



Pharmacy Practice

A MECHANISTIC INSIGHT AND CLINICAL OUTCOMES OF MONTELUKAST IN ASTHMA

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ABSTRACT Montelukast is an orally administered, non-steroidal medication which is a selective cysteinyl-leukotriene type-1 (cysLT₁) receptor antagonist. It was invented in the early 1990s and was approved by the U.S. Food and Drug Administration in 1998 as a treatment of asthma and allergic rhinitis. It is administered on a daily basis and can be used either in isolation or by way of inhaled corticosteroids in selected patients. The mechanisms of effect produced by Montelukast include the inhibition of leukotrienes-dependent bronchoconstriction, increased vascular permeability, mucus secretion and eosinophil recruitment. It leads to anti-inflammatory and bronchodilation. The medication is specifically useful in leukotriene-mediated disorders, e.g. bronchoconstriction during exercise, respiratory disease triggered by aspirin, wheezing induced by virus, and allergic rhinitis-associated asthma. The montelukast absorption rate is fast and the highest levels of plasma are obtained after 2-4 hours of oral administration. It is strongly bound to plasma proteins (>99%); mainly metabolized in the liver using CYP2C8, with a minor role played by CYP3A4 and CYP2C9. Most of the metabolites are excreted via bile. The elimination half-life is 2.7 to 5.5 hours, which justifies the use of once-daily dose in all age groups in the right formulations. The trials in clinics have demonstrated that montelukast is better in the symptoms of asthma, pulmonary performance, and rates of exacerbation than inhaled corticosteroids, though they are still better. It is usually generally tolerable, but the issue of the neuropsychiatric adverse effects has caused more strict safety warning.

KEYWORDS : Montelukast; Leukotriene Receptor Antagonists; Asthma; Pharmacokinetics; Neuropsychiatric Adverse Drug Reaction.

1. INTRODUCTION

Selective leukotriene receptor antagonist (LTRA) has been developed as Montelukast, commonly prescribed orally to treat asthma and allergic rhinitis. It was created by Merck & Co. in early 1990s after which it received the approval of the U.S. Food and Drug Administration (FDA) in 1998 and is sold under the brand name Singulair(r)¹. It was created as an oral, once-a-day, non-steroidal treatment in the patients who required additional therapy over inhaled corticosteroids or those who preferred a pill-based treatment².

Montelukast acts by inhibiting the actions of leukotrienes by blocking the cysteinyl leukotriene receptor type 1 (CysLT₁). These are the most important inflammatory mediators that are based on arachidonic acid and which are very critical in bronchoconstriction, mucus production, and airway inflammatory³. Among the leukotrienes produced by the airways of asthmatics, LTC₄, LTD₄ and LTE₄ have been found to increase their production in the airways of asthmatics and are known to cause airway narrowing and hyper-responsiveness⁴.

The invention of Montelukast was undertaken to meet the need to have specific anti-inflammatory drugs which can regulate the leukotrienes driven pathways without the side-effects associated with corticosteroid administration⁵. It has thus been recommended as a good treatment measure that can be used in the long run prevention and management of asthma in people with mild and moderate persistent asthma, exercise induced bronchoconstriction and coexisting allergic rhinitis⁶.

Unlike bronchodilators which basically reduce the acute symptoms, Montelukast is a controller medication. It is also capable of reducing both diurnal and nocturnal symptoms and improving pulmonary functions when it is used as monotherapy or in combination with inhaled corticosteroids⁷. Its convenience of administration in an oral form, good safety profile and demonstrated effectiveness in adult and pediatric patients has cemented its presence in the international asthma management guidelines⁶.

Asthma is a long-term inflammatory airway condition marked by symptoms such as cough, airway inflammation, which results in mucus hypersecretion, structural remodelling of airway wall, and bronchial hyperresponsiveness (BHR) improved airway smooth muscle cell response to nonspecific triggers, such as cold air. Asthma is a disease that is typical of childhood (childhood-onset asthma), although it may also occur in adulthood (late-onset asthma). These two phenotypes differ in their features; particularly those with late-onset asthma have a higher probability of asthma severity, less frequently accompanied with allergic sensitization, than childhood-onset asthma. Among the risk factors in persistent asthma among the paediatric population are atopy, lung and respiratory tract infections (and rhinovirus infections in particular). The correlation between airway inflammation in asthmatic children and the pathogenicity of respiratory viruses is not well-established, and it is also unclear whether repeated viral infections at an early age predispose people to asthma development. Considering that the pathogenesis of asthma is significantly based on inflammation, the main treatment objectives

include the regulation of symptoms as well as the presence of inflammation in the airways to prevent the occurrence of a new attack⁷.

The positive effects of oral montelukast, a leukotrienes receptor antagonist, on the outcome of asthma (e.g., reduced asthma exacerbations), asthma symptoms, and lung function have been reported in a number of large clinical trials in adults with chronic asthma^{8,9}. Moreover, the studies conducted with patients with asthma, including adults and children, have revealed that the treatment adherence levels are much greater in the case of oral montelukast than of inhaled asthmatics^{10,11,12}.

Montelukast is a systemically active pharmaceutical drug that is described as having a dual mechanism of action, which is both a bronchodilator and anti-inflammatory agent. Montelukast across all ages has shown a good safety profile and has also been tolerated well by patients. In the conditions of monotherapy or concomitant use with inhaled corticosteroids, montelukast has provided clinically significant improvements in different outcomes related to asthma, symptom severity, pulmonary function outcomes, quality of life, or frequency of asthma attacks. Also, montelukast has shown bronchoprotective effects to specific and non-specific bronchoconstrictive stimuli¹⁷.

2. Asthma

Asthma is a long-term inflammatory lung disease which is marked by wheezing, dyspnea, cough, and a tight feeling in the chest. Even though its etiology is still unclear, genetic predisposition and environmental factors are very vital factors in the development of the disease¹³. The pathogenesis of asthma is the complex allergic and autoimmune inflammatory processes, which are usually correlated with the increase of IgE in allergic phenotype¹³.

The main outcome of asthma is immune dysregulation, where immune homeostasis is lost, and there is excessive inflammation. This entails the hyperactivity of immune cells, excess secretion of pro-inflammatory cytokines, airway hyperresponsiveness, and the inflammatory control¹⁴. There is generally an overproduction on T helper 2 (Th2) cells¹⁵. At the expense of regulatory T cells (Tregs), which have a role in unregulated immune activation¹⁶.

Th2 cytokines are significant in allergic inflammation. Interleukin-4 (IL-4) stimulates the production of IgE and the recruitment of eosinophils^{17,18}, whereas IL-5 triggers the differentiation of eosinophils and their infiltration of the airways that cause tissue destruction¹⁹. The IL-13 plays a role in airway hyperresponsiveness, hypersecretion of mucus and eosinophilic inflammation²⁰. Also, IL-17 produced by Th17 cells is a neutrophilic cytokine, and tumor necrosis factor-alpha (TNF-α) further augments airway inflammation and remodelling²¹. These cytokines interact to maintain chronic inflammation in the airway and bronchoconstriction typical of asthma²¹.

2.1 Etiology of Asthma

Asthma is a complex condition that develops through a mix of various factors, including allergic and non-allergic triggers, environmental influences, infections, genetics, and individual characteristics. All these elements contribute to airway inflammation, hyper-responsiveness, and symptoms like wheezing, coughing, and shortness of breath. Extrinsic or allergic asthma is often linked to IgE-mediated reactions to allergens such as dust mites, pollen, mold, certain foods, and pet dander. These allergens activate immune pathways dominated by Th2 cells, leading to eosinophilic inflammation in people with atopy^{22,23}. On the other hand, intrinsic (non-allergic) asthma can be triggered by things like exercise, cold air, emotional stress, and irritants, which highlight increased airway sensitivity and neurogenic reflexes²⁴. Environmental factors, including tobacco smoke, air pollution, damp indoor conditions, and occupational exposures like isocyanates or flour dust, can cause oxidative stress and damage to the airway lining, making bronchoconstriction more likely^{25,26}. Respiratory viral infections, particularly RSV and rhinovirus during early childhood, can disrupt the epithelial barriers and worsen airway inflammation, playing a significant role in the onset and worsening of asthma²⁷. Genetic factors are also crucial, as a family history of atopy and variations in immune-regulating genes like IL-4, IL-13, and ORMDL3 can heighten the risk of developing the disease²⁸. Additionally, factors related to the individual, such as hormonal changes, gastroesophageal reflux disease (GERD), sensitivity to aspirin or β-blockers, obesity, and psychological stress, can further influence how the airways respond²⁹. All

these mechanisms come together to create ongoing airway inflammation and bronchial hyperresponsiveness, characterized by the activation of eosinophils and mast cells, the release of cytokines, and structural changes in the airways that define asthma²³.

2.2 Epidemiology of Asthma

There are about 260-300 million cases of asthma cases across the world, with a high geographical variation in prevalence, morbidity, and mortality³⁰. In spite of the fact that since 1990 the age-standardized rates and DALYs decrease, the absolute cases increase because of population growth and aging. In most high-income countries, prevalence has stagnated, whereas in a number of low- and middle-income countries with fast urbanization, it is on the rise^{31,32}. In children, boys have a greater tendency to get asthma and, in females, it occurs more frequently after adolescence^{33,34}.

South Asia especially India is a significant contributor to the international burden^{30,32}. The prevalence of Indians is highly varied as there is a pooled prevalence of 7.9 in children with greater prevalence being in urban regions and in boys³⁵. The major contributors are urbanization, air pollution, exposure to biomass fuel, and indoor allergens^{36,37}. The prevalence in the rural areas is approximately 2 per cent, as opposed to more than 10 per cent in urban areas^{38,39}. Even after reducing mortality, high absolute cases prevail, as a result of under-diagnosis and poor accessibility to inhaled corticosteroids^{31,32}. The household air pollution, PM2.5 exposure, tobacco use, and socioeconomic impediments to regular treatment are major risk factors in India^{35,38}.

2.3 Major Epidemiological Studies on Asthma

These results suggest that there are complicated mechanisms between genetic susceptibility and environmental exposures that determine asthma prevalence. Asthma has been attributed to rapid urbanization, air pollution, indoor biomass smoke, and viral infections with children being considered especially vulnerable to asthma. Although the world has been vigilant to these issues by monitoring them via ISAAC, ECRHS and GAN, there are still significant regional differences, focusing on healthcare disparities, diagnosis, and the environment at risk³⁴.

The population of children with asthma in India approximated 1 in 12 makes it important to highlight that there is a serious burden on the population health. The high degree of heterogeneity among the studies indicates inconsistencies in diagnostic standards and reporting requirements, and the importance of the necessity of standardized surveillance systems and focused measures in the area of the prevention and management of asthma strengthens the need to develop standard surveillance systems and develop specific targeted interventions in the field of asthma prevention and management⁷.

2.4 Pathophysiology of Asthma

Asthma is a multifactorial disease in which there are numerous interactions between inflammatory and resident airways cells, which results in the inflammation of the airways, bronchial tube hyperirritability and blocking of airways at times⁴⁰. The pathophysiology of asthma is shown in figure 1. This sustained inflammation in airway walls, which is mediated by the infiltration and activation of various immune cells (e.g. dendritic cells, eosinophils, neutrophils, lymphocytes, innate lymphoid cells and mast cells) is the primary characteristic of airway narrowing⁴¹. Airway remodelling complicates everything in the severe asthma cases. The change in structure involves thickening of airway smooth muscle, alteration of goblet cells and excessive deposition of collagen below the epithelium which contribute greatly to permanent dysfunction of the airway^{40,41}. Although asthma is usually divided into Th2-high and Th2-low, the reality is more complicated: more often than not, the disease is a combination of inflammatory reactions. It is also worth mentioning that a patient can be classified as one or a combination of two types of inflammation that will further cause persistent inflammation of the airways⁴². Their structural alteration due to a complex interplay between genetic factors, environmental influences, and irregularities in the immune system. In the genetically determined, airway destruction may occur due to an encounter with allergens, pollutants or respiratory infections. This injury leads to the release of some cytokines by the epithelium, such as interleukin (IL)-33, interleukin (IL)-25 and thymic stromal lymphopoietin (TSLP), which are also referred to as alarmins⁴². The alarmins in turn trigger the dendritic cells, which is essential in processing and presenting the inhaled antigens to the naive CD4+ T lymphocytes to induce them to differentiate into T-

helper type 2 (Th2) cells⁴¹. Th2 cells become activated and produce IL-4, IL-5, and IL-13 that cause the allergic inflammatory response. IL-4 makes B-cells change their classes and produce allergen-specific immunoglobulin E (IgE), whereas IL-5 stimulates the migration of eosinophils and their entry into the airways. The IL-13 increases the goblet cells and this causes more production of mucus and constriction of the airway smooth muscles². IgE binds to high-affinity FcR1 receptors on mast cells and basophils priming them to rapidly degranulate again in response to the allergen re-exposure. This degranulation discharges histamine, leukotrienes (LTC4, LTD4, LTE4), and prostaglandin D2 which cause immediate bronchoconstriction and lead to early symptoms (wheezing, coughing and shortness of breath)²³. Within several hours, a later phase reaction ensues characterized by the influx of eosinophils, Th2 lymphocytes, neutrophils and macrophage into the airway mucosa. These inflammatory cells begin to release eosinophil cationic protein and major basic protein which are the cytotoxic proteins as well as, chemokines and cytokines which continue to promote the epithelial damage⁴³. The result of this continuous inflammation is airway hyperresponsiveness in which the bronchial smooth muscle is over responsive to non-specific stimuli, such as cold air, smoke, or even exercise⁴². Airway remodelling, that is, smooth muscle thickening, cell proliferation, subepithelial fibrosis caused by the accumulation of collagen, goblet cell changes, mucus gland enlargement and the development of new blood vessels occur when inflammation is chronic⁴⁴. These changes lead to permanent airway contraction, reduced elasticity, and airflow obstructions that can frequently be irreversible to initiate chronic asthma and contrast with its previous phases, which were reversible^{23,43}. The continuum of inflammation, epithelial damage and remodelling continue to drive airway hyperactivity and the relapse of symptoms⁴¹. In conclusion, asthma pathophysiological starts with genetic predisposition and exposure to environmental factors. It is mediated by epithelial activation and cytokine release which is followed by Th2-mediated inflammation and bronchoconstriction caused by mast cells, and finally by chronic remodelling. The understanding of these mutually supporting processes has led to the development of specific biologic therapeutics, including anti-IL-5, anti-IL-4Ra and anti-IgE monoclonal antibodies, which negatively impact the cytokine pathways based on which the asthma development occurs^{23,42}.

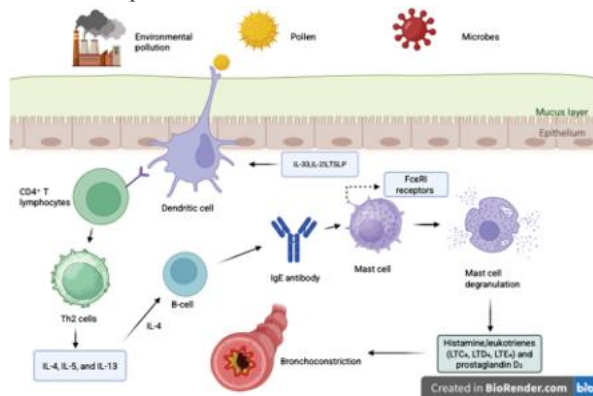


Figure 1. Pathophysiology of Asthma⁴⁵

Environmental triggers and genetic predisposition initiate airway epithelial cells resulting in the release of alarmins (IL-33, IL-25, TSLP) and Th2 differentiation mediated by dendritic cells. Th2 cytokines (IL-4, IL-5, IL-13) increase IgE, eosinophilic inflammation, mucus secretion and bronchoconstriction. The mast cell degranulation triggered by allergens leads to the early bronchospasm, whereas the ongoing inflammation causes the airway hyperresponsiveness, as well as structural remodelling that also leads to chronic airflow limitation.

2.5 Asthma-immunological and Inflammatory Processes

Asthma is characterized by persistent inflammation of the airways, variable restrictions of airflow and excessive bronchial tube overreaction. The activation of naive T cells is triggered by antigen-presenting cells such as dendritic cells when allergens are met and the cells are differentiated into Th2 lymphocytes. These cells in turn produce major cytokines like IL-4, IL-5 and IL-13 which are instrumental in asthma development^{46,47}. The action of IL-4 stimulates B cells to produce IgE, IL-5 stimulates eosinophils, and IL-13 enhances the number of goblet cells and androgynous production of mucus^{40,48}. IgE binds to FcR1 of high affinity in mast cells. On re-

exposure to allergens, these mast cells discharge their contents such as histamine, leukotrienes and prostaglandins leading to instant bronchoconstriction and inflammation^{49,50}. The late-phase response that is mainly mediated by eosinophils and Th2 cytokines leads to the destruction of the epithelial layer, fibrosis below and alteration of airways structure¹. Other current studies have also reported the role of innate lymphoid cells (ILC2) and epithelial cytokines including TSLP, IL-25, and IL-33, in initiating and maintaining type-2 inflammation^{51,52}. This expanding knowledge has led to the emergence of novel directed biologic therapies. Simply put, the imbalance in the type-2 immune response in the lungs with allergen-specific IgE-mediated bronchospasms and Th2 cytokines and CysLTs increasing the intensity of inflammation and airway sensitivity characterizes asthma⁴⁷.

3. History of Montelukast

Montelukast is a cysteinyl leukotriene antagonist drug, which was developed in 1998 to treat asthma, prevent exercise-induced bronchoconstriction, and control allergic rhinitis. The proposed adult dosage is 10mg per day⁵³. Even though it is generally seen as a safe treatment and is used more often as a substitute or a supplement to inhaled corticosteroids, the rare adverse reactions have been raised, as well as the possible neuropsychiatric complications, such as anxiety, depression, sleep impairments, and suicidality⁴⁰.

Montelukast has been considered as a repurposed anti-inflammatory agent in neurodegenerative diseases because it has systemic anti-inflammatory effects, and has in addition been shown to exert an effect in brain tissue, but this potential is limited by neuropsychiatric adverse effects⁵⁴. FDA has documented continued safety issues related to mental health side effects, including suicidal behavior, that resulted in the inclusion of a Boxed Warning and contraindication of first-line use in mild allergic rhinitis. Even though not all observational studies demonstrated the increased risk in comparison with inhaled corticosteroids, the evidence is still scarce and montelukast has already been found to penetrate the blood-brain barrier in animal models⁵⁵.

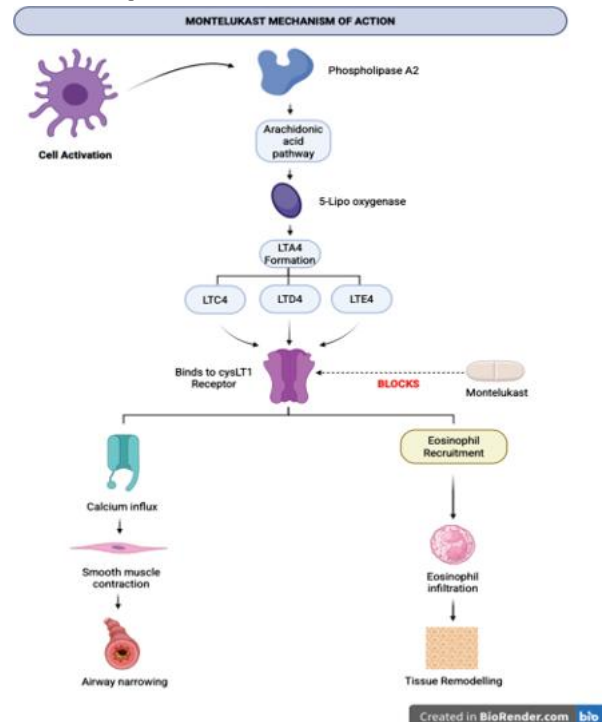


Figure 2. Mechanism of Action of Montelukast⁴⁵

3.1 Mechanism of Action of Montelukast

Montelukast is a drug that is called a selective antagonist to cysteinyl leukotriene type 1 (CysLT1) receptor and it is usually administered to control asthma. Cysteinyl leukotrienes (LCT4, LTD4, LTE4) are synthesized from arachidonic acid through the 5 lipoxigenase (5-LOX) enzyme in the mast cells and eosinophils. The compounds are important to cause airways inflammation, bronchoconstriction, vascular permeability increase, and mucus^{3,56}. The effect that montelukast produces is the attachment to CysLT1 receptor of bronchial smooth muscle cells and other inflammatory cells, blocking

the chain reaction caused by leukotrienes. This will facilitate bronchoconstriction reduction and reduce airway inflammation^{57,58}. This mechanism does not only ensure excessive bronchial responsiveness is avoided, but it also contributes to the reduction of airway remodeling that is usually observed in patients with chronic asthma⁵⁹. Recent studies have shown that Montelukast may also inhibit the 5-LOX-activating protein (FLAP) which results in a direct reduction in the production of leukotrienes⁶⁰. Also, it has been experimentally demonstrated that Montelukast is able to reduce eosinophilic inflammation as well as the IL-4 and IL-5 concentrations leading to higher FEV1 and peak air flow rate in individuals with asthma^{24,61,62}. Figure 2 shows the mechanism of action of montelukast.

Montelukast inhibits the action of leukotrienes (LTC4, LTD4, LTE4) synthesized through the 5-lipoxygenase pathway by selectively blocking the action of cysteinyl leukotrienes type 1 (CysLT1) receptors on bronchial smooth muscle and inflammatory cells. This inhibition lowers bronchoconstriction, airway inflammation, mucus secretion, and vascular permeability which enhances lung performance and constrains airway hyperresponsiveness and remodelling.

3.2 Comparative Efficacy of Montelukast with Other LTRA'S

There is clinical evidence that montelukast, zafirlukast and pranlukast all some provide comparable overall benefits in asthma control, though each possesses its own, clinically and statistically significant differences in latency and resistance to effect, ease of administration, the type of symptoms they address, and the characteristics of patients who respond to them⁶³. Montelukast has a faster acting effect, it exhibits quantifiable bronchodilation within 2 hours only. However, it is generally 2-3 doses before zafirlukast initiates its effects whereas pranlukast requires a bit more time to do so based on Japanese clinical trials. In patients with unremitting asthma, montelukast daily lowers daytime symptoms, night awakenings, and rescue medication requirements, and its effect sizes are comparable to zafirlukast and pranlukast. Nevertheless, some studies have found that zafirlukast has marginally greater effect in FEV1 whereas montelukast is more effective in asthma due to exercise induced bronchoconstriction where it will benefit with up to 24-hour protection following a single dose, a property which zafirlukast does not always exhibit⁶⁴. Also, montelukast has better support in lowering virus-induced wheezing, childhood attacks, and symptoms in patients with asthma and allergic rhinitis, and this may be because of its stable pharmacokinetics and long-lasting receptor occupancy. In the case of allergic rhinitis, all leukotrienes receptor antagonists (LTRAs) are somewhat effective, but montelukast has been demonstrated to be more effective than zafirlukast in direct comparisons, but none is as effective as intranasal corticosteroids⁶⁵. Pranlukast has shown a few additional anti-inflammatory effects such as lessening eosinophilic infiltration in some Japanese studies but these extra effects have not translated into better clinical effects when compared with montelukast. The differences in safety and compliance also contribute to the effectiveness of said treatments in the real-life context: once-a-day dosing of Montelukast makes it easier to adhere to the treatment than taking zafirlukast (twice daily). Also, montelukast can lessen the interaction with other drugs, whereas zafirlukast is more likely to cause liver damage. Pranlukast on the other hand has a more region-specific tolerability data. In general, despite the similarity in the effectiveness of all leukotrienes receptor antagonists (LTRA), montelukast is characterized by its ability to have persistent clinical advantages in different types of asthma. It provides superior safeguarding against physical activity of bronchoconstriction, more convenient to take, and the risk of drug interaction is also decreased hence, it is the pharmaceutical of choice in this category of drugs^{3,64}.

3.3 Montelukast Pharmacokinetic Profile

3.3.1 Absorption

Montelukast is readily and well absorbed in the oral route and has an absolute bioavailability ranging around 64 percent in healthy adults. Usually, Cmax done 2-4 hours (Tmax) after a 10-mg or so dose⁶⁶. Curiously, food has a little effect on the absorption rate but a high-fat food will increase the Tmax a bit but does not affect the systemic exposure (AUC) experience⁶⁷. The tablet formulation is oral, and hence the tablet form is extensively absorbed and therefore excellent in terms of once-daily dosage in asthma management⁶⁸. Absorption is also rather effective in children, but in this case, there are age effects on Tmax and Cmax as children have a developing physiology⁶⁹. In addition, montelukast is not extensively metabolized in the small intestine and this implies that a large percentage of the dose which is

absorbed does not undergo first-pass metabolism and thus ends up in the liver in its original form⁶⁶. This fast absorption is crucial in its use to prevent exercise-induced bronchoconstriction in case of taking at least two hours prior to the activity⁶¹.

3.3.2 Distribution

Montelukast has a binding capacity of more than 99 percent to the plasma proteins, primarily albumin, which implies that an insignificant amount of the drug is in the bloodstream. This potent protein binding contributes to maintaining the levels of free drug steady, and also contributes to the reduction of the risk of side-effects due to drug toxicity⁶⁶. Its effective volume of distribution appears very small implying that it does not diffuse much into the peripheral tissues despite the fact that it penetrates the leukotriene receptors in the respiratory tract effectively⁶⁸. Cysteinyl leukotriene type-1 (CysLT1) receptor has a high affinity with montelukast that ensures its pharmacodynamic action and is associated even in the case of moderate plasma half-life⁷⁰. This narrow distribution to the central nervous system may be critical to future research on the possible neuropsychiatric side effects, despite the fact that the relationship between pharmacokinetics and CNS exposure remains not to be well comprehended⁷¹.

3.3.3 Metabolism

The liver is the main site of metabolism of montelukast, and the CYP2C8 enzyme is instrumental in its metabolism. Other enzymes such as CYP3A4 and CYP2C9 also come to their rescue by forming hydroxylated metabolites which are then coupled with glucuronides⁷². Interestingly, not all the metabolites of montelukast are active at leukotriene receptors and this indicates that it is the original drug that is providing the therapeutic effect⁶⁸. But when you use a CYP2C8-inhibitor, such as gemfibrozil, then it may cause a dramatic rise in the amount of montelukast in your system-to 4 to 5 times higher⁷³. Also, Phase II conjugation contributes to the synthesis of polar metabolites most of which are released in bile⁷². It is worth considering that in case one has liver problems, then it may slow the rate at which drug is eliminated out of the body but in most cases, mild to moderate liver problems do not necessitate any adjustments to the dosage according to clinical pharmacokinetic studies⁶⁷.

3.3.4 Elimination

Mostly, Montelukast is excreted in the bile and very minimal is excreted in the urine in its original form. This implies that, in relation to dosing, renal function is not such a big issue⁶⁶. The quantity of the dose that is present in the faeces as metabolites is over 80 percent in healthy adults, a fact that underscores the extent to which the body depends on the hepatobiliary excretion⁷². Its excretion pathway through the bile after it has undergone intense hepatic metabolism indicates the high lipophilicity of montelukast and high hepatic metabolism. Enterohepatic cycling is also discussed, on the basis of profile of its metabolites, but its clinical significance is regarded as low⁶⁸.

3.3.5 Half Life

The half-life of montelukast in adults taking normal dose of 10-mg is usually 2.7-5.5 hours⁶⁶. Although this half-life is quite brief, in spite of it, montelukast still can provide a sustained pharmacodynamic response due to its ability to keep the receptors occupied longer⁷⁰. The half-life in children is usually lower given the faster clearance by the liver and thus we have to change the dosing according to age⁶⁹. Its moderate half-life and high receptor affinity allows it to be used once daily in the treatment of chronic asthma and allergic rhinitis⁷⁰.

3.3.6 Clearance

Montelukast is excreted at an average rate out of the liver primarily under oxidative metabolism through CYP2C8⁷². Surprisingly, the younger children are quicker in clearing it than adults due to the differences in the functioning of liver enzymes⁶⁹. Although it does not appear that smoking significantly influences the clearance of montelukast, it is the same thing with other drugs such as theophylline where it can be greatly influenced⁶⁸. Moreover, the association with drugs that either suppress or promote CYP2C8, CYP3A4, or CYP2C9 can actually alter montelukast processing and as such, healthcare providers have to monitor these variables carefully⁷³.

3.3.7 Toxicity (Pk Related)

The drug Montelukast is generally well tolerated, and toxicity does not tend to be associated with plasma concentration due to its high protein binding and the existence of inactive metabolites⁶⁶. Irritability, sleep disturbances, anxiety and depression have however been reported to

have some neuropsychiatric effects. Such problems may be more concerned with individual difference in the penetration of the drug into the central nervous system than with the dosage⁷¹. Liver enzyme increases, although mild, may be demonstrated in few patients, which is a manifestation of the high metabolism of the drug in the liver⁶⁷. Liver toxicity is serious and has been reported to occur but very seldom, particularly in those patients who already have liver problems or are taking other drugs that influence CYP enzymes⁷¹. Because of the presence of bile in the urine of most individuals, patients with severe liver dysfunction may have increased systemic contact through the use of montelukast, which might theoretically increase the chances of toxicity⁶⁷.

3.4 Dosage and Administration of Montelukast

Montelukast is administered orally and with the dosage depending on the age of the patient and the condition under treatment. In adults and adolescents (15 years and above) the standard dose used to control asthma or allergic rhinitis is 10 mg per day and usually in the evening^{64,74}. In children between 6 and 14 years old, the usual dosage is 5 mg/kg/day in form of chewable tablets and in little children between the ages of 2 and 5 the dosage is 4 mg/kg/day in either form of chewable tablet or oral granules^{74,75,76}. A study indicates that the optimal dose of 4 mg of leukotriene receptor blockage and clinical response in children between 2-5 years is the optimal dose^{75,77}. In the case of children aged 6-23 months of age, administration should be in the form of the 4 mg granule taken once daily which should be discontinued by suddenly adding half a dose of soft food immediately before administration, as has been supported by pharmacokinetic and safety studies^{74,77}. Montelukast 10 mg two-hour pre-exercise protection is strongly beneficial in exercise-induced bronchoconstriction in both adolescents and adults, but it is not to be used instead of long-term controller therapy^{78,79}. The randomized controlled trials conducted among children have also proved evidence about taking it once a day in the evening to keep the symptoms of asthma at control^{75,76}. Montelukast may be administered with or without food, does not require any renal impairment adjustments, and in general, should not be administered to those with profound liver dysfunction due to scarcity of information^{64,74}.

3.5 Uses of Montelukast

Montelukast is a favorite medication in the treatment of chronic asthma. This is achieved through enhancing lung capacity, airway inflammation, and decreasing asthma outbursts. It achieves this through inhibition of cysteinyl-leukotriene receptors that contribute to bronchoconstriction and mucus secretion⁵. It is particularly effective in patients with mild persistent asthma who are unable to take inhaled corticosteroids, as well as it may be used with treatment in patients with moderate persistent asthma to control the symptoms and decrease the necessity of using rescue medications^{5,80}. It has been noted to work in a variety of asthma types that are extremely leukotrienes dependent, including the wheezing associated with viruses in children, asthma caused by allergic rhinitis, or in smokers and obese patients whose steroid response may be more less than ideal⁸⁰. Montelukast is also licensed to prevent exercise-induced bronchoconstriction (EIB) which can prevent up to 24 hours and greatly reduce the post-exercise reduction of FEV1⁵. It is also commonly applied to seasonal as well as perennial allergic rhinitis, and research has indicated that it is effective in treating nasal congestion, runny nose, sneezing, and nighttime symptoms. Even moderate cases can be treated with a combination of it and antihistamines, giving even greater results⁸¹.

3.6 Effect of Montelukast in Children

Montelukast has undergone many studies in its use in the treatment of asthma and airway allergies in children. It has demonstrated tremendous effects in symptom management, flare-up reduction, as well as, an improvement in the overall quality of life of different forms of childhood conditions. Systematic reviews and meta-analyses suggest that montelukast is an effective treatment in children and adolescents to reduce asthma symptoms and enhance the management of the disease over a placebo, but inhaled corticosteroids remain the preferred treatment option to maximally reduce symptoms⁸². In children, especially those in preschool age and school-going age, who suffer occasional or virus mediated wheezing, long-term montelukast use has been associated with less asthma attacks caused by virus and less acute exacerbations⁸³. Also, montelukast is useful to prevent bronchoconstriction in response to exercise in young patients, reducing post-exercise bronchoconstriction in lung function, when administered as one daily dose⁸⁴. In children with allergic rhinitis, montelukast has demonstrated to be effective in reducing the

symptoms of the nose and overall disease control, especially children who are unable or unwilling to use intranasal steroids⁸⁵. Its oral administration daily dose makes it simpler to follow the treatment in kids as opposed to inhaled administration. The available safety data of randomized controlled trials of thousands of children aged between 6 months and 14 years indicate the general well tolerability of montelukast. A concern has however been raised in the recent past with respect to the possible neuropsychiatric side effects; nevertheless meta-analysis of such trials has not revealed a significant increase in risks as compared to the placebo⁸⁶.

3.7 Off-label Uses of Montelukast

Montelukast has an off-label application in inflammatory disorder. It is mostly used as an adjunct therapy with aspirin-aggravated respiratory disease (AERD), which is typified by leukotrienes excess. It has been shown that leukotriene receptor antagonists may be used to relieve the symptoms of asthma as well as improve its nasal functionality and serve as an additive to overall disease management in a complex treatment regimen⁸⁷. It is also used as an adjunct treatment of chronic spontaneous urticaria and systematic reviews have demonstrated that it is capable of alleviating symptoms in patients who do not respond to antihistamines. It is still in the experimental stages of its usage in atopic dermatitis, where it has been found that it gives mixed results and only slight improvements in some forms of atopy⁸⁸.

3.8 Side Effects and Adverse Drug Reactions of Montelukast

Montelukast, which is prescribed to people with asthma, allergic rhinitis, etc., has been reported to be increasingly linked to numerous adverse drug reactions, especially those of the nervous system and sleep. In depth examination of case reports has shown that there are side effects such as agitation, anxiety, depression, hallucinations, insomnia, nightmares, tremors, dizziness, drowsiness, neuropathy and seizures and rare immune related disorders such as eosinophilic syndromes and hypersensitivity reactions⁸⁹.

A significant research study among children showed that about 15.1% of children treated with montelukast had sleep disturbances, 10.4% said that they felt agitated and that behavioral complications such as hyperactivity and irritability were common-thus neuropsychiatric adverse drug reactions may be more common than actually though⁹⁰.

The U.S. Food and Drug Administration (FDA) has issued a boxed warning in the year 2020 to alert healthcare facilities and patients that there are serious mental health risks such as suicidal ideation or behavior, intense nightmares, behavioral changes, and mood disorders associated with the use of the drug. The FDA suggested that before prescribing, the risks and benefits must be evaluated carefully particularly in low severity conditions such as allergic rhinitis^{55,67}.

Subsequent systematic reviews and observational studies have all implicated risk of anxiety and sleep disorders associated with use of montelukast in adults⁹¹. Montelukast has been found to cause neuropsychiatric symptoms in patients. The symptoms have been experienced in adults, teenagers and children. These could be but not restricted to anxiety, depression, aggression, restlessness, attention and memory deficits, sleep disturbances (including insomnia, sleepwalking, and strange dreams), seizures, unusual sensations (tingling, numbness), and suicidal thoughts or behavior^{92,93}.

Although taking montelukast, a small number of asthma patients can develop systemic eosinophilia, sometimes with the addition of vasculitis, which is in keeping with the Churg-Strauss syndrome (a rare condition).

Montelukast has other side effects such as, but not limited to:

- Headaches, fever, and fatigue
- Respiratory tract symptoms: runny nose, sore throat, laryngitis, sinusitis and nose bleed.
- Problems with ears such as otitis.
- Symptoms of lower respiratory tract such as cough, pneumonia, and wheezing.
- Eye-related complications like conjunctivitis.
- Such infections as flu and chicken pox.
- Skin responses such as itching, eczema, atopic dermatitis, angioedema, hives, rashes, bruising, erythema multiforme, erythema nodosum, toxic epidermal necrolysis and Stevens-Johnson syndrome.
- Such musculoskeletal pains as joint pains and muscle pains.
- Anaphylaxis and eosinophilic liver infiltration hypersensitivity reactions.

Liver toxicity: During clinical trials, liver enzymes underwent mild elevations in 1 to 2 percent of patients receiving long-term montelukast, but like other controls, the rate was the same in placebo. The enzyme elevations are usually of mixed type that involves the liver cells as well as the bile flow. Anaphylactic reactions and the development of auto antibodies were rare. The liver damage normally heals in 1-4 months of discontinuation of the drug. Its likelihood rating is B, which means that it is an infrequent and yet most likely cause of apparent liver damage⁵³.

WHO pharmacovigilance database has reported the following side effects like depression, headaches, aggression, suicidal thoughts, anxiety, insomnia, unusual behaviour, nightmares, difficulty breathing, abdominal pain, nausea, rash, dizziness, muscle pain and muscle spasms⁹⁴.

FDA advised taking caution when prescribing montelukast and other LTRAs due to potential risks of adverse neuropsychiatric effects including depression and suicidal ideation as precaution^{94,95,96}.

4. CONCLUSION

Montelukast is a significant drug in respiratory therapy since it is an oral medication that directly disrupts the leukotrienes pathway. It has certain obvious advantages in terms of compliance and convenience, particularly about individuals with leukotrienes-sensitive obesity-induced bronchoconstriction, AERD, wheezing provoked by viruses, and asthma with allergic rhinitis. Although there is strong evidence that it offers significant benefits in comparison to a placebo, inhaled corticosteroids also outcompete it in regards to overall performance in treating persistent asthma and should be used at all opportunities. The question of safety is a large one with the mounting neuropsychiatric side effects evidence and the boxed warning issued by regulators lately. This implies that physicians must be able to participate in shared decision-making, inform the patient and his family about possible dangers, and observe closely any behaviour or mood changes during the treatment. Montelukast should be reserved as an option to be used in certain situations: an oral alternative to inhalers when they are not available or suitable, another option when inhaled corticosteroids are insufficient, and specific asthma phenotypes when leukotrienes blocking may have additional benefits. In the future, additional studies are required to identify the mechanisms of the neuropsychiatric signatures, to optimize predictors by asthma phenotype and to evaluate the safety of montelukast in the long term in diverse populations to further incorporate montelukast in the management of asthma in a more personalized way.

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Author Contribution

Constructing an idea or hypothesis for the manuscript – SS, UKM, BSB, PMS, SKP, AMK

Designing – SS, UKM, BSB, PMS,

Organizing and supervising the course of the article – SS

Literature review, material, data collection and processing – UKM, PMS, BSB, SKP, AMK

Interpretation and presentation of the results – AMK, BSB, PMS, SKP, UKM

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Not applicable as this is a review article.

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