

Recent advances in antileukotriene therapy

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Purpose of review

Despite profound effects of leukotrienes in experimental models, clinical responses to antileukotriene drugs are highly heterogeneous. This review discusses recent advances concerning the molecular mechanisms of antileukotrienes as well as their efficacy in various clinical scenarios and patient groups.

Recent findings

Appreciation of the role of leukotriene E4 and the existence of its distinct receptors may explain the limited efficacy of current leukotriene receptor antagonists. Pharmacogenetic studies highlight the influence of several leukotriene pathway genes on clinical responsiveness. Benefits of addition of antileukotrienes to inhaled corticosteroids in chronic adult asthmatics have been shown, but their role in acute asthma is unclear. Evidence suggests they are not a first-line treatment for allergic rhinitis or urticaria, but may provide useful additional therapy. In children antileukotrienes provide symptomatic benefit in preschool wheezers, but have no clear role in bronchiolitis or acute asthma. Adherence to montelukast appears superior to inhaled corticosteroids. Use in sleep-disordered breathing and eosinophilic gastroenteropathies warrants further investigation. Despite recent concerns thorough analysis of existing data suggests antileukotrienes are well tolerated drugs. The possible link with Churg-Strauss syndrome requires further investigation.

Summary

The leukotriene pathway remains an attractive target in asthma and allergic disease, particularly in light of renewed appreciation of the role of leukotriene E4. Clarification of the clinical role of antileukotrienes is needed.

Keywords

antileukotriene, asthma, LTE4, pharmacogenetics, rhinitis

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Introduction

Characterization of the leukotrienes began following their identification as components of the slow-reacting substance of anaphylaxis (SRS-A) [1,2]. They are metabolites of cellular arachadonic acid and contribute to smooth muscle contraction, eosinophilic inflammation and mucus production. The leukotriene pathway is outlined in Fig. 1. Current antileukotriene therapies include the ‘-lukasts’ – cysteinyl leukotriene receptor blockers – and inhibitors of the enzyme 5-lipo-oxygenase. This article considers recent basic and clinical advances in antileukotriene therapy.

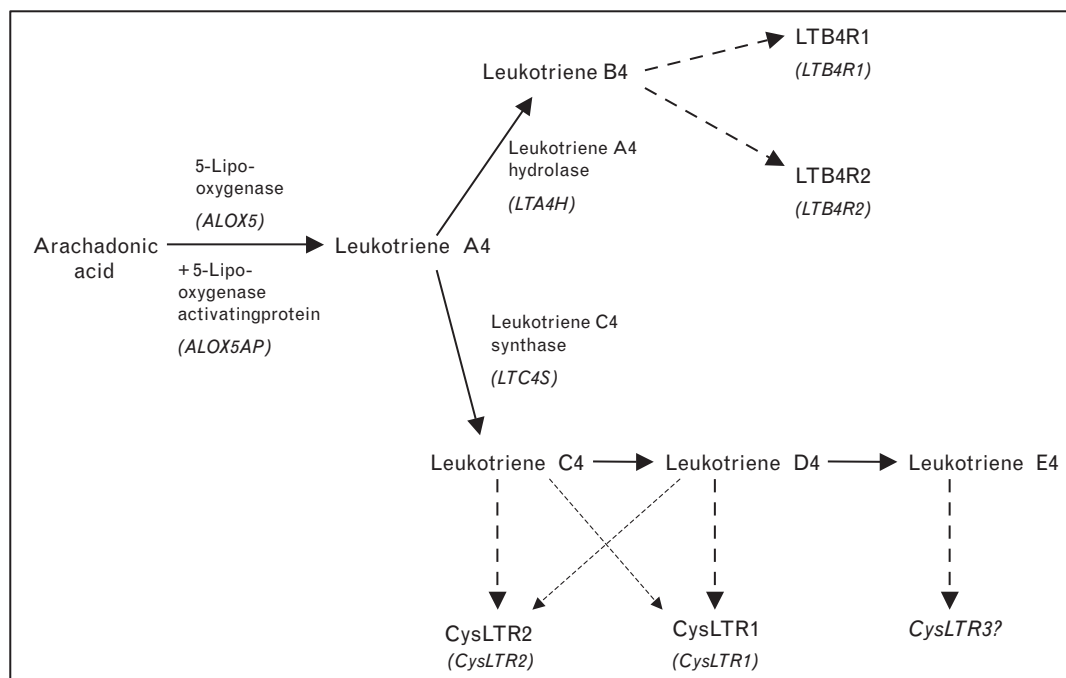
Leukotriene pathway genetics and pharmacogenetics

Leukotriene pathway gene polymorphisms have been associated with asthma, atopy, aspirin-sensitive asthma and response to leukotriene modifiers. Findings have

recently been extensively reviewed [3*,4*]. The most reproducible associations have been for polymorphisms of the ALOX5, LTC4S and CysLTR1 genes; LTC4S polymorphisms in particular have been associated with response to antileukotrienes. The population-attributable effect of polymorphisms identified thus far is, however, relatively minor.

Duroudier *et al.* [5*] evaluated a large, predominantly Caucasian, UK cohort for association of CysLTR1 gene promoter polymorphisms with asthma, atopy and related phenotypes. Interestingly, the wild-type allele for a common A>G single-nucleotide polymorphism (SNP) was significantly associated with atopy, but only in females [5*]. The potential mechanisms for this finding require further investigation.

Via *et al.* [6] investigated associations of ALOX5AP and LTA4H gene polymorphisms with asthma, lung function and total IgE in two Latino populations. They

Figure 1 Leukotriene 5-lipo-oxygenase pathway showing molecules, receptors, enzymes and genes (*italics*)

Within myeloid cells arachadonic acid is converted to leukotriene A4 by 5-lipo-oxygenase with the assistance of 5-lipo-oxygenase activating protein. Subsequent conversion to leukotriene B4 or C4 occurs under the influence of leukotriene A4 hydrolase or leukotriene C4 synthase, respectively. These leukotrienes exit into the extracellular space. Leukotriene B4 binds to leukotriene B4 receptor 1 (LTB4R1), which is predominantly expressed on leukocytes, and receptor 2 (LTB4R2), which has a more ubiquitous expression. Leukotriene C4 has a higher affinity for cysteinyl leukotriene receptor 2 (CysLTR2) than receptor 1 (CysLTR1); it also undergoes further metabolism in the extracellular space to leukotriene D4 and then leukotriene E4 by sequential removal of glutamic acid and glycine moieties. Leukotriene D4 has a preferential effect at CysLTR1. Leukotriene E4 is postulated to exert effects through at least one distinct receptor. Cysteinyl leukotriene receptors are expressed on leukocytes but also appear to be expressed on lung smooth muscle cells and other tissues.

identified polymorphisms associated with protection from asthma, but, paradoxically, also with lower FEV1. Furthermore, one polymorphism associated with protection had previously been positively associated with asthma in a UK population [7]. Whilst both studies suggest a role for the LTB4 arm of the pathway, the disparate results suggest associations may be population-specific.

Mougey *et al.* [8^{*}] demonstrated a role *in vitro* for membrane proteins OATP2B1 and OATP1A2 in carrier-mediated transport of montelukast. OATP2B1 is expressed in a wide range of tissues, including small intestine. They analysed results of a randomized trial for associations between polymorphisms within the gene coding for OATP2B1 (*SLCO2B1*), and both plasma concentration and clinical responsiveness to montelukast. Heterozygosity for the same minor allele was associated with reduced responsiveness and lower plasma concentrations, with correlation between plasma concentration and response at 6 months.

ALOX5, LTC4S and CysLTR1 appear to be amongst the strongest candidates in the identification of leukotriene-

pathway genes affecting clinical asthma and allergy phenotypes. Whilst there may be important pharmacogenetic implications of polymorphisms within these and other genes, we are some way off practical use of genotyping to predict clinical responsiveness.

Leukotriene E4

Attention has recently focused on the pathobiological role of leukotriene E4 (LTE4) following re-evaluation of previous data [9^{*},10^{*}] and new work implying the existence of distinct LTE4 receptors in mice [11,12^{••}] (summarized below). This represents a shift from the assumption that LTE4 was largely inert based on its poor affinity for CysLTRs 1 and 2 *in vitro*.

Evidence for a distinct pathobiological role of leukotriene E4 in asthma and allergic inflammation and the existence of distinct LTE4 receptors (adapted from references [9^{*},10^{*},11,12^{••}]):

(1) Animal studies

- (a) LTE4 causes greater contraction of guinea pig trachea *in vitro* than LTC4 or LTD4.

- (b) LTE4 enhances hyper-responsiveness of guinea pig smooth muscle to histamine; LTC4 and LTD4 do not.
- (c) LTE4 has maintained or enhanced effect on skin swelling and lung inflammation in CysTLR1 and 2 receptor double knockout mice.
- (2) Human studies
 - (a) Injected LTE4 gives equal skin wheal and flare response to LTC4 and LTD4.
 - (b) LTE4 enhances lung eosinophilia in asthmatics; LTD4 does not.
 - (c) LTE4 alone shows an exaggerated bronchoconstrictor response in asthmatic lungs compared with effect in normal controls.
 - (d) Aspirin-sensitive asthmatics have enhanced hyper-responsiveness to LTE4 compared with nonaspirin-sensitive asthmatics.
 - (e) LTE4 is the most stable cysteinyl-leukotriene *in vivo*.

Maekawa *et al.* [11] studied skin swelling in response to injected leukotrienes in single or double CysLTR1 and 2 knockout mice. The response to LTE4 was enhanced in double knockouts. Paruchuri *et al.* [12**] showed LTE4 to be a potent mast cell mitogen and mediator of lung inflammation. Again, the response was maintained in double receptor knockout animals. They identified the known platelet receptor P2Y12 as a mediator of this effect. The P2Y12 antagonist clopidogrel inhibited LTE4-mediated lung inflammation, but not the skin response to LTE4, suggesting the existence of distinct LTE4 receptors at these two sites.

Clinical responsiveness

Antileukotrienes are viewed as add-on or second-line therapy in current guidelines for the treatment of asthma, rhinitis/rhinosinusitis and urticaria [13–15]. Patients with asthma exhibit heterogeneous responses to all classes of asthma medication. In clinical trials based on FEV1 changes, 34–53% of adults and up to 78% of children with asthma were nonresponders to montelukast [16–18]. Previous observations of associations between cigarette smoke exposure and responsiveness to montelukast have been repeated [19]. Clinical characteristics, biomarkers of inflammation and genetic polymorphisms associated with treatment responsiveness have recently been reviewed [20*] and are summarized in Table 1 [4*,8*,16,19,21–23,24*,25–27].

Adult asthma: chronic

Bronchial asthma often remains uncontrolled despite treatment with inhaled corticosteroids (ICS) with or without long-acting beta (2)-agonists (LABA). In a Swiss study [28*] of 1380 patients with initially inadequately controlled asthma multiple regression techniques were

Table 1 Phenotypic, environmental and genetic factors associated with response to antileukotrienes

Phenotype	References
Children	
Younger age	[16]
Shorter duration of asthma symptoms	[16]
Fewer baseline asthma control days	[21]
Female	[19]
Environmental tobacco smoke exposure	[19]
Higher urinary LTE4: exhaled nitric oxide ratio	[19]
Adults	
Smoking	[22]
Genes	
ALOX-5	
Tandem repeat polymorphisms in promoter region associated with response to montelukast	[23]
SNPs associated with improvement in lung function on montelukast	[4*,24*,25]
SNPs associated with improvement in lung function on zileuton	[4*]
LTC4 synthase SNP (-444A>C)	[26]
HLA-DPB1*0301	[26]
CYSLTR1/R2 SNPs	[25]
SLCO2B1 (OATP2B1 transport protein)	
SNP associated with montelukast responsiveness and plasma levels	[8*]
IL-13	
1112C/T polymorphism in EIA	[27]
CC 77.4% respond, CT or TT 51.9% respond	
MRP1	[24*]
Intron SNP associated with FEV1 response to montelukast	
LTA4H	[24*]
5' UTR polymorphism affects asthma exacerbations on montelukast	

EIA, exercise induced asthma; LTA4H, leukotriene A4 hydrolase; MRP1, multidrug resistant protein; SNP, single-nucleotide polymorphism; UTR, untranslated region.

used to identify predictors of improved control, defined as an absolute decrease of 0.5 points or more in the Asthma Control Questionnaire between the baseline (V1) and follow-up visit (V2).

Asthma control improved in 85.7% with add-on montelukast treatment reported in 82.9%. Significantly, withholding montelukast halved the probability of achieving improved asthma control [odds ratio (OR) 0.51, 95% confidence interval (CI) 0.33–078].

In a prospective, open-label study [29*] patients over 17 years (n = 1681) with mild-to-moderate asthma received oral montelukast 10 mg added to ICS or ICS + LABA, and were followed for 6 months. Mean Asthma Control Test (ACT) scores (primary endpoint) improved from 14.6 ± 4.6 (baseline) to 19.4 ± 4.4 (month 6; *P* < 0.0001). The percentage of patients with uncontrolled (57.5%) or poorly controlled (25.0%) asthma at baseline decreased at month 6 (17.6 and 21.7%, respectively); the percentage of patients with well controlled (13.9%) or completely controlled (1.2%) asthma at baseline increased at month 6 (47.5 and 11.4%, respectively). Mini AQLQ scores and FEV1 also improved significantly.

Both authors concluded that in patients insufficiently controlled with ICS or ICS + LABA, daily add-on montelukast improved asthma control.

Adult asthma: acute

A randomized, double-blind, placebo-controlled trial [30] evaluated oral montelukast in older patients (mean age 52) hospitalized with acute asthma. Patients received montelukast ($n=50$; 43 F) or placebo ($n=50$; 36 F). No significant effect was seen on length of stay, peak flow, FEV1, oxygen saturation or symptoms.

A double-blind, placebo-controlled, parallel study [31] evaluated montelukast added to standard care for 5 weeks in 77 patients hospitalized with acute severe asthma. Despite significant improvement in peak expiratory flow rate (PEFR) the morning after admission, the primary endpoint – length of hospitalization – was unaffected.

The addition of 7 mg intravenous montelukast to standard care in adults with acute asthma was studied in a multicenter randomized double-blind placebo-controlled study [32]. Recruited patients had FEV1 50% of predicted after 1 h of standard care alone; 291 then received in addition montelukast and 292 placebo. Montelukast significantly improved the primary endpoint: the change from baseline in FEV1 was 0.32 l (least-squares mean; 95% CI 0.27, 0.37) with montelukast vs. 0.22 l (0.17, 0.27) with placebo ($P < 0.001$). FEV1 improved at 10 min post-dose and for 2 h after administration. Treatment failure and hospitalization were lower with montelukast, but not significantly so (26.8 vs. 29.9% and 17.1 vs. 21.8%, respectively).

Allergic rhinitis

Recent studies confirm that montelukast is not a first-line treatment for uncomplicated allergic rhinitis. In a USA-wide study [33[•]] new allergic rhinitis patients prescribed montelukast (16% of 13703) as first-line therapy had higher medical costs and resource utilization than those prescribed oral antihistamines. These differences persisted after adjustment for patient-fixed effects, available confounders, and treatment propensity scores. The most effective allergic rhinitis treatment, topical nasal corticosteroid, was not considered in this study.

Lu *et al.* [34[•]] investigated concomitant use of montelukast and loratadine in seasonal allergic rhinitis (SAR) in two studies. The first showed the combination improved combined symptom scores compared with either drug alone, but was still inferior to nasal beclomethasone; the second failed to show superiority [34[•]].

Nasal polyps

Nasal polyposis is a chronic inflammatory disease of the upper respiratory tract affecting 2–4% of the population and two-thirds of patients with aspirin-sensitive asthma. Polyp histology is similar to that of asthma with abundant eosinophils, mast cells and high levels of proinflammatory cysteinyl leukotrienes. Di Capite *et al.* [35[•]] used immunohistochemistry, enzyme immunoassay, and cytoplasmic calcium ion (Ca^{2+}) imaging on cultured and acutely isolated human mast cells from patients with polyposis. They demonstrated that Ca^{2+} influx into mast cells via calcium release activated channels (CRAC) stimulated LTC4 production, which then activated further Ca^{2+} influx. A combination of low concentrations of a CRAC channel blocker and a leukotriene receptor antagonist was as effective at suppressing mast cell activation as a high concentration of either antagonist alone. Further trials are needed to establish whether this can be translated into clinical usefulness.

Urticaria

According to recent guidelines [15] leukotriene-receptor antagonists (LTRAs) are considered as potential add-on therapy in chronic urticaria in individuals who fail to respond to four times the standard daily dose of non-sedating antihistamines. Convincing evidence for their efficacy in the treatment of urticaria in large clinical trials is lacking.

Paediatric use

Antileukotrienes are a recognized add-on therapy to asthma in children which is uncontrolled by standard dose inhaled corticosteroids; consideration has been given to their use as monotherapy, particularly in viral-induced wheeze in younger children. Antileukotrienes may be indicated in the treatment of allergic rhinitis in children, whilst experimental uses have included the treatment of bronchiolitis, sleep-disordered breathing and eosinophilic gastrointestinal disease.

A randomized trial of 7-day courses of montelukast vs. inhaled budesonide vs. placebo for intermittent viral wheeze in preschool children showed no differences in frequency or duration of episodes between groups [36]. Symptoms were reduced in both interventional groups, with neither superior. Use of montelukast acutely in proven [37] or suspected [38] bronchiolitis has undergone further investigation following previous studies of efficacy in preventing recurrent symptoms [39]. Administration beginning acutely on admission had no effect on length of stay, severity or nasal cytokine profiles [38]. Similarly, 4 weeks, treatment with montelukast following admission had no benefit over placebo on recurrent symptoms [39].

Multivariate analysis of the Paediatric Asthma Controller Trial has been used to identify phenotypes amongst school-age children with persistent asthma that might predict response to inhaled corticosteroids or montelukast [40^{••}]. Several indicators of classical atopic, eosinophilic asthma – total IgE, blood eosinophils, exhaled nitric oxide, methacholine PC20 – as well as a history of parental asthma, predicted superior asthma control with inhaled fluticasone. No factors predicted improved control with montelukast. A cross-sectional study of antileukotrienes in Puerto Rican and Mexican-American children demonstrated augmented bronchodilator response to albuterol in the former only [41[•]]. Recently, the variability of response to different asthma controller medications has been highlighted in a large randomized cross-over study [42[•]]. The relative responses of 7–16-year-old asthmatics uncontrolled on 100 mcg fluticasone twice daily to step-up therapy with addition of a LABA, montelukast or increased dose fluticoid were compared. Strikingly, 98% showed differential responses. Of note, children were equally likely to have an optimal response to montelukast or increased fluticasone, although the greatest proportion had an optimal response to LABA addition. Black children had a lower rate of optimal response to montelukast than other ethnic groups.

The potential steroid-sparing effect of montelukast has also been investigated. Children with acute asthma stabilized in the emergency department and deemed fit for discharge were randomized to receive 5 days of oral prednisolone or montelukast in a noninferiority trial [43[•]]. Treatment failure and requirement for additional pharmacotherapy were both significantly greater in the montelukast group. An attempt at investigating use of montelukast or azithromycin as inhaled steroid-sparing agents in children with moderate-to-severe asthma was prematurely terminated due to problems with compliance and improvements in control under observation during the run-in phase [44]. However, a futility analysis suggested that even with adequate randomization neither intervention was likely to prove significant.

Improved adherence to antileukotrienes compared with inhaled corticosteroids has been cited as an advantage of the former in the ‘real world’ setting [45]. Over 1 year, adherence to combined inhaled fluticasone and montelukast was recorded in an observational study [46[•]] of economically disadvantaged African American children with asthma. ‘As-prescribed’ adherence was greater for montelukast, although adherence to both was low and fell during the study. When divided into high and low compliance groups for each medication, symptom scores were better for the compliant vs. the poorly adherent montelukast group, whereas this was not the case for fluticasone. Conversely, healthcare utilization was significantly

reduced in the compliant fluticasone group, a feature not seen for montelukast.

The benefit of additional antileukotriene in children with asthma and persistent allergic rhinitis already taking fexofenadine was studied over 16 weeks in a randomized trial [47]. Symptom scores were improved at 4 weeks but not thereafter.

Following the success of a previous trial of antileukotrienes in the treatment of sleep-disordered breathing in children [48], investigators attempted to elucidate the molecular mechanisms involved. *In vitro*, adenotonsillar cell proliferation of affected children was found to be enhanced by LTD4 and suppressed by antileukotriene drugs [49[•]]. Urine cysteinyl leukotriene level also proved a positive predictor of elevated obstructive apnoea-hypopnoea index in a separate study [50[•]]. Whether this association is causal and independent of adenotonsillar size remains to be proven.

The use of montelukast to treat dyspepsia in children with biopsy-confirmed duodenal eosinophilia was the subject of a small open trial [51]. Despite an 83% symptom response rate to combined montelukast and ranitidine no histological changes were identified following repeat biopsy, nor were there any changes in serum cytokine levels. Firmer evidence is needed both to clarify if montelukast is an effective treatment for gastrointestinal eosinophilic conditions and, if so, to demonstrate the mechanism of action.

Adverse events

In June 2009, based on postmarketing surveillance data, the US Food And Drug Administration (FDA) requested that manufacturers of antileukotriene drugs include within drug-prescribing information the potential risk of neuropsychiatric events. Analysis by Merck of double-blinded, placebo-controlled trials revealed no differences in behaviour-related adverse events between montelukast and placebo, nor increased risk of suicidal tendency [52,53]. The authors note, however, that most trials involved treatment periods of less than 2 months and were not designed to identify adverse psychiatric outcomes. A safety and tolerability review of Merck-sponsored paediatric double-blind, placebo-controlled trials and their open-label extensions revealed similar safety profiles for montelukast and placebo/active control [54].

The possible link between use of antileukotrienes and development of Churg-Strauss syndrome (CSS) remains controversial. Whilst a mechanism for this has yet to be demonstrated and links have not been identified in prospective studies, a recent retrospective analysis

[55•] of the FDA Adverse Event Reporting Database found leukotriene receptor antagonist drugs to be implicated in 163 of 181 cases of suspected drug-induced CSS. Furthermore, most of these cases could not be explained by steroid withdrawal.

Hepatotoxicity associated with zileuton, the only currently licensed 5-lipoxygenase inhibitor, has limited its clinical use. A potential mechanism for toxicity may be via the formation of the reactive metabolite, 2-ABT-S-oxide. Recently, this has been shown to irreversibly inhibit liver glutathione transferases *in vitro*, hence reducing the ability of the liver to detoxify 2-ABT-S-oxide via conjugation with glutathione [56].

Despite these issues, antileukotrienes, in particular montelukast, are generally well tolerated and have a good safety profile. Postmarketing surveillance continues to be important; large prospective studies aimed at clarifying whether a link exists between LTRAs and CSS would also be beneficial.

Conclusion

Given the variable efficacy of antileukotrienes in clinical practice, the genetic, pharmacogenetic and environmental factors affecting responsiveness are valuable areas for further study.

The appreciation of a pathobiological role for LTE₄ is a significant advance. It may explain the relatively modest clinical effect of antileukotrienes despite profound effects in experimental models of allergy and asthma. Here is a potential area for drug development and perhaps a clue to the mechanism of aspirin desensitization. Recent work confirms an add-on role for antileukotrienes in chronic asthma treatment; there is insufficient evidence to recommend them for use in acute asthma. Acute and chronic steroid-sparing effects are unclear. Antileukotrienes remain a second-line treatment for allergic rhinitis; further study of their use in eosinophilic nasal polyposis is warranted.

Antileukotrienes confer symptomatic benefit in pre-school recurrent wheezers, but are not of proven benefit in bronchiolitis. Use in childhood sleep-disordered breathing and eosinophilic gastroenteropathies deserves further study. They are generally well tolerated medicines; the rare but important link with CSS requires further investigation.

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References and recommended reading

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- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

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