ELSEVIER

Pharmacological modulation of the leukotriene pathway in allergic airway disease

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Leukotrienes (LTs), including cysteinyl LTs (CysLTs) and LTB_4, are potent lipid mediators that have an important pathophysiological role in asthma and allergic rhinitis. Most of the effects of CysLTs that are relevant to the pathophysiology of asthma are mediated by the activation of the $CysLT_1$ receptor, one of the receptor subtypes for CysLTs. LTB_4 might be functionally involved in the development of airway hyperresponsiveness, acute and severe asthma and allergic rhinitis. $CysLT_1$ receptor antagonists can be given as monotherapy or in addition to inhaled glucocorticoids. The potential anti-remodeling effect of $CysLT_1$ receptor antagonists might be relevant for preventing or reversing airway structural changes in asthmatic patients. Here, we examine the role of LTs in asthma and allergic rhinitis, and the therapeutic implications of the pharmacological modulation of the LT pathway for allergic airway disease.

Introduction

Asthma is a chronic inflammatory disease characterized by increased numbers and activation of inflammatory and immune cells within the airways, including eosinophils, T helper 2 (Th2) lymphocytes, mast cells, neutrophils and macrophages [1]. Cytokines produced by Th2 cells are particularly important in the pathophysiology of asthma; interleukin (IL) 4 promotes Th2 cell differentiation, induces IgE production and upregulates IgE receptors; IL-5 promotes development, differentiation, recruitment, activation and survival of eosinophils; IL-13 is necessary for allergen-induced airway hyperresponsiveness (AHR) [2]. Leukotrienes (LTs), including cysteinyl LTs (CysLTs; these include LTC_4, LTD_4 and LTE_4) and LTB_4, are pivotal biomolecules in the complex network of inflammatory mediators that characterizes allergic airway disease [3–5]. LTs are potent lipid mediators derived from arachidonic acid through the 5-lipoxygenase (5-LO) pathway [3]. Specific enzymes for the synthesis of LTs are present in several types of inflammatory cells and become activated during allergic airway inflammation [3,6].

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CysLTs are released from inflammatory cells that participate in the pathogenesis of allergic rhinitis [5], are elevated in patients with perennial allergic rhinitis [7], and are released following allergen exposure [8]. The $CysLT_1$ receptor, a receptor subtype for CysLTs, is expressed in nasal inflammatory cells and nasal mucosal glands [9], and CysLT administration reproduces the symptoms of allergic rhinitis. Moreover, $CysLT_1$ receptor antagonists reduce the symptoms and signs of allergic rhinitis, reducing nasal allergic inflammation [5]. LTB_4, the main LT formed in the nasal mucosa, is also likely to have a fundamental role in the pathophysiology of allergic rhinitis [10].

LTs have an important pathophysiological role in asthma and allergic rhinitis [3–5]. CysLTs induce pathophysiological responses similar to those associated with asthma, and elevated CysLT concentrations have been detected in biological fluids [e.g. bronchoalveolar lavage (BAL) fluid, sputum and exhaled breath condensate (EBC)] from patients with asthma and in nasal fluids from patients with allergic rhinitis [3,5,7,11]. The CysLTs also have a pivotal role in airway remodeling, which characterizes persistent asthma [12].

Two G protein-coupled receptor subtypes for CysLTs ($CysLT_1$ and $CysLT_2$) have been identified [13,14]. Most of the effects of CysLTs that are relevant to the pathophysiology of asthma are

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mediated by activation of the $CysLT_1$ receptor [3], which is expressed in different types of inflammatory and structural cells in the airways [13,15].

The most convincing evidence for a causative role of CysLTs in asthma comes from the clinical effectiveness of $CysLT_1$ receptor antagonists (e.g. montelukast, zafirlukast and pranlukast) and 5-LO inhibitors (e.g. zileuton) in patients with asthma [4]. Anti-LTs are effective in preventing asthmatic responses induced by allergen-challenge [16], exercise [17] and aspirin [18]. $CysLT_1$ receptor antagonists improve pulmonary function, symptoms and quality of life, and reduce β-agonist use, eosinophilia, asthma exacerbations and the required dose of inhaled glucocorticoids in asthmatic patients [19,20].

$CysLT_1$ receptor antagonism has a significant anti-airway remodeling effect in an animal model of human asthma [21] and inhibitory effects in asthmatic subjects on structural cells that have a central role in airway remodeling [22].

As a potent chemoattractant for neutrophils, LTB_4 can be functionally involved in the neutrophilic inflammation characterizing severe asthma and asthma exacerbations [23], whereas its role in mild-to-moderate persistent asthma is less clear. Elevated LTB_4 concentrations in EBC have been reported in adults and children with stable asthma [24–26]. The lack of effect of LTB_4 receptor antagonists in allergen-induced early- or late-phase airway obstruction in asthmatic patients [27] argues against an important role for LTB_4 in acute bronchoconstriction. However, it is likely that LTB_4 is involved in AHR [3].

Here, we examine the role of LTs in asthma and allergic rhinitis, and the therapeutic implications of the pharmacological modulation of the LT pathway for allergic airway disease.

Biosynthesis and metabolism of LTs

LTs are the products of the 5-LO pathway (Figure 1). Arachidonic acid, which is esterified on plasma membrane phospholipids, is released by the action of different phospholipase A_2 (PLA_2) enzymes and converted into LTA_4, which is subsequently metabolized by LTA_4 hydrolase into LTB_4 and, by LTC_4 synthase or different members of the membrane-associated proteins in the eicosanoid and glutathione metabolism superfamily (MAPEG), such as microsomal glutathione transferase 2, into LTC_4 [6]. This

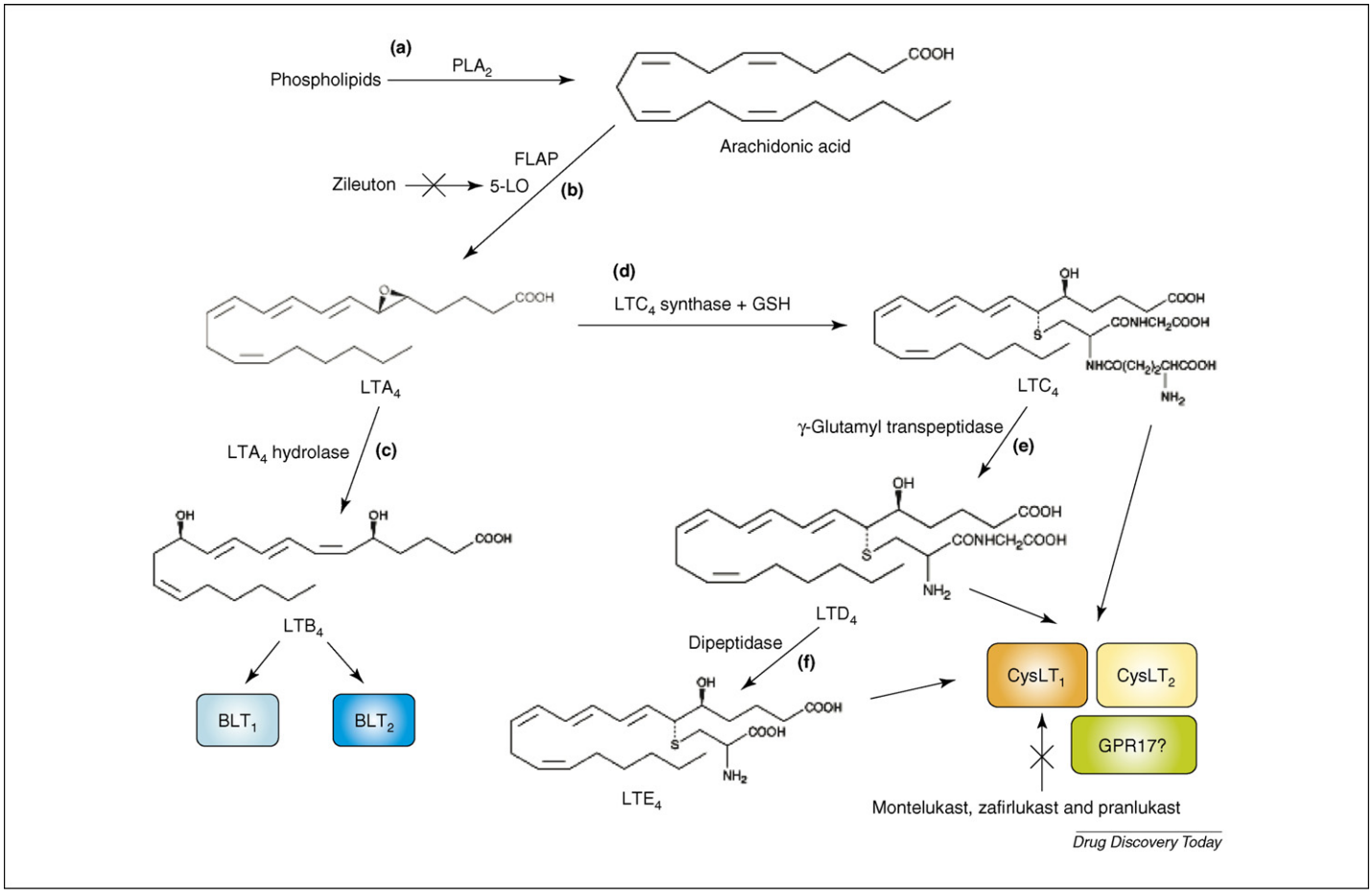

FIGURE 1

Biosynthetic pathway of LTs, LT receptors and mechanisms of action of anti-LT drugs. **(a)** Arachidonic acid, which is esterified on plasma membrane phospholipids, is released by the action of PLA_2 enzymes and converted into LTA_4 through 5-LO activity **(b)** [6]. This reaction requires the FLAP-mediated translocation of 5-LO from the cytosol to the nuclear membrane [3]. LTA_4 is then metabolized by LTA_4 hydrolase into LTB_4 **(c)** and by LTC_4 synthase, which conjugates reduced glutathione (GSH) into LTC_4 **(d)** [6]. This is, in turn, metabolized by a γ-glutamyl transpeptidase into LTD_4 **(e)**, which is then metabolized by a dipeptidase into LTE_4 **(f)**. LTC_4, LTD_4 and LTE_4 are known as CysLTs, which stimulate $CysLT_1$ and $CysLT_2$ receptors [13,14]. The presence of a third receptor subtype for CysLTs, known as GPR17, which responds to CysLTs and to uracil nucleotides, has been hypothesized [289]. LTB_4 activates BLT_1 and BLT_2 receptors [35]. Zileuton is a 5-LO inhibitor, whereas montelukast, zafirlukast and pranlukast are selective $CysLT_1$ receptor antagonists. The role of the $CysLT_2$ receptor is largely unknown, and BLT_1 and BLT_2 receptor antagonists are not yet approved for clinical use. Abbreviations: GPR17, G-protein-coupled receptor-17; GSH, glutathione.

TABLE 1

Expression of LT receptor subtypes, LT biosynthetic pathway enzymes and LT production in different cell types[a]

Cell type	$CysLT_1$ receptor	$CysLT_2$ receptor	BLT_1 receptor	BLT_2 receptor	5-LO	FLAP	LTC_4 Synthase	CysLT production	LTB_4 production
Eosinophils	+	+	–	–	+	+	+	+	+
Basophils	+	+	–	–	+	+	–	+	+
Mast cells	+	+	+	+	+	+	+	+	+
Monocytes	+	–	–	–	+	+	+	+	–
Macrophages	+	–	–	–	+	+	+	+	+
Neutrophils	+	–	–	–	+	+	–	+	+
T lymphocytes	+	–	+	–	–	–	–	+	–
B lymphocytes	+	–	–	–	–	–	–	–	–
Hematopoietic stem cells	+	–	–	–	+	–	–	–	–
Endothelial cells	+	+	–	–	–	–	–	–	–
Glandular cells	+	–	–	–	–	–	–	–	–
Smooth muscle cells	+	–	–	–	–	–	–	–	–
Fibroblasts	+	–	+	–	+	+	+	+	+
Platelets	–	–	–	–	–	–	+	+	+
Erythrocytes	–	–	–	–	–	–	+	+	+
Epithelial cells	–	–	–	–	–	–	+	+	+

[a] +, presence of receptors or enzymes or production; –, absence or lack of evidence of receptors or enzymes or production, to the best of our knowledge.

is metabolized by a γ-glutamyl transpeptidase into LTD_4, which is then metabolized by a dipeptidase into LTE_4. The estimated half-life of the highly reactive LTA_4 is <3 seconds [6]. LTC_4 and its metabolites, LTD_4 and LTE_4, are designated as CysLTs owing to the common cysteine in the side chain. Biosynthesis of LTs requires cellular activation, such as IgE receptor cross-binding on the mast cell surface, and involves a 5-LO-activating protein (FLAP), which binds to 5-LO and facilitates the metabolism of arachidonic acid [3]. The intracellular distribution of 5-LO varies between different cells (Table 1). 5-LO is predominantly expressed in granulocytes, monocytes, macrophages, mast-cells and B lymphocytes [3]. Eosinophils and mast cells can produce large amounts of LTC_4 from an endogenous pool of arachidonic acid. Human bronchial fibroblasts constitutively express 5-LO, FLAP, LTA_4 hydrolase and LTC_4 synthase, and generate CysLTs and LTB_4 spontaneously *in vitro* [28]. Other cells, such as platelets, erythrocytes, endothelial cells and epithelial cells, which do not express 5-LO, can also generate CysLTs and/or LTB_4 through the transcellular metabolism of LTA_4 synthesized by activated neutrophils [6]. After their intracellular formation, CysLTs and LTB_4 are released to the extracellular space through specific carrier proteins, which are potential targets for future anti-LT drugs [3].

Receptors and mechanism of action of LTs

As stated earlier, two G protein-coupled receptor subtypes for CysLTs ($CysLT_1$ and $CysLT_2$) have been identified [13,14] (Figure 1) and, recently, a third receptor was shown to respond to both CysLTs and uracil nucleotides [29]. Most of the effects of CysLTs that are relevant to the pathophysiology of asthma are mediated by activation of the $CysLT_1$ receptor [3], which is expressed in monocytes and macrophages, eosinophils, basophils, mast cells, neutrophils, T cells, B lymphocytes, pluripotent hematopoietic stem cells ($CD34^+$), interstitial cells of the nasal mucosa, airway smooth muscle cells, bronchial fibroblasts and vascular endothelial cells [13,15,28] (Table 1). The $CysLT_2$ receptor is expressed in human peripheral basophils [30], endothelial cells [31], cultured mast cells [14], and in nasal eosinophils and mast cells in patients with active seasonal allergic rhinitis [32] (Table 1). $CysLT_2$ activation might enable the CysLTs to elicit IL-8 generation by human cultured mast cells, potentially leading to neutrophilic inflammation [14], which characterizes acute and severe asthma. $CysLT_2$ receptor expression on eosinophils is increased in patients, especially in nonatopic subjects, during asthma exacerbation, and is upregulated by interferon-γ, indicating a role for this receptor subtype in asthma exacerbations [33]. However, at present, the role of the $CysLT_2$ receptor in allergic inflammation is poorly known [31]. $CysLT_1$ and $CysLT_2$ receptor activation involves an increase in intracellular calcium [13,34], although the complete signal transduction pathway has not yet been established. In murine cell cultures, protein kinase C activity is involved in rapid agonist-dependent internalization and rapid agonist-dependent desensitization [34].

Two subtypes of LTB_4 receptor (BLT_1 and BLT_2), which are expressed in a human mast cell line (HMC-1) [35], have been identified (Figure 1). BLT_1 receptors are expressed in human bronchial fibroblasts [28] and in a subset of effector memory IL-13-producing $CD8^+$ T cells in bronchoalveolar lavage fluid of asthmatic patients [36] (Table 1). The BLT_1 receptor is required for effector $CD8^+$ T cell-mediated, mast cell-dependent AHR in mice [36], indicating a possible role for LTB_4 in AHR.

Biological effects of LTs in the airways

CysLTs induce pathophysiological responses similar to those associated with asthma [3] (Figure 2). CysLTs are the most potent endogenous bronchoconstrictors known. LTC_4, LTD_4 and LTE_4 have similar contractile activity on human airway smooth muscle

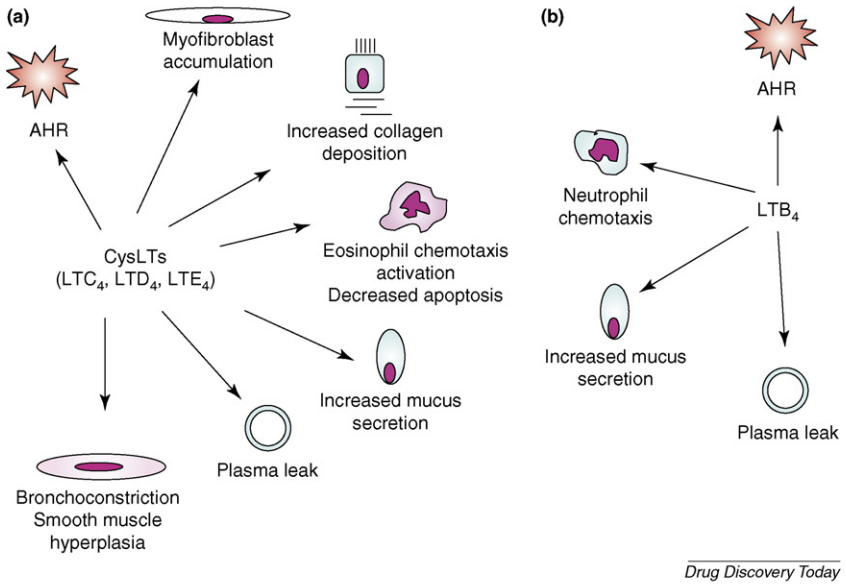

FIGURE 2

Biological effects of CysLTs, including LTC_4, LTD_4 and LTE_4, and LTB_4 in the airways. **(a)** CysLTs have a pathophysiological role in asthma because they are potent bronchoconstrictors, increase AHR, mucus secretion and capillary permeability, cause eosinophil recruitment and activation, and decrease eosinophil apoptosis [3]. CysLTs are also involved in airway remodeling, in that they promote myofibroblast accumulation and airway smooth muscle hyperplasia [12,21,22]. **(b)** LTB_4, a potent chemoattractant for neutrophils, contributes to airway obstruction in asthma, increasing mucus secretion and capillary permeability [3]. LTB_4 is probably involved in the development of AHR [36].

in vitro, and this has been confirmed by bronchoprovocation studies in healthy subjects [3]. Asthmatic patients are hyperresponsive to LTC_4, LTD_4 and LTE_4 inhalation [3]. CysLTs increase microvascular permeability in the lungs in experimental animals and stimulate mucus secretion in isolated animal and human airways [3]. Inhalation of CysLTs in asthmatic patients causes recruitment of eosinophils into the airway mucosa and increases the number of sputum eosinophils [37]. However, the mechanism(s) of the eosinophil chemotactic effect induced by CysLTs need to be clarified. CysLTs reproduce many clinical features of allergic rhinitis, including rhinorrhea and nasal congestion, and increase the responsiveness of nasal sensory nerves to histamine [5].

Asthma and allergic rhinitis are the result of a systemic inflammatory process involving several cell types and mediators in the airways, blood, peripheral lymphoid tissue and bone marrow [4,5]. Apart from their local effect in the airways, CysLTs are multifunctional mediators with a pivotal role in the inflammatory process that characterizes asthma and allergic rhinitis [4,5]. CysLTs: (i) prime progenitor cells to differentiate into mature blood cells and modulate leukopoiesis induced by granulocyte-macrophage-colony-stimulating factor, IL-5 and IL-3; (ii) promote leukocyte migration from the bone marrow into the circulatory system; (iii) are chemoattractant for eosinophils, increasing their cellular adhesion and transendothelial migration across the vessel wall into the airways; (iv) increase eosinophil survival in response to paracrine signals from mast cells and lymphocytes; and (v) activate eosinophils, monocytes, basophils, mast cells and T lymphocytes [4,5]. CysLTs regulate the Th2 cell-dependent inflammatory response, which is a central component of asthma, as shown by the reduced allergen-induced lung inflammation in LTC_4 synthase-null mice [38].

Experimental data support the hypothesis that CysLTs contribute to airway remodeling, which includes the eosinophil cell inflammatory response, mucus gland hyperplasia, mucus hypersecretion, airway smooth muscle cell hyperplasia, and collagen deposition beneath the epithelial layer and in the lung interstitium at sites of leukocyte infiltration [12]. Montelukast has a significant anti-inflammatory effect on allergen-induced lung inflammation and fibrosis in an animal model of the airway remodeling changes observed in patients with persistent asthma [21].

LTB_4 has no bronchoconstrictor effect in healthy or asthmatic subjects [3] but might contribute to airway narrowing, producing local edema and increasing mucus secretion (Figure 2). Being a potent chemoattractant for neutrophils, LTB_4 might be functionally involved in the neutrophilic asthma that is seen most commonly in patients with severe asthma or asthma exacerbations, but its pathophysiological role in mild-to-moderate persistent asthma is less clear. LTB_4 has an essential role in triggering allergic responses in the lungs of mice by activating BLT_1 receptors on a subset of effector CD8+ T cells [36]. The absence or blockade of BLT_1 receptors on these cells markedly reduces AHR and airway inflammation induced by allergen challenge in mice [36]. $CD8^+$/$BLT_1{}^+$ T cells expressing BLT_1 receptors have been identified in BAL fluid and lung tissue from asthmatic subjects but not from healthy subjects [36]. The number of this subset of $CD8^+$ T cells is increased in patients with steroid-resistant asthma compared with those with steroid-sensitive asthma [36]. However, the biological significance of LTB_4-induced activation of effector $CD8^+$ T cells in

TABLE 2

Main pharmacological characteristics of anti-LTs

Drug	Mechanism of action	Indication	Benefits	Side effects	Dose	Comments
Montelukast	$CysLT_1$ receptor antagonism	Asthma, allergic rhinitis	As monotherapy in children with mild persistent asthma; particularly effective in exercise-induced asthma, ASA[a], allergen-induced asthma; as add-on therapy with ICS	Headache, abdominal pain; possible association with Churg–Strauss syndrome	Adults: 10 mg o.d. Children 6–14 years of age: 5 mg o.d. Children 2–5 years of age: 4 mg o.d.	Most widely prescribed $CysLT_1$ receptor antagonist
Pranlukast	$CysLT_1$ receptor antagonism	Asthma, allergic rhinitis	Particularly effective in exercise-induced asthma, ASA, allergen-induced asthma; as add-on therapy with ICS	Abdominal pain, liver enzyme elevations; possible association with Churg–Strauss syndrome	Adults: 225 mg b.i.d.	Only marketed in Asia
Zafirlukast	$CysLT_1$ receptor antagonism	Asthma	Particularly effective in exercise-induced asthma, ASA, allergen-induced asthma; as add-on therapy with ICS	Headache, abdominal pain, liver enzyme elevations; possible association with Churg–Strauss syndrome	Children $\geq$12 years of age and adults: 20 mg b.i.d. Children 5–11 years of age: 10 mg b.i.d.	First $CysLT_1$ receptor antagonist to be approved; food and drug interactions
Zileuton	5-LO inhibition	Asthma	Particularly effective in exercise-induced asthma and ASA	Headache, abdominal pain; liver enzyme elevations	Adults and children 12 years of age and older: 600 mg q.i.d.	Virtually abandoned because of poor compliance and hepatic toxicity

[a] Abbreviations: ASA, aspirin-sensitive asthma; ICS, inhaled corticosteroids.

asthmatic patients needs to be established. A role for LTB_4 in AHR is also suggested by the fact that chronic treatment with zileuton, which decreases both CysLT and LTB_4 production, significantly reduces AHR in asthmatic patients [10,39] concomitantly with a reduction in *ex vivo* LTB_4 production [39], whereas selective $CysLT_1$ antagonists have a modest effect on AHR [4,40]. LTB_4 is likely to have a central role in nasal symptoms in aspirin-sensitive asthma (ASA) because 5-LO inhibition is effective in causing chronic improvement in nasal function in aspirin-intolerant asthmatics at baseline [10], whereas $CysLT_1$ receptor antagonists, which significantly reduce bronchospastic reactions, have only minor effects on ASA-induced upper airway reactions [41].

Measurement of LTs in biological fluids in subjects with allergic airway disease

LTs have been measured in the urine [42], sputum [43] and BAL fluid [44] in asthmatic patients. Urinary measurement of LTE_4, the most abundant CysLT excreted in the urine, is generally used for assessing the systemic synthesis of CysLTs because circulating concentrations of LTs are below the detection limit of most assays [42]. No or small differences have generally been reported in baseline urinary LTE_4 levels between healthy and atopic asthmatic subjects under basal conditions [42]. By contrast, urinary LTE_4 excretion is elevated after allergen challenge in atopic asthmatics [3,42] in aspirin-sensitive asthmatics under basal conditions [45], in patients with nocturnal asthma [44], during asthma exacerbations [46] and in severe asthma [47]. Measurement of LTs in BAL fluid, sputum and EBC is more likely to reflect pulmonary synthesis of LTs. Sputum CysLT concentrations are elevated in asthmatic patients, reflecting disease severity [43]. LT concentrations are increased in BAL fluid in asthmatic subjects, including those with nocturnal asthma [44]. There are several reports of increased LT levels in EBC in both adults and children with asthma [11,24–26,48,49], but the methodology is new and further studies are required [26].

Patients with seasonal allergic rhinitis during seasonal allergen exposure [32] and with perennial allergic rhinitis [5] have elevated CysLT concentrations in nasal lavage fluids. CysLT levels in nasal lavage in rhinitis patients are increased after allergen challenge, depend on seasonal allergen exposure and are correlated with symptoms [5]. Expression of LT pathway enzymes is increased during allergen exposure in nasal biopsies of patients with seasonal allergy [50]. Nasal fluid LTB_4 levels are increased after nasal provocation in allergic rhinitis patients [51].

Effects of anti-LTs in asthma and allergic rhinitis

Anti-LTs that have been approved for clinical use in asthma include selective $CysLT_1$ receptor antagonists (montelukast, zafirlukast and pranlukast) and zileuton, a 5-LO inhibitor (Table 2). Montelukast is the most prescribed $CysLT_1$ receptor antagonist in Europe and the USA, whereas pranlukast is only marketed in Japan and other Asian countries. Montelukast and pranlukast are also registered for rhinitis [3]. Unlike montelukast, zafirlukast, the first anti-LT to be approved in Europe, has possible food and drug interactions, and requires twice daily administration [3]. The observation that $CysLT_1$ receptor antagonists and 5-LO inhibitors had similar efficacy in short-term treatment studies and challenge models led to the conclusion that most of the antiasthmatic effects of anti-LTs are due to $CysLT_1$ antagonism [3]. At present, the use of zileuton, which is commercially available in the USA, is limited because of a small, but distinct, incidence of hepatic enzyme elevation that is not observed with montelukast [3]. Moreover, zileuton has a short half-life, requiring four daily administrations [3].

However, there are at least two aspects of selective 5-LO inhibitors related to LTB_4 synthesis inhibition that require further

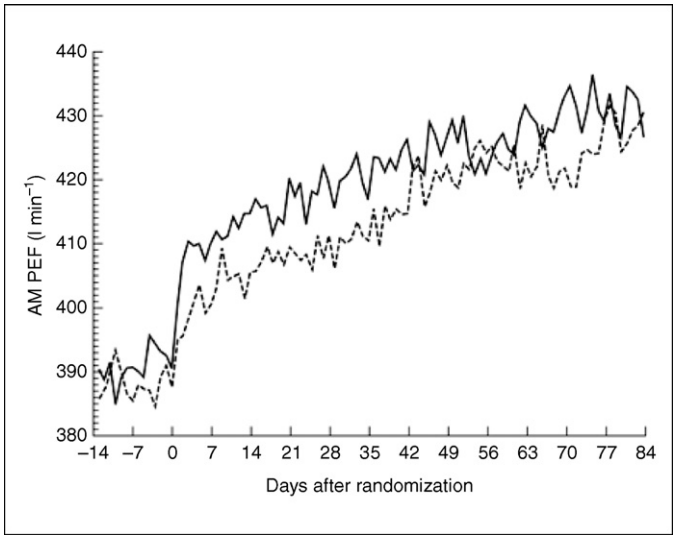

FIGURE 3

Morning peak expiratory flow (AM PEF) during 12 weeks of treatment with oral montelukast (10 mg once daily) plus inhaled budesonide (800 μg daily; unbroken line) or inhaled budesonide (1600 μg daily; dashed line) in adults with asthma inadequately controlled on inhaled budesonide at a dose of 800 μg daily. Data represent the mean AM PEF values over multiple patients measured before administration of the study medication [19]. Reproduced, with permission, from Ref. [19].

investigation: (i) their effect on AHR in asthmatic patients [10,39], which is slightly affected by $CysLT_1$ antagonists [4]; (ii) the potential therapeutic role of these drugs in rhinitis and rhinopolyposis in light of their high efficacy in reducing nasal symptoms in patients with ASA [10].

$CysLT_1$ receptor antagonists improve lung function and symptoms, and reduce the use of rescue β_2 bronchodilators, exacerbation rate, and airway and blood eosinophilia in adults and children with asthma of varying severity [3,4]. Cys-LT_1 receptor antagonists provide a prompt improvement in asthma control (Figure 3), although the group mean effects of inhaled glucocorticoids after a few weeks of therapy is greater [19]. Intravenous montelukast (7 or 14 mg) improves forced expiratory volume in one second (FEV_1) when added to standard therapy in adults with acute asthma, suggesting a possible indication for $CysLT_1$ receptor antagonists in severe asthma exacerbations [52]. $CysLT_1$ receptor antagonists inhibit early and late asthmatic responses induced by allergen inhalation [16,53]. In contrast to budesonide, montelukast attenuates the maximal early asthmatic response, whereas both drugs are effective on the late asthmatic response [16]. However, inhaled glucocorticoids reduce allergen-induced AHR to a greater extent than do anti-LTs [16]. AHR is multifactorial and relatively independent of the acute, LT-mediated inflammatory response. Inhaled glucocorticoids inhibit several airway inflammatory cells and mediators that are pivotal in the pathogenesis of AHR, whereas anti-LTs selectively block LT-mediated eosinophilic inflammation [16]. $CysLT_1$ receptor antagonists are also effective in allergen-induced asthma in children [54]. Treatment with montelukast (10 mg once daily) protects against exercise-induced bronchoconstriction over a 12-week period in asthmatic adults [17]. $CysLT_1$ receptor antagonists reduce the maximal decrease in FEV_1, the time to recovery from the maximal decrease in FEV_1 and the area under the FEV_1 versus time curve after exercise [17]. These effects are observed as soon as two hours after a single oral dose of montelukast (10 mg) and persist up to 24 hours [55]. The effect of montelukast is greater than that of salmeterol in the chronic treatment of exercise-induced bronchoconstriction over a period of eight weeks in adults with mild asthma, as demonstrated by effect size, maintenance of effect and fewer adverse events during the study period [56]. Likewise, $CysLT_1$ receptor antagonists protect against exercise-induced bronchoconstriction in children [57]. $CysLT_1$ antagonism and 5-LO inhibition prevent the fall in FEV_1 in response to aspirin challenge [3] and improve asthma control in aspirin-sensitive patients over and above the therapeutic response to glucocorticoids independently of baseline urinary LTE_4 [10,18].

Some aspects of the clinical pharmacology of $CysLT_1$ receptor antagonists should be emphasized: (i) their role as monotherapy in patients with asthma; (ii) their efficacy and the possibility of steroid tapering as add-on therapy; (iii) the variability in their therapeutic response; (iv) their potential effect on airway remodeling; (v) their tolerability.

In the USA, monotherapy with $CysLT_1$ receptor antagonists is a common therapeutic option for patients with intermittent asthma, whereas in Europe, it is limited to montelukast in 2–5-year-old children, although anti-LTs are less effective than inhaled glucocorticoids as first-line agents [58].

In Europe, $CysLT_1$ receptor antagonists are currently indicated for preventing exercise-induced bronchoconstriction and as add-on therapy in asthmatic patients not sufficiently controlled by inhaled glucocorticoids alone [3]. In these patients, the addition of

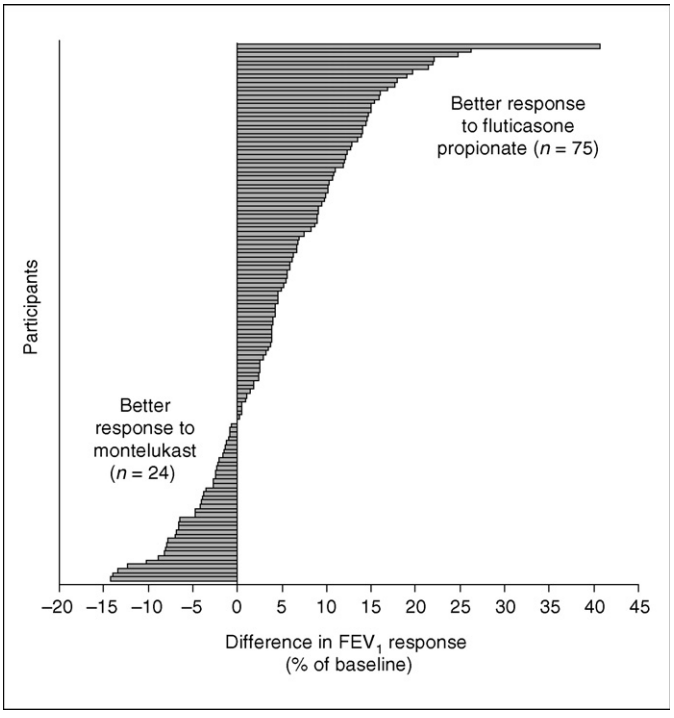

FIGURE 4

Difference in FEV_1 response between inhaled fluticasone proprionate (100 μg twice daily) and oral montelukast (5 mg once daily) for children with mild-to-moderate asthma. Each line designates a single participant [58]. The 'zero' point does not represent zero benefit, but rather equal response to fluticasone and montelukast; the negative numbers indicate a stronger response to montelukast. Reproduced, with permission, from Ref. [58].

montelukast to a constant dose of inhaled budesonide improves asthma control [59], to a level comparable to that achieved by doubling the dose of budesonide [19]. This might reduce the risk of side effects due to long-term administration of high-dose inhaled glucocorticoids [19]. In patients whose symptoms remain uncontrolled with inhaled fluticasone, the addition of montelukast can be taken into consideration [60], although the addition of a long-acting β_2-agonist is generally superior to a $CysLT_1$ receptor antagonist for preventing exacerbations requiring systemic steroids, and for improving lung function, symptoms and the use of rescue β_2 agonists [61].

Add-on therapy with $CysLT_1$ receptor antagonists enables a reduction in the dose of inhaled glucocorticoids required to control asthma with an equivalent therapeutic response (Figure 3) [19,62]. The rationale for combining inhaled glucocorticoids and $CysLT_1$ receptor antagonists in asthmatic patients is based on the relative steroid resistance of the LT pathway [63]. AHR to LTD_4, and urinary LTE_4 concentrations in adults with mild asthma were not affected by inhaled fluticasone (500 μg b.i.d. for two weeks) [63]. After treatment with inhaled fluticasone (100 μg b.i.d. for four weeks), LTE_4 concentrations in EBC in children with intermittent and mild persistent asthma were reduced by 18% [25].

Taken together, this evidence indicates that neither the biosynthesis nor the actions of LTs seem to be sensitive to inhaled glucocorticoids [63]. There is variability in the therapeutic response to LT receptor antagonists as well as to inhaled glucocorticoids in both adults and children with asthma [20,58] (Figure 4). Identification of responders to LT receptor antagonists and/or inhaled glucocorticoids might have important clinical implications, given the importance of considering an individualized approach to asthma management and assessment rather than a strategy directed to the best outcome in a group of patients [58]. Some phenotypic characteristics, including higher exhaled nitric oxide concentrations, total eosinophil counts, serum IgE and eosinophil cationic protein levels and lower levels of pulmonary function, are associated with a favorable response to fluticasone in asthmatic children [58]; a favorable response to montelukast is associated with younger age, shorter disease duration [58] and, possibly, elevated LTE_4 levels in EBC [11]. Studies on biomolecule profiles in biological fluids and genetic polymorphisms of 5-LO cascade and CysLT receptors could help to predict the therapeutic response to $CysLT_1$ receptor antagonists.

In an animal model of human asthma, $CysLT_1$ receptor antagonists not only prevent allergen-induced airway changes, but also reverse structural changes such as airway smooth muscle cell layer thickening and subepithelial fibrosis, which are not affected by glucocorticoid treatment [21]. These findings could provide new insight into the pathophysiology of airway remodeling and have important implications for the management of patients with asthma because they might clarify the role of $CysLT_1$ receptor antagonists in the treatment of these patients. A reduction in basal membrane thickening [64] and subepithelial collagen deposition [65] has also been reported with inhaled glucocorticoids, although these effects seem to have little impact on the clinical evolution of asthma [66]. One biopsy study has shown that montelukast (10 mg once daily for eight weeks) reduces myofibroblast accumulation in the airways of asthmatic individuals following low-dose allergen challenge [22]. However, more studies are required to determine whether $CysLT_1$ receptor antagonists prevent airway remodeling and/or reverse established airway structural changes in patients with asthma.

LT receptor antagonists are generally well tolerated, with headache and gastric discomfort being the most common side effects [3]. An initial worry that $CysLT_1$ antagonism specifically might trigger Churg–Strauss syndrome has been excluded [3].

$CysLT_1$ receptor antagonists improve symptoms in patients with perennial and seasonal allergic rhinitis [67,68]. Although $CysLT_1$ receptor antagonists are less effective than nasally inhaled glucocorticoids as monotherapy, their combination with antihistamines generally provides a similar therapeutic response to inhaled glucocorticoids alone [5]. By antagonizing the effects of relevant pathophysiological mediators in the airways, oral administration of $CysLT_1$ receptor antagonists provides a single therapeutic approach to asthma and allergic rhinitis, potentially increasing the efficacy and reducing the number of side effects compared with increasing the dose of inhaled glucocorticoids alone for asthma therapy [19]. The fact that a combination of oral montelukast and inhaled budesonide is more effective than a double dose of inhaled budesonide alone in asthmatic patients with concomitant allergic rhinitis supports the validity of this therapeutic strategy [69].

Conclusions

Most of our knowledge of the pathophysiological role of LTs in allergic airway disease is currently limited to $CysLT_1$ receptor-mediated effects, whereas the role of the $CysLT_2$ receptor still remains to be clarified. $CysLT_1$ receptor antagonists provide a therapeutic alternative to glucocorticoids in patients with allergic airway disease. In combination with inhaled glucocorticoids, $CysLT_1$ receptor antagonists improve asthma control and enable the dose of inhaled glucocorticoids to be reduced while maintaining similar efficacy. Identifying those subjects who are more likely to respond to $CysLT_1$ receptor antagonists might be relevant for a more rational therapy of patients with asthma and allergic rhinitis. The potential effect of $CysLT_1$ receptor antagonists in preventing and reversing airway remodeling, as well as the role of LTB_4 in allergic airway disease, requires further study.

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