Leukotriene receptor antagonists and biosynthesis inhibitors: potential breakthrough in asthma therapy

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ABSTRACT: Cysteinyl leukotrienes are potent bronchoconstrictors, inducers of airway microvascular leakage and oedema, and of mucus secretion, in addition to causing an eosinophilic airway infiltration. Increased urinary excretion of the cysteinyl leukotriene E4 (LTE4) has been demonstrated following allergen challenge and during acute asthma attacks.

Strategies for inhibition of cysteinyl leukotriene effects include antagonism of cysteinyl leukotriene receptors and inhibition of 5-lipoxygenase activity. In experimental challenge studies in asthmatic patients, these compounds can inhibit bronchoconstriction in response to exercise, aspirin and allergen. Results from clinical studies using receptor antagonists, such as ICI 204,219 and MK-571, and synthesis inhibitors, such as zileuton, demonstrate beneficial effects, with improvement in symptoms and forced expiratory volume in one second (FEV1), and a reduction in the use of β2-adrenergic relief medication. Further studies are needed to clarify the exact mechanisms by which these compounds provide beneficial effects.

Cysteinyl leukotrienes are important mediators of asthma, and inhibition of their effects may represent a potential breakthrough in the therapy of asthma. Eur Respir J., 1995, 8, 1203–1213.

In recent years, there have been major advances in asthma both in the understanding of the pathophysiological processes in the airways and in the effective use of anti-inflammatory therapy [1, 2]. Examination of bronchial mucosal biopsies obtained from the proximal large airways reveals a cellular infiltrate typically of eosinophils and lymphocytes, and epithelial damage and desquamation [3], with the expression of several cytokines, such as interleukins (IL-) 3, 4 and 5, and granulocyte-macrophage colony stimulating factor (GM-CSF), particularly by lymphocytes and other cell types [4–6]. Several mediators, such as histamine, cysteinyl leukotrienes, kinins, and eosinophil products such as eosinophil cationic protein (ECP), have been detected in the asthmatic airway. Priming for release of mediators, in particular cysteinyl leukotrienes, especially from the eosinophil, may occur [7]. Mediators may act on target cells within the airways to induce features typical of asthma, such as bronchoconstriction, mucus plugging, airway wall oedema through microvascular leakage, eosinophil infiltration and bronchial hyperresponsiveness [8].

Although many mediators are likely to play a role in inducing these features, there is now compelling evidence for an important role for cysteinyl leukotrienes in asthma. This will be reviewed and the potential therapeutic importance of inhibiting the effects of leukotrienes in asthma will be discussed.

Generation of leukotrienes (fig. 1)

Leukotrienes are synthesized from arachidonic acid, a normal constituent of the phospholipid bilayer, which is liberated by the action of phospholipases in response to various stimuli. Leukotrienes are formed by the activation of 5-lipoxygenase (5-LO) enzyme on arachidonic acid to form an unstable intermediate, 5-hydroperoxyeicosatetraenoic acid (5-HPETE) which is converted to epoxide leukotriene (LT)A4 [9]. 5-LO is a member of a family of lipoxygenases, and is an iron-containing enzyme consisting of 673 amino acids, which is dependent on Ca++, adenosine triphosphate and several cofactors for maximal activity [10]. 5-LO translocates from the cytosol to the nuclear cell membrane to initiate leukotriene biosynthesis. 5-HPETE is formed through the action of 5-LO and the 5-lipoxygenase-activating protein (FLAP), a nuclear membrane protein to which 5-LO binds to make a stable complex [11].

LT A4 is the pivotal intermediate from which all other leukotrienes are synthesized. LT A4 hydrolase is a zinc-containing cystolic metalloproteinase possessing intrinsic aminopeptidase activity [12], with considerable homology to the aminopeptidase N family of enzymes. LT A4 enzymatic activity can be inhibited by metallohydrolase inhibitors, such as bestatin. LT A4 is unstable and may be hydrolysed to the dihydroxyacid LT B4 by LT A4.
Fig. 1. – Proposed mechanism for the involvement of 5-LO and FLAP in the regulation of cellular leukotriene biosynthesis, and for various ways of inhibiting the effects of cysteinyl-leukotrienes. An inflammatory stimulus (R) leads to receptor-mediated intracellular influx of calcium (Ca++) ions, allowing cytosolic PLA₂ and 5-LO to translocate from the cytosol to the cell membrane to make a stable complex. PLA₂ cleaves AA from membrane phospholipids, and AA is converted by 5-LO in the presence of FLAP to 5-HPETE. 5-HPETE is converted by 5-LO to LTA₄ which is converted by LTA₄ hydrolase to LTB₄, or by LTC₄ synthase to LTC₄, and subsequently to LTD₄ and LTE₄. Three sites of action for drugs are illustrated: FLAP inhibitors which prevent 5-LO binding with FLAP; 5-LO inhibitors which inhibit 5-LO activity and cysteinyl-leukotriene receptor antagonists which inhibit the effects of cysteinyl-leukotrienes.

Hydrolase, or glutathione is incorporated to form the peptidoleukotriene LTC₄ by the enzyme LTC₄ synthase. LTC₄ synthase has been recognized as an 18 kDa integral microsomal membrane protein and has recently been cloned. The nucleotide and deduced amino acid sequences of its complementary deoxyribonucleic acid (cDNA) show no significant homology to glutathione S transferases but share amino acid identity with FLAP. Interestingly, MK-886, a FLAP inhibitor, inhibits LTC₄ synthase activity.

The subsequent conversion of LTC₄ to LTD₄ is a cysteinyl glycinyl derivative, is via the action of α-glutamyl transpeptidase. LTD₄ is further metabolized to the cysteinyl derivative, LTB₄, by the action of a dipeptidase. Leukotrienes are rapidly metabolized and removed from the circulation. Peptidoleukotrienes undergo oxidation, resulting in biliary and urinary elimination of biologically less active and inactive metabolites. LTE₄ is an important urinary metabolite that can be used to monitor the production of leukotrienes in man.

The location of leukotriene synthesis is determined by the cellular distribution of the enzymes controlling each step of the pathway. The distribution of 5-lipoxigenase is limited to myeloid cells, including neutrophils, eosinophils, monocytes, macrophages, mast cells and basophils. LTC₄ synthase has been identified not only in mast cells and eosinophils but also in endothelial cells and platelets. LTA₄ hydrolase has been found in human plasma, human erythrocytes, inflammatory cells, bronchoalveolar lavage fluid and airway epithelial cells. Because these enzymes are distributed among different cell types, various inflammatory cells, in concert with noninflammatory cells, such as endothelial cells or epithelial cells, can participate in the transcellular synthesis of leukotrienes.

Actions of leukotrienes relevant to asthma

In in vitro and in vivo studies on human isolated bronchus, and in normal or asthmatic subjects following aerosol administration, respectively, LTC₄ and LTD₄ are approximately 1,000 times more potent than histamine in contracting human isolated bronchus [20–23]. Both large and small airways of normal and asthmatic patients are constricted by cysteinyl leukotrienes [22, 23]. Inhaled LTC₄ and LTD₄ are 1,000–5,000 times more potent than histamine, with a long duration of action [22, 24].
Although LTE₄ is equipotent with LTC₄ and LTD₄ on isolated human bronchi, in vivo LTE₄ is approximately one tenth as potent as LTD, but with a longer duration of action [25].

LTC₄ and LTD₄ are also potent stimulants of mucous glycoproteins from human airways in vitro [26, 27]. In vivo, they enhance secretion of mucus [28], and stimulate secretion of chloride across the epithelium in dog trachea [29]. LTC₄, D₄ and E₄ cause vasoconstriction and increase microvascular permeability in the airways of guinea-pigs [30, 31], being at least 100-1,000 times more active than histamine. In human skin, LTC₄ and LTD₄ are potent vasodilators, producing wheal and flare responses at low concentrations [32, 33]. Maximal airway narrowing induced by methacholine is augmented by LTD₄ in normal subjects, an effect attributed to induction of airway oedema [34]. Inhalation of LTE₄ by asthmatic subjects led to an increase in the number of eosinophils, and to a lesser extent of neutrophils, in bronchial mucosal biopsies 4 h after inhalation [35].

Production of leukotrienes in asthma

Increased production of leukotrienes can be demonstrated in asthmatic patients. Measurement of LTE₄ excretion in urine is a convenient method for examining leukotriene production in vivo. Thus, increased urinary leukotrienes have been demonstrated following allergen challenge, during acute asthma, and aspirin-induced asthma [36–41]. However, no increase in LTE₄ excretion was shown after exercise-induced asthma [42], despite the fact that leukotriene antagonists inhibit this response [43]. Raised levels of leukotrienes, particularly LTE₄ have been found in bronchoalveolar lavage fluid of asthmatic volunteers [44–46], with further increases after endobronchial allergen challenge [47].

Strategies for inhibition of leukotriene effects

In view of the properties of cysteinyl leukotrienes in mimicking several features of asthma, and of the strong evidence for their production in asthma, it was reasonable to hypothesize that inhibition of leukotriene effects would provide clinical benefit. Two basic modes of action are available for inhibition of leukotriene effects: 1) inhibition of synthesis; and 2) antagonism of leukotriene receptors [48] (fig. 1). Many different approaches are available for inhibiting leukotriene synthesis, including antagonism of FLAP, iron chelation, redox-activity, and inhibition of 5-LO active site. Inhibitors of 5-LO have the added advantage of also preventing the synthesis of LTB₄ in addition to that of cysteinyl leukotrienes. Antagonism of leukotriene receptors is mainly achieved by using specific cysteinyl leukotriene receptor antagonists and blocking the actions of cysteinyl leukotrienes.

Inhibitors of 5-lipoxygenase

Inhibitors of 5-lipoxygenase reactions can act through a number of mechanisms, which include trapping of radi-
been reported to inhibit both responses [67, 69–71]. MK-886 and MK-0591 protected against the late asthmatic response between 3–8 h, but this was subsequently lost [67, 69]. These compounds had no effect on allergen-induced airway hyperresponsiveness, despite effective blockade of LTB4 biosynthesis and LTE4 excretion at the time of measurement of airway responsiveness. In the study with a single oral dose of 800 mg zileuton [66], there was an almost complete blockade of LTB4 biosynthesis \textit{ex-vivo}, and a nearly 50% inhibition of urinary LTE4, whilst in the MK-886 studies, LTB4 biosynthesis \textit{ex-vivo} was reduced by 54%, with an 80% reduction in LTE4 urinary excretion at 3–9 h postchallenge. Almost complete blockade of LTB4 biosynthesis and LTE4 urinary excretion were observed with MK-0591. Zileuton also reduced allergen-induced nasal congestion, and selectively blocked leukotriene release in nasal lavage fluid in patients with allergic rhinitis [73].

Clinical asthma

Despite the relative lack of effect of zileuton on allergen responses, in a 4 week placebo-controlled trial in patients with mild to moderate asthma, it improved airway function and symptoms. At the highest dose of 2.4 gm-day\(^{-1}\), there were a mean increase in FEV1 of 13.4%, a decrease in \(\beta\)-agonist usage by 24%, an improvement in morning peak expiratory flow rate of 10%, a decrease in overall symptom scores of 37%, and a decrease in urinary leukotriene excretion by 39% [72]. There were no significant side-effects reported. Another long-term study with zileuton examined its protective effect against cold, dry air-induced bronchoconstriction after 13 weeks of pretreatment. The protection observed was found to persist for up to 10 days after discontinuation of zileuton, which has a half-life of only 2.3 h [74].

**Leukotriene receptor antagonists**

There are two classes of receptors for leukotrienes, those for the dihydroxy-leukotrienes, LTB4, termed BLT-receptors, and those for cysteinyl leukotrienes, CysLT-receptors, according to the recent International Union of Pharmacology (IUPHAR) receptor nomenclature. Specific membrane CysLT-receptors have been described, using functional receptor assays on isolated smooth muscle preparations and receptor ligand-binding studies in mammalian lung tissues [75]. Although few synthetic agonists for CysLT-receptors now exist, many antagonists have been produced. Two broad subgroups of Cys
LT-receptors have been recognized, those blocked by known antagonists (Cys-LT₁-receptors) and those that are resistant to blockade (Cys-LT₂-receptors). One recent antagonist appears to have activity both for Cys-LT₁-receptors and Cys-LT₂-receptors [76]. In human airway smooth muscle, LTC₄, LTD₄ and LTE₄ all activate a Cys-LT₁-receptor, although a subclass of Cys-LT₁-receptor may be activated specifically by LTE₄ alone. In human pulmonary vasculature, a Cys-LT₂-receptor has been identified. Cys-LT₁-receptor is likely to be G-protein-coupled, leading to calcium mobilization on activation [77].

Early compounds in the development of receptor antagonists were relatively weak in activity. The first leukotriene receptor antagonist of the hydroxyacetophenone class described was FPL-55712 [78], which exhibited poor bioavailability and a short half-life. Other compounds within the same class, e.g. LY 171883, L-649,923, and YM-16638, were synthesized, but did not possess sufficient potency to act effectively as an LTD₄ receptor antagonist. In addition to having no effect on allergen-induced responses, L-649,923 was poorly-tolerated, with a high incidence of gastrointestinal effects [79].

The newer generation of leukotriene antagonists, such as ICI 204,219 (or Accolate), the quinolones MK-571 and RG-12,525, ONO-1078 (pranuklast) and SK&F 104,353 are more promising. SK&F 104,353 has little oral activity and has been studied via the inhaled route. These compounds are at least 200 fold more potent than earlier leukotriene antagonists in [³H]-LTD₄ binding assays [80]. The efficacy and safety of potent leukotriene receptor antagonists against leukotriene-induced bronchoconstriction in normals and asthmatics has been shown in several studies. ICI 204,219, at a single oral dose of 40 mg, shifted the LTD₄-induced bronchoconstriction dose-response curve by 100-fold and provided significant antagonism for at least 24 h in normal subjects, with no apparent side-effects [81]. MK-571 provided a shift of greater than 88 fold in asthmatic patients [82]. The introduction of these potent antagonists has been critical in defining the role of LTD₄ in bronchial asthma.

**Table 2.** Effect of leukotriene receptor antagonists on clinical challenges in asthma

<table>
<thead>
<tr>
<th>Challenge</th>
<th>Compound</th>
<th>Effect</th>
<th>First author</th>
<th>Year</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise</td>
<td>ICI 204,219 20 mg, oral</td>
<td>↓ by 40% FEV₁*</td>
<td>Finnerty</td>
<td>1992</td>
<td>[83]</td>
</tr>
<tr>
<td></td>
<td>ICI 204,219 400 µg, inhaled</td>
<td>↓ by 49% FEV₁</td>
<td>Makker</td>
<td>1993</td>
<td>[84]</td>
</tr>
<tr>
<td></td>
<td>SK&amp;F 104,353 800 µg, inhaled</td>
<td>↓ by 50% FEV₁</td>
<td>Robuschi</td>
<td>1992</td>
<td>[85]</td>
</tr>
<tr>
<td></td>
<td>MK-571 160 µg, oral</td>
<td>↓ by 68% FEV₁</td>
<td>Manning</td>
<td>1990</td>
<td>[43]</td>
</tr>
<tr>
<td>Allergen</td>
<td>ICI 204,219 40 mg, oral</td>
<td>↓ EAR 81% FEV₁</td>
<td>Taylor</td>
<td>1991</td>
<td>[86]</td>
</tr>
<tr>
<td></td>
<td>ICI 204,219 1,600 µg, inhaled</td>
<td>↓ LAR 55% FEV₁</td>
<td>O'Shaughnessy</td>
<td>1993</td>
<td>[90]</td>
</tr>
<tr>
<td></td>
<td>ICI 204,219 40 mg, oral</td>
<td>↓ AHR</td>
<td>Findlay</td>
<td>1992</td>
<td>[87]</td>
</tr>
<tr>
<td></td>
<td>MK-571 450 mg, infused</td>
<td>↓ EAR 88% FEV₁</td>
<td>Rasmussen</td>
<td>1994</td>
<td>[88]</td>
</tr>
<tr>
<td></td>
<td>ICI 204,219 20 mg, oral</td>
<td>↓ LAR 68% FEV₁</td>
<td>Dahlén</td>
<td>1994</td>
<td>[89]</td>
</tr>
<tr>
<td>Aspirin</td>
<td>SK&amp;F 104,353 893 µg, inhaled</td>
<td>↑ 5.5 fold in allergen dose</td>
<td>Christie</td>
<td>1991</td>
<td>[91]</td>
</tr>
<tr>
<td></td>
<td>MK-0679 750 mg, oral</td>
<td>↑ aspirin dose by 4.4 fold</td>
<td>Dahlén</td>
<td>1993</td>
<td>[92]</td>
</tr>
<tr>
<td>Dipyrone</td>
<td>ONO-1078 225 mg, oral</td>
<td>↑ 14 fold in dipyrone dose</td>
<td>Yamamoto</td>
<td>1994</td>
<td>[93]</td>
</tr>
<tr>
<td>PAF (normal subjects)</td>
<td>ICI 204,219 40 mg, oral</td>
<td>↓ 59% of fall in sGaw after PAF</td>
<td>Kidney</td>
<td>1993</td>
<td>[94]</td>
</tr>
<tr>
<td></td>
<td>SK&amp;F 104,353 1.2 mg, inhaled</td>
<td>↓ 12.6% of fall in sGaw after PAF</td>
<td>Spencer</td>
<td>1991</td>
<td>[95]</td>
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</tbody>
</table>

* Indicates attenuation of the induced fall in FEV₁. sGaw: Specific airways conductance; PAF: platelet-activating factor. For further abbreviations see legend to table 1.
with asthma, such as exercise, allergen, and aspirin. Exercise-induced asthma is partially inhibited by approximately 50% in most studies [43, 83–85], despite the likelihood that the degree of leukotriene receptor antagonism achieved in each study could have been different. The studies using allergen challenge are of interest because both the early and late phase responses are inhibited by the leukotriene antagonists, ICI 204,219 (40 mg orally) and MK-571 [86–88]. ICI 204,219 also inhibited airway hyperresponsiveness to histamine at 6 h after allergen challenge [86]. ICI 204,219 inhibited the airway response to cumulative allergen challenge by 5.5 fold increase in allergen dose, associated with a shorter recovery time [89]. When administered by inhalation, ICI 204,219 (1.6 mg) reduced the early but not the late asthmatic response [90]. Inhaled L-648051 administered over 7 days attenuated the early and late responses to inhaled allergen [96]. In normal subjects, PAF-induced bronchoconstriction was inhibited by the LTD₄ leukotriene antagonists, ICI 204,219 [94] and SK&F 104,353 [95], in accordance with the observation that platelet-activating factor (PAF)-induces an increase in urinary LTE₄ excretion [97].

The profile of activities demonstrated by the leukotriene antagonists is different from that observed with single doses of inhaled or oral corticosteroids, which do not inhibit exercise or the acute response to allergen challenge. Aspirin-induced bronchoconstriction in aspirin-sensitive asthmatics was inhibited by the leukotriene receptor antagonists MK-069 and SK&F 104,353 [91, 92]. These results contrast with those obtained with potent receptor antagonists of PAF, which demonstrate little or no significant activity against allergen- or exercise-induced bronchoconstriction [98–100], and in trials involving moderately severe asthmatic patients [101]. Oral pranlukast (ONO-1078), after one week of treatment, causes a small (half of one doubling dilution of methacholine provocative concentration producing a 20% decrease in forced expiratory volume in one second (PC20)) improvement in bronchial hyperresponsiveness in stable asthmatic patients [102]. Inhaled L-648051 also improved bronchial hyperresponsiveness by 1.5 doubling dilutions of methacholine, after 9 days of treatment [96]. These studies indicate that, as after inhaled steroids, bronchial hyperresponsiveness improves after treatment with leukotriene antagonists. They are also in agreement with studies showing that LTC₄ interacts synergistically with histamine and prostaglandin D₂ [103], and that LTE₄ increases histamine airway responsiveness in asthmatics but not in normal subjects [104, 105]. It is possible that further improvement may occur with longer periods of treatment with leukotriene antagonists.

Studies in clinical asthma (table 3)

Single dosing. Results from several studies show that leukotriene antagonists, like synthesis inhibitors, produce significant improvement in airways function, together with a reduction in symptoms. In a study of 10 patients with mild-to-moderate asthma, a single oral dose of ICI 204,219 induced significant bronchodilation, with a mean increase of 8% in FEV₁ (range 2–14%) [106]. However, inhaled ICI 204,219 (1,600 μg dose) did not induce bronchodilatation [107], whilst SK&F 104,353 by inhalation was effective (5% mean increase in FEV₁) [108]. In 12 moderately severe asthmatics, infusion of MK-571 resulted in a mean 20% increase in FEV₁ noticed 20 min after the start of infusion, and persisting for the 5 h observation period [109, 115]. The bronchodilator properties of LT antagonists and of the β₂-adrenergic agonist, salbutamol, appear to be additive. In addition, the degree of baseline airway obstruction was correlated with the degree of bronchodilation achieved with MK-571. Similarly, in eight patients with aspirin-sensitive asthma, MK-679, the (R)-enantiomer of MK-571, by oral administration, induced a 5–34% (mean 18%) improvement in FEV₁, lasting for at least 9 h [110]. These studies suggest that persistent activation of leukotriene receptors to increase airway tone is present in patients with chronic asthma. The bronchodilator response correlated strongly with the severity of asthma and with aspirin sensitivity. It is interesting to note that leukotriene receptor antagonists do not induce bronchodilatation in normal volunteers [81, 82].

Multiple dosing. The earlier relatively weak leukotriene receptor antagonist LY 171,883 (600 mg b.i.d. for 6 weeks) caused a small improvement in basal lung function, with some reduction in the use of β₂-adrenergic agonist relief medication [111]. It is possible that this beneficial effect may have resulted from its other properties, such as phosphodiesterase inhibition. Studies using more potent and specific antagonists have recently been completed. MK-571 administered orally for 6 weeks resulted in a mean increase in FEV₁ of 8–14%, a decrease in daytime symptom scores by 30%, a decrease in β₂-agonist inhaler use by 30% and improved diurnal variation in peak expiratory flow rate [112]. Development of MK-571 has been suspended, in favour of the (R)-enantiomer, MK-679. However, this has also been abandoned because of hepatotoxicity, which is unrelated to its leukotriene receptor antagonism.

In a 6 week study of ICI 204,209 (5, 10 or 20 mg b.i.d.) in patients with mild to moderate asthma, a dose-dependent improvement in symptoms was observed. The 40 mg kg⁻¹ dosage led to a significant improvement of evening peak expiratory flow, rescue β₂-agonist inhaler use (reduced by 30%), nocturnal awakenings (reduced by 46%), morning asthma symptoms and daytime symptoms (reduced by 26%) [113]. ICI 204,219 was more effective in subjects who had the lowest predicted FEV₁ at entry to the study, and a linear response was observed with increasing doses of the antagonist [113].

In general, leukotriene receptor antagonists and inhibitors were well-tolerated in studies where the treatment period was over one week. Only mild adverse events have been reported, such as headaches and gastrointestinal disturbances. Some patients on zileuton have reported dyspepsia [72], and LY-171,883 was associated with mild diarrhoea in some patients [111]. However, in many studies, the incidence of reported adverse effects was similar to that reported in the placebo group [72, 111, 113].
Inhibition of leukotriene: effects in asthma therapy

Although it is likely that many mediators are involved in the pathogenesis of the asthmatic diathesis, inhibition of the effects of leukotrienes by receptor antagonism or inhibition of synthesis leads to improvement in symptoms and bronchodilation in patients with asthma. Although leukotriene receptor antagonists appear to be more effective than the synthesis inhibitors in blocking the late asthmatic response, the limited clinical trials that have been published show that both classes have similar effects in clinical improvement. It is too early to say whether there will be an advantage of one class over the other, despite the theoretical advantage of leukotriene 5-LO inhibitors in blocking leukotriene B4 synthesis.

Further clinical studies of inhibitors of leukotriene effects should clarify their exact place in asthma therapy, but it is important to consider the mechanism of action of these drugs in asthma. Some of the improvement may be secondary to inhibition of airway microvascular leakage and oedema. Their mechanism of bronchodilator effect in asthma would be similar to that provided by anti-inflammatory agents, such as corticosteroids, in that these effects are "indirect". Whether leukotriene receptor antagonists or inhibitors improve bronchial responsiveness to bronchoconstrictor stimuli, such as histamine or methacholine, on a longer term basis as do topical corticosteroids needs investigation, as do their potential effects on the cellular influx of inflammatory cells, in particular, eosinophils in the airway. They may also prevent the long-term consequences of asthma, such as worsening decline in lung function, as supported by results in a rat model [116].

Current guidelines for the therapy of asthma emphasize the central role of inhaled corticosteroid therapy with the use of bronchodilators, mainly short-acting β-adrenergic agonists on an as-needed basis [2]. Inhibitors of leukotriene effects may be considered at all stages of asthma therapy. Firstly, they could be introduced at Step 1 of the guidelines as regular therapy in patients with symptoms or β-agonist usage of more than 3–4 times per week. Secondly, they could be introduced, together with inhaled steroid therapy, for a potential synergistic or additive effect, to limit or reduce the dose of inhaled steroid therapy. In this respect, it would be important to determine any steroid-sparing properties of these compounds. Leukotriene receptor antagonists or synthesis inhibitors appear to provide useful bronchodilation over and above what β2-adrenergic agonists may provide. Most of these drugs are active by the oral route, and this may possess the advantage of improved patient compliance with once or twice daily oral dosing over

Table 3. Effect of leukotriene receptor antagonists in clinical asthma

<table>
<thead>
<tr>
<th>Compound</th>
<th>Type of asthma</th>
<th>Effects</th>
<th>First author</th>
<th>Year</th>
<th>[Ref]</th>
</tr>
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<tr>
<td><strong>Single dosing</strong></td>
<td></td>
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</tr>
<tr>
<td>ICI 204,219</td>
<td>Mild-moderate</td>
<td>↑ 8% FEV₁* (2–14%)</td>
<td>Hui</td>
<td>1991</td>
<td>[106]</td>
</tr>
<tr>
<td>40 mg, oral</td>
<td>(n=10)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICI 204,219</td>
<td>Moderate</td>
<td>Nil</td>
<td>Kips</td>
<td>1993</td>
<td>[107]</td>
</tr>
<tr>
<td>1,600 µg, inhaled</td>
<td>(n=10)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>SK&amp;F 104,353</td>
<td>Moderately severe</td>
<td>↑ 22% FEV₁</td>
<td>GADDY</td>
<td>1992</td>
<td>[109]</td>
</tr>
<tr>
<td>800 µg, inhaled</td>
<td>(n=12)</td>
<td></td>
<td></td>
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<tr>
<td>MK-571</td>
<td>Aspirin-sensitive</td>
<td>↑ 18% FEV₁ (5–34%)</td>
<td>DAHLÉN</td>
<td>1993</td>
<td>[110]</td>
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<td>776 mg over 6 h, infused</td>
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<tr>
<td>MK-0679</td>
<td>(n=8)</td>
<td></td>
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<tr>
<td>825 mg, oral</td>
<td>Mild-moderate</td>
<td>At 40 mg·day⁻¹↓ rescue β-agonist (30%)</td>
<td>SPECTOR</td>
<td>1994</td>
<td>[113]</td>
</tr>
<tr>
<td>5, 10 or 20 mg</td>
<td>(n=276)</td>
<td>↓ nocturnal awakening (46%)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>b.i.d. for 6 weeks</td>
<td></td>
<td>↓ day symptom (26%)↑ FEV₁ (11%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Multiple dosing</strong></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>ICI 204,219</td>
<td>Mild-moderate</td>
<td>↑ 8–14% FEV₁ ↓ 30% symptom scores</td>
<td>MARGOLSKIE</td>
<td>1991</td>
<td>[112]</td>
</tr>
<tr>
<td>5, 10 or 20 mg</td>
<td>(n=43)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>b.i.d. for 6 weeks</td>
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<tr>
<td>MK-571</td>
<td>75 mg t.i.d., 2 weeks, then 50 mg t.i.d. for 4 weeks</td>
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<tr>
<td>LY-171,883</td>
<td>Mild-moderate</td>
<td>↑ Mean weekly FEV₁ of 4.5% ↓ use of β-agonist</td>
<td>CLOUD</td>
<td>1989</td>
<td>[111]</td>
</tr>
<tr>
<td>600 mg b.i.d., 6 weeks</td>
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</tr>
<tr>
<td>RG 12525</td>
<td>↑ 7.9% FEV₁</td>
<td></td>
<td>WAJEDNA</td>
<td>1992</td>
<td>[114]</td>
</tr>
<tr>
<td>50 mg q.i.d. 10 days</td>
<td></td>
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</tbody>
</table>

* Indicates change in FEV₁ from baseline.
inhaled therapy. With a relatively safe profile of unwanted side-effects so far, compliance may be better than with the use of regular twice daily inhaled steroid therapy [117].

The introduction of leukotriene antagonists and synthesis inhibitors in the therapy of asthma will represent an important breakthrough in asthma therapy. These drugs represent the first class of mediator antagonists that have provided clinical benefit in asthma, in contrast to the disappointing results seen with very potent histamine antagonists. Although further work needs to be done, one should be optimistic as to their future contribution in the management of asthma; they are likely to become an established class of anti-asthma drugs.

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References


