available to test the hypothesis (Tables 1, 2, and 3).

Effects in models of asthma

Bronchodilation. Several studies have shown that leukotriene D₄-receptor antagonists and 5-lipoxygenase-inhibitors have a significant bronchodilating effect in asthma. Hui & Barnes (27) observed that the oral intake of 40 mg of the leukotriene D₄-receptor antagonist ICI 204 219 resulted in a signif-

icant increase in FEV₁ over baseline in 10 mild-to-moderate asthmatics. FEV₁ was significantly higher above baseline 1–4 h after dosing, with a maximum increase of 8% above baseline at 3.5 h. At 4 h after intake of ICI 204 219, 5 mg of salbutamol was administered via nebulizer, resulting in an additional bronchodilation in both treatment groups, but the difference in FEV₁ between the ICI 204 219- and placebo-treated group remained. The highest bronchodilating activity of a leukotriene D₄-receptor antagonist ever published was the one measured by Gaddy et al. (24). The intravenous infusion of the leukotriene D₄-receptor antagonist MK-571 caused a 22% increase in FEV₁ over baseline during the time of the infusion compared to 1% during placebo infusion. The inhalation of salbutamol caused an additional bronchodilation. Other studies have observed more modest bronchodilating effects of leukotriene D₄-receptor antagonists such as inhaled SK&F 104 353 (33), intravenous MK-571 (36), intravenous MK-679 (29), inhaled MK-679 (42), inhaled ICI 204 219 (37), oral MK-0476 (62), and oral RG 12 525 (69, 71).

An interesting observation was made by Dahlen et al. (13), who studied the bronchodilating effect of the oral leukotriene D₄-receptor antagonist MK-0679 in aspirin-sensitive asthmatics. MK-0679 caused bronchodilation with an average peak improvement of the FEV₁ of 18% and a duration of the bronchodilating effect of at least 9 h. The bronchodilating effect correlated significantly with the severity of the asthma and the aspirin sensitivity, suggesting the possibility that aspirin-sensitive patients benefit the most from leukotriene D₄-receptor antagonists.

The 5-lipoxygenase-inhibitor zileuton also produced an acute bronchodilating effect in the study by Israel et al. (32). They investigated the effect of zileuton in mild-to-moderate asthma and studied both the acute bronchodilating effect and the long-term antiasthma effects. A single oral dose of 600 mg zileuton caused a significant bronchodilation 1 and 2 h after intake. The maximum mean increase in FEV₁ after zileuton was 14.6%.

Similarly, the 5-lipoxygenase-inhibitor BAY1005 caused significant bronchodilation after administration of a single oral dose (49). The mean percentual FEV₁ increase in 17 asthmatics was 11% after 250 mg, 13% after 750 mg, and 5% after placebo.

In summary, leukotriene-antagonists and 5LO-inhibitors have been shown to cause acute bronchodilation in patients with asthma. It appears that this bronchodilating effect is only clinically relevant in moderate-to-severe asthma. The bronchodilating effect of these compounds is much more trivial in mild asthma and is absent in healthy volunteers.

Table 1. Leukotriene receptor antagonists in development

Drug code	Drug name	Company	Dosage
ICI 204219	Accolate	Zeneca	Oral
ONO 1078	Pranlukast	Ono	Oral
SKF 104353	Pobilukast	SKB	Inhaled
SKF 106203		SKB	Oral
RO-24 5913		Rioche	Oral
RG-12525		RPR	Oral
RG-14524		RPR	
CGP 457154		Ciba-Geigy	Oral/inhaled
CGP-44826		Ciba-Geigy	
BAY X 7195		Bayer	Oral/inhaled
MK-476		Merck	Oral
LY 290324		Lilly	
LY-287192		Lilly	
AS 35		Tanabe	Inhaled
DS-4574		Daichi	

Table 2. 5 Lipoxygenase inhibitors under development

Drug code	Drug name	Company	Dosage
A 64077	Zileuton	Abbott	Oral
A-79175		Abbott	Oral
ZD2138		Zeneca	Oral
TMK-688		Terumo	Oral

Table 3. FLAP-inhibitors under development

Drug code	Company	Dosage
Mk-591	Merck	Oral
BAY X 1005	Bayer	Oral
Bay Y 1015	Bayer	Oral

Allergen challenge

Taylor et al. (64) studied the effect of a single dose of the leukotriene D_4 -receptor antagonist ICI 204 219 on the early and late asthmatic reaction following bronchial allergen challenge. ICI 204 219 significantly attenuated the early and the late bronchoconstriction to inhaled allergen and suppressed the allergen-induced increase in histamine responsiveness. This protective effect of leukotriene D_4 -receptor antagonists on the early and late asthmatic reaction and on the increase in nonallergenic airway responsiveness has been confirmed for other leukotriene D_4 -receptor antagonists such as MK-571 (54), MK-886 (22), and L-648 051 (55). Other investigators have only studied the effect of leukotriene D_4 -receptor-antagonist on the immediate reaction following allergen challenge and shown significant protective effect (14, 19, 65). The ICI 204 219 given via inhalation protects only against the immediate reaction and does not affect the late reaction (52). The most likely explanation of this observation is the rapid disappearance of the inhaled drug from the airways.

A single dose of the 5-lipoxygenase-inhibitors zileuton or ZD2138 failed to protect against the allergen-induced bronchial reactions despite good *ex vivo* evidence of 5LO-inhibition in isolated and stimulated leukocytes (28, 51). The FLAP-inhibitor MK591 inhibited the early and late bronchoconstriction following allergen challenge, although a closer look at the curves suggests that the effect of these drugs on the late reaction is rather a delaying of the reaction than a real inhibition (17). Two explanations are offered for the discrepancy between leukotriene D_4 -receptor antagonists and 5-lipoxygenase-inhibitors with regard to protective effect on allergen challenge: insufficient inhibition of leukotriene synthesis and shift of arachidonic acid metabolism towards bronchoconstrictor prostaglandins or lipoxins. The clinical relevance of this finding can only be studied in comparative controlled clinical trials.

Exercise challenge

Exercise challenge in asthma is generally regarded as a challenge with a physiologically and clinically relevant stimulus. Leukotriene D_4 -receptor antagonists have been shown to inhibit exercise-induced bronchoconstriction. Intravenously administered MK-571 inhibited the exercise-induced fall in FEV_1 in 12 subjects with stable asthma by 69% (46). Both oral and inhaled ICI 204 219 and inhaled SK&F 104 353 also protected against exercise-induced bronchoconstriction (20, 44, 56).

Aspirin challenge

Aspirin-sensitive asthmatics have a high urinary LTE_4 excretion, and leukotriene D_4 -receptor-antagonists have significant bronchodilating effects in aspirin-sensitive asthmatic patients (13). Christie et al. (8) investigated in aspirin-sensitive subjects the effect of the inhaled leukotriene D_4 -receptor antagonist SK&F 104 353 on the bronchoconstriction induced by the oral intake of aspirin. Pretreatment with SK&F 104 353 inhibited the bronchoconstriction by a mean of 47%. The inhibition was partial, with one subject showing no inhibition. The protective effect in the other five subjects ranged from 43 to 74%. The inhibitory effect of leukotriene D_4 -receptor-antagonists on aspirin-induced bronchoconstriction was confirmed by Dahlen et al. (12), using MK-0679 in a challenge study using inhaled lysine-aspirin. Similarly, Yamamoto et al. demonstrated that ONO-1078 inhibited the bronchoconstriction caused by the inhalation of inhaled dipyrone by aspirin-sensitive asthmatics (73).

Israel et al. (31) studied the effect of the 5-lipoxygenase inhibitor zileuton on challenge with oral aspirin in eight subjects with aspirin-sensitive asthma. Zileuton significantly inhibited the aspirin-induced bronchoconstriction, increase in urinary LTE_4 excretion, and nasal, gastrointestinal, and dermal symptoms. The protective effect of 5-lipoxygenase inhibitors on aspirin-induced asthma was confirmed by Nasser et al. using ZD2138 (50).

Other challenges

A single dose of 800 mg zileuton was shown to increase significantly the amount of cold dry air needed to reduce the FEV_1 by 10% (30).

Two studies investigated the effect of a short 1-week treatment with a leukotriene D_4 -receptor antagonist on methacholine responsiveness in asthma. Fujimura et al. (23) observed that ONO-1078 caused a small but significant decrease in methacholine airway responsiveness. In the study by Rasmussen et al. (55), the effect of L-648 051 was similar, but the difference with placebo did not reach statistical significance.

Effects in clinical studies on asthma

Only a few of the large-scale clinical studies on leukotriene D_4 -receptor antagonists and 5-lipoxygenase inhibitors have yet appeared in full publication, and some of the information given below will therefore be based on material presented at meetings and published in abstract form. The first evidence of the clinical potential of leukotriene D_4 -receptor antagonists in asthma came from a double-blind, placebo-

controlled, parallel designed study of 6 weeks treatment with LY171 883 in 136 patients with asthma (11). Treatment with LY171 883 significantly decreased the severity of the daytime and nighttime wheezing and breathlessness score but had no effect on the frequency of asthma attacks. At the end of the 6-week treatment period, mean FEV_1 was significantly increased in the LY171 883-treated patients compared with the placebo-treated patients ($+0.3$ l vs -0.1 l), although no differences in diurnal peak flows were observed during or at the end of treatment. There was a significant decrease of the use of rescue metaproterenol in patients using more than 23 mg of metaproterenol per week and treated with LY171 883.

Treatment with the oral leukotriene D_4 -receptor-antagonist MK-571 had also significant therapeutic effects in a 6-week, placebo-controlled parallel study in mild-to-moderate asthma (47). MK-571 improved all measured efficacy parameters compared to placebo, including a 30% decrease in symptom scores and in use of salbutamol as rescue inhaler, and an 8–14% improvement in FEV_1 measured at the clinic visits.

ICI 204 219 was tested in a 6-week dose-ranging study in patients with mild-to-moderate asthma (26, 63, 64). The study was double-blind, randomized, placebo-controlled, and parallel. In the first part, patients were randomized to 10 mg, 20 mg, or placebo bid. In the 20-mg group, 72% of the subjects responded to treatment based on one or more efficacy criteria. No difference was observed between the 10-mg group and placebo (51% and 53% response, respectively). The 20-mg treatment had significant effects on morning peak flow (increase 321 min vs 101 min on placebo), nighttime awakenings, and daytime asthma score. In a second part of the study, 2 and 40 mg of accolate bid were compared to placebo. Six weeks of treatment with 40 mg accolate bid improved nighttime awakenings, first morning asthma, and PEF in the evening, although the overall interpretation of the data is difficult due to a confounding large placebo effect.

A 4-week treatment with the 5-lipoxygenase inhibitor zileuton at a dose of 600 mg qid significantly improved, in patients with moderate-to-severe asthma treated only with inhaled beta agonists, the asthma symptom score, the rescue use of beta-agonist, the morning PEF, and the FEV_1 measured at the clinic (32). The effect was already observed after 1 week of treatment and persisted for the whole duration of the study. Treatment with 800 mg zileuton bid had far less significant effects.

An important study with regard to the positioning of antileukotriene therapy in asthma evaluated the therapeutic effect of adding MK-0591, a FLAP inhibitor, to treatment with inhaled steroids (6). The

addition of MK-0591, 125 mg bid, to inhaled steroids (mean daily dose of beclomethasone or budesonide: 850 g) in this 4-week, double-blind, randomized, and placebo-controlled trial caused a significant improvement in FEV_1 , morning and evening PEF, and decrease in use of rescue beta₂-agonist.

An important question in the development of new compounds for the treatment of chronic diseases is their safety. The normal physiological role of leukotrienes is not known, and there is always the fear that by using potent antagonists or synthesis inhibitors one might eliminate an important normal physiological mechanism. Many of the compounds that have been developed either as leukotriene-antagonists or synthesis inhibitors have been stopped for toxicity reasons, often hepatic toxicity, but no class-specific side-effects have yet been noted, and some of the compounds currently under development appear to be remarkably free of toxicity. It is somewhat reassuring that experiments in mice show that a disruption of the 5-lipoxygenase gene, resulting in animals that are incapable of synthesizing leukotrienes, does not have a major impact on the life of these animals (7). 5-Lipoxygenase-deficient mice show no apparent abnormalities under normal physiological conditions.

Conclusion

Leukotriene D_4 -receptor-antagonists, 5-lipoxygenase inhibitors, and FLAP inhibitors have established themselves quite firmly as a potential new class of antiasthma drugs. Several clinical studies have indeed shown that the concept of LTD₄-receptor antagonism or synthesis inhibition is a valid approach in the treatment of this disease. Chronic treatment with potent LTD₄-antagonists results in a decrease of asthmatic symptoms, improvement of lung function, and decreased use of rescue bronchodilators. A very relevant question regarding the future of these compounds is their efficacy and safety relative to already existing antiasthma therapy; more specifically, low doses of inhaled steroids. No comparative study with established antiasthma therapy has yet been published. The relative merit and efficacy of leukotriene D_4 -receptor antagonism, 5-lipoxygenase inhibition, and FLAP inhibition need also to be studied in comparative clinical trials. The clinical therapeutic results suggest that LT-antagonists, 5LO-inhibitors, and FLAP inhibitors might find a place of their own in the treatment of mild persistent asthma or in combination therapy in more severe asthma. The availability of oral preparations should enhance the compliance during long-term treatment.

The demonstration that the inhalation of LTE₄ causes airway inflammation in asthmatic patients suggests that leukotriene antagonists could have

anti-inflammatory activity in asthma. No study has yet been published on the effect of leukotriene antagonists on chronic airway inflammation in asthma.

References

1. ADELROTH E, MORRIS M, HARGREAVE FE, O'BYRNE PM. Airway responsiveness to leukotriene C_4 and D_4 and to methacholine in patients with asthma and normal controls. *N Engl J Med* 1986; 315: 480-4.
2. ARM JP, SPUR BW, LEE TH. The effects of inhaled leukotriene E_4 on the airway responsiveness to histamine in subjects with asthma and normal subjects. *J Allergy Clin Immunol* 1988; 82: 654-60.
3. BARNES NC, PIPER PJ, COSTELLO JF. Comparative effects of inhaled leukotriene C_4 , leukotriene D_4 and histamine in normal human subjects. *Thorax* 1984; 39: 500-4.
4. BJÖRCK T, DAHLEN S-E. Leukotrienes and histamine mediate IgE-dependent contractions of human bronchi: pharmacological evidence obtained with tissues from asthmatic and non-asthmatic subjects. *Pulm Pharmacol* 1993; 6: 87-96.
5. CHAN CC, MCCKEE K, TAGARI P, CHEE P, FORD-HUTCHINSON AW. Eosinophil-eicosanoid interactions: inhibition of eosinophil chemotaxis *in vivo* by an LTD $_4$ -receptor antagonist. *Eur J Pharmacol* 1990; 191: 273-80.
6. CHAPMAN KR, FRIEDMAN BS, SINGO S, HEYSE J, REISS T, SPECTOR R. The efficacy of an oral inhibitor of leukotriene synthesis (MK 0591) in asthmatics treated with inhaled steroids. *Am J Respir Crit Care Med* 1994; 149: A215.
7. CHEN X-S, SHELLER JR, JOHNSON EN, FUNK CD. Role of leukotrienes revealed by targeted disruption of the 5-lipoxygenase gene. *Nature* 1994; 372: 179-82.
8. CHRISTIE PE, SMITH CM, LEE TH. The potent and selective sulfidoepoxide leukotriene antagonist, SK&F 104353 inhibits aspirin induced asthma. *Am Rev Respir Dis* 1991; 144: 957-8.
9. CHRISTIE PE, TAGARI P, FORD-HUTCHINSON AW, et al. Urinary leukotriene E_4 after lysine aspirin inhalation in asthmatic subjects. *Am Rev Respir Dis* 1992; 146: 1531-4.
10. CHRISTIE PE, TAGARI P, FORD-HUTCHINSON AW, et al. Increased urinary LTE $_4$ excretion following inhalation of LTC $_4$ and LTE $_4$ in asthmatic subjects. *Eur Respir J* 1994; 7: 907-13.
11. CLOUD ML, ENAS GC, KEMP J, et al. A specific LTD $_4$ LTE $_4$ receptor antagonist improves pulmonary function in patients with mild, chronic asthma. *Am Rev Respir Dis* 1989; 140: 1336-9.
12. DAHLEN B, KUMLIN M, MARGOLSKEE DJ, et al. The leukotriene receptor antagonist MK-0679 blocks airway obstruction induced by inhaled lysine aspirin in aspirin sensitive asthmatics. *Eur Respir J* 1993; 6: 1018-26.
13. DAHLEN B, MARGOLSKEE DJ, ZETTERSTRÖM O, DAHLEN SE. Effect of the leukotriene receptor antagonist MK-0679 on baseline pulmonary function in aspirin sensitive asthmatic subjects. *Thorax* 1993; 48: 1205-10.
14. DAHLEN B, ZETTERSTRÖM O, BJÖRCK T, DAHLEN S-E. The leukotriene antagonist ICI 204,219 inhibits the early airway reaction to cumulative bronchial challenge with allergen in atopic asthmatics. *Eur Respir J* 1994; 7: 324-31.
15. DAHLEN S-E. Pulmonary effects of leukotrienes. *Acta Physiol Scand* 1983; 512 (Suppl.): 1-51.
16. DAHLEN S-E, HEDQVIST P, HAMMARSTRÖM S, SAMUELSSON B. Leukotrienes are potent constrictors of human bronchi. *Nature* 1980; 228: 484-6.
17. DIAMANT Z, TIMMERS MC, VAN DER VEEN H, et al. The effect of MK-591, a potent oral leukotriene biosynthesis inhibitor, on allergen-induced airway responses in asthmatic subjects. *Eur Respir J* 1993; 6: 253s.
18. DRAZEN JM. Comparative contractile responses to sulfidoepoxide leukotrienes in normal and asthmatic human subjects. *Ann N Y Acad Sci* 1988; 524: 289-97.
19. FINDLAY SR, BARDEN JM, EASLEY CB, GLASS M. Effect of the oral leukotriene antagonist, ICI 204219 on antigen induced bronchoconstriction in subjects with asthma. *J Allergy Clin Immunol* 1992; 89: 1040-5.
20. FINNETT JP, WOOD-BAKER R, THOMSON H, HOLGATE ST. Role of leukotrienes in exercise-induced asthma. Inhibitory effect of ICI 204219, a potent leukotriene D $_4$ receptor antagonist. *Am Rev Respir Dis* 1992; 145: 746-9.
21. FORD-HUTCHINSON AW, GRESSER M, YOUNG RN. 5-Lipoxygenase. *Annu Rev Biochem* 1994; 63: 383-417.
22. FRIEDMAN BS, BEL EH, BUNTINX A, et al. Oral leukotriene inhibitor (MK-886) blocks allergen-induced airway responses. *Am Rev Respir Dis* 1993; 147: 839-44.
23. FUJIMURA M, SAKAMOTO S, KAMIO Y, MATSUDA T. Effect of a leukotriene antagonist, ONO-1078, on bronchial hyperresponsiveness in patients with asthma. *Respir Med* 1993; 87: 133-8.
24. GADDY JN, MARGOLSKEE DJ, BUSH RK, WILLIAMS VC, BUSSE WW. Bronchodilation with a potent and selective leukotriene D $_4$ (LTD $_4$) receptor antagonist (MK-571) in patients with asthma. *Am Rev Respir Dis* 1992; 146: 358-63.
25. HOLTZMAN MJ. Arachidonic acid metabolism in airway epithelial cells. *Annu Rev Physiol* 1992; 54: 303-29.
26. HOWLAND W, SEGAL A, GLASS M. 6 Weeks therapy with the oral leukotriene receptor antagonist, ICI 204,219 in the treatment of asthma. *J Allergy Clin Immunol* 1994; 93: A581.
27. HUI KP, BARNES NC. Lung function improvement in asthma with a cysteinyl-leukotriene receptor antagonist. *Lancet* 1991; 337: 1062-3.
28. HUI KP, TAYLOR IK, TAYLOR GW, et al. Effect of a 5-lipoxygenase inhibitor on leukotriene generation and airway responses after allergen challenge in asthmatic patients. *Thorax* 1991; 46: 184-9.
29. IMPENS N, REISS TF, TEAHAN JA, et al. Acute bronchodilation with an intravenously administered leukotriene D $_4$ antagonist MK 679. *Am Rev Respir Dis* 1993; 147: 1442-6.
30. ISRAEL E, DERMARKARIAN R, ROSENBERG M, et al. The effects of a 5-lipoxygenase inhibitor on asthma induced by cold, dry air. *N Engl J Med* 1990; 323: 1740-4.
31. ISRAEL E, FISCHER AR, ROSENBERG MA, et al. The pivotal role of 5-lipoxygenase products in the reaction of aspirin sensitive asthmatics to aspirin. *Am Rev Respir Dis* 1993; 148: 1447-51.
32. ISRAEL E, RUBIN P, KEMP JP, et al. The effect of inhibition of 5-lipoxygenase by zileuton in mild to moderate asthma. *Ann Intern Med* 1993; 119: 1059-66.
33. JOOS GF, KIPS JC, PAUWELS RA, VAN DER STRAETEN ME. The effect of aerosolized SK&F 104353Z2 on the bronchoconstrictor effect of leukotriene D $_4$ in asthmatics. *Pulm Pharmacol* 1991; 4: 37-42.
34. KAYE MG, SMITH LJ. Effects of inhaled leukotriene D $_4$ and platelet activating factor on airway reactivity in normal subjects. *Am Rev Respir Dis* 1990; 141: 993-7.
35. KIKAWA Y, MIYANOMAE T, INOUE Y, et al. Urinary leukotriene E_4 after exercise challenge in children with asthma. *J Allergy Clin Immunol* 1992; 89: 111-19.
36. KIPS JC, JOOS GF, DE LEPELIERE I, et al. MK-571, a potent antagonist of leukotriene D $_4$ -induced bronchoconstriction in the human. *Am Rev Respir Dis* 1991; 144: 617-21.
37. KIPS JC, JOOS GF, PELEMAN RA, PAUWELS RA. The effect of inhaled ICI 204,219 on baseline lung function in moderate asthma. *Am Rev Respir Dis* 1993; 147: A297.
38. KNAPP HR, SLADEK K, FITZGERALD GA. Increased excretion of leukotriene E_4 during aspirin induced asthma. *J Lab Clin Med* 1992; 119: 48-51.
39. KUMLIN M, DAHLEN B, BJÖRCK T, ZETTERSTRÖM O, GRANSTRÖM E, DAHLEN SE. Urinary excretion of leukotriene E_4 and 11-dehydro-thromboxane B $_2$ in response to

- bronchial provocations with allergen, aspirin, leukotriene D₄ and histamine in asthmatics. *Am Rev Respir Dis* 1992; 146: 96-103.
40. LAITINEN LA, LAITINEN A, HAAHTELA T, VILKKA V, SPIR BW, LEE TH. Leukotriene E₄ and granulocytic infiltration into asthmatic airways. *Lancet* 1993; 341: 989-90.
41. LAM S, CHAN H, LERICHE JC, CHAN-YEUNG M, SALARI H. Release of leukotrienes in patients with bronchial asthma. *J Allergy Clin Immunol* 1988; 81: 711-17.
42. LAMMERS JWJ, VAN DAELE P, VAN DEN ELSHOUT FMJ, et al. Bronchodilator properties of an inhaled leukotriene D₄ antagonist (Verlukast - MK-6679) in asthmatic patients. *Pulm Pharmacol* 1992; 5: 121-5.
43. LINDGREN JA, EDENUS C. Transcellular biosynthesis of leukotrienes and lipoxins via leukotriene A₄ transfer. *TIPS* 1993; 14: 351-4.
44. MAKKEK HK, LAU LC, THOMSON HW, BINKS SM, HOLT-GATE ST. The protective effect of inhaled leukotriene D₄ receptor antagonist ICI 204,219 against exercise-induced asthma. *Am Rev Respir Dis* 1993; 147: 1413-18.
45. MANNING PJ, ROKACH J, MALO JL, et al. Urinary leukotriene E₄ levels during early and late asthmatic responses. *J Allergy Clin Immunol* 1990; 86: 211-20.
46. MANNING PJ, WATSON RM, MARGOLSKIE DJ, WILLIAMS VC, SCHWARTZ JJ, O'BYRNE PM. Inhibition of exercise-induced bronchoconstriction by MK-571, a potent leukotriene D₄-receptor antagonist. *N Engl J Med* 1990; 323: 1736-9.
47. MARGOLSKIE D, BODMAN S, DOCKHORN R, et al. The therapeutic effects of MK-571, a potent and selective leukotriene (I T) D₄ receptor antagonist in patients with chronic asthma. *J Allergy Clin Immunol* 1991; 87: A677.
48. MAROM Z, SHELLHAMER JH, BACH MK, MORTON DR, KALINER MA. Slow reacting substances, leukotrienes C₄ and D₄, increase the release of mucus from human airways *in vitro*. *Am Rev Respir Dis* 1982; 126: 449-51.
49. MELTZER SS, JOHNS MA, RECHSTEINER EA, JUNGERWIRTH S, D'AMICO JM, BLEEKER ER. Bronchodilatory effects of BA1005, a 5-lipoxygenase inhibitor, in mild to moderate asthma. *J Allergy Clin Immunol* 1994; 93: A792.
50. NASSER SMS, BELL GS, FOSTER S, et al. Effect of the 5-lipoxygenase inhibitor ZD1218 on aspirin induced asthma. *Thorax* 1994; 49: 749-50.
51. NASSER SMS, BELL GS, HAWKSWORTH RJ, et al. Effect of the 5-lipoxygenase inhibitor ZD1218 on allergen-induced early and late asthmatic responses. *Thorax* 1994; 49: 743-8.
52. O'SHAUGHNESSY KM, TAYLOR IK, O'CONNOR B, O'CONNELL I, THOMSON H, DOLLERY CT. Potent leukotriene D₄ receptor antagonist ICI 204,219 given by the inhaled route inhibits the early but not the late phase of allergen-induced bronchoconstriction. *Am Rev Respir Dis* 1993; 147: 1431-5.
53. PIACENTINI GL, KALINER MA. The potential roles of leukotrienes in bronchial asthma. *Am Rev Respir Dis* 1991; 143: S96-9.
54. RASMUSSEN JB, ERIKSSON LO, MARGOLSKIE DJ, TAGARI P, WILLIAMS VC, ANDERSSON KE. Leukotriene D₄ receptor blockade inhibits the immediate and late bronchoconstrictor responses to inhaled antigen in patients with asthma. *J Allergy Clin Immunol* 1992; 90: 193-201.
55. RASMUSSEN JB, ERIKSSON LO, TAGARI P, STAHL EG, ANDERSSON KE. Reduced nonspecific bronchial reactivity and decreased airway response to antigen challenge in atopic asthmatic patients treated with the inhaled leukotriene D₄ antagonist, L-648,051. *Allergy* 1992; 47: 604-9.
56. ROBUSHI M, RIVA E, FUCELLA LM, et al. Prevention of exercise-induced bronchoconstriction by a new leukotriene antagonist (SK&F 104353). *Am Rev Respir Dis* 1992; 145: 1285-8.
57. SAMUELSSON B. Leukotrienes: mediators of immediate hypersensitivity reactions and inflammation. *Science* 1983; 220: 568-75.
58. SLADEK K, DWORSKI R, FITZGERALD GA, et al. Allergen-stimulated release of thromboxane A₂ and leukotriene E₄ in humans. *Am Rev Respir Dis* 1990; 141: 1441-5.
59. SLADEK K, DWORSKI R, SELLER JR, NIZANKOWSKA E, OATES JA, SZCZELIK A. Eicosanoids in bronchoalveolar lavage fluid of aspirin-intolerant patients with asthma after aspirin challenge. *Am J Respir Crit Care Med* 1994; 149: 940-6.
60. SMITH CM, CHRISTIE PE, HAWKSWORTH RJ, THIEN F, LEE TH. Urinary leukotriene E₄ levels after allergen and exercise challenge in bronchial asthma. *Am Rev Respir Dis* 1991; 144: 1411-13.
61. SMITH LJ, GREENBERGER PA, PATTERSON R, KRELL R, BERNSTEIN PR. The effect of inhaled leukotriene D₄ in humans. *Am Rev Respir Dis* 1985; 131: 368-72.
62. SORKNESS CA, REISS TF, ZHANG J, et al. Bronchodilation with a selective and potent leukotriene D₄ antagonist (MK-4676) in patients with asthma. *Am J Respir Crit Care Med* 1994; 149: A216.
63. SPECTOR SL, GLASS M, MINKWITZ MC. ICI ASTHMA TRIAL GROUP. The effect of six weeks of therapy with oral doses of ICI 204,219 in asthmatics. *J Allergy Clin Immunol* 1993; 91: A16.
64. SPECTOR SL, SMITH LJ, GLASS M, ACCOLATE ASTHMA TRIALISTS GROUP. Effects of 6 weeks of therapy with oral doses of ICI 204,219, a leukotriene D₄ receptor antagonist, in subjects with bronchial asthma. *Am J Respir Crit Care Med* 1994; 150: 618-23.
65. TANIGUCHI Y, TAMURA G, HONMA M, et al. The effect of an oral leukotriene antagonist, ONO-1078, on allergen induced immediate bronchoconstriction in asthmatic subjects. *J Allergy Clin Immunol* 1993; 92: 507-12.
66. TAYLOR GW, TAYLOR I, BLACK P, et al. Urinary leukotriene E₄ after antigen challenge and in acute asthma and allergic rhinitis. *Lancet* 1989; i: 584-8.
67. TAYLOR IK, O'SHAUGHNESSY KM, FULLER RW, DOLLERY CT. Effect of cysteinyl-leukotriene receptor antagonist ICI 204,219 on allergen induced bronchoconstriction and airway hyperactivity in atopic subjects. *Lancet* 1991; 337: 690-4.
68. TAYLOR IK, WELLINGS R, TAYLOR GW, FULLER RW. Urinary leukotriene E₄ excretion in exercise-induced asthma. *J Appl Physiol* 1992; 73: 743-8.
69. WAHEDNA I, WISNIEWSKI AFZ, WONG CS, TATTERSFIELD AE. Effects of multiple dose of RG 12525, an oral leukotriene D₄ antagonist, in chronic asthma. *Am Rev Respir Dis* 1993; 147: A16.
70. WARDLAW AJ, HAY H, CROMWELL O, COLLINS JV, KAY AB. Leukotrienes LTC₄ and LTB₄ in bronchoalveolar lavage in bronchial asthma and other respiratory diseases. *J Allergy Clin Immunol* 1989; 84: 19-26.
71. WELCH MJ, NELSON HS, PAULL BR, SMITH JA, FEISS G, TOBEY RE. Effect of RG 12525, a new leukotriene antagonist, on pulmonary function of asthmatic adults. *Ann Allergy* 1994; 72: 348-52.
72. WENZEL SE, LARSEN GL, JOHNSTON K, VOELKEL NF, WESTCOTT JY. Elevated levels of leukotriene C₄ in bronchoalveolar lavage fluid from atopic asthmatics after endobronchial allergen challenge. *Am Rev Respir Dis* 1990; 142: 112-19.
73. YAMAMOTO H, NAGATA M, KURAMITSU K, et al. Inhibition of analgesic-induced asthma by leukotriene receptor antagonist ONO-1078. *Am J Respir Crit Care Med* 1994; 150: 254-7.

This document is a scanned copy of a printed document. No warranty is given about the accuracy of the copy. Users should refer to the original published version of the material.