Historically, the structural and functional differences within the respiratory tract have served as the basis for separating the airway into upper and lower components. As such, asthma and allergic rhinitis have been diagnosed and managed by clinicians as distinct upper and lower airway diseases, respectively. Consistent with this idea of distinct diseases, researchers have developed drugs in years past for specific treatment of either asthma or allergic rhinitis. However, during the past decade, the focus of study has shifted to the role of the arachidonic acid metabolic pathway and other inflammatory mediators in the pathophysiology and treatment of upper and lower airway disease. Recent advances in inflammatory mediators have prompted members of the medical and scientific communities to recognize asthma and allergic rhinitis as being a continuum of inflammation within one common airway.¹

Leukotrienes (LTC₄, LTD₄, LTE₄) are important proinflammatory mediators in asthma. They are appropriately named as the leukotrienes are produced by leucocytes and their chemical structure contains three double bonds, a triene. These eicosanoids are derived from the metabolism of membrane phospholipids within alveolar macrophages, eosinophils, mast cells and neutrophils, that are involved in the pathophysiology of this disease.² The production of LTs by these cells depends on the selective expression of the enzymes involved in the metabolic pathway. LTA₄ may be directly released into the extracellular environment and they are metabolized by other cells (transcellular biosynthesis). This pathway results in LTB₄ production by bronchial epithelial cells, despite 5-lipoxygenase enzyme is absent. These eicosanoids bind to cysteinyl leukotriene (CysLT) receptors.

CysLTs activate type 1 and type 2 leukotriene receptors (CysLT1 and CysLT2) on cell membranes. CysLT1 receptors are localised primarily on pulmonary smooth muscle cells. Activation of these receptors by CysLT leads to decreased activity of respiratory cilia, increased mucus secretion, increased venopermeability and promotion of eosinophils into the airways. This, in turn, induces airway smooth-muscle proliferation and may play a role in the development of airway remodeling. Moreover, CysLTs are the most potent bronchoconstrictive agents...
discovered, being 100–1000 times more potent than histamines. The synthesis and release of leukotrienes appear not to be blocked by corticosteroid therapy.\textsuperscript{3,4}

CysLTs receptor antagonists bind the LTD4 receptor and prevent the interaction between the receptor and its physiological ligands.\textsuperscript{5} Due to this receptor obstruction, LTs cannot activate the signal transduction that leads to bronchoconstriction. Among LTRAs, zafirlukast, pranlukast and montelukast have been approved in several countries for asthma treatment of adults and children. Montelukast, is the most specific and powerful LTs receptor antagonist, and is the only LTRA that has been approved for preschool children use in several countries. In addition to its use as controller drug in allergic and viral-induced asthma, it decreases also bronchial hyperreactivity and prevents bronchial obstruction induced by physical activity at preschool and school age. Montelukast binds with high affinity and selectivity to the CysLT1 receptor (in preference to other pharmacologically important airway receptors, such as the prostanoid, cholinergic, or \( \beta \)-adrenergic receptor). Montelukast inhibits physiologic actions of LTD4 at the CysLT1 receptor without any agonist activity.\textsuperscript{6}

It is rapidly absorbed after administration reaching peak plasma concentration (Cmax) in 3 to 4 hours with a mean bioavailability of 64% following a 10 mg oral administration. For the 5 mg chewable tablet, the mean Cmax is achieved in 2 to 2.5 hours with a mean bioavailability of 73% fasting versus 63% with the standard meal. Montelukast is more than 99% bound to plasma proteins with minimal distribution across the blood-brain barrier. Excretion occurs almost exclusively in bile with a half-life from 2.7 to 5.5 hours in healthy adults. The pharmacokinetic profile is similar in females and males, young and elderly.\textsuperscript{7}

**Montelukast in Allergic Rhinitis**

LTRAs can be considered an established treatment option for asthma, with published clinical evidence for their efficacy and tolerability in this indication dating back to the early 1990s. More recently, evidence has also started to accumulate in support of their utility in the treatment of AR.\textsuperscript{8}

**Monotherapy:** A multicentre, double-blind trial involving 450 men and 852 women with spring seasonal allergic rhinitis randomised to once-daily montelukast (10 mg), loratadine (10 mg) or placebo for 2 weeks showed that the change from baseline in daytime nasal symptoms score was significantly \((p < 0.001)\) greater with montelukast and loratadine than with placebo, but that nighttime symptoms were better controlled with montelukast. Peripheral blood eosinophil counts were significantly \((p < 0.001)\) decreased with montelukast but not with loratadine or placebo.\textsuperscript{9} A study by Chervinsky et al showed similar improvement of symptoms in patients treated with montelukast in comparison to placebo in an evaluation of the results of three prospective clinical trials in fall AR patients.\textsuperscript{10}

**Combination Therapy:** Montelukast traditionally used as anti-inflammatory drugs in the long-term treatment of asthma in adults, adolescents, and school-age children. Now a days its use in allergic rhinitis has gained importance. Furthermore, there are many combinations of montelukast with levocetrizine or desloratidine are in market for the treatment of allergic rhinitis. In one study, a combination of montelukast and loratadine has been found to be superior to either montelukast or loratadine alone in seasonal allergic rhinitis.\textsuperscript{11} In patients with persistent AR, the combination of montelukast and either desloratidine or levocetirizine were more effective than monotherapy with either of these three medications.\textsuperscript{12} Montelukast in combination with cetirizine showed better control of the clinical nasal symptoms and reduced eosinophil counts better than either montelukast or cetirizine alone in seasonal AR patients.\textsuperscript{13}

**Montelukast in Bronchial Asthma**

Although LTRAs were considered as first line therapy in the management of mild to moderate persistent asthma since their discovery, a Cochrane review consisting of 13 randomised controlled trials, concluded that low doses of inhaled glucocorticoids were superior to LTRAs.\textsuperscript{14} Various current international guidelines (Global Initiative for Asthma,GINA; British Thoracic Society, BTS; National Institute of Health, NIH) recommend the use of low-dose inhaled corticosteroids (ICSs) as the preferred controller therapy, with LTRAs as an alternative, for the management of persistent asthma in children (5–11 years of age) and adolescents. In patients unresponsive to ICSs alone, the alternative options are the addition of LTRAs or long-acting beta-agonsist (LABA), or an increase of ICS dosage.

**Montelukast as Monotherapy**

Leukotriene receptor antagonists have beneficial clinical effect in all age groups and are proposed in GINA and NAEPP guidelines as an option for monotherapy. Montelukast was found to be effective in mild persistent asthmatics with near normal lung functions.\textsuperscript{15}

The clinical efficacy of montelukast in adults and children with persistent asthma, including patients sensitive to aspirin, has been evaluated in several randomised, double-blind, placebo controlled trials. Montelukast have demonstrated an important role in aspirin-induced asthma. It has long been known...
that 5-10% of asthmatics are exquisitely sensitive to aspirin, so that ingestion of even a very small dose causes profound bronchoconstriction and symptoms of systemic release of histamine, such as flushing and abdominal cramping. Because this reaction to aspirin is not associated with any evidence of allergic sensitisation to aspirin or its metabolites and because it is produced by any of the nonsteroidal anti-inflammatory agents, it is thought to result from inhibition of prostaglandin synthetase (cyclooxygenase), shifting arachidonic acid metabolism from the prostaglandin to the leukotriene pathway. Support for this idea was provided by the demonstration that leukotriene pathway inhibitors impressively reduce the response to aspirin challenge and improve overall control of asthma on a day-to-day basis.\[16\] Lee et al in a study found that a single 10 mg dose of montelukast partially protected against the local effects of nasal lysine-aspirin challenge.\[17\]

In a study on asthmatic patients greater than 15 year age, Reiss et al found that Montelukast improved FEV1, peak expiratory flow rates, daytime asthma symptoms, nocturnal awakening significantly as compared to placebo. Also need of rescue medications (β agonists) was significantly less in patients taking Montelukast as compared to placebo.\[18\] In another study, Montelukast was associated with significantly better protection against exercise induced asthma as compared to placebo. The maximum decrease in exercise induced FEV1 was significantly improved in patients taking Montelukast as compared to patients taking placebo.\[19\]

### Montelukast in combination therapy

Various studies have assessed the role of Montelukast in combination therapy with other asthma medications or as an add on therapy to ICS. Montelukast provides improvement symptoms and in lung function, decrease in acute exacerbations and dose of ICS. Apart from these, many studies have evaluated the role of Montelukast on quality of life of asthma patients and found consistent improvement in QOL with Montelukast as compared to placebo. Blood eosinophil count was found to be decreased during Montelukast treatment in many studies.\[20\]

Montelukast as an add on therapy to ICS improves control in mild to moderate asthma compared to ICS monotherapy with similar safety profile. In active controlled studies, montelukast + ICS was clinically less effective as compared to salmeterol + ICS in most of the 12 weeks trials. However, 48 week trials showed comparable proportion of patients with ≥ 1 exacerbation in both the groups. Until recent, there were no comparative studies for ICS + LABA and ICS + LABA + montelukast, which is compared in recently published MONICA study.

The MONtelukast In Chronic Asthma (MONICA) study was an open-label study in which add-on montelukast therapy in a real-world setting over 3 and 6 months improved asthma control in patients with mild to moderate persistent asthma who were not sufficiently controlled by ICS or the combination of ICS and LABA. Asthma control was assessed by the Asthma control test (ACT), a short and relatively simple, validated, patient based, five-item questionnaire that is one of the assessment tools for asthma control recommended by GINA. The control of asthma was found to be improved after addition of montelukast as assessed by ACT score.

Additionally, clinically meaningful improvement in quality of life of patients were observed after addition of montelukast when the same was assessed using mini-Asthma quality of life questionnaire (mini-AQLQ).\[21\]

### Montelukast in Patients with Concomitant Allergic Rhinitis and Asthma

Individuals with AR are at a 3- to 12-fold greater risk of also having asthma or developing it later in life. These two medical conditions have interacting manifestations of a common underlying etiology. They share pathophysiological features such as early- and late-response components, infiltration of the mucosa by eosinophils, and mediation of key inflammatory events by CysLT. Many studies have evaluated role of montelukast in concomitant asthma and allergic rhinitis.\[22\] In a study, Busse et al found that montelukast improved asthma symptoms the use of asthma rescue medications.\[23\]

The first demonstrations of the efficacy of montelukast in asthma were obtained in the mid-1990s, when the results of both comparative studies of montelukast versus placebo and studies of the protective effect of montelukast on bronchoconstriction induced by exercise or other nonspecific stimuli were published.\[24\] Montelukast improved symptoms, rescue medication use and pulmonary function, and reduced the rate of exacerbation and the level of blood eosinophils, in mild-to moderate asthmatics not treated with ICS. Montelukast also protected against bronchoconstriction induced by exercise better than long acting beta2-agonists (LABAs).\[25\] These data led to the introduction of montelukast into the market at the end of the 1990s.

After the results of montelukast in monotherapy and its potential additive effect to ICS, many studies have been performed in order to assess the efficacy of montelukast as add-on therapy. When added to ICS, montelukast induced further improvement in
symptoms and pulmonary function, particularly in patients still symptomatic despite treatment with ICS.\textsuperscript{26} Although in short-term studies the combination of ICS plus LABA was more effective on symptoms and pulmonary function than ICS plus montelukast,\textsuperscript{27,28} in a 1-year study especially designed to assess efficacy with regard to rate of severe exacerbations, fluticasone plus montelukast provided equivalent clinical control to fluticasone plus salmeterol, and was associated with a greater reduction in blood eosinophilia.\textsuperscript{29} A recent systematic review suggests that different conclusions may be drawn when either short term or long-term trials are considered: in 12-week trials, efficacy with regard to rate of exacerbations is higher for salmeterol plus ICS than montelukast plus ICS, with a similar safety profile, whereas in 48-week trials, the two treatments are similar, with a lower rate of adverse events for montelukast plus ICS.\textsuperscript{30}

**Safety and Tolerability of Montelukast**

Montelukast is well tolerated with a safety profile that is similar in adult and paediatric populations. Studies have demonstrated no clinical or laboratory difference in adverse experiences of montelukast as compared to placebo.\textsuperscript{22} Most common adverse effects include headache, gastrointestinal disturbances, fatigue, pharyngitis, upper respiratory tract infection and rash. These adverse events occurred more than 1% that of placebo. Isolated reports of Churg-Strauss syndrome (CSS), a rare systemic vasculitis associated with asthma, have been reported in asthma patients treated with montelukast. The prevalence of CSS is 60 per million asthma patients whereas in general population it affects 2 to 7 people per million. The cause is unknown but it is often preceded by tapering of steroid treatment. The possible explanation for slight higher prevalence of CSS among patients taking montelukast is that, inhaled or oral corticosteroid treatment in these patients may mask the underlying vasculitis that develops as the glucocorticosteroid doses are reduced in patients with severe asthma being treated with leukotriene receptor antagonists (LTRAs).

Particular attention should be given to the consideration of periodically monitoring liver function tests during treatment with LTRA. Most recently, the FDA has published reports of agitation, aggression, anxiety, depression, sleep disturbances, hallucinations, restlessness, suicide, suicidal ideation, and tremor associated with the use of montelukast and other LTRAs based upon post marketing reports published by the drug manufacturer.

**Conclusion**

To conclude, montelukast is highly specific CysLT1 receptor antagonist. The efficacy in both AR and asthma is better than placebo. It can be useful as monotherapy in patients with mild persistent asthma with near normal lung functions and for the control in aspirin induced asthma. Montelukast is a suitable option as add on therapy when asthma is not controlled on ICS monotherapy or combination of ICS and LABA. The safety and tolerability is good among patients but a rare possibility of Churg Strauss syndrome should be kept in mind.

**References**

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