Update Article

Anti-leukotrienes in Childhood Asthma

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Abstract

Bronchial asthma is an inflammatory condition. The inflammatory actions of leukotrienes (LT) B₄, C₄, D₄, and E₄ have been shown experimentally to play a role in inflammatory mechanisms, producing asthma. Antileukotrienes (ALT) or leukotrienes antagonists (LA) is a new class of anti-asthma drugs with anti-inflammatory role. LT modifiers from the groups of 5 lipoxygenase inhibitor and Cys LT₁ receptor antagonists, are found useful in asthma therapy. LAs are of main use in young infants and toddler with recurrent wheezing, children with moderate to severe chronic asthma on steroid therapy and in allergic rhinitis. In chronic asthma they are required to be used for prolonged periods with other anti-asthma agents. Except for Montelukast and Zafirlukast, which can be used in children above two and six years of age respectively, the paediatric use of other agents is yet to be established. However, these agents are essentially safe. The cost of LAs is reasonably high. At present, with available evidence, these drugs are considered promising in management of asthma in children. However, there is need to do more long term clinical trials for ascertaining their effectivity in different types of asthma to compare their effects with long acting B₂ agonists and chromones, so as to optimally explore their utility.

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Asthma is an inflammatory disease. The effective therapeutic intervention is based on use of anti-inflammatory drugs. At present, steroids are being used in aerosol/oral and parenteral forms. Corticosteroid therapy has inherent difficulties of administration and side effects. Therefore, newer group of drugs called ALT, LA or leukotrienes modifiers are being explored. The ALT represent a new class of mediator specific, anti-inflammatory anti-asthma drugs. Consequent to the studies showing their effectiveness in paediatric age group, ALT are soon going to establish their place in childhood asthma management [1,2].

Leukotrienes synthesis

LTs belong to group of eicosanoids. These molecules are so named, because the parent molecule was first isolated from leucocytes, and its organic structure contained three double bonds in series, which constitute a triene. LTs are synthesised from precursor fatty acid, arachidonic acid [AA], by way of 5-lipoxygenase pathway. The AA is cleaved from cell membrane phospholipids by phospholipase A₂ [3]. The nuclear-membrane protein called as 5-lipoxygenase-activating protein (FLAP) presents AA to 5 lipoxygenase (LO), which in turn with sequential catalytic actions produces LT A₄ from AA. Zileuton inhibits this conversion by 5 lipoxygenase [4]. LT A₄ is unstable molecule and is quickly converted to LT C₄ by LT C₄ synthase in eosinophils, mast cells and alveolar macrophages, the cells of significance in asthma. Thereafter,

a specific transmembrane transporter exports the LT C₄ to extra-cellular space where further cleavages result in production of LT D₄ and LT E₄. As LTs C, D and E₄ all contain the amino acid cysteine; they are called as cysteinyl LTs (Cys-LT). They are degraded rapidly in extracellular space and the liver. In neutrophils, LT A₄ is converted to LT B₄, a dihydroxy compound as against cysteinyl, by enzyme LT A₄ epoxide hydrolase. LT B₄ is degraded in various tissues by multiple pathways.

The LTs exert their actions by binding to and activating various receptors. The Cys-LTs act on two receptors Cys LT₁ and Cys LT₂. Most of Cys LTs actions are mediated through Cys LT₁ receptors. These actions include airway smooth muscle contraction, chemotaxis and increased vascular permeability. The LTs, C₄ and D₄ have equal effects on stimulation of smooth muscle contraction while LT E₄ has significantly lesser effect [5]. The class of drugs which block binding of LTs to Cys LT₁ receptors are given the generic suffix-lukast. They include Zafirlukast, Montelukast, Pranlukast etc. The Cys LT₂ receptors, mediate constriction of pulmonary vascular smooth muscle to a much lesser degree. The Cys LT₁ receptor has recently been cloned and thus has opened up a new vista of further research.

The receptor for noncysteinyl LT, LT B₄ is known as B leukotriene receptor (BLT). The BLT predominantly mediates chemotaxis [6]. It is observed that LT B₄ may not be involved in chronic asthma, although it may be associated with neutrophilia seen during acute

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asthma or as late response to allergen challenge [7]. The BLT antagonists eg. LY-293111, have not been found to be of significance in management of asthma.

The LTs are synthesised by various cells in response to different stimuli, including antigen challenge to the sensitised tissues. It has been observed that more LTs production occurs in bronchial asthma, wheezy infants due to viral infection, severe bronchopulmonary dysplasia and in children with cystic fibrosis.

Leukotrienes in the pathogenesis of asthma

Asthma is a chronic inflammatory disease that is associated with widespread but variable airflow obstruction due to broncho-constriction, mucosal oedema, increased secretion of mucus and eosinophil rich inflammatory cell infiltrate. Various mediators of inflammation are important in the pathogenesis of asthma, which include histamine, acetylcholine, bradykinin, adenosine, prostaglandins D2 and F2 alpha, thromboxane A2, LTs, PAF and various cytokines. Previously identified as slow release substances of anaphylaxis (SRS-A), are the present LTs B4, C4, D4 and E4 have been shown experimentally to play a role in each of these inflammatory mechanisms responsible for asthma [3,4]. Inhaled LT C4 and LT D4 are the most potent broncho-constrictors found in human subjects and are about 100 to 1000 times more potent than histamine [4] LT C4 and LT D4 also may cause migration of inflammatory cells into the asthmatic airway. The Cys-LTs seem to have a direct chemotactic activity on eosinophils. LT D4 specifically increases blood flow and increases the vascular permeability in human skin and airway mucosa producing edema. The escape of plasma proteins into the tissue provides the source of potent plasma protein-derived inflammatory mediators, including the kinins, complement and clotting systems, producing mucus plugs, inhibit mucociliary clearance and fuel the inflammatory process, Cys-LTs may have an effect on airway remodelling in chronic asthma. Cys-LTs also cause a dose related nasal obstruction, but not the reflex-mediated symptoms of allergic rhinitis, such as nasal itching, sneezing, or secretion. The significant nasal blockage still present in allergic rhinitis after antihistamine treatment may be attributable to Cys-LTs induced nasal mucosal engorgement and hence may be reduced by 5-LO inhibition. Increased urinary concentrations of LTs have been demonstrated in asthma patients, reflecting increased production [8,9]. Therefore, the Cys-LTs are the pivotal mediators in asthma and virus induced wheezing.

Leukotrienes Antagonists and Asthma therapy

The ALT hold great promise as new therapies to treat asthma [10]. The 5 LO inhibitor and Cys LT1 receptor antagonists are found useful in asthma management. The FLAP, Cys LT2 and BLT receptor antagonists are not of any significance in asthma management (Table-1). The selective Cys LT receptor antagonists eg., Zafirlukast [11], Pranlukast and Montelukast as well as Zileuton, a direct inhibitor of 5-LO, have been found useful in management of asthma and of broncho-constriction induced by exposure to allergens, exercise, aspirin, cold air and inhaled LTs.

TABLE I
Leukotrienes antagonists in asthma

Drug class	Drug	Usefulness	Pediatric use
5-lipoxygenase inhibitor	Zileuton	Yes	No
Cyst LT antagonist	Montelukast	Yes	Yes
	Pranlukast	Yes	No
	Zafirlukast	Yes	Yes
FLAP antagonist	BAY X 1005	No	No
	MK-886	No	No
BLT antagonist	LY-293111	No	No

Mode of action of LT Modifiers

LTA have bronchodilatory properties, which in asthmatics are additive to the activity of β_2 -agonists [12]. This makes them useful as adjunctive therapy, but they should never substitute for β_2 -agonists in rescue therapy because of their slow onset of action. However, studies in acute asthma with intra-venous formulations are in progress. LT modifiers provide some anti-inflammatory properties, as shown by reduced airway eosinophilia, reduced FeNO levels, and modified microvascular permeability. However, the inflammation is not checked to the same extent as with corticosteroids. Therefore, LT modifiers could not substitute steroids for anti-inflammatory control. Cys-LT receptor antagonists (Cys-LTRA) have been found to have complementary effects to those of corticosteroids in chronic asthma. This is because the steroids do not affect the release of LTs. Dose tapering from the required high dose corticosteroid monotherapy was facilitated by addition of Cys-LTRAs [13-16]. Patients do not appear to develop tolerance to LT modifiers, even in 24 month extensions of clinical trials. There is no rebound effect observed after the treatment has ended. Many studies suggest that Cys-LT production is unchecked by corticosteroids in vivo and hence the significance of LTA in asthma management in addition to steroid therapy.

Effects

LAs have produced significant relief in asthma symptoms and signs, decreased the need of steroids and bronchodilators. As yet, there is no way of distinguishing LT related asthma from other types, it is likely, however, that LT intervention may be useful in some patients with specific forms of the disease only; for example, aspirin-sensitive asthma [17,18].

Indications

LAs are of definite role in management of wheezy infants and toddler and moderate to severe chronic asthma. They have significant preventive and therapeutic roles, in asthma induced by allergens, exercise, aspirin or NSAID, cold air and hyperventilation. Their usefulness is also observed in allergic rhinitis. They are not useful in acute attack of asthma as the onset of action may take from one to many days. ALT may be useful in controlling polyposis and symptoms secondary to allergic sino-nasal disease [19,20].

Drug Dosage

Drug details are as shown in Table-2. LAs are administered orally.

TABLE 2
Leukotrienes antagonists

Drug	Company	Tablet	Frequency	Age limits
Montelukast (Singulair)	Merck and Co, Inc, Whitehouse Station, NJ	10 mg, adult; 5 mg, child (Chewable)	OD, HS	2 years and above
Pranlukast (Onon, ultair)	SKB	225 mg	BD	Above 12 years
Zafirlukast (Accolate)	Zeneca, INC., Zeneca, Wilmington, DE	20 mg	BD, 1 hr AC or 2 hrs PC	Above 6 years
Zileuton (Zyflo)	Abbot Lab.	600 mg	QID	Above 12 years

Side effects

These agents are safe, well tolerated and have minimal side effects. Zileuton produces dyspepsia and transient elevation of liver enzymes [21]. Therefore, baseline and subsequent periodic monitoring of liver enzymes in patients treated with Zileuton is considered essential. Montelukast may produce headache, GIT disturbances and upper respiratory symptoms. Zafirlukast may produce Churg-Strauss syndrome, a systemic disease characterised by inflammation of lung with resultant wheeze, fever, muscle-ache, weight loss and worsening of lung functions, but the reported incidence of this syndrome is extremely low [22]. Occasionally, Montelukast may also produce

eosinophilic syndrome.

Drug Interactions

LAs especially Zileuton and Montelukast, may affect hepatic metabolism. Therefore, there is need to modify dosage of Theophylline, Warfarin and Propranolol when patients are on LAs.

Cost

The use of LAs on an average, incurs approximately monthly expense of about Rs. 3000.00. This is a reasonably costly therapy in a developing country.

Paediatric Experiences

The paediatric evidence has been limited to 5 randomised controlled trials (RCTs) [23-26].

With Zafirlukast

The therapeutic effects of Zafirlukast have been reported in one RCT in children. In a randomized, double-blind, 3 way, crossover study of 39 asthmatic children from 6 to 14 year old, Zafirlukast 5, 10, 20 and 40 mg and placebo were tested for their effects on exercise induced bronchospasm. At exercise challenge, at 4 hours after dosing, treatment with Zafirlukast attenuated the maximal percentage decrease in FEV1, compared with placebo, with no apparent dose response relation in the range of 5 to 40 mg [25].

With Montelukast

Montelukast is an orally bio-available Cys-LTRA, administered once daily. The drug has been approved for the treatment of asthma in children 2 years and older. The food does not have a clinically important influence with chronic administration. Therapeutic concentrations of montelukast do not inhibit cytochrome P450 isoenzymes. The studies show that the treatment effect of montelukast was additive to that of concurrent corticosteroid treatment. Montelukast has produced clinically significant bronchoprotection for the difficult asthmatic toddlers. Montelukast caused a significant reduction in days with symptoms, daytime asthma symptom scores, days of β_2 agonist use, use of corticosteroid rescue and peripheral blood eosinophils [24]. Montelukast caused significant improvement in asthma control in patients 2 to 5 year old. In summary, Cys-LTRAs have proved moderately effective in asthmatic children from 2 years of age and older, an effect which appears to be complementary to current corticosteroid treatment.

Asthmatic Infants and Toddlers

Most children with chronic asthma first show

symptoms as infants and toddlers. LT modifiers present an interesting option for young wheezy children, because of their oral administration, good safety profile, prolonged effect, and partial anti-inflammatory effects. Two of the 4 reported paediatric studies addressed the effect of Montelukast on 2-5 year old asthmatic children [23,24]. Based on evidence thus far, LT modifiers may play an important role as first-line treatment of young wheezy children with mild recurrent symptoms.

Moderate to Severe Asthma

Children with moderate to severe asthma symptoms, may require high doses of inhaled corticosteroids, but their symptoms may not be sufficiently controlled by such steroids. Accordingly, there is a good rationale for positioning LT modifiers as complementary to corticosteroid treatment in children whose symptoms are not optimally controlled with a moderate dosage of steroids such as 400 µg/day. To support such positioning, RCTs should assess the potential of LT modifiers as corticosteroid-sparing drugs for children. Long-term trials are necessary, and it may be worthwhile to investigate the potential additive effects of LT modifiers on very low doses of inhaled corticosteroids and compare the use of long acting β_2 -agonists and Chromones [27,28].

Exercise Induced Asthma (EIA)

The EIA is a cardinal symptom of paediatric asthma. The long-term coverage is preferable in children for protection against EIA, as the activity of children is more spontaneous than planned. Hence, short acting β_2 agonists are not always effective. EIA improves with better asthma control. Inhaled corticosteroids can be used to treat EIA and provide full-time coverage. Long-acting β_2 agonists generally provide 12 hour coverage against EIA, but some tolerance may develop. Also, β_2 agonists offer no anti-inflammatory action of significance [29]. Therefore, there is a need for an asthma medication that provides long lasting broncho-protection with an anti-inflammatory component. LT modifiers may provide both of these. The broncho-protective effect of LT modifiers should be compared with long acting β_2 agonists as complementary treatment for children with poorly controlled asthma despite being on steroid treatment.

To conclude, the LAs are probably useful agents in management of chronic asthma but are not of any established use in acute attack of asthma. In chronic asthma, they are required to be used for prolonged periods with other agents viz. inhaled steroids and β_2 agonists. They should be continued even if the patient

is asymptomatic. Except for Montelukast and Zafirlukast, which can be used in children above two and six years of age respectively, paediatric use of other agents is yet to be established. Given their efficacy, partial anti-inflammatory activity, safety and oral availability, ALT may be used as first line treatment of young wheezy preschool children with mild recurrent symptoms. In asthmatic school children, these drugs should be used as complementary treatment to be added to inhaled corticosteroids. However, till further details about long-term disease control, long-term safety, effects on development and progression of disease in later life of ALT do not become available, these drugs should be used with caution and under observation. In future researches, it is also important to compare the efficacy of Cys-LTRAs with those of inhaled steroids and inhaled β_2 agonists. Viral infection induced young infant wheezers should be specifically addressed in future studies of ALT, so as to establish confidence in newer therapeutic modality: This comprehensive information will help to formulate the final asthma management guidelines in paediatrics.

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