Role of leukotrienes in bronchial asthma. How efficacious are leukotriene antagonists as compared to β2-agonist in the management of asthma

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ABSTRACT

Asthma is a disease of the bronchial tubes (the “airways”) that typically presents with “wheezing”, a high pitched whistling sound heard during breathing, especially when breathing out. Asthma most commonly develops in early childhood, and more than three-quarters of children who develop asthma symptoms before age 7 no longer have symptoms by age 16. However, asthma can develop at any stage in life, including adulthood. It is clinically classified according to the frequency of symptoms, forced expiratory flow rate in one second (FEV1), and peak expiratory flow rate.[9] Asthma may also be classified as atopic (extrinsic) or non-atopic (intrinsic).

Asthma is a chronic inflammatory disease of the airways that is characterized by activation of mast cells, infiltration of eosinophils, and T helper 2 (Th2) lymphocytes. Leukotrienes play a major role in the pathophysiology of asthma hence leukotrienes are considered to be one of the major targets for developing the antiasthma drug. In this article, different comparative studies comparing the efficacy of standard antiasthma drugs with anti-leukotriene agents have been reviewed. In conclusion, it is observed that anti-leukotriene drugs appear to be more potent than long-acting β2-agonists in treatment for exercise-induced and acetyl salicylic acid-sensitive asthma; but anti-leukotriene drugs are less effective than long-acting β2-agonists as add on therapy in patients with chronic asthma and in patients who are not well controlled on an inhaled corticosteroid.

Keywords: Asthma, Leukotriene, Bronchial tubes.

1. INTRODUCTION

Asthma is a common chronic inflammatory disease of the airways characterized by variable and recurring symptoms, reversible airflow obstruction and bronchospasm.[1] Common symptoms include wheezing, coughing, chest tightness, and shortness of breath.[2]

Asthma is thought to be caused by a combination of genetic and environmental factors.[3] Its diagnosis is usually based on the pattern of symptoms, response to therapy over time and spirometry.[4] It is clinically classified according to the frequency of symptoms, forced expiratory volume in one second (FEV1), and peak expiratory flow rate.[5] Asthma may also be classified as atopic (extrinsic) or non-atopic (intrinsic).[6]

Treatment of acute symptoms is usually with an inhaled short-acting β2 agonist (such as salbutamol) and oral corticosteroids.[7] In very severe cases, intravenous corticosteroids, magnesium sulfate, and hospitalization may be required.[8] Symptoms can be prevented by avoiding triggers, such as allergens [9] and irritants, and by the use of inhaled corticosteroids.[10] Long-acting β2 agonists (LABA) or leukotriene antagonists may be used in addition to inhaled corticosteroids if asthma symptoms remain uncontrolled.[11]

2. BURDEN OF DISEASE

Till 2011, 235–330 million people worldwide are affected by asthma,[12,13,14] and approximately 250,000-345,000 people die per year from the disease[15,16]. Rates vary between countries with prevalences between 1 and 18%. It is more common in developed than developing countries.[15] In the United States, asthma affects more than 22 million persons and it is one of the most common chronic diseases of childhood, affecting more than 6 million children [1]. Asthma affects approximately 7% of the population of the United States [16] and 5% of people in the United Kingdom [17]. In India, COPD and Asthma are the greatest burdens compared to other non-communicable diseases. The population prevalence of Asthma reported in different field studies is variable and ranges from 2.4-6.4%.[18] Among school children, higher prevalence rates have been reported.
Within developed countries, asthma is more common in those who are economically disadvantaged while in contrast to developing countries it is more common in the affluent. The reason for these differences is not well known.\[15\]

While asthma is twice as common in boys as girls,\[15\] severe asthma occurs at equal rates.\[17\] In contrast, adult women have a higher rate of asthma than men\[45\] and it is more common in the young than the old.\[17\]

From 2000-2010, the average cost per asthma-related hospital stay in the United States for children remained relatively stable at about $3,600, whereas the average cost per asthma-related hospital stay for adults increased from $5,200 to $6,600.\[20\] Despite the availability of effective medications and treatment strategies, many patients continue to report hospitalizations, missed school or work days, and suboptimal pharmacotherapy.\[5\]

### 3. PATHOPHYSIOLOGY

Asthma is a chronic inflammatory disease of the airways that is characterized by activation of mast cells, infiltration of eosinophils, and T helpers 2 (Th2) lymphocytes. Mast cell activation by allergens and physical stimuli releases bronchoconstrictor mediators, such as histamine, leukotriene D\(_4\), and prostaglandin D\(_2\), which cause bronchoconstriction, microvascular leakage, and plasma exudation. Many of the symptoms of asthma are due to airway smooth muscle contraction, and therefore bronchodilators are important as symptom relievers.\[21,22\]

### 4. ROLE OF LEUCOTRIENES IN ASTHMA

Leukotrienes are formed from the metabolism of arachidonic acid, which is derived from the action of phospholipase A\(_2\) acting on the cell membrane. Arachidonic acid is metabolized by two major pathways, the cyclooxygenase pathway which forms prostaglandins and thromboxanes and the 5'-lipoxygenase pathway which produces leukotrienes.

Several stimuli, including IgE-receptor activation, antigen-antibody interaction, and microorganisms, can activate phospholipase A\(_2\) to speed the formation of arachidonic acid.\[23\]

In the late 1970s, it became evident that the cysteinyl leukotrienes i.e. leukotriene C\(_4\), leukotriene D\(_4\), and leukotriene E\(_4\) represented the component molecules of the slow-reacting substance of anaphylaxis.\[24\]

Cysteinyl leukotrienes are found to produce smooth muscle spasm, increase vascular permeability, enhance mucus production, decrease mucociliary transport, and attract eosinophils into the airway.\[20\] Inhaled leukotrienes C\(_4\) and D\(_4\) are up to 1000 times more potent than histamine in causing airway obstruction in healthy people, and their effect also lasts longer than histamine. Inhaled leukotrienes C\(_4\) and D\(_4\) also appear to increase bronchial hyperresponsiveness to both histamine and methacholine\[27\]. Thus, cysteinyl leukotrienes have potent effects on airway function, inducing bronchoconstriction, airway hyperresponsiveness, plasma exudation, mucus secretion, and eosinophilic inflammation.\[28\]

### 5. ANTI-LEUKOTRIENE DRUGS IN ASTHMA

Anti-leukotriene drugs act by blocking the leukotriene pathways. Currently, two groups of leukotriene modifiers are available, which include of 5'-lipoxygenase (5-LO) enzyme inhibitors such as zileuton and antagonists of the cysteinyl leukotrienes type-1 (cys-LT\(_1\)) receptor such as montelukast, zafirlukast.\[21\]

Anti-leukotriene drugs have been intensively investigated in clinical studies. They inhibit approximately 50% of bronchoconstriction induced by a variety of challenges, including allergen, exercise, and cold air.\[29\] Zileuton, zafirlukast, and montelukast are associated with rare cases of hepatic dysfunction and Churg-Strauss syndrome.\[21\]

### 6. \(\beta_2\)–AGONISTS IN ASTHMA

Inhaled \(\beta_2\) agonists are the bronchodilator treatment of choice in asthma because they are the most effective bronchodilators and have minimal side effects when used in low doses. These drugs directly bind to \(\beta_2\) receptors and result in the activation of the stimulatory type of G-protein (G\(_{s}\))-adenyl cyclase- cyclic adenosine mono phosphate (cAMP) –phospho kinase-A (PKA) pathway, resulting in phosphorylative events leading to bronchial smooth muscle relaxation.

The molecular mechanisms by which \(\beta_2\) agonists induce relaxation of airway smooth muscle include: lowering of intracellular calcium(Ca\(^{2+}\)) concentration by active removal of Ca\(^{2+}\) from the cytosol into intracellular stores and out of the cell, acute inhibition of the Phopho Lipase-C (PLC)-Inositol tri phosphate (IP\(_3\)) pathway and its mobilization of cellular Ca\(^{2+}\), inhibition of myosin light chain kinase activation, activation of myosin light chain phosphatase, opening of a large conductance Ca\(^{2+}\)-activated K\(^+\) channel which repolarizes the smooth muscle cell and may stimulate the sequestration of Ca\(^{2+}\) into intracellular stores, \(\beta_2\) receptors may also couple to Ca\(^{2+}\)-activated K\(^+\) channel via G, so that relaxation of airway smooth muscle may occur independently of an increase in cAMP.\[21\]

Inhaled short-acting \(\beta_2\) agonists such as salbutamol and terbutaline are the most widely used and effective bronchodilators in the treatment of acute asthma. When inhaled, they are convenient, easy to use, rapid in onset, and without significant systemic side effects. The long-acting inhaled \(\beta_2\) agonists (LABA) such as salmeterol, formoterol have a bronchodilator action which lasts for...
β₂-agonists rarely produce side effects such as muscle tremor, palpitation, tachycardia, hypokalemia, restlessness, and hypoxemia. Continuous treatment with an agonist often leads to tolerance, which may be due to down-regulation of the receptor [21]. But TRUST trial proved that there is no exacerbation of asthma with regular use of inhaled salbutamol [30].

7. COMPARISON OF EFFICACY OF LEUKOTRIENE MODIFIERS AND β₂ AGONISTS IN ASTHMA:

Anti-leukotriene drugs are effective in tablet form which increases compliance with chronic therapy and makes treatment of children easier. Montelukast is effective as a once-daily preparation in a dose of 10 mg in adults and 5 mg in children. Since many mediators besides cysteinyl leukotrienes (cys-LTs) are involved in the pathophysiology of asthma, anti-leukotriene drugs are less effective than β₂-agonists, which act as functional antagonists and reverse bronchoconstriction irrespective of the contractile agent [21].

In patients with mild to moderate asthma, anti-leukotriene drugs can cause a significant improvement in lung function and asthma symptoms, with a reduction in the use of rescue inhaled β₂-agonists [31]. But anti-leukotriene drugs are less effective than long-acting inhaled β₂-agonists (LABA) as an add-on therapy in patients who are not well controlled on inhaled corticosteroid (ICS) [32]. A recent Cochrane Review summarized the addition of a long-acting β₂-agonist compared with a leukotriene receptor agonist in patients receiving inhaled steroids. This study also concluded that in adults with chronic asthma inadequately controlled by low-dose inhaled steroids, the addition of a long-acting β₂ agonist was superior in preventing exacerbations requiring systemic steroids [33].

A randomized, double-dummy, blinded and placebo-controlled trial concluded that anti-leukotrienes provide prompt effective and persistent defense against exercise-induced asthma, with efficacy similar to that of long-acting β₂-agonist [34]. In a recent report, montelukast (10 mg daily for 12 weeks) was associated with significant inhibition (47.4%) of the exercise-induced fall in FEV1. This protective effect was well sustained, and there was no evidence of tolerance or rebound worsening of lung function after 3 months of continuous montelukast therapy [35]. The same cannot be said of long-acting β₂-agonists, which lose some effectiveness over time when given continuously to prevent exercise-induced symptoms [36]. Research suggests that Acetyl Salicylic Acid (ASA) triggers attacks of wheezing in susceptible individuals by blocking cyclooxygenase mediated metabolic degradation of arachidonic acid and by directing larger amounts of this substrate down the lipoxygenase (leukotriene-producing) pathway. Leukotriene-receptor antagonists have been shown to protect against bronchospasm associated with oral ASA challenge [37].

8. CONCLUSION

Convincing evidence suggests that cysteinyl leukotrienes have an important role as inflammatory mediators in the pathophysiology of asthma. Asthma symptoms triggered by physiologic, environmental, and allergic stimuli are alleviated by anti-leukotriene drugs. At present, inhaled corticosteroids remain first-line therapy for control of air way inflammation. Anti-leukotriene drugs appear to be more potent than long-acting β₂-agonists in treatment for exercise-induced and acetyl salicylic acid-sensitive asthma, but anti-leukotriene drugs are less effective than long-acting β₂-agonists as add-on therapy in patients with chronic asthma and in patients who are not well controlled on an inhaled corticosteroid.

9. FUTURE PERSPECTIVES

The role of the cys-LT₂ receptor in asthma is unknown, as is the value of its blockade in asthma. Cys-LT₂ receptors may be important in vascular and airway smooth muscle proliferative effects of cys-LT and are not inhibited by current cys-LT₁-receptor antagonists [38].

10. REFERENCES