LEUKOTRIENE RECEPTOR ANTAGONISTS IN THE MANAGEMENT OF CHILDHOOD ASTHMA

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SUMMARY

Leukotrienes play an important role in the pathophysiology of asthma. Leukotriene blockade in the lungs cause bronchodilatation, reduce eosinophilia and decrease inflammation – all essential in the treatment of chronic asthma. However, there have been very few studies on the role of Leukotriene receptor antagonists (LTRAs) in the management of childhood asthma. Current evidence suggests that inhaled corticosteroids are still more effective than LTRAs in the management of chronic asthma. However, LTRAs have a role to play as add-on therapy to inhaled corticosteroids (ICS), in exercise-induced asthma and as an alternative to ICS for a select group of children.

Keywords: Leukotriene receptor antagonists, childhood asthma

INTRODUCTION

Leukotriene receptor antagonists (LTRAs) are a new group of asthma medications that hold the promise of being an alternative to inhale corticosteroids (ICS) for the management of chronic childhood asthma. Its easy once-a-day oral dosing and minimal side effects make it an attractive option for children. However, its role in the management of childhood asthma has yet to be fully established. This review attempts to examine the mode of action of LTRAs and to define their role in childhood asthma.

Leukotrienes and their role in the pathophysiology of asthma

The leukotrienes are eicosanoids that are produced de novo from the cell membrane phospholipid arachidonic acid by the activity of 5-lipoxygenase in conjunction with 5-lipoxygenase-activating protein (Figure 1). The cysteinyl leukotrienes LTC_4 and LTE_4 (formerly known collectively as the slow-reacting substance of anaphylaxis [SRS-A]) play a key role in the pathophysiology of asthma by exhibiting multiple effects.

In the lungs, the cysteinyl leukotrienes are potent bronchoconstrictors. They increase airway blood flow and vascular permeability, allowing the exudation of plasma macromolecules and contribute to airway edema. They also induce mucus secretion, reduce respiratory ciliary motility, and hamper mucociliary clearance. They contribute significantly to the airway inflammation[1] and serve as specific chemoattractants for eosinophils and neutrophils.

Therefore, the LTRAs work by causing bronchodilatation and reducing airway eosinophilia[2] and inflammation[3]. Moreover, the bronchodilator properties of the LTRAs are additive with those of $beta_2$-agonists[4].

LTRAs in the management of childhood asthma

There have been limited clinical studies on the use of LTRAs in children. The LTRAs e.g. montelukast, zafirlukast, and pranlukast work by specific antagonism of the Type 1 leukotriene receptor ($CysLT_1$). Pharmacological blockade of the cysteinyl leukotrienes have also been studied via the direct inhibition of 5-lipoxygenase activity with Zileuton (MK-886) but the use of Zileuton (MK-886) has been limited due to its relatively low potency and short half-life in vivo.

Are LTRAs effective as monotherapy in childhood asthma?

Studies of montelukast used as monotherapy in children with chronic asthma have shown that compared to placebo, their use resulted in a *mild improvement* of FEV1, asthma symptoms and the need for $beta_2$-agonists or oral corticosteroids. However, there was *no difference* between placebo and montelukast on daytime asthma symptoms, physician's global evaluation, patient's global evaluation, number of asthma-control days, percentage of patients experiencing asthma attacks or improvement in quality-of-life scores[5,6]. Moreover, when compared to inhaled cortocosteroids as monotherapy, LTRAs offer no major advantages with regards to clinical efficacy.

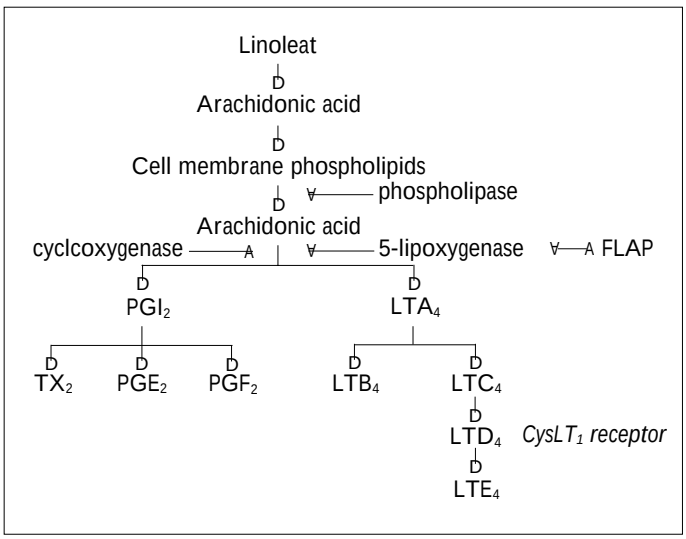

Figure 1: Schematic showing pathway of eicosanoid biosynthesis. $CysLT_1$ receptor = cysteinyl leukotriene Type 1 receptor. FLAP = 5-lipoxygenase activating protein. LT = leukotriene. PG = prostaglandin. Tx = thromboxane.

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How do LTRAs compare to inhaled corticosteroids (ICS)?

A recent meta-analysis of adult and paediatric randomised controlled trials that compared LTRAs with ICS were recently published in the Cochrane Review[7]. They reported that ICS at 400mcg/day of beclomethasone-equivalent was *more effective* than LTRAs given in the usual licensed doses. This was true for most asthma outcomes including risk of exacerbations requiring systemic steroids, improvement in FEV1, symptom scores, nocturnal awakenings, rescue medication use and quality of life. The only advantage LTRAs have is greater patient compliance and satisfaction. In two paediatric studies comparing LTRA to ICS, children and parents showed a significantly higher overall satisfaction for montelukast than for inhaled beclomethasone. According to parents, montelukast was more convenient, less difficult to use, and was used as instructed more of the time compared to beclomethasone[8,9].

Are LTRAs useful in exercise-induced asthma?

In exercise-induced asthma (EIA), LTRAs are more effective than placebo in children and adults. Studies have shown a dose-related protective effect of LTRAs to EIA[10,11]. This effect was observed in a study of asthmatic children, aged 6-14 years, using 5 mg montelukast or placebo once nightly for 2 days in a crossover fashion[12].

Are LRTAs useful as add-on therapy to inhaled corticosteroids (ICS)?

As corticosteroids appear to act through a mechanism that does not involve the leukotrienes[13,14], concomitant leukotriene blockade should provide additive benefits to corticosteroid therapy. Although no comparative studies between the LTRAs and long acting beta-agonists have been published yet, LTRAs seem to be theoretically the preferential choice as they provide extra anti-inflammatory effects and do not induce tolerance.

The addition of LTRAs to ICS improves asthma control when compared to inhaled corticosteroids alone[15]. In a recent paediatric study by Simons et al., 5 mg montelukast or placebo were added to budesonide 200 mcg twice daily in children with chronic asthma. The addition of montelukast produced significant improvement in lung function parameters, decrease in exacerbation days by 23% and reduced blood eosinophil counts[16]. In addition to providing additional clinical benefit to patients receiving concomitant ICS, the use of montelukast can also reduce the need for inhaled corticosteroids[17].

Conclusion

Evidence shows that the LTRAs can attenuate airway inflammation in both children and adults with asthma. This observation suggests that the LTRAs represent a novel therapeutic approach, one that may provide benefits that are additive to corticosteroid therapy. Although there is a paucity of data with regards to its efficacy in childhood asthma, there is currently good evidence that LTRAs are beneficial as add-on therapy to ICS. Its role as monotherapy and in EIA is still not fully substantiated and requires further studies. However, it may be an attractive alternative for selected patients – those who are steroid-phobic with low compliance to intra-bronchial medication or in patients with a poor inhalation technique.

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