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REVIEW

# Leukotriene modifiers for asthma treatment

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**Summary**

Leukotrienes (LTs), including cysteinyl LTs (CysLTs) and $LTB_4$, are potent lipid mediators that have a role in the pathophysiology of asthma. At least two receptor subtypes for CysLTs, $CysLT_1$ and $CysLT_2$, have been identified. The activation of the $CysLT_1$ receptor is responsible for most of the pathophysiological effects of CysLTs in asthma, including increased airway smooth muscle activity, microvascular permeability, and airway mucus secretion. $LTB_4$ might have a role in severe asthma, asthma exacerbations, and the development of airway hyperresponsiveness. $CysLT_1$ receptor antagonists can be given orally as monotherapy in patients with mild persistent asthma, but these drugs are generally less effective than inhaled glucocorticoids. Combination of $CysLT_1$ receptor antagonists and inhaled glucocorticoids in patients with more severe asthma may improve asthma control and enable the dose of inhaled glucocorticoids to be reduced while maintaining similar efficacy. The identification of subgroups of asthmatic patients who respond to $CysLT_1$ receptor antagonists is relevant for asthma management as the response to these drugs is variable. $CysLT_1$ receptor antagonists have a potential anti-remodelling effect that might be important for preventing or reversing airway structural changes in patients with asthma. This review discusses the role of LTs in asthma and the role of LT modifiers in asthma treatment.

## Introduction

Leukotrienes (LTs), including cysteinyl LTs (CysLTs) ($LTC_4$, $LTD_4$, and $LTE_4$) and $LTB_4$, are potent lipid mediators that derive from arachidonic acid through the 5-lipoxygenase (5-LO) pathway [1–5]. The pathway for the complete synthesis of CysLTs is highly expressed in several types of inflammatory cells and becomes activated during allergic airway inflammation [3, 5]; other cell types like platelets and endothelial cells, while lacking the complete synthetic pathway, can produce CysLTs from the chemically reactive intermediate $LTA_4$ via mechanisms of intercellular transfer [5].

LTs have a central role in asthma [1–4, 6], but their importance may vary among asthmatic patients. CysLTs induce a variety of pathophysiological responses that contribute to asthma, while the role of $LTB_4$ in disease expression may be more restricted.

This review will examine the role of LTs in asthma and the therapeutic implications of LT pathway inhibition for asthma.

## Biosynthesis and metabolism of leukotrienes

LTs derive from the enzymatic activity of 5-LO (Fig. 1). Arachidonic acid, esterified in plasma membrane phospholipids, is cleaved by the action of various phospholipase $A_2$ isoenzymes and the released fatty acid is transformed by 5-LO into $LTA_4$. This LT is subsequently metabolized by $LTA_4$ hydrolase into $LTB_4$ and by $LTC_4$ synthase or other members of the membrane-associated proteins in eicosanoid and glutathione metabolism (MAPEG) superfamily, including microsomal glutathione transferase 2, into $LTC_4$ [5]. This, in turn, is metabolized by a γ-glutamyl transpeptidase into $LTD_4$, which is then cleaved by a dipeptidase to $LTE_4$. The highly reactive $LTA_4$ has an estimated half-life of $< 3$ s [5]. $LTC_4$, $LTD_4$ and $LTE_4$ are known as CysLTs due to the common cysteine in the side chain. Initiation of LT biosynthesis requires cellular activation of phospholipase $A_2$ and 5-LO by stimuli including IgE receptor cross-linking on mast cells, and also involves the five-lipoxygenase-activating protein (FLAP) that binds and facilitates the transfer of arachidonic acid to 5-LO [2, 3, 5]. The intracellular compartmentalization of 5-LO varies between different cell types. 5-LO is mainly expressed in granulocytes, monocytes, macrophages, and mast cells [3]. Eosinophils and mast cells can produce large amounts of $LTC_4$ from an endogenous pool of arachidonic acid. Human bronchial fibroblasts, that constitutively express 5-LO, FLAP, $LTA_4$ hydrolase, and

$LTC_4$ synthase, produce CysLTs and $LTB_4$ *in vitro* [7]. However, fibroblasts and other structural cells have a lower capacity for LT synthesis than do leucocytes [1]. Cells that do not express 5-LO, including platelets, erythrocytes, and endothelial cells can also produce CysLTs and/or $LTB_4$ through the transcellular metabolism of $LTA_4$ synthesized by activated neutrophils [5]. After their intracellular formation, CysLTs and $LTB_4$ are released to the extracellular space through specific carrier proteins that are potential targets for new anti-LT drugs [3].

### Receptors, mechanism of action, and biological effects of leukotrienes in the airways

Two G-protein coupled receptor subtypes for CysLTs ($CysLT_1$ and $CysLT_2$) have been identified [8, 9] (Fig. 1). Evidence supporting the existence of other CysLT receptors is growing rapidly [10–14]. In mice lacking $CysLT_1$ and $CysLT_2$ receptors, $LTE_4$ increases vascular permeability, suggesting the existence of a third CysLT receptor that responds preferentially to $LTE_4$ [10]. In sensitized mice, intranasal $LTE_4$ potentiates pulmonary inflammation in response to low-dose aerosolized antigen [12]. This effect persists in mice lacking both $CysLT_1$ and $CysLT_2$ receptors but not in mice lacking $P2Y_{12}$ receptors, indicating that the $P2Y_{12}$ receptor is required for pro-inflammatory effects of $LTE_4$ [12]. Although $LTE_4$ has little activity at $CysLT_1$ and $CysLT_2$ receptors [13], inhalation of $LTE_4$ increases airway inflammatory cells [15, 16] and airway hyperresponsiveness (AHR) in asthmatic patients [17], particularly in those with aspirin-sensitive asthma (ASA) [13]. A G-protein-coupled receptor (GPCR) GPCR17, that responds both to CysLTs and uracil nucleotides [14], is a ligand-independent, constitutive negative regulator for the $CysLT_1$ receptor at the cell membrane [11]. GPR17 negatively regulates $CysLT_1$ receptor-mediated inflammation in the lung following intranasal sensitization and challenge with the house dust mite in mice [18]. Many of the effects of CysLTs that are relevant to the pathophysiology of asthma are mediated by the activation of the $CysLT_1$ receptor [1, 2], which is expressed in mast cells, monocytes, and macrophages, eosinophils, basophils, neutrophils, T and B lymphocytes, pluripotent haemopoietic stem cells ($CD34^+$), airway smooth muscle cells, bronchial fibroblasts, and vascular endothelial cells [7, 8, 19]. The $CysLT_2$ receptor is expressed in human peripheral basophils [20], endothelial cells [21], cultured mast cells [9], in peripheral blood eosinophil from patients with asthma [22], and in nasal mast cells and eosinophils in patients with active seasonal allergic rhinitis (AR) [23]. In human cultured mast cells, $CysLT_2$ activation induces IL-8 synthesis that may promote neutrophilic inflammation [9], a characteristic of acute and severe asthma. The role of the $CysLT_2$ receptor in acute asthma, and more generally in allergic airway inflammation is currently largely unknown. The development of selective $CysLT_2$ antagonists [24] should facilitate its elucidation. $CysLT_1$ and $CysLT_2$ receptor activation triggers increased intracellular calcium [8, 25], but the complete signal transduction pathway from each receptor is incompletely understood.

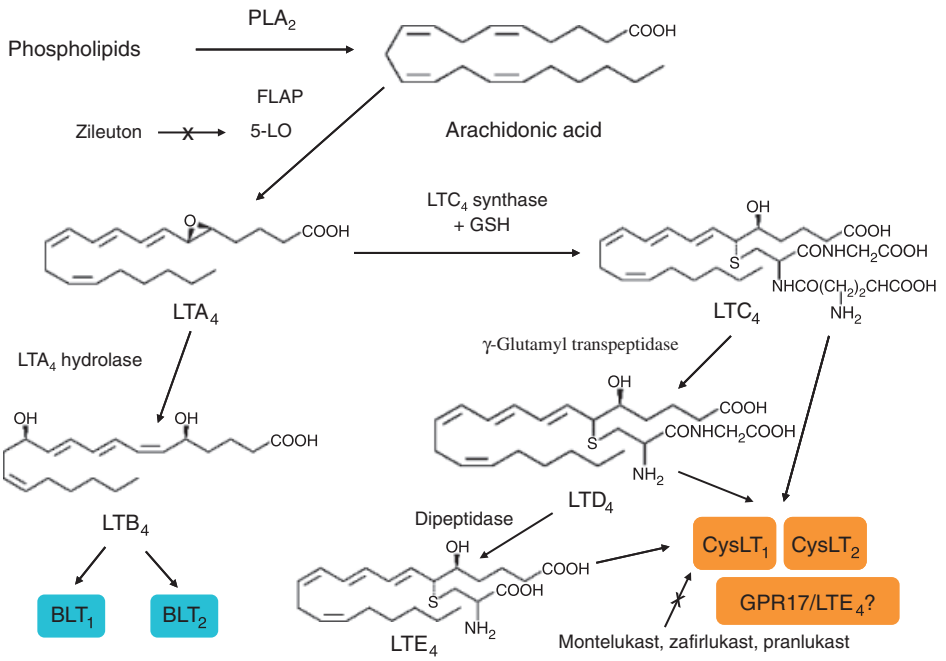


**Fig. 1.** Biosynthetic pathway of leukotrienes (LTs), LT receptors, and mechanisms of action of anti-LT drugs (modified with permission from Montuschi et al. [2]). CysLT, cysteinyl leukotrienes; FLAP, five-lipoxygenase-activating protein; GSH, glutathione; 5-LO = 5-lipoxygenase; $PLA_2$, phospholipase $A_2$.

Two $LTB_4$ receptor subtypes ($BLT_1$ and $BLT_2$), that like $CysLT_1$ and $CysLT_2$ are cell-surface G protein-coupled seven transmembrane domain receptors, have been identified [26, 27]. Both receptor subtypes are expressed in a human mast cell line (HMC-1) [28]. $BLT_1$ receptors are expressed in human bronchial fibroblasts [7], neutrophils, and monocytes/macrophages [29]. A subset of $CD8^+$ T cells expressing $BLT_1$ receptors have been identified in BAL and lung tissue from patients with asthma, but not from healthy subjects [30]. $BLT_1$ expression on Ag-primed T cells [30] and dendritic cells [31] is required for the development of AHR in mice. The absence of $BLT_1$ receptors or their antagonism on these cells markedly reduces allergen challenge-induced AHR and airway inflammation in mice [30–32]. Taken together, these data suggest a possible role for $LTB_4$ in AHR and allergic airway inflammation in asthmatic patients. Glucocorticoids upregulate $BLT_1$ expression on corticosteroid-resistant inflammatory cells including neutrophils, monocytes, and effector memory $CD8^+$ T cells [29, 33]. The number of $CD8^+$ T cells is increased in patients with steroid-resistant asthma compared with those with steroid-sensitive asthma [30]. This corticosteroid-resistant $LTB_4/BLT_1$ pathway may contribute to the development of inflammation in allergic diseases that do not respond to glucocorticoids [29], including steroid-resistant asthma for which the inhibition of this pathway might have a therapeutic benefit. However, the biological significance of $LTB_4$-induced activation of effector $CD8^+$ T cells in asthmatic patients is yet to be established. The lack of effect of $LTB_4$ receptor antagonists in allergen-induced early or late-phase airway obstruction in asthmatic patients [34] argues against an important role for $LTB_4$ in acute bronchoconstriction. A possible contribution of $BLT_2$ to airway inflammation and asthma is beginning to be appreciated [35]. $LTB_4$ is a physiologically relevant peroxisome proliferator-activated receptor (PPAR) activator in cells of the immune system [36]. PPAR-$\alpha$ activation, a direct effect of intracellularly generated $LTB_4$ binding to the nuclear receptor and not of secreted $LTB_4$ acting through its cell-surface receptors [36], reduces levels of $LTB_4$ by stimulating its degradation, thereby limiting the pro-inflammatory effects of $LTB_4$ [36].

CysLTs induce pathophysiological responses similar to those that are observed in patients with asthma [1–3]. $LTC_4$, $LTD_4$, and $LTE_4$, the most potent endogenous bronchoconstrictors, have similar contractile activity on human airway smooth muscle *in vitro*, an effect that has been confirmed by bronchoprovocation studies in healthy subjects [3]. Patients with asthma are hyperresponsive to inhalation of $LTC_4$, $LTD_4$, and $LTE_4$ [3]. CysLTs are elevated in adults and children with exercise-induced bronchoconstriction (EIB) [37, 38]. CysLTs increase pulmonary microvascular permeability in experimental animals and increase mucus secretion in isolated animal and human airways [3]. These effects can contribute to bronchial obstruction in patients with asthma. CysLT inhalation in asthmatic patients increases sputum eosinophil counts and induces the recruitment of eosinophils into airway mucosa [39]. However, the role of direct vs. indirect mechanisms in the eosinophil chemotactic effect of CysLTs remains to be completely defined.

In addition to their local airway effects, CysLTs exert several effects that contribute to the inflammatory process that characterizes asthma [4, 40]. CysLTs (1) modulate leukopoiesis induced by granulocyte–macrophage colony-stimulating factor, IL-5, and IL-3 and prime progenitor cells to differentiate into mature blood cells; (2) cause leucocyte migration from the bone marrow into the circulatory system; (3) induce chemotaxis of eosinophils, increasing their cellular adhesion and transendothelial migration into the airways; (4) increase eosinophil survival in response to mast cell and lymphocyte paracrine signals; and (5) activate mast cells, eosinophils, T lymphocytes, monocytes, and basophils [4, 40]. CysLTs have a central role in pulmonary inflammation induced by allergen challenge, as reflected by the reduced $Th_2$ cell-dependent inflammatory response in $LTC_4$ synthase null mice [41].

CysLTs might participate in the process of airway remodelling that includes eosinophilic inflammation, airway smooth muscle cell hyperplasia, mucus gland hyperplasia, mucus hypersecretion, and collagen deposition beneath the epithelial layer and in the lung interstitium at sites of leucocyte infiltration [42].

$LTB_4$ may contribute to airway narrowing by producing local oedema and increasing mucus secretion, although $LTB_4$ has no bronchoconstrictor effect in healthy subjects and patients with asthma [2, 3]. $LTB_4$ might be functionally involved in the neutrophilic phenotype of asthma that characterizes patients with severe asthma [43] or asthma exacerbations due to its potent chemoattractant activity for neutrophils. $LTA_4$ hydrolase inhibition attenuates allergic airway inflammation and AHR in a mast cell-dependent murine model of allergic airway inflammation [44]. Persistently elevated plasma $LTB_4$ concentrations in children 1 month after an asthma exacerbation [45], and elevated $LTB_4$ concentrations in EBC in adults with mild asthma [46] and children with mild-to-moderate persistent asthma [47], could indicate a pathophysiological role of $LTB_4$ in persistent asthma of lesser severity [48]. However, the pathophysiological role of $LTB_4$ in asthma is not completely defined and requires further studies. Selective $CysLT_1$ receptor antagonists have only a modest inhibitory effect on AHR [4, 49]. By contrast, a possible role for $LTB_4$ in AHR is suggested by the fact that chronic treatment with zileuton, which reduces the synthesis of both CysLTs and $LTB_4$, decreases AHR in asthmatic patients [50, 51] concomitant with a reduction of *ex vivo* $LTB_4$ production [51]. Unlike $CysLT_1$ receptor antagonism [52], 5-LO inhibition is very effective in promoting chronic improvement in nasal function in patients with ASA at baseline [50]. These data suggest that $LTB_4$ may have a pathophysiological role in the nasal manifestations of ASA. Alternatively, or

additionally, nasal symptoms in patients with ASA could be due to activation of $CysLT_2$ receptors or distinct $LTE_4$ receptors [10–14], which are not blocked by $CysLT_1$ receptor antagonists.

### Measurement of leukotrienes in biological fluids in patients with asthma

LTs have been measured in EBC [46, 47, 53–61], sputum [55, 62, 63], BAL fluid [64], and urine [65–67] in patients with asthma. Several studies reported increased LT concentrations in EBC in both adults and children with asthma [46, 47, 53–61], but this methodology requires standardization [56, 68, 69]. Sputum CysLT concentrations are elevated in asthmatic patients, reflecting asthma severity [63]. LT concentrations are increased in BAL fluid in patients with asthma, including those with nocturnal asthma [64]. Measurement of LTs in BAL fluid, sputum, and EBC is likely to reflect pulmonary synthesis of these mediators.

Urinary measurement of $LTE_4$, the stable end-metabolite of CysLTs and therefore the most abundant CysLT excreted in the urine, is used for assessing the systemic synthesis of CysLTs, because circulating concentrations of LTs are usually undetectable [65]. No or slight differences have generally been reported in urinary $LTE_4$ concentrations between healthy and atopic asthmatic subjects under basal conditions [65]. By contrast, urinary $LTE_4$ excretion is elevated after allergen challenge in atopic patients with asthma [3, 65], in aspirin-sensitive asthmatics under basal conditions [66, 70], in patients with nocturnal asthma [64], in severe asthma [71], and during asthma exacerbations [67].

### The effects of leukotriene modifiers in asthma

Selective $CysLT_1$ receptor antagonists that have been approved for clinical use in asthma include montelukast, zafirlukast, and pranlukast. Zileuton, a 5-LO inhibitor, has been approved for the prevention and chronic treatment of asthma in adults and children 12 years of age and older in the United Kingdom and United States. FLAP inhibitors such as MK-886 [72], MK-0591 [73], and veliflapon (BAY-X-1005, DG-031) [74] were shown to be effective in clinical trials with patients with asthma in the mid-1990s, but, unlike $CysLT_1$ receptor antagonists, these compounds were not marketed [75]. Novel FLAP inhibitors including 2190914 (AM-103) [76, 77] and GSK-2190915 have entered phase II trials for the treatment of asthma [75].

Montelukast is the most prescribed $CysLT_1$ receptor antagonist in Europe and North America, whereas pranlukast is only marketed in Japan and other Asian countries. Zafirlukast was the first anti-LT that was approved in Europe, but it is not frequently prescribed due to possible food and drug interactions, and the twice-daily administration regimen [2, 3]. Selective $CysLT_1$ receptor antagonists and 5-LO inhibitors appear to have similar efficacy in short-term treatment studies and challenge models, suggesting that most of the anti-asthmatic effects of anti-LTs are due to $CysLT_1$ antagonism [3]. However, the strength of this assumption is limited by the lack of direct comparisons of the two classes of agents in large patient populations. The use of zileuton has been limited by a modest but distinct incidence of hepatic enzyme elevation that is not observed with montelukast, and its short half-life, which initially demanded four times daily administration [3]. A twice-daily controlled-release formulation of zileuton was subsequently approved by the Food and Drug Administration (FDA) [1].

At least two properties of selective 5-LO inhibitors that distinguish them from $CysLT_1$ receptor antagonists deserve emphasis and further investigation: (1) their greater effects on AHR in asthmatic patients than those of $CysLT_1$ receptor antagonists [4]; and (2) their greater efficacy in reducing nasal symptoms in patients with ASA [50].

$CysLT_1$ receptor antagonists improve symptoms and lung function, and reduce exacerbation rate, the use of $\beta_2$ bronchodilators, and airway and blood eosinophilia in adults and children with asthma of varying severity [1–4]. In patients with persistent asthma who are undertreated and remain symptomatic while taking short-acting $\beta_2$-agonists alone, $CysLT_1$ receptor antagonists provide a prompt improvement in asthma control, although low-dose inhaled glucocorticoids are generally more effective than $CysLT_1$ receptor antagonists as first-line maintenance therapy [78].

As add-on therapy, LTRAs are effective for acute asthma [79, 80]. When added to standard therapy in adults with asthma exacerbations, intravenous montelukast (7 mg) significantly improves airway obstruction throughout the 2 h after administration, with the onset of action as early as 10 min, indicating a possible therapeutic role for $CysLT_1$ receptor antagonists in severe acute asthma [79, 80]. However, the utility of oral montelukast in this setting has not been studied and intravenous formulation is not being clinically developed at present.

$CysLT_1$ receptor antagonists are effective in reducing early and late asthmatic responses induced by allergen inhalation [81, 82]. Unlike budesonide, montelukast inhibits the maximal early asthmatic response, whereas both drugs attenuate the late asthmatic response [81]. However, anti-LTs reduce allergen-induced AHR to a lesser extent than do inhaled glucocorticoids [81]. This could be explained by the fact that AHR is multifactorial and relatively independent of the acute inflammatory response mediated by LTs. Moreover, inhaled glucocorticoids inhibit numerous airway inflammatory cells and mediators that are pivotal in the AHR pathophysiology, whereas anti-LTs selectively block LT-mediated eosinophilic inflammation [81]. However, while the anti-inflammatory effects of glucocorticoids are undoubtedly broader than those of anti-LTs, effects of anti-LTs may be unexpectedly pleiotropic, in part via their ability to exert indirect

inhibitory effects on the synthesis or actions of cytokines [1, 40]. $CysLT_1$ receptor antagonists are also effective in reducing allergen-induced asthmatic response in children [83].

In Europe, $CysLT_1$ receptor antagonists are currently indicated for preventing EIB [3]. Montelukast given at a dose of 10 mg once daily protects against exercise-induced bronchconstriction over a 12-week period in adults with asthma [84]. Treatment with $CysLT_1$ receptor antagonists reduces the time to recovery from the maximal decrease in forced expiratory volume in 1 s ($FEV_1$), the maximal decrease in $FEV_1$, and the area under the $FEV_1$ vs. time curve after exercise [84]. These effects are observed as soon as two hours after a single oral dose of montelukast (10 mg) and are maintained up to 24 h [85, 86]. Montelukast is more effective that salmeterol in the chronic treatment of EIB over a period of 8 weeks in adults with mild asthma, as demonstrated by effect size, persistence of effect and higher tolerability during the study period [87]. $CysLT_1$ receptor antagonists are effective in EIB in children [88], although generally less effective than inhaled glucocorticoids in children with EIB with persistent asthma [89].

$CysLT_1$ receptor antagonism and 5-LO inhibition protect against the reduction 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, an effect that is independent of the baseline urinary $LTE_4$ [50, 90].

Some aspects of the clinical pharmacology of $CysLT_1$ receptor antagonists deserve further discussion: (1) their role as monotherapy in patients with asthma; (2) their additive efficacy with inhaled glucocorticoids and their possible steroid-sparing action; (3) the variability in their therapeutic response across the population; (4) their potential anti-remodelling effect in the airways and (5) their safety.

In North America, monotherapy with $CysLT_1$ receptor antagonists is a common therapeutic option for patients with mild asthma [91, 92]. However, inhaled glucocorticoids are generally preferred because of their greater efficacy as first-line agents in both adults and children with asthma [93, 94]. Nonetheless, LTRAs are not an unreasonable choice for a controller in patients who cannot tolerate inhaled glucocorticoids or prefer a non-steroid agent [91, 92].

In patients with asthma not sufficiently controlled with inhaled glucocorticoids alone, add-on therapy with montelukast to a constant dose of inhaled budesonide improves asthma control [95] to a level comparable to that achieved by doubling the dose of budesonide [96]. The advantage of this therapeutic strategy would be the reduced risk of side-effects due to long-term administration of high-dose inhaled glucocorticoids [96]. In patients whose symptoms remain uncontrolled with inhaled fluticasone alone, the addition of montelukast is a therapeutic option [97], although the addition of a long-acting $\beta_2$-agonist (LABA) is generally more effective for preventing exacerbations requiring systemic steroids, and for improving lung function, symptoms and the use of rescue $\beta_2$-agonists [98, 99]. In patients with well-controlled asthma based on symptoms and lung function testing, the addition of pranlukast to the combination of inhaled glucocorticoids and LABAs gives better control of airway inflammation compared with therapy with the combination of inhaled glucocorticoid/LABA alone [100, 101]. In children with mild persistent asthma, montelukast withdrawal can result in enhanced airway inflammation, as reflected by fractional-exhaled nitric oxide ($F_ENO$) concentrations, and worsening of lung function [102].

Add-on therapy with $CysLT_1$ receptor antagonists enables a reduction in the dose of inhaled glucocorticoids required to control asthma [96, 103]. As the LT pathway is relatively steroid-resistant [104], the combination of LTRAs and inhaled glucocorticoids can increase therapeutic efficacy in subgroups of patients whose asthma is LT-driven. AHR to $LTD_4$ and urinary $LTE_4$ concentrations in adults with mild asthma are not affected by inhaled fluticasone (500 μg b.i.d. for 2 weeks) [104]. Treatment with inhaled fluticasone (100 μg b.i.d. for 4 weeks) reduces $LTE_4$ concentrations in EBC by 18% in children with intermittent and mild persistent asthma [60]. Taken together, this evidence indicates that inhaled glucocorticoids have limited, if any, effects on the biosynthesis of CysLTs and AHR to CysLTs in patients with asthma [104].

The therapeutic response to $CysLT_1$ receptor antagonists in both adults and children with asthma is variable [96, 105, 106], but this is also true for inhaled glucocorticoids, and undoubtedly, all classes of medications. Identification of LTRA and/or inhaled glucocorticoid responders might have important clinical implications, as a tailored, individualized approach to asthma management and assessment is preferable for asthma control than a strategy directed to the best outcome in a group of patients [94]. Certain phenotypic features have been linked to a therapeutic response to inhaled fluticasone; these include higher $F_ENO$ concentrations, serum IgE, and eosinophil cationic protein concentrations, total blood eosinophil counts, and lower levels of methacholine $FEV_1$ provocative concentration $(PC)_{20}$ and of pulmonary function [94, 105]. A therapeutic response to montelukast is associated with younger age, shorter disease duration, higher urinary $LTE_4$ concentrations [94, 105], and elevated $LTE_4$ concentrations in EBC [53]. In patients with asthma, the response to inhaled glucocorticoids decreases with the increasing body mass index, whereas the response to montelukast remains intact [107]. Studies on biomolecule profiles in biological fluids and genetic polymorphisms of the 5-LO pathway and CysLT receptors [108] may in the future help to predict the therapeutic response to $CysLT_1$ receptor antagonists. At present, it is not possible to predict in individual patients whether they will respond to LTRAs mandating that a therapeutic trial be performed.

In a mouse model of asthma, $CysLT_1$ receptor antagonists not only prevent allergen-induced airway changes but also reverse established structural changes including subepithelial fibrosis and airway smooth muscle cell layer thickening – effects not achieved by glucocorticoid treatment [109]. These findings suggest a possible role of CysLTs in airway remodelling [42] and may have important implications for the management of patients with asthma as they might indicate new therapeutic effects of $CysLT_1$ receptor antagonists. In patients with asthma, inhaled glucocorticoids also reduce basal membrane thickening [110] and subepithelial collagen deposition [111], although these effects seem to have limited impact on the clinical evolution of asthma [112]. In one study, montelukast at a dose of 10 mg once daily for 8 weeks reduced myofibroblast accumulation in the airways observed in biopsies of patients with asthma following low-dose allergen challenge [113]. However, whether $CysLT_1$ receptor antagonists prevent airway remodelling and/or reverse established airway structural changes in asthmatic patients require further research.

$CysLT_1$ receptor antagonists are generally considered to be safe and well tolerated, with headache and gastric discomfort being the most common side effects [3]. However, an association between treatment with $CysLT_1$ receptor antagonists and severe adverse events including Churg–Strauss syndrome [114] and suicidality [115] has been reported. An aetiologic role for $CysLT_1$ receptor antagonists in the Churg-Strauss syndrome has been deemed previously unlikely [3]. However, a recent analysis of the FDA adverse event reporting system database has shown that LTRA therapy was a suspect medication in most confirmed cases of Churg–Strauss syndrome reported [114]. In the majority of cases treated with an LTRA, Churg–Strauss syndrome could not be explained by either glucocorticoid withdrawal or pre-existing Churg–-Strauss syndrome [114]. Based on a limited number of postmarketing suicide-related adverse experience reports, the FDA issued a warning raising concerns about the suicidality potential of montelukast and other $CysLT_1$ receptor antagonists [115]. However, no completed suicides were reported in any studies [115], and in fact, data from clinical studies indicate that adverse experiences possibly related to suicidality were rare and were similar between montelukast and placebo or active-control groups [115, 116]. There are limited prospective, comparative studies examining the safety of $CysLT_1$ receptor antagonists in pregnancy [117]. Montelukast does not appear to increase the baseline rate of major malformations [117, 118]. The lower birth weight observed in infants born to women treated with montelukast could be attributed to severity/control of the maternal asthma [117, 118].

Oral administration of $CysLT_1$ receptor antagonists provides a single therapeutic approach to both AR and asthma. In asthmatic patients with AR, a combined treatment approach that includes montelukast and budesonide is more effective in reducing airflow obstruction compared with doubling the dose of budesonide, indicating that this strategy increases therapeutic efficacy, potentially reducing the number of side-effects [119].

## Conclusions

Most of the knowledge of the pathophysiological role of LTs in asthma is currently limited to $CysLT_1$ receptor-mediated effects, whereas the roles of the $CysLT_2$ receptor and other emerging receptors are largely unknown. $CysLT_1$ receptor antagonists are generally less effective than inhaled glucocorticoids, but there is a substantial heterogeneity of clinical responsiveness among individual patients. It is not currently possible to predict whether an individual asthmatic will respond to these agents. Among responders, $CysLT_1$ receptor antagonists provide a therapeutic alternative to inhaled glucocorticoids in mild persistent asthma. In patients with more severe asthma who respond to $CysLT_1$ receptor antagonists, the addition of these drugs to inhaled glucocorticoids improves asthma control and enables the dose of inhaled gluococorticoids to be reduced without compromising efficacy. LTRAs are also useful in exercise-induced asthma.

The potential effect of $CysLT_1$ receptor antagonists or novel LT synthesis inhibitors in preventing and reversing structural changes that characterize airway remodelling, as well as the role of $LTB_4$ in asthma, requires further study.

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