

REVIEW

Leukotriene receptor antagonists Pranlukast and Montelukast for treating asthma

ABSTRACT

Introduction The prevalence of bronchial asthma, which is a chronic inflammatory disorder of the airway, is increasing worldwide. Although inhaled corticosteroids (ICS) play a central role in the treatment of asthma, they cannot achieve good control for all asthmatics and medications such as leukotriene receptor antagonists (LTRAs) with bronchodilatory and anti-inflammatory effects often serve as alternatives or add-on drugs.

Areas covered Clinical trials as well as basic studies of montelukast and pranlukast in animal models are ongoing. This review report clarifies the current status of these two LTRAs in the treatment of asthma and their future direction.

Expert opinion Leukotriene receptor antagonists could replace ICS as first-line medications for asthmatics who are refractory to ICS or cannot use inhalant devices. Furthermore, LTRAs are recommended for asthmatics under specific circumstances that are closely associated with cysteinyl leukotrienes (cysLTs). Considering the low incidence of both severe adverse effects and the induction of tachyphylaxis, oral LTRAs should be more carefully considered for treating asthma in the clinical environment. Several issues such as predicted responses, effects of peripheral airway and airway remodeling and alternative administration routes remain to be clarified before LTRAs

could serve a more effective role in the treatment of asthma.

Key words: airway hyperresponsiveness, bronchodilation, inflammation, pulmonary function, tachyphylaxis

Abbreviations

AHR, airway hyperresponsiveness

AIA, aspirin intolerant asthma

AR, allergic rhinitis

ASM, airway smooth muscle cells

COX, cyclooxygenase

CSS, Churg Strauss syndrome

CVA, cough variant asthma

CysLT, cysteinyl leukotriene

DC, dendritic cell(s)

EIB, exercise-induced bronchoconstriction

FEV1.0, forced expiratory volume in one second

FLAP, 5-lipoxygenase (5-LO)-associated protein

ICS, inhaled corticosteroid;

LABA, long acting β 2 agonist

LTRA, leukotriene receptor antagonist

NSAID non steroidal anti inflammatory drug

PMA, premenstrual asthma

RCT, randomized control trial

SABA, short acting β 2 agonist

SRS-A, slow reacting substance of anaphylaxis

URI, upper respiratory tract infection

Introduction

1. Pathophysiology and epidemiology of asthma

Bronchial asthma is a respiratory disease that affects an estimated 315 million individuals of all ages worldwide [1]. Asthma is clinically characterized by the acute onset of dyspnea with expiratory stridor and reversible airway obstruction. The primary pathophysiology of asthma is airway hyperresponsiveness (AHR) to various stimuli associated with allergic airway inflammation. Various types of cells and mediators are involved in the development and exacerbation of allergic airway inflammation [2]. Asthma is also characterized by structural change of the airway wall, especially following long periods. The term “airway remodeling” includes goblet cell metaplasia, thickening of the reticular layer beneath the true basement membrane, smooth muscle, fibroblast and myofibroblast hyperplasia [3-5]. Such airway remodeling is thought to be associated with AHR and the irreversible airway obstruction found in patients with chronic asthma. Asthma is primarily a chronic respiratory disorder, while acute exacerbation occasionally occurs following upper respiratory tract infection and could be fatal. Recent advances in the treatment of asthma have reduced the incidence of fatalities among asthmatics. Nonetheless, the prevalence of asthma in both children and adults is increasing worldwide. The annual direct medical expenditure for asthma

treatment in the USA in 2007 was USD 37.2 billion [6]. In Europe, the estimated annual direct cost of asthma is EUR 7.9 billion [7]. Furthermore, the total incremental cost (including indirect costs) of asthma to society in the USA was USD 56 billion during 2007 [8].

2. Leukotrienes

2.1 History

In 1960, Brocklehurst discovered a substance in guinea pigs that could constrict smooth muscle and was distinct from histamine. He named his discovery slow reacting substance of anaphylaxis (SRS-A) due to its delayed onset and protracted activity [9]. Thereafter, Samuelsson and colleagues identified SRS-A as cysteine-containing conjugated triene derivatives of the fatty acid arachidonic acid and collectively called them leukotrienes (LT) [10]. Samuelsson received the Nobel Prize in Physiology or Medicine for this discovery in 1982.

2.2 Biosynthesis and receptors of LTs

Inflammatory cells including eosinophils, mast cells and macrophages in the airway predominantly produce leukotrienes (**Figure 1**). Many stimuli including allergens and viral infections initiate LT production from arachidonic acid in the cellular membrane

by activating phospholipase A2 (PLA2). First, the enzyme 5-lipoxygenase (5-LO) and its helper protein, 5-LO-activating protein (FLAP) produces LTA4, which is converted by LTC4 synthase to LTC4 or by LTA4 hydrolase to LTB4. Neutrophils in asthmatic airways produce LTB4, which is less well characterized. Leukotriene C4 is then converted to LTD4 and LTE4. Slow reacting substance of anaphylaxis comprises LTC4, D4 and E4 that are now termed cysteinyl LTs (cysLTs) and they are predominantly produced from eosinophils and mast cells in asthmatic airways. All cysLTs act through G protein-coupled receptors on the cell surface. The best characterized cysLTs receptors are cysLT1R and cysLT2R. The binding affinity of CysLT1R is LTD4 > LTC4 or LTE4, whereas that of cysLT2R is LTC4 = LTD4 > LTE4. The ligation of cysLTs and cysLTR1 results in bronchoconstriction, mucous secretion and edema. The ligation of cysLTs and cysLTR2 results in airway inflammation and fibrosis [11], although their primary roles in the pathogenesis of asthma remain uncertain. Leukotriene E4 binds poorly to both cysLT1R and cysLT2R, suggesting the involvement of LTE4 receptors [12]. The receptors for LTB4 include BLT1 and BLT2.

2.3 Action of cysLTs in asthma

Several studies have determined higher concentrations of cysLTs in the airways and urine of asthmatics compared with non-asthmatic individuals [13]. The production of

cysLTs is increased in asthmatics, particularly during the early phase of bronchoconstriction that follows allergen challenge [14]. Cysteinyl LTs have far more powerful bronchoconstrictive effects than either methacholine or histamine, they induce AHR, vascular permeability and mucous production and exert proinflammatory effects including chemotactic activity for eosinophils and cytokine production from lymphocytes [15, 16]. All of these actions are closely associated with the pathogenesis of asthma. Cysteinyl LTs also have mitogenic effects on airway smooth muscle cells (ASM) that might be closely associated with airway remodeling [17]. Taken together, cysLTs seem to be critically involved in the symptoms, acute exacerbation and persistence of asthma.

3. Leukotriene receptor antagonists

3.1 Drug development

Since their discovery, cysLTs have been regarded as candidate drugs for treating asthma and pranlukast became commercially available in Japan during 1995 as a new class of antiasthma drugs, followed by montelukast in Mexico during 1997. Two classes of anti-LT drugs, 5-LO inhibitor (zileuton) and LT receptor antagonists (LTRA; pranlukast, montelukast, zafirlukast) are currently available. The present review focuses

on pranlukast and montelukast (**Figure 2**). Both are specific cysLTR1 antagonists that do not antagonize cysLTR2. Montelukast is administered once daily, whereas pranlukast is administered twice daily. Their clinical benefits seem comparable despite some differences in their pharmacokinetics.

3.2 Pharmacology

As predicted from the biological effects of cysLTs, LTRAs reduce bronchoconstriction in response to various stimuli. Leukotriene receptor agonists significantly reduce anaphylactic bronchoconstriction in passively sensitized human lung parenchyma in vitro compared with other anti-allergic drugs [18]. Leukotriene receptor agonists also have anti-inflammatory effects in a murine model of allergic asthma as they reduce airway eosinophilia and cytokine production from T lymphocytes [16]. Heterogeneous effects are characteristic of LTRAs. Although the reason for this heterogeneity remains unclear, some genetic and acquired factors have been suggested. This heterogeneity also results in some specific indications for which LTRAs are particularly effective as will be described in detail later. At present, however, no laboratory measures can predict responses to LTRAs including cysLT production in urine or sputum. Although pranlukast might have anti-inflammatory effects via a mechanism distinct from cysLTR1 antagonism, the clinical relevance remains unknown

[19, 20].

4. Clinical use of LTRA for asthma

4.1 Asthma treatment guidelines

The current asthma treatment guidelines consider that asthma is a chronic inflammatory disorder of the airways and that inhaled corticosteroid (ICS) is a first line therapy. Leukotriene receptor antagonists are classified as acceptable alternative first line therapies for mild asthma and also considered an alternative to long acting β 2 agonists (LABA) as ICS add-on therapy in moderately persistent asthma.

4.2 First-line therapy

Inhaled corticosteroids are the standard first-line therapy for any severity of asthma. Although the anti-inflammatory properties of LTRAs are less powerful than those of ICS, LTRA monotherapy might be effective for mild asthma. Randomized control trials (RCT) of montelukast have shown significant improvements in lung function, symptoms, QOL, rescue with short acting β 2 agonists (SABA) and exacerbation [21, 22]. A meta-analysis has also shown that LTRA monotherapy is significantly less clinically effective against mild to moderate asthma than low-dose ICS [23]. Considering compliance, monotherapy with LTRA could be substituted for that with

ICS in mild asthmatics for whom inhalers are not an option. In fact, whereas therapeutic compliance with ICS is low in the clinical setting, the effects on pulmonary function and QOL are comparable between monotherapy with montelukast and ICS [24].

4.3 Add-on therapy

The most common role of LTRA is that of add-on therapy for uncontrolled asthma on patients treated with ICS. The rationale for this is that steroids cannot inhibit cysLT production [25]. Similarly to other chronic diseases such as hypertension and infection, combined medications are potentially more effective than simply increasing the dose of a single drug. Adding pranlukast or montelukast to ICS significantly improves symptoms and pulmonary functions to a degree comparable to that of doubling the ICS dose for patients with uncontrolled asthma [26, 27]. As add-on medication to ICS, the asthma treatment guidelines also recommend slow-release theophylline and LABA as well as LTRA. The bronchodilatory effects of add-on pranlukast to medium doses of ICS are comparable to those of theophylline [28]. Combinations of ICS and LABA comprise the most prevalent option for treating moderate, to severe asthma. Many RCT have found that adding LABA to ICS results in significantly better outcomes than those generated by LTRA [29-32]. However, these studies might have some critical limitations. Firstly, participants in RCT generally have bronchial obstruction that is

reversible by SABA, which potentially proves the effectiveness of LABA at entry. Secondly, individuals with obesity, a smoking history and recent viral respiratory infection who might be good responders to LTRA are generally excluded from RCT. In fact, a clinic-based, real-world study from which participants could not be strictly excluded found comparable add-on effects between LTRA and LABA [24]. Thirdly, many RCT have compared bronchodilatory effects such as peak expiratory flow and forced expiratory flow volume in one second (FEV_{1.0}) between LTRA and LABA and have found that LABA are more effective than LTRA, which are primarily considered as anti-inflammatory controllers despite having bronchodilatory effects that are inferior to those of LABA. One study found that LABA improved bronchodilatory effects more effectively, whereas montelukast had better anti-inflammatory effects including peripheral blood eosinophil counts [33]. Although the clinical relevance of the anti-inflammatory properties of LTRA remain to be determined, adding LTRA to ICS over the long-term could probably prevent the progression of airway remodeling, since LTRA have anti-remodeling effects in humans and other animals with asthma as described below. Montelukast has also been added to ICS and LABA. This triple combination significantly improved the QOL of patients compared with a combined ICS and LABA [34]. Even when pulmonary function is normal in asthmatics on high-dose

ICS and LABA, cysLTs can be detected in induced sputum. Adding on pranlukast for these patients significantly attenuated cysLTs and pro-inflammatory cytokines in induced sputum [35]. Taken together, the current asthma treatment guidelines might under-represent the usefulness of LTRA, especially in the real-world setting and under the following specific situations.

4.4 Established situations for which LTRAs are preferential

Leukotriene receptor agonists are currently prescribed for all asthmatics. However, they might be particularly effective for treating subsets of asthmatics.

Exercise induced bronchoconstriction (EIB)

Over half of all asthmatics develop exercise-induced bronchoconstriction. Although the underlying mechanisms of EIB remain unknown, several inflammatory mediators including cysLTs might be involved [36]. The administration of SABA, disodium cromoglycate and LTRA before exercise can prevent EIB. Montelukast prevents pulmonary function from maximally decreasing after exercise in children with EIB significantly more effectively than ICS [37]. Repeated administration with β 2-agonists results in tachyphylaxis, whereas that of LTRA does not. Montelukast persistently prevents EIB even after four and eight weeks of administration, whereas the preventive effects of salmeterol, a LABA, were attenuated [38].

Aspirin intolerant asthma (AIA)

About 10% of adult asthmatics develop acute severe bronchoconstriction after being medicated with non-steroidal anti-inflammatory drugs (NSAIDs) including aspirin. The prevalence of AIA is higher among 40 – 50-year-old women than among men. Common complications include nasal polyps and anosmia. The shunt theory states that the 5-LO pathway dominates the cyclooxygenase (COX) pathway in patients with AIA. Inhibition of the COX pathway by NSAIDs activates arachidonic acids through the 5-LO pathway to produce excessive amounts of cysLTs in AIA, which results in bronchoconstriction. Significantly more CysLTs are produced in patients with aspirin-intolerant, than tolerant asthma [39]. Thus, LTRA should be useful for treating AIA. In fact, adding montelukast to ICS to treat patients with symptomatic AIA significantly improves their QOL [40]. Pranlukast partially, but significantly reduces the fall in oral aspirin-induced FEV1.0 in patients with AIA [41, 42].

Perimenstrual asthma (PMA)

Symptoms worsen in 30% - 40 % of pre-menopausal women with asthma during the premenstrual or menstrual period. Although the exact mechanism of PMA remains unknown, cysLTs as well as sex hormones seem to be involved [43]. Perimenstrual asthma includes severity that warrants treatment with systemic corticosteroids [44, 45].

Both pranlukast and montelukast significantly improve asthma symptoms and pulmonary functions, indicating that LTRAs could be effective against PMA [46, 47].

Cough variant asthma (CVA)

Chronic persistent cough is one of the most prevalent symptoms worldwide. Although chronic cough has many causes, CVA is the most frequent source when both chest X ray and auscultation findings are normal. Cough variant asthma is defined as asthma with cough as the predominant or sole symptom with minimal bronchoconstriction. Airway hyper-responsiveness with eosinophilic airway inflammation is also found in CVA. Bronchodilators can relieve cough associated with CVA and ICS is the mostly frequently recommended medication. However, patients with CVA in the real world cannot inhale deeply and severe coughing interrupts breathing; thus oral LTRAs might be reasonable add-ons or alternatives for such patients. Montelukast has significantly reduced cough symptoms and suppressed airway inflammation [48]. One study compared the antitussive effects of pranlukast and LABA in patients with CVA and found that pranlukast can significantly reduce cough scores [49].

Asthma with concomitant allergic rhinitis (AR)

Allergic rhinitis is a comorbidity associated with the severity of asthma that affects

30% - 60% of asthmatics [50]. Treating AR improves asthma symptoms and intranasal steroids reduce asthma-related symptoms as well as AHR [51]. From this perspective, LTRAs are ideal because they can treat both AR and asthma. For uncontrolled moderate persistent asthma, the effects of adding montelukast to moderate-dose ICS on pulmonary function are considered comparable to double doses of ICS. While, in the subgroup of asthmatic patients with AR, a combined treatment approach that included montelukast and ICS provided significantly greater efficacy in reducing airflow obstruction compared with doubling the dose of ICS [52]. Accordingly, the current Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines recommend LTRAs for treating asthma in patients with AR who are unable to use ICS [53].

Infection-induced asthma

Upper respiratory infection (URI) caused by respiratory viruses exacerbates about 50% of adult asthmatics and 80% of children with asthma and it is treated similarly to asthma due to other causes. Systemic CSs and SABA are central medications for URI-induced acute asthma. Treatment of URI-induced acute asthma remains complicated by several issues. Firstly, systemic CSs are extremely effective against acute asthma, but they potentially inhibit anti-viral immunity [54]. Secondly, viral infection attenuates the anti-inflammatory effects of CSs [55]. Thirdly, viral infection

also attenuates the effects of β_2 agonists [56]. These problems can be overcome by adding other drugs to CSs and SABA. From this perspective, LTRAs are attractive because cysLTs increase in the airway after URI [57-59], cysLTR1 also increases in the airway of acute exacerbated asthma [60], LTRAs have acute bronchodilator effects and they selectively inhibit pro-inflammatory cytokines in contrast to CS, which non-selectively inhibits cellular immunity [61]. In fact, adding pranlukast to systemic CSs significantly shortened the duration of symptoms and reduced the total dose of systemic CS compared with systemic CS therapy alone in patients with questionnaire confirmed URI-induced acute asthma [62]. Daily montelukast also prevents the development of URI-induced acute asthma exacerbation in 30% of children with asthma [63].

Obesity

Obesity has recently emerged as a potential critical risk factor for developing and exacerbating asthma and it causes CS resistance in patients with asthma. The mechanism of obesity-exacerbated asthma includes physical obstruction by fat tissue and systemic inflammation associated with fat tissue [64]. Fat tissue produces many pro-inflammatory mediators [65], among which are cysLTs. Body mass index (BMI) is associated with LTE4 production in adult asthmatics [66]. The therapeutic responses of

asthmatics to ICS decrease with increasing BMI, whereas those to montelukast remain stable [67].

Smoking

Smoking is also regarded as a critical risk factor for worsening asthma. Smoking inhibits almost all steroid-related anti-inflammatory effects and thus causes CS resistance in asthmatics who smoke [68]. One mechanism of CS resistance is smoking-induced cysLT production. Habitual cigarette smoking causes a dose-dependent increase in cysLT production [69]. One study found that the response to ICS is attenuated in smokers with mild asthma, whereas the response is greater in asthmatic smokers treated with montelukast, suggesting that cysLTs could be important for treating such individuals [70]. Patients with a smoking history of less than 11 pack years tend to show more benefit with ICS, whereas those with a smoking history of greater than 11 pack years tended to show more benefit with montelukast [71].

Elderly persons with asthma

Asthma is common disorder in not only young generation but also in elderly patients. Elderly asthmatics are frequently misdiagnosed such as chronic heart failure or chronic obstructive pulmonary diseases. Even when asthma is adequately diagnosed, anti-asthma therapies for the elderly are often difficult to implement due to poor

inhalation technique, poor compliance with inhaled medicines, decreased cognitive function and comorbidities. The recent increase in the mortality rate due to asthma among elderly patients might thus be associated with insufficient diagnosis and treatment [72]. Leukotriene receptor agonists are valuable medications for elderly persons since they are orally administered and have less severe adverse effects. Montelukast as add-on therapy to ICS for severe asthmatics aged > 60 years reduces asthma exacerbation events and increases the number of symptom-free days [73].

4.5 Uncertain areas regarding LTRA preference

Sex

Sex differences in cysLT production have recently been identified [74]. Significantly more cysLTs are produced by stimulated white blood cells from women than from men. The distribution of enzymes in white blood cells that synthesize LTs differs between men and women. Male sex hormones inhibit cysLT production by white blood cells from women. The prevalence of AIA, which is closely related to cysLTs, is higher and asthma is more frequently severe in women, which might be partially associated with sex differences in cysLT production. Although a clinical study has found increased cysLT-related albuterol usage and a greater tendency towards montelukast responsiveness in girls than in boys exposed to tobacco smoke [75], whether the clinical

effects of LTRAs are in fact associated with sex with remains undetermined.

Peripheral airways

Recent findings support the concept that not only central, but peripheral airways are involved in allergic airway inflammation and obstruction, especially in severe asthma [76, 77]. Furthermore, the density of inflammatory cells is greater in the outer, than in the inner airway walls of asthmatic peripheral airways [78]. Additionally, more cysLTR1 is expressed in fibroblasts from the peripheral, than the central airway [79]. Since inhaled medicines cannot easily penetrate the outer walls of peripheral airways, oral LTRAs that can be delivered to peripheral airways via the bloodstream might be a useful add-on therapy to inhibit peripheral airway inflammation. Montelukast inhibits allergic inflammation in the small airways of guinea pigs in vitro [80] and both pranlukast and montelukast attenuate peripheral airway inflammation and obstruction in humans with asthma [81, 82].

Airway remodeling

Airway remodeling is currently thought to be associated with fixed airway obstruction and AHR. Considerable evidence suggests that cysLTs are involved in the development of airway remodeling. The ideal therapy for asthma should prevent both airway inflammation and remodeling. However, whether or not regular therapy with

ICS affects airway remodeling remains controversial [83-87]. Montelukast has reversed established airway smooth muscle cell layer thickening and sub-epithelial fibrosis in a murine model of allergic asthma [88] and Kelly et al. showed using endobronchial biopsy specimens that eight weeks of montelukast treatment attenuated the increase in myofibroblasts subsequent to allergen challenge in patients with mild asthma [89]. Thus, LTRAs have the potential to attenuate airway remodeling in asthma. However, data supporting this notion remain scant.

Prevention of asthma

Cysteinyl LTs are involved in not only the worsening and maintenance of established asthma but also in its development. Primary antigen-presenting dendritic cells (DC) in the airway express cysLT₁R and produce cysLTs upon antigen stimulation [90, 91]. Intranasal inoculation with allergen-sensitized DCs into the airway of naïve mice results in allergic airway inflammation and incubating allergen-sensitized DCs with LTRAs inhibited the subsequent development of allergic airway inflammation in a murine model [92]. Thus, LTRAs might prevent the development of subsequent asthma in susceptible individuals including those with AR, although data from humans is presently unavailable.

4.5. Safety

The safety as well as the efficacy issue of control medications should be considered. Both pranlukast and montelukast are generally well tolerated and the incidence of severe adverse effects low [93]. A long-term follow-up study has confirmed the safety of LTRAs as well as the absence of the tachyphylaxis induced by β 2-agonists [94]. Despite a small sample size, a recent study of perinatal outcomes in asthmatics administered with LTRAs or SABA and in those without asthma found that the use of LTRAs during pregnancy does not result in adverse perinatal outcomes including specific structural abnormalities [95]. Montelukast is presently classified as a grade B drug for pregnant women. The present safety concerns regarding LTRAs comprise the induction of Churg Strauss Syndrome (CSS) and neuropsychiatric disorders [93]. However, data supporting a relationship between LTRA and these adverse events remain conclusive. Adult patients with asthma severe enough to require high-dose ICS and/or systemic CS generally develop CSS. Since the clinical symptoms of CSS generally develop during CS reduction by add-on LTRAs, LTRAs might unmask, rather than induce CSS. Physicians should carefully reduce ICS by adding LTRAs for patients with severe asthma who require high-dose ICS and/or oral steroids. Although the development of neuropsychiatric disorders might be due to allergies or severe asthma

itself, a history of behavioral disturbances should be carefully assessed before administering LTRAs to patients.

5. Conclusion

Since the initiation of their clinical use, several studies have helped to clarify the status of LTRAs including pranlukast and montelukast in the treatment of asthma. Asthma treatment guidelines primarily consider LTRAs as alternative or add-on medications to ICS because their anti-inflammatory effects are less powerful than those of ICS. However, adherence, especially with inhaled CS, is relatively poor. Furthermore, elderly patients often have difficulties with handling inhaled devices due to decreased cognitive function and comorbidities. Oral problems associated with ICS can also prevent compliance with ICS among the elderly, who have reduced salivary production. Thus, LTRAs could be substituted ICS as a first-line medication for asthmatics who are poorly compliant with ICS or cannot use inhaled devices. In fact, a recent real-world study has confirmed that the effects of LTRAs as a first line therapy with ICS and add-on therapy are comparable to those of LABA. Similarly, LTRAs are especially recommended for asthmatics under specific situations that are closely associated with cysLTs such as EIB, AIA, PMA, CVA, asthma with concomitant AR, infection-induced

asthma, obesity and smoking. In addition, oral LTRAs should be considered more often for treating asthma in the clinical setting because of the low incidence of both severe adverse effects and the induction of tachyphylaxis.

6. Expert opinion

A critical defect in the clinical use of LTRAs also involves their variable effects on asthma. The notion that asthmatics who produce more cysLTs in urine or sputum are higher responders to LTRAs therapy is simply untrue and predictors of better responders to LTRAs before initiation are unavailable. Identifying genetic factors or surrogate markers that could predict responses to LTRAs will be important.

The findings of basic and/or clinical, but not of practical research, indicate that LTRAs significantly affect peripheral airway and airway remodeling. However, peripheral airway and airway remodeling require specific modalities such as high-resolution computed tomography, fractional exhaled nitric oxide detectors, impulse oscillometry and endobronchial biopsies. Longer term and larger scale prospective studies as well as the development of non-invasive and clinically repeatable measures will definitely be important to conclude whether or not LTRAs are effective against peripheral airway and airway remodeling in asthma.

Chemoprevention for allergic diseases does not exist. Cysteinyl leukotrienes are critically involved in innate immunity and LTRAs act upon DCs to prevent the induction of allergic airway inflammation in mice. Future studies should determine whether LTRAs can prevent the subsequent development of asthma among patients with AR who are susceptible to the development of asthma.

Since LTRAs have bronchodilatory as well as anti-inflammatory effects, intravenous montelukast was developed as a medication to relieve acute asthma [96] and inhalant montelukast was developed to directly deliver medications to the airway [97]. Although these forms of montelukast exert significant anti-asthmatic effects, they have not yet been marketed.

Current LTRAs antagonize cysLT₁R but not cysLT₂R and since cysLT₂R might be involved in the pathogenesis of asthma, the development and clinical application of dual antagonists might be a promising asthma treatment [98]. Besides cysLTs, antagonism of the LTB₄ pathway is also of interest. An inhibitor of LTA₄ hydrolase that inhibits LTB₄ production significantly attenuated allergic airway inflammation in a murine model of allergic asthma [99].

Besides asthma and AR, cysLTs are also associated with other human diseases [100]. The expression of cysLTR₁ increases in the airway of patients with acute exacerbated

COPD and cysLT levels are increased in bronchoalveolar fluids from patients with idiopathic pulmonary fibrosis. Cysteinyl leukotrienes are also potentially associated with cardiovascular diseases and malignancy. The clinical benefits of LTRAs for these diseases will also become research topics of interest.

Article highlights box

- Pranlukast and montelukast are leukotriene receptor antagonists, which are specific cysLT1R antagonists.
- Leukotriene receptor antagonists are classified as acceptable alternative first line therapies for mild asthma and also considered an alternative to LABA as ICS add-on therapy in moderately persistent asthma.
- Leukotriene receptor antagonists might be particularly effective for treating subsets of asthmatics including EIB, AIA, PMA, CVA, asthma with concomitant AR, infection-induced asthma, obesity, smoking and elderly subjects.
- Both pranlukast and montelukast are generally well tolerated and the incidence of severe adverse effects low.
- Several issues such as predicted responses, effects of peripheral airway and airway remodeling and alternative administration routes remain to be clarified before leukotriene receptor antagonists could serve a more effective role in the treatment of asthma.

Figure legends

Figure 1. Biosynthesis and receptors of leukotrienes.

BLT, LTB₄ receptor; CysLT, cysteinyl LT; CysLTR, cysLT receptor; FLAP, 5-LO associated protein; LT, leukotriene; LTA₄H, LTA₄ hydrolase; LTC₄S, LTC₄ synthase; PLA₂, phospholipase A₂; 5-LO: 5-lipoxygenase.

Figure 2. Leukotriene receptor antagonists.

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Figure 1

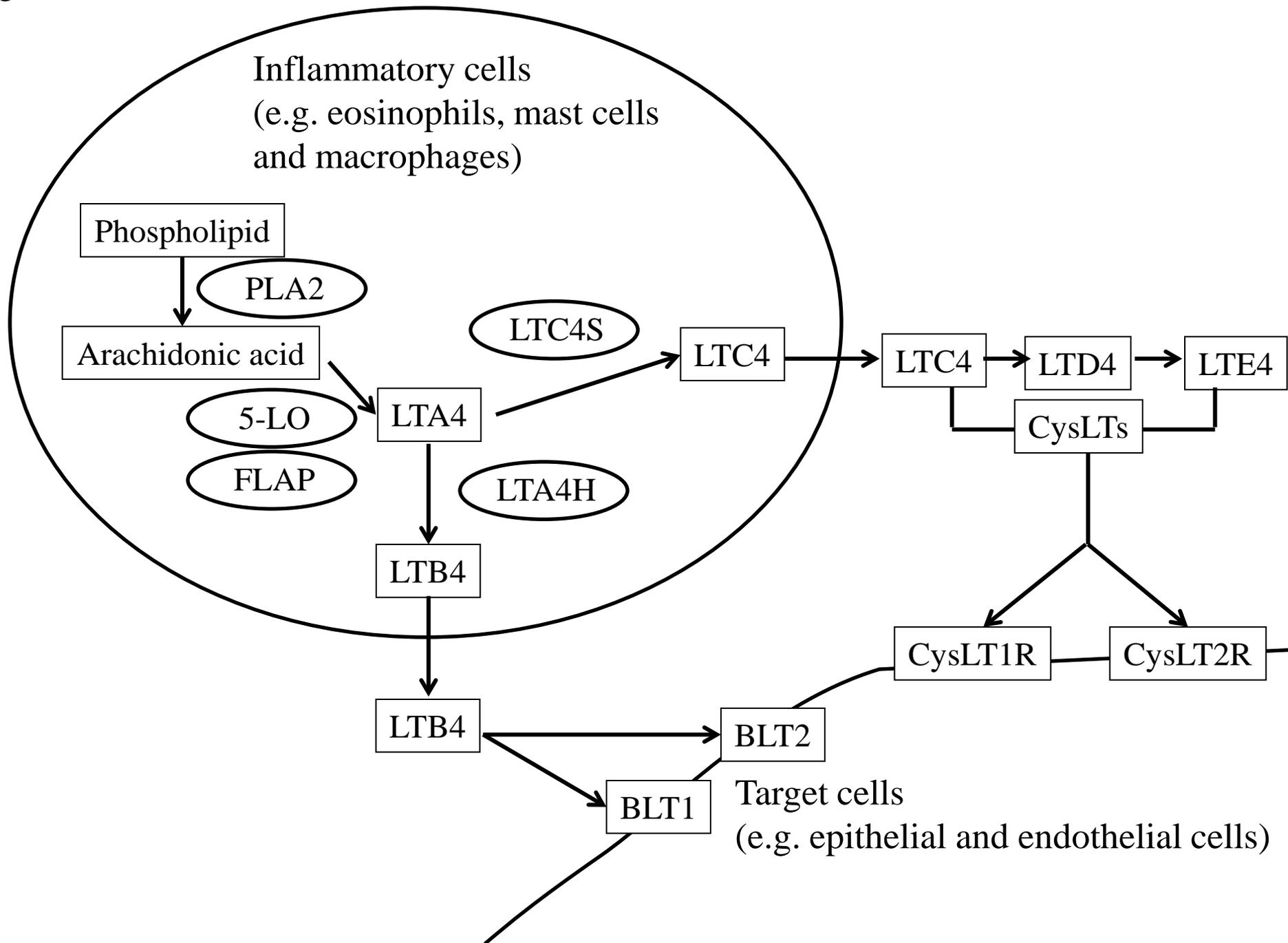
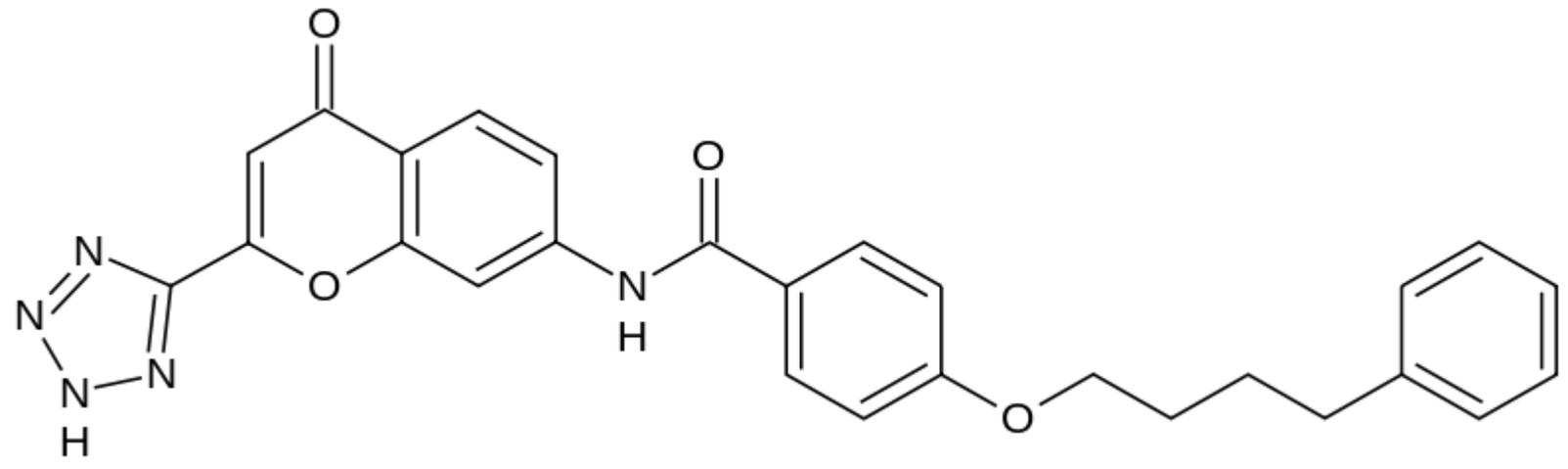


Figure 2

Pranlukast



Montelukast

