Drug therapy

Anti-leukotriene therapy in asthma

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Abstract

There is ample evidence that leukotrienes are important inflammatory mediators of asthma. Anti-leukotriene therapy is a novel, specific anti-asthma strategy providing both reliever and controller effects. Currently, two types of anti-leukotriene drugs are being registered in several countries: leukotriene receptor antagonists and leukotriene biosynthesis inhibitors. Both types of drugs have shown comparable bronchodilator effects, and provided protection against bronchoprovocation tests with cold dry air, exercise, allergen and aspirin. Moreover, beneficial effects have been shown in the treatment of day-to-day asthma resulting in improvement of clinical symptoms, lung function parameters, and a reduction in β2-agonist- and corticosteroid-use. Furthermore, some studies showed a decrease in the airway eosinophil counts after longterm administration of anti-leukotriene drugs, suggestive of anti-inflammatory effects. Because of these properties in combination with generally mild adverse effects, anti-leukotrienes seem promising in the treatment of patients with various types and severities of asthma, including children. However, their definitive place in the management of asthma will eventually depend on their effectiveness to modulate the chronic airway inflammation, which induces the structural changes within the airways, determining the severity of clinical symptoms of asthma. © 1998 Elsevier Science B.V. All rights reserved.

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1. Introduction

Asthma is a chronic disorder of the airways, associated with atopy, and characterized by a spectrum of abnormalities on various levels, including: (1) clinical symptoms (chest tightness, dyspnoea, coughing, and/or wheeze), (2) pathophysiological parameters (variable airway obstruction, bronchial hyperreactivity to a variety of physical, pharmacological, chemical, or physiological (e.g. exercise) stimuli), and (3) histopathological parameters (mainly eosinophilic airway inflammation, resulting in structural changes within the airways: the so-called airway remodelling) [1,2]. This disease entity may occur in various degrees of severity ranging from intermittent to severe persistent [3].

Airway inflammation plays a central role in the pathogenesis of asthma [1]. Hence, according to
modern guidelines of management of asthma, anti-inflammatory therapy (the so-called controller medication, mostly inhaled corticosteroids) is being advocated as first-line treatment of persistent asthma, in combination with on demand bronchodilators [3]. Despite the well-known effectiveness and relative safety of these drugs, still too many asthmatic patients are being treated suboptimally, resulting in a poor quality of life [4]. Besides, a worldwide trend of increasing prevalence in morbidity and mortality of asthma has been observed in the last decade [3]. Therefore, several researchers have been putting effort into investigating alternative anti-inflammatory drugs, possessing a favourable pharmacokinetic profile to enhance patients’ compliance, and preferably combined with bronchodilator properties. The anti-leukotrienes seem to comply with this profile.

2. Models for asthma research

In preclinical studies, exacerbations of asthma can be mimicked by various validated models including exercise, cold, dry air and aspirin challenge, inhalations of allergen, ozone, and hypertonic saline, experimental virus infections, or controlled withdrawal of regular anti-asthma treatment [5].

Owing to its characteristics, allergen challenge is one of the most suitable models for intervention studies with experimental anti-asthma therapy. Inhalation of a specific allergen by a sensitive asthmatic patient induces acute airway narrowing, the so-called early asthmatic response (EAR), which is defined as a fall in forced expiratory volume in 1 s (FEV₁) of at least 20% from baseline [6]. The EAR involves IgE-triggered mast cell mediator release, predominantly causing acute airway smooth muscle contraction, occurring within 10 min after allergen inhalation and mostly recovering within 3 h [6,7]. In approximately 50% of the cases, the EAR is followed by a late asthmatic response (LAR) which represents a fall in FEV₁ of at least 15% from baseline up to 24 h after allergen challenge [6]. The LAR is characterized by inflammatory events within the airways in which activated eosinophils are likely to play a key role by releasing pro-inflammatory mediators that are capable of inducing the associated non-specific airway hyperresponsiveness which may last for several weeks [7–9].

Despite several advantages, the models of asthma provide only information on the acute inflammatory processes within the airways during experimental exacerbations of asthma. Therefore, long-term follow-up studies in patients with persistent asthma are essential to evaluate the treatment effects of novel, potential anti-asthma therapy on the chronic, structural changes which mainly determine the clinical parameters. Both types of interventions have been applied with anti-leukotriene drugs [10].

3. Effects of leukotrienes within the airways

Leukotrienes (LTs) are lipid metabolites of the arachidonic acid via the 5-lipoxygenase (5-LO) pathway (Fig. 1) [11,12]. These eicosanoids represent a heterogeneous group of biologically active mediators [12]. For translation and activation of the enzyme 5-LO, the 5-LO activating protein (FLAP), an 18 kD nuclear membrane-bound protein, is essential [11,12]. First, the arachidonic acid is converted by 5-LO to 5-hydro-peroxy-eicosatetraenoic acid (5-HPETE) which is then converted to the unstable LTA₄, and subsequently to either LTB₄ or to the cysteinyl leukotrienes (cysLTs: LTC₄, LTD₄, and LTE₄), depending on the cell type. LTC₄ is metabolized via LTD₄ to the stable endproduct LTE₄, which is predominantly excreted in urine [11,12]. While LTB₄ is predominantly synthesized by monocytes, macrophages, and neutrophils, cysLTs are mainly produced by mast cells, basophil and eosinophil granulocytes [11–18]. Both categories of leukotrienes possess distinct biologic properties which may account for features of asthma and of other diseases as well [11,12,19,20]. LTB₄ is a chemoattractant and activator of leukocytes in several species in vitro and in vivo [11,12,21,22], whereas cysteinyi leukotrienes contract airway and pulmonary vascular smooth muscle, increase microvascular permeability resulting in oedema, and stimulate mucus secretion [11,12]. Furthermore, recent evidence shows that cysLTs also possess chemoattractant activity both in animals and humans [22–25]. These pro-inflammatory effects are most likely mediated by stimulation of specific re-
Fig. 1. Arachidonic acid metabolism: 5-lipoxygenase pathway. Sites of interaction for leukotriene receptor antagonists and leukotriene biosynthesis inhibitors are indicated. Abbreviations: 5-LO = 5-lipoxygenase; FLAP = 5-lipoxygenase activating protein; (cys)LT = (cysteinyl) leukotriene; 5-HPETE = 5-hydroperoxy-eicosatetraenoic acid; cysLTRAs = cysteinyl leukotriene receptor antagonists.

ceptors [11,26,27] or through release of other pro-inflammatory mediators, such as neuropeptides [28].

In symptomatic patients with atopic asthma, increased levels of LTB4 and/or cysLTs have been demonstrated in exhaled air and in biological fluids, such as blood, urine, sputum, and bronchoalveolar lavage fluid [29–39]. This generation of leukotrienes may either result from direct activation of inflammatory cells [7,15], or from secondary release by other mediators, such as platelet activating factor (PAF) [40], or bradykinin [41]. Despite conflicting data on the cysteinyl leukotriene production following exercise or isocapnic hyperventilation of cold and/or dry air [42–47], several intervention studies using anti-leukotriene drugs have attested that leukotrienes are likely to be involved in the bronchoconstriction induced by these challenges [10,48]. In aspirin-sensitive asthmatic patients, who are mostly non-atopic [49], the basal production of cysLTs is relatively even higher, as reflected by increased urinary LTE4 levels as compared with aspirin-tolerant asthmatics [50]. Presumably, this increase in enhanced cysLT synthesis may be caused by the increased numbers of mast cells and eosinophils which have been demonstrated at baseline in bronchial biopsies of aspirin-sensitive patients in comparison with aspirin-tolerant asthmatics [51]. In addition, evidence exists for a selective target organ hypersensitivity for LTE4 in patients with aspirin-induced asthma [52,53].

Upon inhalation, cysLTs induce clinical symptoms of asthma, including bronchoconstriction [54–56] and airway hyperresponsiveness [54,57–59] in both nonasthmatic and asthmatic individuals, although late phase responses to cysLTs could not be demonstrated [60]. In addition, recent studies in asthmatic patients have shown airway eosinophilia in bronchial biopsies [24], and hypertonic saline-induced sputum [25], 4 h upon inhalation of LTE4 and LTD4, respectively. Furthermore, strong evidence exists from animal studies that cysLTs may contribute to the development of structural changes within the airways [61–63]. This so-called airway remodelling, characterized by a loss of airway epithelium and thickening of the airway wall through depositions of fibronectin and collagen along with airway smooth muscle hypertrophy/hyperplasia...
[2,64], is a major determinant for excessive airway narrowing which may rise serious clinical symptoms [65].

Despite involvement of various other pro-inflammatory mediators such as histamine, prostanoids, and platelet activating factor [30–32], so far anti-inflammatory therapy has shown disappointing results in the treatment of asthma, with the exception of anti-leukotriene drugs. Currently, two categories of anti-leukotriene agents have been introduced: (1) leukotriene (cysLT1 and BLT) receptor antagonists, and (2) leukotriene biosynthesis inhibitors (5-LO inhibitors and FLAP-antagonists) (Fig. 1).

3.1. Leukotriene B4 (BLT) receptor antagonists

Based on its chemotactic properties on neutrophils and eosinophils both in vitro [20], and in vivo [21], and on evidence of increased LTB4 levels in body fluids of symptomatic asthmatics [35,37], specific BLT receptor antagonists have been developed recently. So far, only a few of such compounds have been applied in human studies of asthma. Although in sensitized guinea pigs in vivo U-75302 has considerably reduced the peribronchial eosinophil infiltration without affecting the neutrophil migration following allergen challenge [66], this could not be demonstrated in humans in vivo, using a different BLT receptor antagonist [67]. In this study, LY-293111 failed to protect against allergen-induced bronchoconstriction despite a significant decrease in the number of neutrophils and myeloperoxidase level in the BAL fluid, 24 h after the challenge [67].

Although the role of neutrophils in allergen-induced airway responses in humans is still under debate [7,8,68], BLT receptor antagonists may be used more appropriately in models in which neutrophilic inflammation is more prominent, such as ozone inhalation, COPD, occupational asthma, or experimental virus infections.

3.2. Cysteinyl leukotriene (cysLT) receptor antagonists

The cysteinyl leukotriene receptor antagonists (cysLTRAs) antagonize the effects of cysLTs at the site of the cysLT1 receptor [28]. The first drugs of this category to be evaluated in humans in vivo included FPL-55712, L-648051, L-649923, LY-171883 (tomelukast), LY-170680 (sulukast), RG-12525 and SKF-104353 (pobilukast) [69–75]. These compounds had a relatively low potency, producing a rightward shift in the dose-response curve for LTD4 of merely 3 to 12-fold [69–75]. Hence, due to lack of potency or undesirable side effects most of these compounds have been abandoned. In the past decade, more potent and/or selective cysLTRAs have been developed among which pranlukast (SB-205312, Ultair), zafirlukast (ICI 204219, Accolate), and montelukast (MK-0476, Singular) have recently obtained registration in a number of countries. These compounds are being administered orally at a recommended dose of once or twice daily.

The cysLTRAs have a dual mechanism of action. First, these agents have bronchodilator properties, which are additive to β2-agonists in patients with mild to moderate persistent asthma [76,77]. Second, evidence exists for anti-inflammatory activities [78–82]. Based on various studies in asthmatic patients, cysLTRAs have been shown to provide protection against various bronchoconstrictor stimuli, including challenges with allergen, exercise, cold dry air, aspirin or other non-steroid anti-inflammatory drugs (Table 1), and to improve clinical and pathophysiological parameters in asthma, suggesting modulation of the underlying disease processes (Table 2).

3.3. Clinical effects

An ever increasing number of long-term studies applying cysLTRAs in asthma are currently being performed. Consequently, many results are not yet published in full. From several long-term follow-up studies in patients with different gradations of asthma, it has been shown that pranlukast, zafirlukast and montelukast, alone or in combination with controller anti-asthma therapy (mostly theophylline or inhaled corticosteroids), are capable of improving both clinical and lung function parameters (Table 2). In these studies, more or less comparable dose- and duration of therapy dependent increases in lung function parameters (FEV1 and peakflow) have been measured, often accompanied by clinically significant decreases in day- and nighttime symptom scores and β2-agonist use in patients with mild to moderate, or with moderate to severe persistent asthma (Table 2; [83–86]).
Table 1
Effects of cysLT₁ receptor antagonists and leukotriene biosynthesis inhibitors on various bronchoprovocation tests in asthma

<table>
<thead>
<tr>
<th>Compound</th>
<th>type</th>
<th>stimulus</th>
<th>effect (% mean inhibition)</th>
<th>dose, route</th>
<th>reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICI-204,219</td>
<td>cysLTRA</td>
<td>allergen</td>
<td>EAR(max) ↓ 88% LAR(max) ↓ 54%</td>
<td>40 mg, p.o.</td>
<td>Lancet 1991;337:690</td>
</tr>
<tr>
<td></td>
<td></td>
<td>exercise</td>
<td>↑ 52%</td>
<td>0.4 mg, i.v.</td>
<td>ARRD 1993;147:1413</td>
</tr>
<tr>
<td></td>
<td></td>
<td>eosinophils¹</td>
<td>↓ 45%</td>
<td>20 mg, p.o.</td>
<td>ARRD 1992;145:746</td>
</tr>
<tr>
<td>MK-571</td>
<td>cysLTRA</td>
<td>allergen</td>
<td>EAR(AUC₁₀) ↓ 88% LAR(AUC₁₀) ↓ 63%</td>
<td>450 mg, i.v.</td>
<td>JACI 1992;90:193</td>
</tr>
<tr>
<td>MK-0476</td>
<td>cysLTRA</td>
<td>allergen</td>
<td>EAR(AUC₅₈) ↓ 75% LAR(AUC₅₈) ↓ 57% LAR(max) ↓ 36%</td>
<td>2×10 mg, p.o.</td>
<td>AJRCCM 1996;153:A346</td>
</tr>
<tr>
<td>SK and F104,353</td>
<td>cysLTRA</td>
<td>exercise</td>
<td>↓ 41%</td>
<td>10 mg, p.o.</td>
<td>AJRCCM 1995;151:A377</td>
</tr>
<tr>
<td>MK-0679</td>
<td>cysLTRA</td>
<td>aspirin</td>
<td>↓ 47%</td>
<td>893 µg, i.v.</td>
<td>ARRD 1991;144:957</td>
</tr>
<tr>
<td>ONO-1078 = SB205,312</td>
<td>cysLTRA</td>
<td>aspirin</td>
<td>↑ 4.4-fold aspirin dose</td>
<td>750 mg, p.o.</td>
<td>ERJ 1993;6:1018</td>
</tr>
<tr>
<td>(pranlukast⁺; Ultair⁺)</td>
<td>cysLTRA</td>
<td>dipyrone</td>
<td>↑ 14-fold dipyrone dose</td>
<td>225 mg, p.o.</td>
<td>AJRCCM 1994;150:254</td>
</tr>
<tr>
<td></td>
<td></td>
<td>exercise</td>
<td>↓ 45%</td>
<td>14(1×450 mg), p.o.</td>
<td>AJRCCM 1997;155:A662</td>
</tr>
<tr>
<td>Drug</td>
<td>Type</td>
<td>Condition</td>
<td>Effect</td>
<td>Dose</td>
<td>Source</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
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<td>--------</td>
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<td>----------------------</td>
</tr>
<tr>
<td>A-64077 (zileuton(^a); Leutrol = Zyflo(^b))</td>
<td>5-LO inhibitor</td>
<td>cold, dry air</td>
<td>↑47% cold, dry air extra for ↓10% FEV(_1)</td>
<td>800 mg, p.o.</td>
<td>NEJM 1990;323:1740</td>
</tr>
<tr>
<td></td>
<td></td>
<td>exercise</td>
<td>↓41%</td>
<td>4×600 mg, p.o.</td>
<td>AJRCCM 1996;153:931</td>
</tr>
<tr>
<td></td>
<td></td>
<td>aspirin</td>
<td>↓76%</td>
<td>6–8(4×600 mg), p.o.</td>
<td>ARRD 1993:148:1447</td>
</tr>
<tr>
<td></td>
<td></td>
<td>eosinophils(^c)</td>
<td>↓66%</td>
<td>8(4×600 mg), p.o.</td>
<td>JACI 1996;97:646</td>
</tr>
<tr>
<td>ZD2138</td>
<td>5-LO inhibitor</td>
<td>aspirin</td>
<td>↓76%</td>
<td>2(1×350 mg), p.o.</td>
<td>Thorax 1994;49:749</td>
</tr>
<tr>
<td>MK-886</td>
<td>FLAP-antagonist</td>
<td>allergen</td>
<td>EAR(AUC(_{0-15})) ↓58%</td>
<td>500 + 250 mg, p.o.</td>
<td>ARRD 1993;147:839</td>
</tr>
<tr>
<td>MK-0591</td>
<td>FLAP-antagonist</td>
<td>allergen</td>
<td>EAR(AUC(_{0-1})) ↓79%</td>
<td>3×250 mg, p.o.</td>
<td>JACI 1995;95:42</td>
</tr>
<tr>
<td>BAY-x1005</td>
<td>FLAP-antagonist</td>
<td>allergen</td>
<td>EAR(AUC(_{0-x})) ↓87%</td>
<td>3.5(2×500 mg), p.o.</td>
<td>Thorax 1997;52:348</td>
</tr>
<tr>
<td></td>
<td></td>
<td>cold, dry air</td>
<td>↑34% cold, dry air extra for ↓10% FEV(_1)</td>
<td>750 mg, p.o.</td>
<td>Thorax 1997;52:1074</td>
</tr>
</tbody>
</table>

\(^{a}\) Generic name.
\(^{b}\) Trade name.
\(^{c}\) Airway eosinophils and basophils, respectively, after a segmental allergen provocation test.
Table 2
Effect of cysLT<sub>1</sub> receptor antagonists and leukotriene biosynthesis inhibitors in clinical asthma

<table>
<thead>
<tr>
<th>asthma (n = number of patients)</th>
<th>compound</th>
<th>dose, route</th>
<th>effect</th>
<th>reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild-moderate (n = 43)</td>
<td>MK-571</td>
<td>2 wk (3×75 mg), p.o., 4 wk (3×150 mg), p.o.</td>
<td>† 8–14% FEV&lt;sub&gt;1&lt;/sub&gt;  ¶ 30% β&lt;sub&gt;2&lt;/sub&gt;-agonist use</td>
<td>JACI 1991;87:309</td>
</tr>
<tr>
<td>Moderate-severe (n = 42)</td>
<td>Pranlukast</td>
<td>8 wk (2×450 mg)</td>
<td>† 16% morning/evening PEF  ¶ 40% daytime symptom scores  ¶ 60% nighttime symptom scores  ¶ 34% symptom scores  ¶ 36% rescue medication</td>
<td>AJRCCM 1997;155:A664</td>
</tr>
<tr>
<td>Moderate-severe (n = 586)</td>
<td>Pranlukast</td>
<td>12 wk (2 × 150/300/450 mg)</td>
<td>† 8–12% FEV&lt;sub&gt;1&lt;/sub&gt;  ¶ 34% symptom scores  ¶ 36% rescue medication</td>
<td>AJRCCM 1997;155:A665</td>
</tr>
<tr>
<td>Moderate-severe (n = 79; BDP ≥ 1500 μg/day)</td>
<td>Pranlukast</td>
<td>6 wk (2×450 mg)</td>
<td>steroidsparing effect: ¶ 50% BDP</td>
<td>AJRCCM 1997;155:A663</td>
</tr>
<tr>
<td>Moderate-severe (n = 276)</td>
<td>Zafirlukast</td>
<td>6 wk (2 × 5/10/20 mg)</td>
<td>† 11% FEV&lt;sub&gt;1&lt;/sub&gt;  ¶ 26% daytime symptom scores  ¶ 46% nighttime symptom scores  ¶ 30% β&lt;sub&gt;2&lt;/sub&gt;-agonist use</td>
<td>AJRCCM 1994;150:618</td>
</tr>
<tr>
<td>Moderate-severe (n = 79; BDP ≥ 1500 μg/day)</td>
<td>Zafirlukast</td>
<td>6 wk (2×80 mg)</td>
<td>† morning/evening PEF  ¶ symptom scores  ¶ β&lt;sub&gt;2&lt;/sub&gt;-agonist, ¶ rescue medication</td>
<td>J Invest Med 1997;45:A286</td>
</tr>
<tr>
<td>Moderate-severe (n = 29)</td>
<td>Montelukast</td>
<td>10.3 days (3×200 mg)</td>
<td>† 9–14% FEV&lt;sub&gt;1&lt;/sub&gt;  ¶ 11% day/nighttime symptom scores  ¶ β&lt;sub&gt;2&lt;/sub&gt;-agonist use</td>
<td>JACI 1996;98:528</td>
</tr>
<tr>
<td>Severe level</td>
<td>Treatment</td>
<td>Duration</td>
<td>Dose</td>
<td>Improvement Measures</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
<td>----------</td>
<td>------</td>
<td>----------------------</td>
</tr>
<tr>
<td>Moderate-severe ($n=681$)</td>
<td>Montelukast</td>
<td>12 wk (1 x 10 mg)</td>
<td>↓31% asthma exacerbations ↑37% asthma-free days</td>
<td>AJRCCM 1997;155:A662</td>
</tr>
<tr>
<td>Moderate ($n=226$; ICS 300–3000 μg/day)</td>
<td>Montelukast</td>
<td>12 wk (1 x 10 mg)</td>
<td>40% (M) vs 29% (P) tapering of ICS</td>
<td>AJRCCM 1997;155:A976</td>
</tr>
<tr>
<td>Mild-moderate ($n=40$)</td>
<td>Zileuton</td>
<td>4 wk (1 x 10 mg)</td>
<td>↓48% sputum eosinophils</td>
<td>AJRCCM 1997;155:A977</td>
</tr>
<tr>
<td>Moderate ($n=10$)</td>
<td>Zileuton</td>
<td>13 wk (4 x 400/600 mg)</td>
<td>↑58% cold, dry air for ↑15% FEV$_1$ up to 10 d after cessation of therapy ↓need for corticosteroids during zileuton treatment ↑16% FEV$_1$ ↓26% β₂-agonist use ↓28% daytime symptom scores ↓33% nighttime symptom scores</td>
<td>AJRCCM 1997;155:A977</td>
</tr>
<tr>
<td>Moderate-severe ($n=401$)</td>
<td>Zileuton</td>
<td>13 wk (4 x 400/600 mg)</td>
<td>↓16% FEV$_1$ ↑7–10% PEF ↓37% daytime symptom scores ↓31% nighttime symptom scores ↓31% β₂-agonist use ↓62% need for steroids ↓blood eosinophils</td>
<td>JACI 1996;98:859</td>
</tr>
<tr>
<td>Mild-moderate ($n=373$)</td>
<td>Zileuton</td>
<td>26 wk (4 x 400/600 mg)</td>
<td>↑16% FEV$_1$ ↑7–10% PEF ↓37% daytime symptom scores ↓31% nighttime symptom scores ↓31% β₂-agonist use ↓62% need for steroids ↓blood eosinophils</td>
<td>JACI 1996;98:859</td>
</tr>
</tbody>
</table>

BDP = beclomethasone; ICS = inhalational corticosteroids; P = placebo
Apart from these (mainly) bronchodilator effects, there is growing evidence that cysLT1RAs may also possess anti-inflammatory properties, also depending on dose- and duration of treatment [87,88]. In follow-up studies in patients with moderate to severe persistent asthma, 6 to 12 weeks of treatment with the aforementioned cysLT1RAs resulted in a steroidsparing effect [81–83]. Moreover, after one week of treatment with oral pranlukast already a slight, though significant decrease in airway hyperresponsiveness to methacholine was noticed in patients with stable asthma [82]. Likewise, one week of treatment with oral zafirlukast produced a significant decrease in basophils and eosinophils in the BAL fluid of atopic patients with mild to moderate asthma, 48 h following segmental allergen challenge [78]. Similarly, four weeks of treatment with oral montelukast provided a significant reduction of sputum eosinophils in patients with mild to moderate persistent asthma [88].

4. Leukotriene biosynthesis inhibitors

Apart from the cysLTs, LTB4 may also contribute to the chronic airway inflammation in asthma. Hence, pharmacological compounds have been developed which block the effects of both type of mediators. This can be achieved at different levels of the arachidonic acid and 5-lipoxygenase metabolic pathways, of which inhibition of the 5-lipoxygenase (by the so-called 5-LO-inhibitors) and of the 5-LO activating protein (by the so-called FLAP-antagonists) represent the most commonly applied interventions (Fig. 1). Although less currently tried in long-term clinical studies, leukotriene biosynthesis inhibitors provide comparably beneficial effects on clinical and lung function parameters in asthma as the cysLT1RAs (Table 2).

4.1. Clinical effects

In follow-up studies in asthma, by far the most experience has been accomplished with the first generation 5-LO inhibitor zileuton (Zyflo), mostly at oral doses of either 400 or 600 mg q.i.d. [89]. This drug has been registered for treatment of asthma in the United States since the end of 1996. Although the FLAP-antagonists, MK-0591 and BAY-x1005, have also shown some improvement in clinical and lung function parameters after four to six weeks of treatment [90,91], so far in this category of drugs zileuton has provided the most promising results in follow-up studies in asthma (Table 2).

Considerable dose-dependent improvements in clinical symptoms and lung function parameters together with a steroid-sparing effect were observed in patients with mild to moderate persistent asthma after six months of treatment with oral zileuton [92]. Using a similar treatment strategy, a steroidsparing effect was demonstrated after 13 weeks of treatment in patients with moderate to severe persistent asthma [93]. Further evidence for possible anti-inflammatory properties of this 5-LO inhibitor has been provided from other long-term studies [94,95]. In aspirin-sensitive asthmatic patients using corticosteroids, six weeks of treatment with oral zileuton produced a significant, additional improvement in clinical symptoms, lung function, and non-specific airway hyperresponsiveness [96]. In patients with mild to moderate persistent asthma, 13 weeks of treatment with oral zileuton provided adequate protection against bronchoconstriction induced by cold, dry air [94]. Unexpectedly, this protection persisted for up to 10 days after discontinuation of this short-acting drug (half life: 2.3 h), suggesting the potentially anti-inflammatory effect of leukotriene modulation [94]. In another study in asthmatic patients treated with inhaled corticosteroids for at least six months, one single dose of oral zileuton 400 mg already provided a considerable protection against airway hyperresponsiveness to inhaled histamine (2.1 doubling doses) and distilled water (1.3 doubling doses), without affecting baseline FEV1 [97]. The mechanism of action of zileuton producing such acute protection against histamine is unclear, since there is no evidence of histamine antagonism in vitro by this drug. Furthermore, eight days of pretreatment with oral zileuton significantly reduced the eosinophil number and LTE4 level in the BAL fluid along with a decreased urinary LTE4 excretion (by approx. 85%), 24 h after segmental allergen instillation in atopic asthmatic individuals [95]. Likewise, in patients with mild to moderate persistent asthma, seven days of treatment with zileuton significantly reduced LTB4...
and cysLT levels in BAL fluid and urinary LTE₄ excretion, while showing a trend for improvement of nocturnal FEV₁. Correspondingly, these protective effects were accompanied by a significant decrease in the percentage of eosinophils both in the BAL fluid and in peripheral blood [98].

4.2. Adverse effects

Although predominantly only mentioned between the lines of the current literature, most anti-leukotriene drugs are generally well-tolerated showing only a few side-effects including headache, gastrointestinal problems, incidental infections, and rash. In addition, there have been a few observations of elevated liver enzymes (transaminases) caused by some drugs, which have been self-limiting in most of the cases after discontinuation of the therapy [48,89].

5. Guidelines for application of anti-leukotriene therapy in the current management of asthma

Recently international consensus has been achieved for long-term management of asthma summarised in a stepwise approach from intermittent to severe persistent asthma [3]. In persistent asthma bronchodilators are recommended in combination with (increasing doses of) anti-inflammatory therapy, depending on the frequency and severity of the clinical symptoms and pathophysiological parameters [3]. The anti-leukotrienes seem to unify these properties: both reliever and controller, despite some recent observations of non-responders [99,100]. Although these drugs are not likely to replace neither the β₂ agonists, nor the corticosteroids, in particular not in the treatment of severe persistent asthma, a place for anti-leukotriene drugs in the management of asthma seems however justified.

Hence, some preliminary suggestions for possible applications of anti-leukotrienes and their possible positioning in the current management of asthma will be made. First, as first-line treatment in specific types of asthma, including most patients with aspirin-induced asthma [52], but also in patients with a mild type of asthma (intermittent to mild persistent), regularly suffering from exercise-induced bronchoconstriction [94]. After all, in studies comparing the effects of pobilukast or zafirlukast and cromoglicate, it has been shown that these cysLTRAs provided at least similar protection against exercise-induced bronchoconstriction in asthma with even a better recovery than cromoglicate [101,102]. Second, in patients with a more severe type of asthma (moderate to severe persistent), who need daily controller medication with high doses of corticosteroids, anti-leukotrienes seem rather promising because of their potential steroid-sparing effect [80,81]. Third, owing to their beneficial effects on both clinical and pathophysiological parameters in combination with relatively little side effects, anti-leukotriene therapy may be promising in children (starting from 0 years) and adolescents [102,103]. An additional advantage is the favourable pharmacokinetic profile of some of these compounds: already one single oral dose may provide protection for 24 h. This will surely contribute to patients’ compliance [81,88,103].

Eventually, after 25 years a novel generation of targeted drugs has been added to the current anti-asthma therapy. Their definitive position in the modern management of asthma will depend upon their effects on the pathophysiological and histopathological parameters in patients with asthma of different severity. To that aim, long-term studies in asthma comparing the effects of anti-leukotriene therapy with adequate doses of (inhaled) corticosteroids on disease modulation are mandatory.

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