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Review article

Leukotrienes and leukotriene modifiers in pediatric allergic diseases

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Abstract
Leukotrienes are potent pro-inflammatory lipid mediators derived from arachidonic acid through several enzymatic pathways. They have an essential role in allergic inflammation, where they induce bronchoconstriction, airway edema, and chemotaxis of the inflammatory cells in the airways, nasal and conjunctival tissues. Leukotriene modifiers include leukotriene receptor antagonists (montelukast, zafirlukast and pranlukast) and leukotriene synthesis inhibitors (zileuton). These medications have been extensively used in childhood allergic diseases. This review will highlight the leukotriene pathway and its role in allergy as well as the effects of leukotriene modifiers in different allergic disorders.

Allergic inflammation is due to a complex interplay between several inflammatory cells, including mast cells, basophils, lymphocytes, dendritic cells, eosinophils, and sometimes neutrophils. These cells produce multiple inflammatory mediators, including lipids, purines, cytokines, chemokines, and reactive oxygen species. Allergic inflammation affects target cells, such as epithelial cells, fibroblasts, vascular cells, and airway smooth muscle cells, which become an important source of inflammatory mediators.[1] Leukotrienes are potent newly formed lipid mediators that are derived from arachidonic acid upon cellular activation, including IgE receptor cross-binding on mast cell surface.[2]

Leukotrienes ("leuko," from white blood cells; and "trienes," three conjugated double bonds) comprise a family of products of the 5-lipoxygenase (5 Lipo-pathway of arachidonic acid metabolism.[3] They are divided into two classes: the chemoattractant LTB4 and the spasmogenic cysteinyl leukotrienes [CysLTs: LTC4, LTD4, and LTE4] which have been termed previously as slow-reacting substance of anaphylaxis (SRS-A).[4]

Biosynthesis of leukotrienes (figure1)

The synthesis of leukotrienes from arachidonic acid is initiated by 5-lipoxygenase (5-LO) in concert with 5-lipoxygenase–activating protein (FLAP). Although FLAP does not have enzymatic activity, it enhances the ability of 5-LO to interact with its substrate.[5] Arachidonic acid, which is esterified on plasma membrane phospholipids, is cleaved by the action of different phopsholipase A2 enzymes, released and metabolized into LTA4. [2] LTA4 is converted by LTA4 hydrolase to LTB4, or it can be conjugated with reduced glutathione by LTC4 synthase to yield LTC4. LTB4 and LTC4 are exported from the cell by specific transporter proteins; the released LTC4 is converted to LTD4 which undergoes conversion to LTE4 by sequential amino acid hydrolysis.[3] LTA4 is highly reactive, with an estimated half-life less than 3 seconds. LTC4 and its metabolites, LTD4 and LTE4, are known as cysteinyl-LTs due to the common cysteine in their side chains.[6]

The enzyme 5-LO is mainly expressed in granulocytes, monocytes, macrophages, mast-cells and B lymphocytes.[7] Mast cells and eosinophils can produce large amounts of LTC4 from an endogenous pool of arachidonic acid. Human bronchial fibroblasts constitutively express 5-LO, FLAP, LTA4 hydrolase, and LTC4 synthase and produce cysteinyl-LTs and LTB4 spontaneously *in vitro*.[8]

Although nonleukocyte cells generally do not have sufficient 5-LO and FLAP to synthesize appreciable amounts of leukotrienes from arachidonate, such cells expressing distal LTA4-metabolizing enzymes can take up leukocyte-derived LTA4 and metabolize it into bioactive leukotrienes, a process that is termed *transcellular biosynthesis*.[6]

Leukotrienes and cytokines can regulate each other; interleukin-13, a product derived from type 2 helper T (Th2) lymphocytes that participates in the development of asthma, can up-regulate both the leukocyte biosynthesis of LTD4 and the expression of cellular type 1 Cys LT receptors (CysLT1). Moreover, LTD4 can up-regulate production of interleukin-13, as well as the expression of its receptor. The result of this cross-talk is a self-perpetuating circuit of inflammation and smooth-muscle contraction in which interleukin-13 and its receptor mediate some of the actions of LTD4, whereas LTD4–CysLT1 mediates some of the actions of interleukin-13.[3]

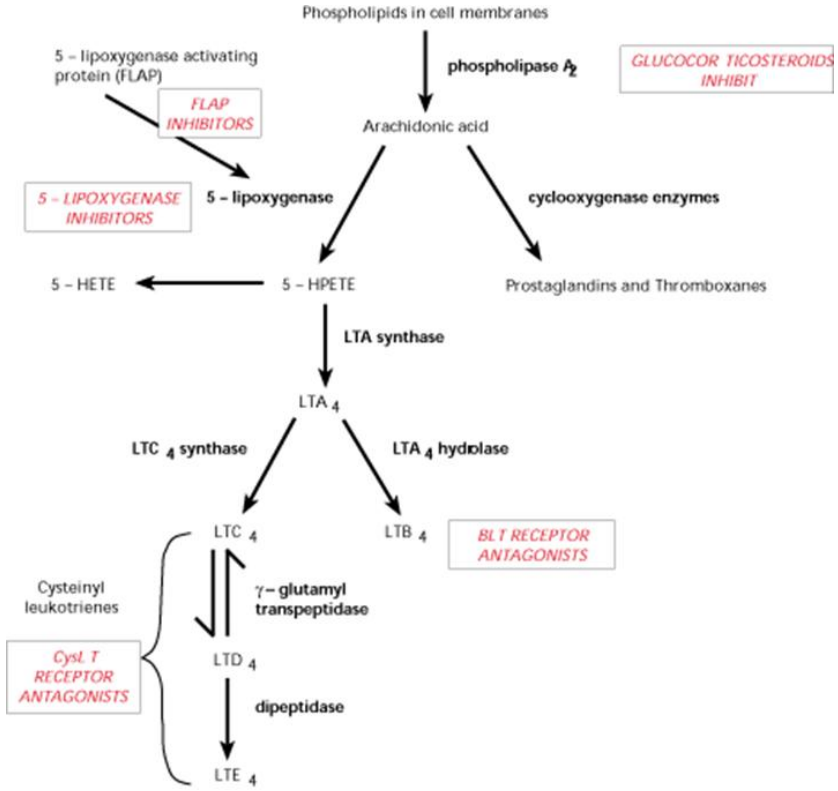

Figure 1. The main pathways to the formation of the leukotrienes and the sites of action of the current drug groups (in boxes) that can attenuate leukotriene responses (Quoted from O'Donnell SR. Leukotrienes: Biosynthesis and mechanisms of actions. Aust Prescr 1999; 22: 55-7.)

Receptors of leukotrienes

Leukotrienes act by binding to specific heptahelical receptors of the rhodopsin class that are located on the outer plasma membrane of structural and inflammatory cells.[9] Once ligated by the leukotriene, these receptors interact with G proteins in the cytoplasm, thereby eliciting increases in intracellular calcium and reductions in intracellular cyclic AMP. These proximal signals activate downstream kinase cascades in ways that alter various cellular activities, ranging from motility to transcriptional activation.[3]

Two G-protein coupled receptor subtypes for CysLTs (CysLT1 and CysLT2), that have 38% amino acid identity, have been identified. [10] The CysLT1 and CysLT2 receptors are broadly expressed by structural and hematopoietic cells. Some cell types (vascular smooth muscle) express mostly Cys-LT1 receptors[11], whereas others (endothelial cells) dominantly express CysLT2 receptors.[12] Both receptors are expressed by cells of the innate (macrophages, monocytes, eosinophils, basophils, mast cells, dendritic cells) and adaptive (T and B lymphocytes) immune systems, implying potentially cooperative functions in immunity and inflammation.[9]

CysLT1 receptor binds LTD4 with high affinity and LTC4 with lesser affinity, whereas CysLT2 receptor binds both LTC4 and LTD4 with equal affinities. Neither receptor exhibits substantial affinity for LTE4 in radioligand binding assays nor does LTE4 elicit strong signalling responses in cells expressing CysLT1 or CysLT2 in isolation.[11, 13] Increased vascular permeability induced by LTE4 in mice lacking CysLT1 and CysLT2 receptors suggests the existence of a third CysLT receptor that responds preferentially to LTE4.[14] Certain reported actions of CysLT are not readily explained by either CysLT1 or CysLT2, raising the possibility of the presence of CysLT1–CysLT2 heterodimers or additional receptors.[15] One candidate is G protein–coupled receptor 17 (GPR17), a dual-uracil nucleotide–CysLT receptor.[16]

Two LTB4 receptor subtypes (BLT1 and BLT2), that are cell surface G protein-coupled

seven transmembrane domain receptors, have been identified. These receptors differ in their affinity and specificity for LTB4 and their expression pattern. BLT1, a specific high affinity receptor for LTB4, is expressed predominantly on leukocytes including granulocytes, monocytes, macrophages, mast cells, dendritic cells, and effector T cells,[17] whereas BLT2, a low affinity receptor which can also bind to other eicosanoids, is expressed ubiquitously and their biological role in humans is unknown.[18]

Role of leukotrienes in allergic inflammation

CysLT1 receptor mediates sustained broncho-constriction, mucus secretion, and edema in the airways (figure 2).[19] CysLT inhalation in patients with asthma increases the number of sputum eosinophils and causes recruitment of eosinophils into the airway mucosa. [20] CysLTs prime progenitor cells to differentiate into mature blood cells, cause chemotaxis of eosinophils increasing their cellular adhesion and transendothelial migration across the vessel wall into the airways, increase eosinophil survival in response to mast cell and lymphocyte paracrine signals and activate eosinophils, mast cells, T-lymphocytes, monocytes and basophils. [21,22] LTB4 serves as a potent chemoattractant through ligation of the high affinity LTB4 receptor-1 (BLT1) on target cells.[23] LTB4 can have a central role in the neutrophilic inflammation that characterises severe asthma and asthma exacerbations.[24]

CysLT levels were found to be elevated in bronchoalveolar lavage[25] and induced sputum[26] from patients with asthma, when compared with levels in healthy volunteers at baseline and following exercise[27] or allergen challenge.[28] In patients with allergic rhinitis, specific allergen challenge provoked significant increases in nasal airway resistance, numbers of neutrophils and eosinophils, and levels of protein, histamine, LTB4, and CysLTs in nasal lavage fluid.[29] Also, LTB4 was found to cause eosinophil and neutrophil emigration into conjunctival tissue. LTB4 and LTC4 levels were reported to be increased in the tears of patients with seasonal allergic conjunctivitis.[30,31]

Several *in vivo* and *in vitro* studies suggest that leukotrienes are involved in the inflammation of the skin in atopic dermatitis, possibly by chemotaxis of inflammatory cells, vasodilatation and oedema, but their role is controversial.[32] The enzymatic activities of LTA4 hydrolase in peripheral blood leukocytes were found to be associated with disease severity in patients with atopic dermatitis and were reduced after improvement of the disease.[33]

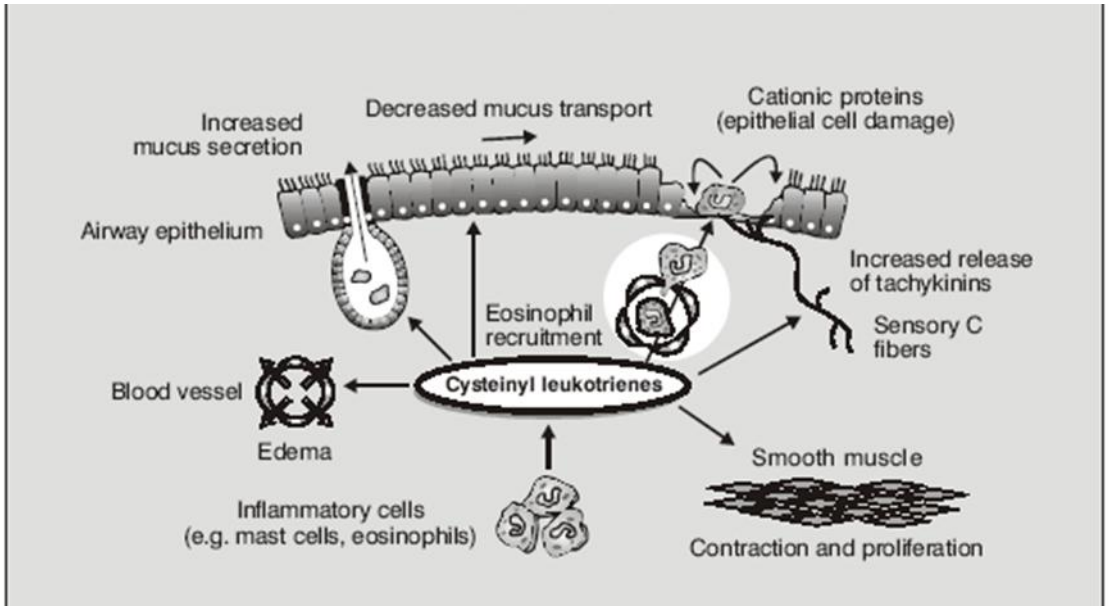

Figure 2. Leukotriene actions on airway structure.
(Hay DW, Torphy TJ, Undem BJ. Cysteinyl leukotrienes in asthma: old mediators up to new tricks. Trends Pharmacol Sci. 1995,16:304-9).

Leukotriene modifiers

Leukotriene modifiers have been available since 1997 for the treatment of asthma. By modifying leukotriene effects, these medications reduce the symptoms of allergies, asthma and possibly sinusitis and nasal polyps.[34] Leukotriene modifiers are classified in two groups; CysLT1 receptor antagonists (LTRAs) – zafirlukast, pranlukast and montelukast – block the binding of CysLTs to CysLT1 receptor and thus block the end organ response of leukotrienes; and leukotriene synthesis inhibitors – zileuton – block the biosynthesis of CysLTs.[35] There are also FLAP inhibitors, GSK2190915[36] and MK886[37] which are not FDA approved, but they have benefits in early and late allergic responses and cold induced asthma.[35]

Montelukast is the most prescribed LTRA in Europe and the USA, whereas pranlukast is only marketed in Japan and other Asian countries. Zafirlukast was the first LTRA that was approved in Europe, but it is not frequently prescribed due to possible food and drug interactions, and its twice daily administration regimen.[38] Montelukast can be used in children from the age of 2 years and has been formulated as a chewable, pink, cherry flavoured tablet.[39] The bioavailability is similar regardless of patient age, and absorption is not affected by food. No drug interactions have been documented.[40]

Zafirlukast is approved for the treatment of asthma in children aged 7 years or older. It is administered orally twice daily and is metabolized by the liver; hepatic cytochrome P450 which is inhibited by therapeutic concentrations.[41] Zileuton is approved for treatment of persistent asthma in patients 12 years or older.[40]

Dosage and route of administration of leukotriene modifiers are listed in table 1.

The role of leukotriene modifiers in pediatric allergic diseases

Bronchial asthma

Two Cochrane Reviews evaluated research comparing leukotriene inhibitors with inhaled corticosteroids in the management of recurrent and persistent asthma in children.[42,43] In 2002, Ducharme and Di Salvio[42], conducted a bibliographic search of randomized controlled clinical trials comparing the efficacy of antileukotrienes with inhaled corticosteroids (ICSs) in asthmatic patients and identified 27 trials of which 13 were of high methodological quality. Mild-to-moderate chronic asthmatic patients treated with LTRAs were 60% more likely to experience an asthma exacerbation requiring oral steroids than those treated with ICSs (in most trials the daily dose of ICSs was 400 mg of beclomethasone or equivalent). After 6 weeks of treatment, those patients who received ICS showed a significantly greater improvement in baseline FEV_1, morning peak expiratory flow rate, fewer nocturnal awakenings and respiratory symptoms, and less use of rescue medication. In 2004, Ng, et al[43] confirmed the earlier findings by Ducharme and Di Salvio[42] that patients on antileukotrienes are more likely to suffer an exacerbation requiring systemic steroids, to exhibit a lesser improvement in lung function, and to report more nocturnal awakenings and respiratory symptoms and greater use of rescue medication. The available evidence convincingly persuades against the use of LTRAs as first-line monotherapy in patients with mild-to-moderate asthma. It must be noted that only 3 of the 13 studies taken in the meta-analysis were conducted among children.[43] Combination therapy is less effective in controlling asthma in children with moderate persistent asthma than increasing to moderate dose of inhaled glucocorticoids.[44] Moreover, montelukast has not been demonstrated to be an effective inhaled glucocorticoid sparing alternative in children with moderate – to - severe persistent asthma.[45] In children with mild persistent asthma, montelukast withdrawal can result in enhanced airway inflammation, as reflected by increased fractional exhaled nitric oxide concentrations (FENO) and worsening of lung function.[46]

Leukotriene modifiers reduce viral-induced asthma exacerbations in young children aged 2-5 years with intermittent asthma.[47] Applications of leukotriene modifiers that remain under investigation are the treatment of persistent respiratory symptoms in children after respiratory syncytial virus infection[48] and the treatment of acute asthma exacerbations in children.[49] There are little data to suggest a role in acute asthma; small investigations demonstrated improvement in PEF but clinical relevance requires more study.[50]

Whether leukotriene modifiers prevent or ameliorate airway remodelling in patients with asthma is still being tested.[3] Using lung function tests and HRCT image technique, it was found that add-on therapy with montelukast improves distal lung function reflected by air trapping, but not airway wall thickness in moderate-to-severe asthma.[51]

Montelukast and zafirlukast provide protection against exercise-induced asthma (EIA) (Evidence A). A single oral dose of montelukast is as effective as inhaled salmeterol, a long-acting β2 agonist, in

preventing EIA. Its protective effects against EIA have been seen to occur as early as 1 hour,[52] and up to 24 hours after a single oral dose.[51] Moreover, its regular use during a 2-month period was not associated with the development of tachyphylaxis, as occurs with the use of salmeterol.[53] Also, zafirlukast is effective against EIA when administered immediately prior to exercise, and a single oral dose has been shown to attenuate EIA in children.[54]

Leukotirene modifiers are beneficial in patients with aspirin-sensitive asthma, a condition in which production of very high levels of CysLTs is typical. They were more beneficial than placebo in improving forced expiratory volume in one second, improving symptoms, decreasing exacerbations, and providing one more night per week of uninterrupted sleep in these patients.[55]

Table 1. Dosage and adverse effects of the leukotrienes modifiers commonly used.

Drug	Recommended oral dose	Adverse effects
Montelukast	- Children two to five years:4 mg before bed - Children six to 14 years: 5 mg before bed - Children ≥ 14 years: 10 mg before bed	Headache, abdominal pain; Concerns about possible association with Churg-Strauss syndrome
Zafirlukast	- Children seven to 11 years: 10 mg twice daily - Patients ≥ 11 years: 20 mg twice daily	Headache, rhinitis, pharyngitis, abdominal pain, liver enzymes elevations; multiple drug interactions. Concerns about possible association with Churg-Strauss syndrome
Zileuton	- Patients > 12 years: 600 mg four times daily	Headache, abdominal pain, liver enzymes elevations and multiple drug interactions

Allergic rhinitis

The FDA has approved montelukast for the treatment of allergic rhinitis.[40] Several pivotal studies have shown that montelukast was more effective than placebo for all nasal and ocular symptoms and that there was no significant difference between montelukast and loratadine, even for nasal obstruction.[56-60] The combined montelukast and cetirizine treatment, when started 6 weeks before the pollen season, was effective in preventing allergic rhinitis symptoms and reduced allergic inflammation in the nasal mucosa during natural allergen exposure.[61] In studies carried out on patients with seasonal allergic rhinitis and asthma, montelukast was found to improve nasal and bronchial symptoms. The use of ß-agonists (puffs/day) was also reduced with montelukast.[62,63] LTRAs are modestly better than placebo, as effective as antihistamines, but less effective than nasal corticosteroids in improving symptoms and quality of life in patients with seasonal allergic rhinitis.[64]

Allergic conjunctivitis

Oral montelukast for 15 days has been shown to produce significant and persistent reduction of ocular signs and symptoms in asthmatic patients with vernal keratoconjunctivitis.[65] In seasonal allergic conjunctivitis, LTRAs are more efficacious than placebo but less efficacious than oral antihistamines in adult patients. Clinical trials should be conducted to determine whether combination treatment with LTRA and oral antihistamine has a synergistic effect. Further research is required to clarify the role of LTRAs in other allergic eye diseases.[66]

Atopic dermatitis

Because the majority of children with atopic dermatitis later develop allergic rhinitis and asthma, it is conceivable that early leukotriene modifiers use could not only treat atopic dermatitis but also modify the disease course of allergic rhinitis and asthma in children. However, there are only a few small studies of the use of leukotriene modifiers in the treatment of atopic dermatitis, most of which are case reports.[40] A significant improvement of skin findings in two patients with severe atopic dermatitis was reported following treatment with oral montelukast at a dose of 10 mg daily for 8 weeks as a single therapeutic agent.[67] However, another study on the use of either montelukast or zafirlukast in seven patients as add-on usage trial in atopic dermatitis showed that leukotriene modifiers did not lead to a sustained benefit for extensive atopic dermatitis.[68] Therefore, the role of leukotriene modifiers in atopic dermatitis has yet to be defined.[40]

Leukotrienes are believed to be involved in the pathogenesis of urticaria. Activated mast cells generate and release leukotrienes in addition to histamine.[69,70] Available evidence suggests that these agents may be useful either as monotherapy or add-on therapy in some patients with chronic

urticaria (CU).[71,72] One subgroup that may respond more predictably to these agents is patients with CU that is exacerbated by ingestion of aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs).[73]

The therapeutic role of LTA in other allergic diseases

Since inflammatory mediators such as leukotrienes have been theorized to play a role in the esophageal inflammation noted in patients with eosinophilic esophagitis (EoE), leukotriene modifiers may be of value for the management of EoE. A small study of 8 patients with EoE examined the efficacy of the leukotriene receptor antagonist, montelukast, and found a significant improvement in symptoms in the majority of subjects, but no improvement in histology.[74] Leukotriene modifiers have been used also for the treatment of eosinophilic gastroenteritis.[75]

Response to leukotriene modifiers

The oral administration of the leukotriene modifiers makes them the only class of commonly prescribed asthma medications with the potential to undergo significant metabolism in the liver, so called "first pass effects". Nonetheless, it has now been shown that montelukast demonstrates significant inter-individual variability in plasma levels.[76] This variability appears to be mediated at least in part via the organic anion transporter, OATP2B1, which is encoded by the gene *SLCO2B1* (solute carrier organic anion transporter family, member 2B1). Polymorphism in SLCO2B1 gene has been associated with variation in plasma montelukast levels, with heterozygous individuals demonstrating a ~30% reduction in levels versus those harbouring the wild type genotype. Clinically, there was concordance with the drug level data in that those harbouring the variant associated with higher drug levels also had a significant improvement in asthma symptoms one and six months following the initiation of montelukast therapy.[77] In patients with asthma who were treated with a 5-lipoxygenase inhibitor, polymorphisms in the promoter of the 5-lipoxygenase gene (*ALOX5*) were associated with diminished improvement in airflow.[78]

Since levels of leukotrienes and their receptors are greatly influenced by substances such as cytokines, analysis of responsiveness to leukotriene modifiers therapy must take into account the genes for molecules that reside outside the leukotriene pathway.[3] Also, several patients' characteristics affect response to leukotriene modifiers where a benefit is more likely in children than in adults[79] and in younger than in older children.[80]

Precautions and adverse effects of leukotriene modifiers

LTRAs are generally considered to be safe and well tolerated, with headache and gastric discomfort being the most common side effects.[7] Because zafirlukast is hepatically metabolized through the p450 system, this drug may interfere with the metabolism of certain drugs such as warfarin, propranolol and theophylline. Other drugs with similar metabolism may require serum monitoring. Mild gastrointestinal discomfort has been primarily reported with zafirlukast compared with montelukast. Based on its metabolism, liver transaminases should be measured at the start and monthly for the first 3 months during zafirlukast therapy, and then quarterly.[81] Approximately 5 percent of patients receiving zileuton had increases in liver enzymes that resolved with discontinuation.[82] The liver enzymes should be monitored as with zafirlukast.[40]

An etiologic role for LTRAs in the Churg–Strauss syndrome is generally excluded.[7] However, a recent analysis of the FDA adverse event reporting system database has shown that LTRA therapy was a suspect medication in most confirmed cases of Churg–Strauss syndrome reported.[83] In the majority of cases treated with a LTRA, Churg–Strauss syndrome could not be explained by either glucocorticoid withdrawal or pre-existing Churg–Strauss syndrome.[83] Because of the potential association, the use of LTRAs in more severe, steroid-dependent patients should be accompanied by intermittent evaluation of blood eosinophils.[81]

Based on a limited number of post marketing suicide-related adverse experience reports, the FDA issued a warning raising concerns about the suicidality potential of montelukast and other LTRAs.[84] At present, there is insufficient data to prove that there is a link between montelukast and suicidality.[85]

In conclusion, leukotrienes play an essential role in allergic inflammation and their biosynthesis pathway is a target for the drug therapy of allergic disorders. Leukotriene modifiers are well tolerated, FDA approved medications for asthma and allergic rhinitis. Their use in allergic conjunctivitis and atopic dermatitis is based on case reports and small non-randomized studies which need controlled trials for evaluation of their efficacy in these disorders. The new discovery about the pharmacogenetics of leukotriene pathway offers better correlates with the clinical response to leukotriene modifiers and targets for new drugs inhibiting this pathway.

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