Curr Allergy Asthma Rep (2015) 15: 64
DOI 10.1007/s11882-015-0564-7

RHINOSINUSITIS (J MULLOL, SECTION EDITOR)

# Antileukotrienes in Upper Airway Inflammatory Diseases

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Published online: 18 September 2015


**Abstract** Leukotrienes (LTs) are a family of inflammatory mediators including $LTA_4$, $LTB_4$, $LTC_4$, $LTD_4$, and $LTE_4$. By competitive binding to the cysteinyl $LT_1$ ($CysLT_1$) receptor, LT receptor antagonist drugs, such as montelukast, zafirlukast, and pranlukast, block the effects of CysLTs, improving the symptoms of some chronic respiratory diseases, particularly bronchial asthma and allergic rhinitis. We reviewed the efficacy of antileukotrienes in upper airway inflammatory diseases. An update on the use of antileukotrienes in upper airway diseases in children and adults is presented with a detailed literature survey. Data on LTs, antileukotrienes, and antileukotrienes in chronic rhinosinusitis and nasal polyps, asthma, and allergic rhinitis are presented. Antileukotriene drugs are classified into two groups: CysLT receptor antagonists (zafirlukast, pranlukast, and montelukast) and LT synthesis inhibitors (5-lipoxygenase inhibitors such as zileuton, ZD2138, Bay X 1005, and MK-0591). CysLTs have important proinflammatory and profibrotic effects that contribute to the extensive hyperplastic rhinosinusitis and nasal polyposis (NP) that characterise these disorders. Patients who receive zafirlukast or zileuton tend to show objective improvements in, or at least stabilisation of, NP. Montelukast treatment may lead to clinical subjective improvement in NP. Montelukast treatment after sinus surgery can lead to a significant reduction in eosinophilic cationic protein levels in serum, with a beneficial effect on nasal and pulmonary symptoms and less impact in NP. Combined inhaled corticosteroids and long-acting β-agonists treatments are most effective for preventing exacerbations among paediatric asthma patients. Treatments with medium- or high-dose inhaled corticosteroids, combined inhaled corticosteroids and LT receptor antagonists, and low-dose inhaled corticosteroids have been reported to be equally effective. Antileukotrienes have also been reported to be effective for allergic rhinitis.

**Keywords** Leukotrienes · Antileukotriene drugs · Asthma · Chronic rhinosinusitis with nasal polyposis · Allergic rhinitis

This article is part of the Topical Collection on *Rhinosinusitis*

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## Introduction

Leukotrienes (LTs) are inflammatory mediators, previously known as slow-reacting substances of anaphylaxis, produced by a number of cell types, including mast cells, eosinophils, basophils, macrophages, and monocytes [1]. LTs are synthesised from arachidonic acid (AA) by the 5-lipoxygenase (5-LO) pathway [2, 3] (Fig. 1). Synthesis of these mediators results from the cleavage of AA in cell membranes. LTs exert their biologic effects by binding to and activating specific adaptors. This occurs in a series of events, leading to the

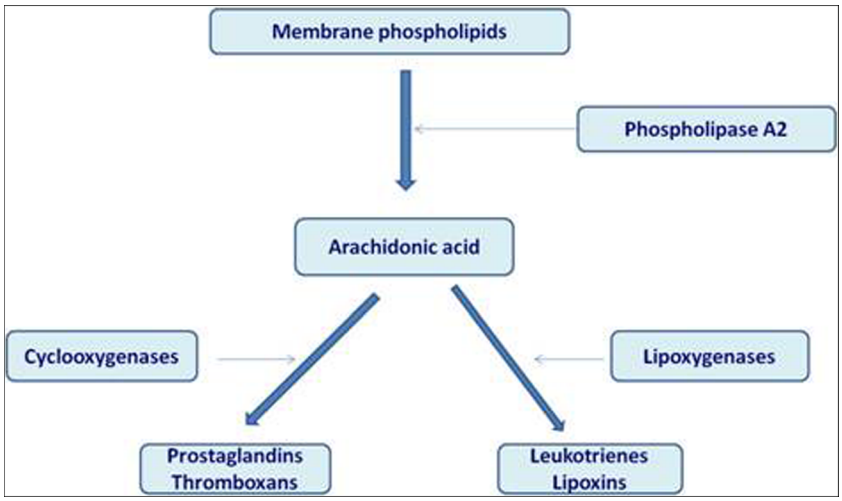


**Fig. 1** Synthesis of leukotrienes from arachidonic acid. Adapted from reference 3

contraction of human airway smooth muscle, cell chemotaxis, and increased vascular permeability [1].

The LT family consists of $LTA_4$, $LTB_4$, $LTC_4$, $LTD_4$, and $LTE_4$ [4••, 5]. An unstable intermediate product, $LTA_4$, is formed and successively converted into $LTC_4$, $LTD_4$, and $LTE_4$. A separate pathway produces $LTB_4$. $LTC_4$ is metabolised enzymatically into $LTD_4$ and subsequently into $LTE_4$, which is excreted in the urine. Several cells such as mast cells, basophils, eosinophils, monocytes/macrophages, dendritic cells, and T lymphocytes can produce LTs in response to receptor-activated, antigen-antibody interactions [2]. By competitive binding to the $CysLT_1$ receptor, LT receptor antagonist (LTRA) drugs, such as montelukast, zafirlukast, and pranlukast, block the effects of cysteinyl LTs (CysLTs), improving the symptoms of some chronic respiratory diseases, particularly bronchial asthma and allergic rhinitis [4••, 5].

CysLTs are potent proinflammatory mediators produced from AA through the 5-LO pathway. They have important pharmacological effects by interacting with at least two different receptors: $CysLT_1$ and $CysLT_2$. $CysLT_1$ mediates sustained bronchoconstriction, mucus secretion, and oedema in the airways. Selective antagonists of $CysLT_1$ approved for the treatment of asthma block the proasthmatic effects of $CysLT_1$. Experiments in mice that are deficient in $CysLT_2$, or that overexpress $CysLT_2$ in the lungs, have indicated that $CysLT_2$ does not mediate bronchoconstriction but rather contributes to inflammation, vascular permeability, and tissue fibrosis [4••].

The two classes of LTs, $LTB_4$ and peptidylcysteinyl LTs, also have important mediator functions in the upper airways. They promote inflammatory cell recruitment and activation (primarily of eosinophils) as well as fibrosis and airway remodelling, with actions such as smooth muscle and epithelial cell proliferation. The CysLTs increase the expression of adhesion molecules such as P selectin. They also promote airway remodelling by increasing the deposition of collagen below the basement membrane, enhancing collagen synthesis and degradation by fibroblasts, and promoting the proliferation of bronchial epithelial cells and smooth muscle cells. LT modifiers can reduce cytokine expression by blocking their actions. The reverse phenomenon is also true: cytokines can modulate LT expression [5].

LTs act by binding to specific receptors of the rhodopsin class that are located on the outer plasma membrane of structural and inflammatory cells [3]. Once ligated by the LT, these receptors interact with G proteins in the cytoplasm, thereby eliciting an increase in intracellular calcium and a reduction in intracellular cyclic AMP. These proximal signals activate downstream kinase cascades in ways that alter various cellular activities, ranging from motility to transcriptional activation [6]. In the bronchi of aspirin-intolerant asthma (AIA) patients, whose asthma is characterised by increased production of CysLTs, there is overexpression of $LTC_4$ synthase. This phenomenon is explained, at least in part, by a genetic polymorphism of the $LTC_4$ synthase gene. A common promoter variant of the gene creates a predisposition to AIA by reinforcing the effector mechanism of bronchoconstriction. Aspirin challenge studies, coupled with the estimation of $LTC_4$ synthase polymorphism and $LTC_4$ urinary excretion, point to some heterogeneity among patients with AIA [3, 7].

In this review paper, we present the efficacy of antileukotrienes in upper airway inflammatory diseases.

## Antileukotrienes

During the early-phase response to antigens, CysLTs are released by mast cells and basophils; however, in the late phase, they are synthesised by eosinophils and macrophages [8]. CysLTs cause contraction of bronchial smooth muscles, mucous production, oedema, and increased vascular

permeability. $LTD_4$ challenge in humans causes an increase in nasal mucosal blood flow and airway resistance [9]. Antileukotriene drugs are classified into two groups based on their mechanism of action: LTRAs (zafirlukast, pranlukast, montelukast), which block the LT receptor and thus block the end-organ response of LTs; and LT synthesis inhibitors (zileuton, ZD2138, Bay X 1005, MK-0591), which block the biosynthesis of cysteinyl LTs and $LTB_4$ [1].

Zafirlukast is an $LTD_4$ receptor antagonist that has been used for $LTD_4$-induced bronchoconstriction, exercise challenge, cold-induced asthma, and chronic asthma. LT synthesis inhibitors block the biosynthesis of cysteinyl LTs. Zileuton is a 5-lipoxygenase inhibitor that has been used in exercise, cold, and aspirin-induced bronchial hyperresponsiveness. LT modifiers represent the first mediator-specific therapeutic option for rhinitis and asthma [10, 11].

The currently used antileukotriene drugs are described in the succeeding paragraphs [12••].

Zileuton (Zyflo) (15-lipoxygenase inhibitor) is indicated for asthma and recommended for adults. It is administered twice daily (b.i.d.) or four times daily (q.i.d.). Adverse effects include dyspepsia (8.2 %) and transaminase elevation (1.9 %).

Montelukast (Singulair, Pluralair, Montecarlo, Lovetas) ($CysLT_1$ antagonist) is indicated for asthma and rhinitis and is recommended for adults and children aged 6 months and older. It is administered as once daily (q.d.). Adverse effects are not observed.

Pranlukast (Onon, Azlaire) ($CysLT_1$ antagonist) is indicated for asthma and rhinitis and is recommended for adults and children aged 1 year and older. It is administered b.i.d. Adverse effects are not observed.

Zafirlukast (Accolate) ($CysLT_1$ antagonist) is indicated for asthma and rhinitis and is recommended for adults and children aged 5 years and older. It is administered b.i.d. Adverse effects are not observed except single reports of hepatoxicity.

## Antileukotrienes in Chronic Rhinosinusitis and Nasal Polyps

In aspirin-exacerbated respiratory disease (AERD), subjects display dramatic upregulation of two essential enzymes involved in CysLT synthesis, LO and $LTC_{4S}$ [13, 14]. This overexpression drives both the constitutive overproduction of CysLTs and life-threatening surge in CysLTs that occurs with ingestion of aspirin and other non-selective COX inhibitors [15]. CysLTs demonstrate important proinflammatory and profibrotic effects that contribute to the extensive hyperplastic rhinosinusitis and nasal polyposis that characterise this disorder. In addition to their overproduction, these patients display greatly enhanced sensitivity to CysLTs, reflecting overexpression of the CysLT receptors [16, 17], including two well-characterised receptors ($CysLT_1$ and $CysLT_2$) and newly described selective $LTE_4$ receptors [18–21].

Chronic hypereosinophilic rhinosinusitis (CHES) is an inflammatory disease characterised by the prominent accumulation of eosinophils in the sinuses and, when present, associated with nasal polyps [21–24]. While NPs frequently occur with CF, AFS, and AERD, in the absence of one of these conditions, the presence of NP (particularly in the concomitant presence of asthma) has been proposed as presumptive evidence for CHES [25, 26]. In CHES, the sinus tissue demonstrates a marked increase in cells that express cytokines (e.g., IL-5 and GM-CSF), chemokines (e.g., $CCL_5$, $CCL_{11}$, and $CCL_{24}$), and proinflammatory lipid mediators (e.g., CysLTs) that are responsible for the differentiation, survival, and activation of eosinophils [22, 27, 28].

Antileukotrienes in chronic rhinosinusitis and nasal polyps are shown on Table 1. In Pérez-Novo et al.'s [29••] study, samples were prepared from sinonasal tissue of patients with CRS with (CRS-NP group, $n=13$) and without nasal polyposis (CRS group, $n=11$), sinonasal tissue of patients with nasal polyposis and aspirin sensitivity (CRS-ASNP group, $n=13$), and normal nasal mucosa from healthy subjects (NM group, $n=8$). IL-5 and eosinophil cationic protein were increased in both groups of nasal polyp tissue compared with in the NM and CRS groups and correlated directly with $LTC_4$, $LTD_4$, and $LTE_4$ concentrations and inversely with PGE 2 concentrations. They concluded that changes of tissue eicosanoid metabolism do occur in CRS, even in the absence of clinical aspirin sensitivity, and these changes appear to be related to the severity of eosinophilic inflammation.

Ulualp et al. [30] studied 18 patients who had all undergone previous sinus surgery. Sixteen received zafirlukast, and two received zileuton. They were evaluated by questionnaires and postoperative sinus endoscopies. After a follow-up of several months to 1 year, the overall benefit on the questionnaire was positive in 12 out of 15 patients (80 %), consistent with changes in symptom scores. Among the 15 subjects, the endoscopic findings demonstrated no abnormalities in 8 (53 %) patients, nasal crusting in 6 (40 %) patients, and erythema with nasal crusting in 1 (7 %) patient. In this uncontrolled study, the authors concluded that anti-LT therapy seemed to be an effective treatment for most patients whose symptoms of CRS persist following sinus surgery. Parnes and Chuma [31] investigated the effects of anti-LT added to the standard treatment in 36 patients with CRS with or without NP. In total, 26 received zafirlukast, 5 received zileuton, and the remaining 5 switched from zafirlukast to zileuton. A statistically significant improvement was noted with respect to headache, facial pain and pressure, ear discomfort, teeth pain, purulent nasal discharge, postnasal drip, nasal congestion and obstruction, olfaction, and fever in patients who received zafirlukast or zileuton. Overall improvement was noted by 72 % of the patients, and side effects occurred in 11 % of the patients.

**Table 1** Antileukotrienes in chronic rhinosinusitis and nasal polyps

| Authors | Main comments |
|---|---|
| Pérez-Novo et al. [29••] | IL-5 and eosinophil cationic protein increased in nasal polyp tissue and correlated directly with LTC 4, LTD 4, and LTE 4 |
| Ulualp et al. [30] | Anti-LT therapy seemed to be an effective treatment for most patients whose symptoms of CRS persist following sinus surgery |
| Parnes and Chuma [31] | In patients with CRS with or without NP, a statistically significant improvement was noted with respect to headache, facial pain and pressure, ear discomfort, teeth pain, purulent nasal discharge, postnasal drip, nasal congestion and obstruction, olfaction, and fever who received zafirlukast or zileuton |
| Kutting et al. [32] | Montelukast (10 mg daily) associated with oral steroids (oral methylprednisolone 40 mg) in nine patients with severe NPs; and no evidence of NP recurrence in five (56 %) patients, one (11 %) with NP reduction, and three (33 %) without changes by nasal endoscopy |
| Mullol et al. [33••] | Montelukast may contribute to the reduction of eosinophilic inflammation in upper-airway inflammatory diseases such as rhinitis and nasal polyposis |
| Ragab et al. [34] | Clinical response to montelukast appeared to be more impressive with respect to asthma than NP, possibly suggesting that LTs are more relevant in the lower than in the upper airway |
| Kieff et al. [37] | Patients with perennial allergies and NPs seem more likely to respond to the montelukast treatment than those without allergy |
| Wentzel et al. [38••] | LTAs are an effective tool for treating CRSwNP, with limited benefit as an adjunctive therapy |
| EPOS 2012 consensus [39•] | In adults with chronic rhinosinusitis with nasal polyps, antileukotriene treatment was mentioned as "negative outcome with no relevance" |

An objective improvement, or at least stabilisation, of NP was seen in 50 % of the patients [3, 31].

Kutting et al. [32] evaluated the effects of montelukast (10 mg daily) associated with oral steroids (oral methylprednisolone 40 mg) in nine patients with severe NPs. Seven patients (78 %) presented with symptomatic improvement (nasal obstruction and rhinorrhea), and four (44 %) were free of nasal symptoms. Endoscopic examinations demonstrated no evidence of NP recurrence in five (56 %) patients, one (11 %) with NP reduction, and three (33 %) without changes. Paranasal sinus MRI findings revealed resolution of the sinus opacification in four (44 %) patients. There were no further side effects of montelukast [32].

Mullol et al. [33••] investigated the effect of montelukast on an in vitro model of upper-airway eosinophil inflammation by reducing proinflammatory cytokines from both nasal mucosa (NM) and polyp (NP) epithelial cells and reducing eosinophil survival primed by epithelial cell secretions. Montelukast's anti-inflammatory effects on epithelial cell cytokine secretion and on eosinophil survival suggest that montelukast may contribute to the reduction of eosinophilic inflammation in upper-airway inflammatory diseases such as rhinitis and nasal polyposis.

Ragab et al. [34] investigated the response to montelukast, as an add-on therapy to topical and inhaled steroids, in patients with NPs and AIA or aspirin-tolerant asthma (ATA). Clinical subjective improvement in NP occurred in 64 % of ATAs and 50 % of AIAs; asthma improvement occurred in 87 % of ATAs and 61 % of AIAs. Objective changes in the peak flow occurred only in ATAs, while acoustic rhinometry, nasal inspiratory peak flow, and nitric oxide levels did not change. They concluded that the clinical response to montelukast appeared to be more impressive with respect to asthma than NP, possibly suggesting that LTs are more relevant in the lower than in the upper airway [3].

Grundmann and Topfner [35] studied 18 patients with AIA diagnosed by oral provocation and treated with montelukast after undergoing sinus surgery. The authors used endoscopic evaluations and determined the eosinophilic cationic protein (ECP) levels in serum. There was a significant reduction in ECP levels, with a further beneficial effect on nasal and pulmonary symptoms, as well as a significant reduction in the number of polyps noted on endoscopic examination. A prospective, double-blind study on 40 patients compared the effects of the LTRA montelukast (10 mg daily) and nasal beclomethasone (400 μg daily) on the postoperative course of patients with NPs [36]. There was a significant reduction in the symptom scores between these two postoperative treatments in the year following surgery. There were no differences in the recurrence rate or need for rescue medications between the groups throughout the study period. In total, 24 patients with symptomatic NPs and nonallergic or perennial rhinitis who had undergone chronic nasal steroid therapy were evaluated for the response to adjunctive oral montelukast therapy.

The NPs were submitted to biopsy to determine their degree of eosinophilia. Kieff et al. [37] concluded that montelukast appears to be beneficial for some patients with NP. Patients with perennial allergies and NPs seem more likely to respond to the treatment than those without allergy [3].

Wentzel et al. [38••] performed a systematic review including studies that assessed the effectiveness of LTAs on clinical outcome measures of CRSwNP. They concluded that LTAs are an effective tool for treating CRSwNP, with limited benefit as an adjunctive therapy.

In the EPOS 2012 consensus, in adults with chronic rhinosinusitis with nasal polyps, antileukotriene treatment was mentioned as "negative outcome with no relevance" [39•]. Antileukotrienes were not recommended for adults or children with chronic rhinosinusitis with or without nasal polyps.

## Antileukotrienes in Asthma

The use of LT inhibitors can reduce the need to use inhaled steroids or systemic steroid treatment, and lead to cost savings. Majak and Stelmach [40] indicated that montelukast seems to be the best therapeutic option for exercise-induced asthma. Interestingly, montelukast may have some preventive activity against viral-induced asthma exacerbations. There is strong evidence for the clinical effectiveness of montelukast in all asthma phenotypes, making this drug the most universal anti-asthma treatment option. However, there is individual variability in the response to montelukast, as observed for all drugs commonly used for the treatment of asthma [40].

The Genome-Wide Association Study [41], which used genome-wide genotype and phenotype data available from the American Lung Association-Asthma Clinical Research Center (ALA-ACRC) cohorts, evaluated changes in $FEV_1$ (at 8 weeks) related to montelukast administration in a discovery population of 133 asthmatics. The top 200 single-nucleotide polymorphisms (SNPs) were then tested in 184 additional samples from two independent cohorts. Twenty-eight SNP associations were replicated. Of these, rs6475448 achieved genome-wide significance (combined $P=1.97\times10^{-9}$), and subjects who were homozygous for rs6475448 showed increased ΔFEV1 from baseline in response to montelukast. The study identified a novel pharmacogenomic locus related to an improved montelukast response in asthmatics.

Zhao et al. [42] investigated the effectiveness and safety of current maintenance therapies including inhaled corticosteroids (ICS), long-acting β-agonists (LABA), and LTRAs for preventing exacerbations and improving symptoms in paediatric asthma. They performed a meta-analysis. They reported that combined ICS and LABA treatments were most effective for preventing exacerbations among paediatric asthma patients. Medium- or high-dose ICS, combined ICS and LTRAs, and low-dose ICS treatments seem to be equally effective.

The risks of using LTRAs as part of a strategy for ICS were investigated for asthmatic patients in a meta-analysis. Only one study addressed the risk of substitution of LTRAs for ICS in stable asthma, limiting any strong conclusions concerning this step-down strategy [43••].

Zileuton, a 5-LO inhibitor, inhibits the formation of LTs, whereas the lukast agents (montelukast, zafirlukast, and pranlukast) are receptor antagonists. Anti-LTs improve airway flow, decrease the need for rescue medication, and diminish the symptoms of asthma [3, 44, 45].

Antileukotrienes have been shown to be efficacious, and they have a good safety profile in patients with moderately severe asthma [46]. In patients with milder but persistent asthma, in whom disease control is not achieved with $\beta_2$-agonists, currently available consensus guidelines on the management of asthma suggest that low doses of ICS are the most effective treatment [47]. It is likely that antileukotrienes will also be effective for some of these patients; however, because low doses of ICS are highly effective for this patient population, antileukotrienes cannot be recommended as the preferred treatment (unless the patient cannot or will not use ICS). If antileukotrienes are chosen as the next line of treatment, a therapeutic trial of 2–4 weeks will allow a decision to be made concerning treatment efficacy. If the treatment is ineffective, it should not be continued beyond this time [46].

A review of the Cochrane database suggested that antileukotrienes are less effective than ICS for chronic asthma [48]. Fourteen trials were evaluated, among which 12 were performed in adults, one was performed in adults and adolescents (≥12 years), and one was performed in children (mean age, 10 years). The duration of intervention ranged from 4 to 37 weeks. The antileukotrienes used were montelukast, pranlukast, and zafirlukast. More patients who received antileukotrienes than ICS had an increased rate of asthma exacerbations. They concluded that, in patients with chronic asthma, daily antileukotrienes are not as effective as ICS and increase asthma exacerbations requiring systemic corticosteroids [48].

Antileukotrienes serve as an alternative monotherapy to ICS in the management of mild persistent asthma in adults and children [49]. As monotherapy in adults and children with persistent asthma and moderate airway obstruction, ICS is superior in most secondary outcomes, including exacerbation requiring hospital admission, $FEV_1$ and other lung function parameters, asthma symptoms, nocturnal awakenings, rescue medication use, symptom-free days, the quality of life, and parent and physician satisfaction [50]. Furthermore, antileukotriene therapy is associated with an increased risk of withdrawals due to poor asthma control and exacerbation requiring systemic corticosteroids. On the other hand, asthma

control may remain suboptimal when relying on ICS because of problems with compliance, poor inhaler technique, and concerns about the side effects of steroids [51]. In this case, montelukast may be an alternative treatment for mild persistent asthma as a monotherapy [11].

LTRAs are indicated as an add-on therapy to ICS and are alternatives to long-acting $\beta_2$-agonists in moderate to severe persistent asthma [49]. Compared to long-acting β2-agonists as an add-on therapy to ICS in patients with moderate to severe persistent asthma, montelukast is less efficacious and costs more [50]. However, LTRAs might decrease small airway/alveolar sites of inflammation when combined with ICS therapy, as shown by a higher reduction in the fractionally exhaled nitric oxide levels, a marker of inflammation, in combination therapy than ICS alone [52]. Antileukotriene agents are also widely used for the treatment of paediatric asthma. In children, maintenance treatment with ICS for pure episodic (viral) wheezing is ineffective, but maintenance as well as intermittent montelukast can play an efficient role in both episodic and multi-trigger wheezing [53]. Furthermore, LTRAs do not affect the short-term growth rate of lower legs in prepubertal children [54]. In addition, they are particularly beneficial for patients with exercise-induced asthma. They can be used prior to exercise to prevent exercise-induced bronchoconstriction similar to short- or long-acting $\beta_2$-agonists [11, 55].

LTRAs also have beneficial effects on aspirin-sensitive rhinitis and asthma [49, 56]. Aspirin sensitivity is characterised by intense eosinophilic inflammation of nasal and bronchial tissues in non-atopic patients with chronic rhinosinusitis and/or nasal polyps [34]. Montelukast reduces peripheral blood eosinophilia but does not affect tissue eosinophilia [11, 56].

Schäper et al. [57••] reported that $LT_1$ receptor blockade by montelukast led to a significant decrease in eosinophil inflammation accompanied by a reduction in other mediators such as neurokinin A and substance P in the nasal lavage fluid of patients with nasal polyps and asthma, with or without aspirin intolerance.

## Antileukotrienes in Allergic Rhinitis

Allergic rhinitis (AR), which is clinically expressed by sneezing, rhinorrhea, nasal itching, and congestion, is an allergen-driven mucosal inflammatory disease that is modulated by immunoglobulin E. Epidemiological studies have indicated that the prevalence of AR continues to increase, and it has been a worldwide health problem that places a significant healthcare burden on individuals and society. Recently, montelukast has exhibited anti-inflammatory properties; therefore, LTRAs may serve a more important role for the treatment of AR [58].

Lu et al. [59] evaluated the treatment outcomes of LTRAs as a monotherapy or combined with second-generation oral $H_1$-histamines for the treatment of allergic rhinitis to provide a basis for optimising clinical therapeutic strategies. Treatment outcomes, including the daytime nasal symptom score (DNSS), nighttime symptom score (NSS), composite symptom score (CSS), daytime eye symptom score (DESS), and the rhinoconjunctivitis quality of life questionnaire (RQLQ), were used to evaluate the therapeutic effects of LTRAs on seasonal and perennial AR. Montelukast statistically significantly reduced the NSS, but not the DNSS, in patients with seasonal AR compared to loratadine. The combination therapy of montelukast and loratadine statistically significantly improved the CSS compared to either montelukast or loratadine monotherapy. Montelukast, a representative LTRA, can be used as first-line therapy for AR, with comprehensive improvement of nasal and ocular symptoms and quality of life in AR patients. Montelukast combined with loratadine can significantly improve diurnal and nocturnal symptoms in patients with seasonal AR, and their curative effects are better than their effects after a single use.

The LTRA montelukast is FDA-approved for the treatment of symptoms of seasonal AR in adults and paediatric patients 2 years of age and older and perennial AR in adults and paediatric patients 6 months of age and older [60•]. While several other LTRAs are available in the USA, montelukast is the only LTRA approved by the FDA for AR. Systematic literature reviews and meta-analyses (predominantly based on controlled studies of montelukast in adults with seasonal AR) have concluded that LTRAs are more effective at controlling symptoms and improving the quality of life than placebo [61–64]. While some studies have shown that LTRAs are as effective as oral antihistamines [61, 63–65], others have shown that LTRAs are less effective [62] than oral antihistamines and INS [61–65]. In a single randomised, double-blind study, montelukast had a similar effect to pseudoephedrine in reducing the symptoms of AR except the symptoms of nasal congestion, for which pseudoephedrine was more effective [66]. In patients with both AR and asthma, montelukast improves both conditions [67–70].

Montelukast is generally well tolerated and is not associated with drowsiness [71]. In placebo-controlled trials, behaviour-related adverse events were infrequent [72]. However, some reports have demonstrated rare drug-induced neuropsychiatric events (including aggression, depression, suicidal thinking, and behaviour) [73]. Suicidal ideation was reported in 1 of 9929 patients (0.01 %) treated with montelukast in clinical trials [74].

Montelukast has traditionally been more expensive than oral antihistamines [75], although the cost differential has been lessened with the introduction of generic montelukast. Because montelukast is currently more expensive and equally as effective as or less effective than oral antihistamines for

AR, and because it is less effective than INS, clinicians should not routinely offer an LTRA as primary therapy for patients with AR. However, there may be a subset of patients who have AR and asthma who may benefit from this medication.

LTRAs should not routinely be used as additive therapy for patients benefiting from INS for AR [76–78]. Three studies with arms that compared INS to INS+LTRA did not show a significant benefit to adding LTRA in their primary outcome. The largest trial enrolled 102 patients [78].

Histamine has long been implicated as a major mediator of AR, primarily causing sneezing, nasal itching, and rhinorrhea. In contrast to histamines, LTs such as $LTC_4$ and $LTD_4$ contribute to vascular permeability and vasodilation, resulting in mucosal swelling, which causes rhinorrhea and nasal congestion [9, 79, 80]. In addition, the nasal allergen challenge-induced release of CysLTs has been correlated with allergic symptoms [8, 81, 82]. Furthermore, nasal congestion in the early phase and late phase is accompanied by a significant increase in CysLTs in nasal lavage fluid from AR patients [81]. Therefore, CysLTs play an important role in AR [83].

The levels of histamine and CysLTs are elevated in the nasal secretion of patients with AR when triggered by IgE-mediated reactions [82]. In addition, the release of histamine and LTs contributes to the allergic nasal symptoms by having selective effects on the nose [84, 85]. Histamine nasal challenge induces neurological responses, such as itching and sneezing, but affects nasal congestion to a lesser degree. Therefore, LTs contribute to the pathophysiology of AR and potentially increase both mucus production and congestion [83].

The concomitant use of loratadine and zafirlukast is significantly more effective for diminishing the response to an inhaled allergen challenge than the use of loratadine or zafirlukast alone [86]. Both histamine and LTRAs have antiallergic and anti-inflammatory properties, including effects on mediator release and chemoattraction of inflammatory cells. These findings suggest that administering antihistamine and LT modifiers together might result in an amplified effect for the treatment of allergic rhinitis.

In recent animal studies, nasal $LTD_4$ challenge was shown to increase nasal airway resistance [87], and anti-LT can inhibit the antigen-induced increase in nasal resistance [88]. Ho et al. [83] showed that both a low dose or high dose of anti-LT, with or without additional antihistamine, improved subjective nasal obstruction and objective nasal resistance. These results indicate that anti-LTs are more powerful for the improvement of nasal congestion than new-generation antihistamines for AR.

CysLTs promote various proinflammatory actions, including microvascular leakage, inflammatory cell chemotaxis (particularly eosinophils), mucus hypersecretion, and neuronal stimulation, all of which are relevant to the pathophysiology of AR [89, 90]. Recent evidence has suggested the involvement of CysLTs in the pathophysiology of AR: CysLTs are released from inflammatory cells that participate in AR [91], receptors for CysLTs are located in nasal tissue [92], CysLTs are increased in patients with AR and are released following allergen exposure [93], nasal administration of CysLTs reproduces the symptoms of AR [89], CysLTs play roles in the maturation and tissue recruitment of inflammatory cells [9], there is a complex interregulation between CysLTs and various inflammatory mediators, CysLTs increase nasal vascular permeability and blood flow, inducing plasma protein exudation and leading to blockage and mucus secretion, and levels of CysLTs rise in ragweed-sensitive patients during ragweed season [90, 93].

The proinflammatory effects of CysLTs have been well described in asthma and rhinitis. CysLTs induce bronchospasm (1000 times more potent than histamines), oedema, mucus, and hypersecretion; attract inflammatory cells such as eosinophils; increase airway hyperreactivity and vascular leakage; and stimulate tachykinins. LT synthesis can be inhibited through two different mechanisms: by inhibiting 5-lipoxygenase-activating protein (FLAP) in the 5-lipoxygenase pathway with the drug Zyleuton, and by blocking the $CysLT_1$ receptor with the drugs montelukast, pranlukast, or zafirlukast. CysLTs play an important role in the pathophysiology of AR and comorbid diseases such as rhinosinusitis and NP. Antileukotrienes are prescribed for the treatment of AR [94].

Antileukotrienes have been shown to be effective for AR, producing significant improvements in daytime nasal symptoms and in the quality of life [3, 45].

Clinical trials of LTRAs and synthesis inhibitors for the treatment of AR have shown a modest effect compared to placebo. A 2-day outdoor study was conducted in Iowa during the ragweed season comparing zafirlukast with placebo. Nasal congestion improved ($p<0.01$) from the evening after dosing through the second day in patients who had received 20 and 40 mg. Small ($p<0.05$) improvements were noted in sneezing and rhinorrhea as well. However, there was little clinical change in the clinical end points in patients who had received 100 mg [95]. Pranlukast (150 and 300 mg) and loratadine (10 mg) were compared in a 4-week double-blind, placebo-controlled trial in patients with seasonal AR. The mean symptom scores were significantly reduced in the group that had received pranlukast (150 mg). There was a trend toward symptom reduction in the loratadine and pranlukast (300 mg) groups. All treatments were well tolerated [96].

Montelukast, a potent, selective LT antagonist, was studied during the spring of 2000 in 1302 subjects with

seasonal AR to a relevant allergen. Subjects were randomised to treatment with 10 mg montelukast, 10 mg loratadine, or placebo. The primary efficacy variable, change from baseline in the daytime nasal symptom scores as well as secondary end points (nighttime and composite symptom scores) significantly ($p<0.01$) favoured the treatment groups over placebo [97]. A small, 33-subject trial in patients with seasonal AR compared 20 mg b.i.d. zafirlukast with 200 mg b.i.d. intranasal beclomethasone or placebo. Symptom scores decreased in the nasal steroid group but not in the zafirlukast or placebo groups. There was a significant increase in activated eosinophils in biopsy specimens of nasal tissue in the zafirlukast and placebo arms of the study [98].

Because LTs clearly produce significant nasal obstruction with little effect on discharge or pruritis, and histamines induce pruritis and drainage with no concomitant nasal obstruction, combination therapy by blocking LTs and histamines seems to be a reasonable approach. A multicentre pilot study in California investigated the hypothesis of combination mediator LT and histamine antagonist therapy in patients with seasonal AR. Four hundred sixty subjects were randomised to 10 mg montelukast combined with 10 mg loratadine, 10 mg montelukast, 20 mg montelukast, and 10 mg loratadine or placebo in the spring of 1997 [25]. The combination group showed significant improvement in the daytime, nighttime, and composite symptom scores. The rhinitis quality of life improved ($p<0.05$) in the combination group as well as in the loratadine and montelukast (10 mg) groups [99]. A similar multicentre study was performed nationally in the fall of 2000 comparing 10 mg montelukast combined with 10 mg loratadine with 10 mg montelukast and 10 mg loratadine or placebo. Significant improvement was noted in the primary efficacy variable, daytime nasal symptom score, in the combination group as well as the montelukast and loratadine groups compared to placebo [100].

## Conclusion

CysLTs (LTC4, LTD4, and LTE4) promote various pro-inflammatory actions, including microvascular leakage, inflammatory cell chemotaxis (particularly eosinophils), mucus hypersecretion, and neuronal stimulation, all of which are relevant to the pathophysiology of allergic rhinitis. They are also effective for asthma and in selected cases of chronic rhinosinusitis with nasal polyposis. For adults and children with chronic rhinosinusitis without nasal polyps, antileukotrienes are not recommended.

**Acknowledgments** With exception of data collection, preparation of this paper including design and planning was supported by Continuous Education and Scientific Research Association.

**Compliance with Ethics Guidelines**

**Conflict of Interest** Drs. Cingi, Mulak, Ipci, and Sahin declare no conflicts of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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