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### Original Article

## Role of Anti-Leukotriens antagonist, Montelukast in Bronchial Asthma

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### ABSTRACT

Asthma is one of the most common chronic diseases globally with a rising incidence in developing countries. Asthma severity is now classified on the basis of the intensity of treatment required to achieve good asthma control. The standard treatment of bronchial asthma depends on the stage of the disease and usually consists of combination of inhaled steroids and long acting beta 2 agonists. Leukotriene receptor antagonists (LTRAs) are a class of drugs which specifically act on leukotriene receptors and they have an established role in the management of chronic asthma. They may also provide benefit, additional to that achieved by current treatment, in acute attack. They have been shown to have acute bronchodilator effect which may be of additional help in acute attack of bronchial asthma. Here we have reviewed the clinical efficacy of anti-leukotriene antagonist, Montelukast in the management of bronchial asthma.

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### Introduction

Asthma is one of the most common chronic diseases globally with a rising incidence in developing countries. Asthma is a problem worldwide with an estimated 300 million affected individuals. The prevalence ranges from 1% to 18% in different countries [1]. According to World Health Organization about 15 million disability adjusted life years (DALYs) are lost annually due to asthma accounting for 1% of incidence of total disease burden. Its incidence is on the rise all across the world, especially in the paediatric population, with bronchial asthma accounting for 4% of the paediatric outpatient visits [2]. India has an estimated 15-20 million asthmatics aged 15 years or more. There has been a constant and variable increase in asthma prevalence worldwide in the last two decades which is also being observed in India. A study conducted in India on epidemiology of asthma, it was observed that the prevalence of asthma in India to be 2.05%: rural-2.28%, urban-1.64% [3]. Pal et al [3] reported that the mean prevalence of asthma was  $7.24 \pm 5.42$  and childhood asthma among children 13 – 14 years of age was lower than that in younger children (6 – 7 years of age). Aggarwal et al [4] reported that the overall prevalence of asthma in the various populations (Delhi, Bangalore, Kanpur) studied was 2.38%. Female sex, advancing age, usual residence in urban area, lower socio-economic status, history suggestive of atopy, history of asthma in a first degree relative, and all forms of

tobacco smoking were associated with significantly higher odds of having asthma.

Factors that influence the risk of asthma can be divided into those that lead to development of asthma and those that trigger asthma symptoms and both. The former include host factors which are mostly genetic and the latter are environmental factors [5]. Host factors includes genetic predisposition, obesity and male sex; while the environmental factors includes allergens, viral infections, occupational sensitizers, pollutants, tobacco smoke and dietary factors. Asthma is an inflammatory disorder of the airways, which involves several inflammatory cells and multiple mediators which result on characteristic patho-physiological changes [6]. Asthma attacks in humans probably involve elements of both the early and late responses. It is observed when atopic individuals are exposed to airway-delivered specific allergens. The final consequences of patho-physiological events in bronchial asthma includes airway narrowing, airway hyperresponsiveness, airway inflammation, and airway remodeling leading to deposition of collagen material under the basement membrane.

More than 100 different mediators have been identified to be involved in asthma and they mediate complex inflammatory response pathways. Some of the important mediators are histamine, chemotactic factors, prostaglandins, cytokines, kinins, and cysteinyl leukotrienes. Prostaglandins and leukotrienes are biologically active derivatives of 20 carbon atoms polyunsaturated essential fatty acids that are released from cell membrane phospholipids [7]. They are the major lipid derived autacoids. The metabolism of the phospholipids occurs by two major enzymatic pathways – cyclooxygenase and lipoxygenase pathways. Lipoxygenase pathway [operates mainly in the lungs, WBC and platelets. The 5-lipoxygenase is the predominant arachidonic acid

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metabolizing enzyme in the neutrophils. This leads to the formation of a compound 5-HPETE (5-hydroperoxyeicosatetraenoic acid) which is unstable and gets reduced to 5-HETE (5-hydroxyeicosatetraenoic acid), lipoxins and family of leukotrienes. The first leukotriene generated is leukotrieneA<sub>4</sub> (LTA<sub>4</sub>) which in turn gives rise to LTB<sub>4</sub> or LTC<sub>4</sub>. LTB<sub>4</sub> is produced by neutrophils and macrophages. LTC<sub>4</sub> and its subsequent metabolites, LTD<sub>4</sub> and LTE<sub>4</sub> are produced in mast cells. Leukotrienes are named so because they were first obtained from leukocytes (leuko) and have three conjugated double bonds (triene). Leukotrienes of biological importance are LTB<sub>4</sub>, LTC<sub>4</sub> and LTD<sub>4</sub>. Cysteinyl Leukotrienes are potent bronchoconstrictors and proinflammatory mediators. They are the only mediators whose inhibition has been associated with an improvement with lung function and asthma symptoms [8]. LTC<sub>4</sub> and D<sub>4</sub> contract most smooth muscles. They also increase mucus secretion of the airways. Thus, leukotrienes are responsible for bronchoconstriction, mucus hypersecretion, recruitment of inflammatory cells, vascular permeability and proliferation of smooth muscles.

### Montelukast in Bronchial Asthma

Up to the end of 1990s, asthma treatment was based only on beta<sub>2</sub> agonists and corticosteroids, with minimal role of theophyllines and cromones [9]. Leukotriene receptor antagonists are the only new class of anti-asthma drugs available in the last 10 years. Their specialty was that they were the first category of drugs which target a specific mechanism, that is binding of leukotrienes to their receptors, which is part of the complex pathway involved in asthma [10]. Drugs which have been developed and launched are montelukast, zafirlukast and pranlukast. Among them, montelukast has shown the best efficacy and safety profile, and has become the most widely used and studied antileukotriene compound. Both montelukast and zafirlukast have similar actions and clinical utility. They competitively inhibit cysLT<sub>1</sub> receptor mediated bronchoconstriction, increased vascular permeability and recruitment of eosinophils [7]. Montelukast is an orally active compound that binds with high affinity and selectivity to the CysLT<sub>1</sub> receptor (in preference to other pharmacologically important airway receptors, such as the prostanoid, cholinergic, or β-adrenergic receptor). It inhibits physiologic actions of LTD<sub>4</sub> at the CysLT<sub>1</sub> receptor without any agonist activity. These drugs are unique in that they demonstrate both bronchodilator and anti-inflammatory properties. They reduce symptoms including cough, improve lung functions, and reduce airway inflammation and asthma exacerbations [11,12]. They are orally active, with the former used at a daily dose of 10mg and the latter given as 20 mg twice daily (in adults). The first study to demonstrate the efficacy of montelukast in asthma was obtained in the mid-1990s, where the comparative studies of montelukast versus placebo was published by Leff et al [13], which showed that once daily treatment with montelukast compared to placebo provided significant protection against exercise-induced asthma showed by improvement in area under FEV<sub>1</sub> curve over a 12-week period. Villaran et al [14] observed that montelukast also protected against bronchoconstriction induced by exercise better than long acting beta<sub>2</sub> agonists. Following these studies montelukast was introduced, for the treatment of asthma. Inhaled corticosteroids are the 'gold standard' for treatment of asthma, therefore, the first evaluation was the comparison between montelukast and low-dose inhaled corticosteroids. In a study done by Busse et al [15] it

was observed that low-dose fluticasone propionate is more effective than montelukast as first-line maintenance therapy for patients with persistent asthma who are undertreated and remain symptomatic while taking short-acting β<sub>2</sub>-agonists alone. However, Barnes et al [16] proposed that when patients with mild asthma were selected, montelukast was still more effective than placebo. Their study showed that there was a significant improvement in FEV<sub>1</sub> in montelukast treated patients (7–8% over baseline) compared with placebo (1–4% over baseline) which was found to be statistically significant ( $p < 0.02$ ). In a recent study by Mc Ivor et al [17] (SIMPLE TRIAL), 534 patients with mild asthma well controlled by low-dose inhaled corticosteroids when replaced with montelukast was associated with good asthma control in more than 75% of patients after 6 weeks, with an increase in compliance to treatment.

### Montelukast as an add on therapy in Bronchial Asthma:

With many studies showing fairly convincing results of montelukast as monotherapy and its potential additive effects to inhaled corticosteroids, many studies were done to evaluate the efficacy of montelukast as an add-on therapy in asthma. A study done by Laviolette et al [18] showed that montelukast provided significant ( $p < 0.05$ ) clinical benefit on addition to inhaled beclomethasone by improving FEV<sub>1</sub>, daytime asthma symptom scores, and nocturnal awakenings. Vaquerizo et al [19] conducted a multicentre double blinded randomised placebo controlled study and found that for patients with mild airway obstruction and persistent asthma symptoms on budesonide treatment, concomitant treatment with montelukast significantly improved asthma control. They evaluated 639 patients aged 18-70 years and found that the median percentage of asthma exacerbation days was 35% lower (3.1% v 4.8%;  $p = 0.03$ ) and the median percentage of asthma free days was 56% higher (66.1% v 42.3%;  $p = 0.001$ ) in the montelukast group as compared to the placebo group. The usage of montelukast has also been studied in patients with severe asthma already treated with maximal therapy (high-dose inhaled corticosteroids plus long acting beta<sub>2</sub> agonists). A study done by Tonelli et al [20] showed that leukotriene receptor antagonists (montelukast 10mg orally once daily or zafirlukast 20mg twice daily) had no significant effect in severe asthmatics not controlled by high dose inhaled corticosteroids and bronchodilators, but a subgroup of these patients could be sensitive to the effects of these drugs and showed a positive response. A recent study by Lemanske et al [21], in a crossover design, the addition of long acting beta<sub>2</sub> agonists or montelukast to low-dose inhaled corticosteroids in children not controlled with inhaled corticosteroids, showed that many patients reported a better response to montelukast plus ICS than to LABA plus ICS. Many clinical and experimental studies were done to test the efficacy and safety profile of montelukast and this finally led to establishing the definite role of this drug in the management of asthma. According to GINA [22], montelukast is recommended as an alternative monotherapy to low-dose inhaled corticosteroids, in a step-down strategy (step 2), and also as an add-on treatment to inhaled corticosteroids plus long acting beta<sub>2</sub> combination, to improve the control and reduce the dose of inhaled corticosteroids in bronchial asthma (steps 3 and 4). Other uses of Montelukasti)

### 1) Asthmatic bronchoconstriction and hyperresponsiveness:

The key function of asthma medication is to counteract the spontaneous reversible bronchoconstriction which develops in mild to moderate asthmatics on withholding bronchodilator therapy. Role of leukotriene modifiers has been assessed in such patients. Administration of these drugs has resulted in acute

bronchodilatation and improvement in airway function within 1-3 hours with increase in FEV1 by 5-30%. They also have an additive effect to beta2 agonists. These drugs have a significant effect on bronchial hyperresponsiveness [23].

**ii) Exercise induced asthma:** Exercise induced bronchoconstriction occurs in 80% of asthma patients. Several studies have shown increased levels of urinary leukotrienes following exercise. They have been shown to inhibit the maximal bronchoconstrictor response after exercise upto 70%. They maintain their bronchoprotective effects over many weeks of treatment. In a study by Edelman et al [24], which was a double blinded placebo controlled study, 191 patients with exercise induced bronchoconstriction were enrolled. Patients treated with montelukast in the study had sustained improvement in symptoms and 67% had maximal decrease in FEV1 less than 20% throughout 8 weeks of the study period.

**iii) Allergic rhinitis:** It is a complex inflammatory disease of the upper airway characterized by sneezing, nasal pruritus, rhinorrhoea and nasal obstruction. Uncontrolled allergic rhinitis is known to precipitate and exacerbate asthma. Cysteinyl leukotrienes are inflammatory mediators common to both the upper and lower airways [25]. This has led to various studies to evaluate their therapeutic potential in allergic rhinitis. Montelukast as monotherapy is effective in the treatment of allergic rhinitis. In a study done by Philip et al [26], 1302 patients with allergic rhinitis, were randomly assigned to receive montelukast 10mg /day. It was observed that there was improvement in day- and night-time nasal symptoms, eye symptoms as well as quality of life parameters in the group that received montelukast. Another study of Van Adelsberg et al [27], a randomized, double-blind placebo controlled trial, 1079 patients with a history of allergic rhinitis and a positive skin test to seasonal pollen allergens were assigned to placebo, montelukast 10 mg, or loratadine 10 mg. It was seen that montelukast was more effective than placebo in improving daytime nasal symptoms, eye symptoms, rhinoconjunctivitis and quality-of-life ( $p \leq 0.006$ ). The treatment effect of montelukast was more persistent than loratadine over all 4 weeks of treatment and was well tolerated

**iv) Aspirin induced asthma:** Aspirin-sensitive asthma may exist in as many as 20% of all asthmatics [28]. It is characterized by bronchoconstriction following aspirin ingestion, and is associated with rhinosinusitis, nasal polyposis. It is caused by aspirin and non-steroidal anti-inflammatory drugs that selectively inhibit cyclo-oxygenase-1 enzyme which shunts arachidonic acid down the 5-lipoxygenase-activating protein pathway, causing the overproduction of cysteinyl leukotrienes. Therefore, elevated levels of cysteinyl leukotrienes can be found in bronchial and nasal aspirates, and in urine following aspirin challenge [29]. Therefore, leukotriene receptor antagonists might play an important role in ameliorating the clinical symptoms of aspirin sensitive asthma. In a study done by Dahlen et al [30], 80 patients with aspirin-sensitive asthma, were randomized to receive placebo or montelukast 10mg /day for 4 weeks and many of them were already treated with steroids. Pulmonary function and symptoms improved in the latter group, suggesting that LTRAs such as montelukast improve asthma control in aspirin-sensitive patients over and above that achieved by inhaled corticosteroids.

**v) Asthma in obese patients:** Studies published in recent years suggested that obesity may affect the response of asthmatic patients to their normal treatment. A study done by Peters-Golden et al [31], analyzed patient's response in relation to BMI in 3000

asthmatic patients who were given one of the following three treatments: placebo, inhaled corticosteroids (beclomethasone), and leukotriene receptor antagonists (montelukast). It was observed that those patients with high BMIs who received montelukast, the clinical benefit was greater than in lean patients, which suggests that leukotrienes play a more important role as mediators of symptoms in obese patients.

**vi) Asthma in smokers:** Cigarette smoking is associated with accelerated decline of lung function in asthmatics, worsening asthma severity, reduction of responsiveness to glucocorticoids and poor asthma control and higher hospital admissions. Smokers with asthma also have a greater need for rescue medications and increased morbidity and mortality rates compared to non-smokers with asthma [32]. Lazarus and colleagues demonstrated that in mild asthmatics who smoked and who showed corticosteroid insensitivity, montelukast produced a statistically significant increase in morning PEF and a decrease in PEF variability in smokers [33]. Montelukast showed greater effects in smokers than non-smokers.

#### Role of Montelukast in acute asthma exacerbations

There is little data to suggest a role for leukotriene antagonists in acute attack of bronchial asthma. LTRAs have an acute bronchodilator effect which is seen within 20-60 minutes of administration of the intravenous drug and within 6 hours of taking the drug orally [34]. In acute attack of asthma there is an increase in cysteinyl leukotriene production as evidenced by increase in urinary LTE4. This points towards the importance of use of these drugs as a novel new therapeutic approach, as these mediators cannot be inhibited by corticosteroids. Few studies have demonstrated improvement in peak expiratory flow values following administration of this drug as an add on therapy with the standard treatment, but clinical relevance requires more research and studies.

Ramsay et al [35] did a randomized, double blind, placebo controlled trial with oral montelukast in acute exacerbations of bronchial asthma in 87 adults requiring hospitalization for the disease. They observed that patients who received montelukast achieved a PEF of  $389.6(+109.7)$  l/min (81.4% predicted) compared with  $332.3(+129.9)$  l/min (69.8% predicted) from placebo ( $p=0.046$ ). The mean difference between treatment groups was 57.4 l/min (95%CI to 1.15 to 113.6 l/min or 1.95-21.2% predicted). They concluded that the administration of oral montelukast results in a significantly higher PEF the morning after admission than that achievable with current standard treatment alone. In another multicentered, double blinded, placebo controlled study by Camargo et al [36], 201 adult patients were randomized and they received standard therapy plus either intravenous montelukast (7 or 14 mg) or matching placebo. It was observed that there was significant improvements in FEV1 after intravenous use of montelukast by 14.8% at 2 hours from baseline compared with 3.6% for placebo ( $p=0.007$ ) and it was concluded that that intravenous montelukast in addition to standard therapy causes rapid benefit and is well tolerated in adults with acute asthma. Another study by Ferreira et al [37], which was a randomized, double blind, placebo controlled, parallel group study, 20 adult patients received the standard therapy and were also administered oral 10mg montelukast (MK) or placebo (PL), it was observed that the montelukast group had a shorter duration of hospital stay and a better evolution of peak-flow values (medium increase of 55% from baseline versus 44% in placebo group) but this did not reach statistical significance. It was concluded that montelukast is a useful additional therapy, which should be considered in the emergency room treatment of the acute asthma.



A randomized, double-blind, placebo-controlled, parallel-group study by Harmanci et al [38] analysed 51 patients of acute attack of bronchial asthma who received either a 4-mg tablet of montelukast or placebo in addition to inhaled salbutamol and were followed up for 4 hours. It was observed that compared to the placebo, the pulmonary index scores and respiratory rates were significantly lower in the montelukast group starting at 90 minutes ( $p=0.01$ ). This difference persisted at 120, 180, and 240 minutes of the study. At the end of the first hour of treatment, the requirement of oral steroids was 20.8% and 38.5% in patients randomized to the montelukast and placebo groups, respectively. Another study by Silverman et al [39], a randomized double blind, multicentre, placebo controlled study, a total of 641 patients presenting with acute asthma received either single-dose zafirlukast 160 mg or 20 mg or placebo as an adjunct treatment to standard care. At the end of the outpatient period, 23.6% treated with zafirlukast and 28.9% treated with placebo relapsed ( $p=0.047$ ), and 9.9% treated with zafirlukast 15.0% treated with placebo required extended care ( $p=0.052$ ). They concluded that when added to standardized care, therapy with zafirlukast reduced the risk of relapse compared with placebo over a 28-day treatment period.

In conclusion, it can be stated that Montelukast has got a definite role in the management of bronchial asthma on day-to-day basis, either in children or in adults [40]. It is one of the fastest moving molecule in the pharmaceutical industry and its role is being defined more and more in different allergic manifestation including allergic rhinitis and atopic dermatitis, and also nowadays it has been found to have some role in acute exacerbations of bronchial asthma.

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