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REVIEW ARTICLE

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Role of montelukast in the treatment of covid – 19 an overview

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ABSTRACT

Introduction: COVID – 19 infections that has shaken the world by leading into a significant health issue. World is in the need for effective therapies in order to improve clinical outcomes of patients. We must consider new approaches in the treatment of COVID-19. In order to bring effectiveness in treatment, it is important to know the exact pathogenesis of the virus so that it will pave a path for an efficient treatment.

Methods: To ensure comprehensive research and discuss the objective of the review of the study, literature collection was collected from the relevant published articles from databases such as "PubMed, Medline, and SCOPUS,"

Results: COVID-19 is linked with severe inflammation. Pro-inflammatory cytokine levels are elevated in the lung and in bronchial cells. Leukotrienes [LTs] are eicosanoids and inflammatory mediators. Leukotrienes are produced by various cell types which includes, leukocytes. Cysteinyl-leukotrienes (CysLTs) are involved in respiratory pathologies such as inflammation, thrombosis and vascular damage, and fibrotic remodeling.

Discussion: Hence there is a rational for LTs inhibition and montelukast usage in respiratory diseases beyond asthma. Various literatures suggest the use of LT receptor antagonist 'Montelukast' in COVID – 19 treatments.

Conclusion: This review article will discuss various aspects of Montelukast in COVID – 19 treatments and reviews the properties of montelukast that could be beneficial in the treatment of COVID-19.

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Introduction

Since the arrival of the SARS-COV-2 virus, the number of cases is in the increasing phase and so does the information regarding the management of this infection. SARS-COV-2, an RNA beta coronavirus, emerged in 2019 Dec in Wuhan, China, has led to clusters of pneumonia outbreaks and infections and is a global concern. The important complications seen with patients of COVID – 19 are acute respiratory distress syndrome and cytokine storm syndrome. Nuclear Factor Kappa light chain enhancer of activated B-cells [NF-kB], a protein complex is involved in the production of cytokines and is said to play a vital role in inflammatory responses. Montelukast, an FDA-approved drug for asthma has shown effective inhibition of NF-kB signaling such as IL – 6, IL-8, IL-10, TNF – alpha,

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Monocyte Chemoattractant Protein- 1 (MCP – 1), and various other proinflammatory mediators (Sanghai *et al*., 2020). SARS-COV-2 enters via the ACE receptors into the cells and causes excessive inflammatory processes. Montelukast effect's on events developing with Angiotensin-converting enzyme (ACE) receptors, and also its anti-inflammatory effect with bradykinin and leukotriene antagonism; could make it a potential drug in COVID – 19 (Norouzi A., 2020). There are various proposals stating that montelukast causes a reduction in proinflammatory mediators and mitigates COVID- 19 symptoms, thereby could serve as a therapeutic for SARS – COV – 2 infection.

Materials and Methods

To ensure a comprehensive research review of the study, search terms were carried out using key text words such as "Covid-19 and Montelukast," "Leukotriene's", "Cytokine storm", "Interleukin". These terms were used individually and in combination to sew up for widening the search window of the literature collection. Relevant published articles from databases such as "PubMed, Medline, and SCOPUS," were selected for disusing the objective of the review.

Discussion:

COVID – 19 pathogenesis and the role of NF-kB

Excessive inflammation accounts for the severity of Covid-19 infection. Increased levels of interleukin-6[IL-6], C-Reactive Protein[CRP], procalcitonin, interleukin-2[IL-2], interleukin-10[IL-10], and Tumor Necrosis Factor [TNF-α] is observed in those who undergo hospitalization. SARS-COV-2 infects alveolar cells directly, and further limits gaseous exchange within the lung (Khan *et al*., 2022).

NF-kB is the first important factor involved in many inflammatory responses and it is associated with cytokine storm. NF-kB pathway is commonly activated upon viral infections resulting in an array of cytokine and chemokine gene expressions (Ludwig *et al*., 2008). RNA viral pathogens are said to activate this factor and also activated NF-kB yields a better environment for viral replication. Multiple studies suggest the evidence of SARS- COV-2 activating the NF-B pathway, and serving as a mediator for cytokine storm, better known as the NF-kB butterfly effect. Hence suppression of NF-kB could help in attenuating proinflammatory cytokine release and tame the cytokine storm by dampening the NF-kB butterfly effect.

Inflammatory responses in COVID – 19

COVID-19 inflammation is said to be partially triggered by virus-induced cell cytolysis in the lungs, which enhances the production of cytokines and chemokines by infected cells. There are increased levels of inflammatory markers in the blood that includes: C-reactive protein, ferritin, and D-dimers, increased neutrophil/lymphocyte ratio, and increased serum levels of several inflammatory cytokines, like IL-1, IL-6, and TNF-α, and chemokines, as well as extensive lymphopenia and infiltration of monocytes, macrophages and neutrophils in the lungs, heart, spleen, lymph nodes, and kidney. Increased vascular leakage and uncontrolled inflammation have been associated with alveolar damage in COVID-19 patients (Dogan *et al*., 2021). The pathogenesis has been presented in Figure 1.

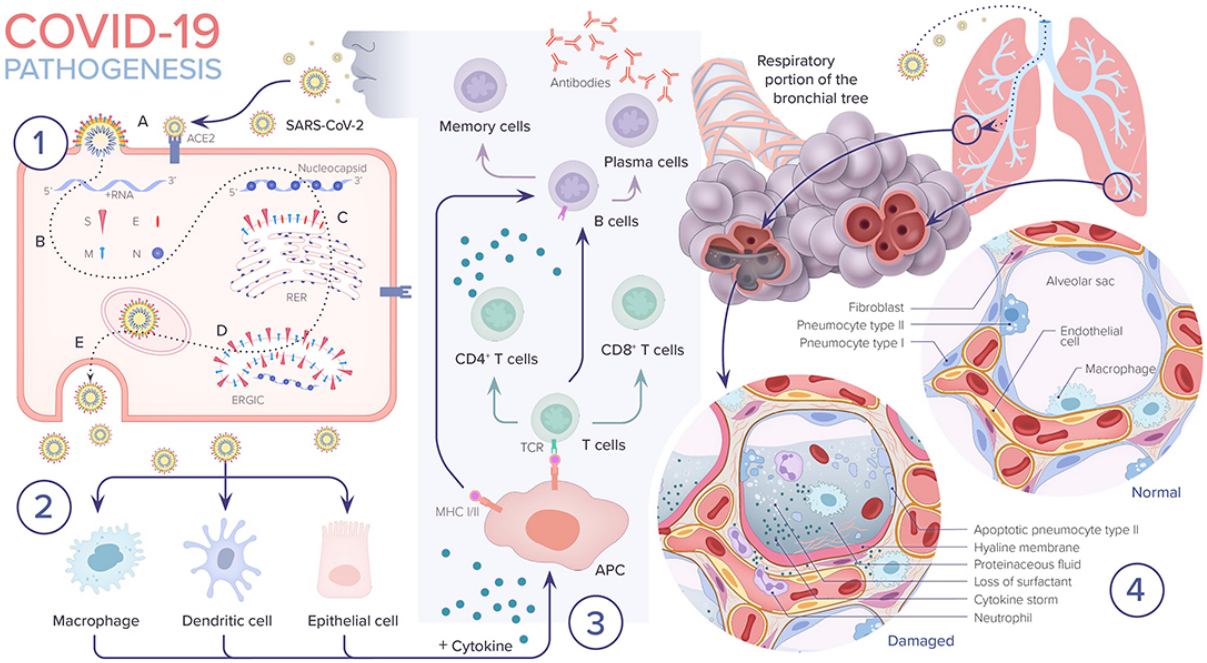


Figure 1: Pathological changes resulting in alveolar damage and collapse impairing gaseous exchange.

Cytokine storm syndrome

Many COVID – 19 patients experience a typical syndrome referred to as cytokine storm syndrome or simply referred to as cytokine storm- where there occurs sudden and severe onset of cytokine cascade which can lead to Acute Respiratory Distress Syndrome [ARDS], multiple organ failure and finally leading to death. This effect is due to the cumulative effects of a combination of several immune-active molecules. This "cytokine storm", due to angiotensin-converting enzyme-2 (ACE2) downregulation by SARS-CoV-2 is said to trigger a proinflammatory environment and hence it is strongly associated with severe tissue damage, contributing to ARDS and fatal outcomes (Barre *et al*., 2020).

Main components of cytokine storm: release of large quantities of interferons, interleukins, chemokines, colony-stimulating factors, and TNF-alpha. This is the most dangerous aspect of COVID – 19.

Acute respiratory distress syndrome [ARDS]

ARDS is an acute inflammatory lung injury, with complex pathogenesis resulting from widespread alveolar injury caused by intense inflammation. Respiratory failure is the most important cause of COVID-19-related deaths and it is progressive and unresponsive to treatment (Fidan *et al*., 2020). It has also been shown that 70 % of death in Covid cases is due to ARDS (Al-Kuraishy *et al*., 2021).

A brief on leukotrienes [LTs]

Leukotrienes are eicosanoids that are produced by leucocytes. These are well known in respiratory medicine as they trigger bronchoconstriction in asthma and cause inflammation. LTs play an important role in the acute phase of respiratory ailments and serve as a mediator of molecular and cellular pathologies in respiratory disease, therefore inhibition of LTs alleviates respiratory pathology.

Leukotrienes in COVID

Targeting leukotrienes is a novel strategy to mitigate hyperinflammatory responses in COVID. There are many similar symptoms such as cough and fever, dyspnoea, pneumonia, respiratory failure, and sepsis between COVID-19-associated and not-associated respiratory conditions, and also there exists similarities in the various aspects of respiratory disease pathology such as inflammation, thrombosis, and vascular damage, and fibrotic reactions. The most potent chemoattractant for neutrophil and lymphocyte subsets is leukotriene B4 [LTB4], which is one of the key mediators in carrying out the huge influx of these cells to airways, leading to profound lymphocytopenia in severe COVID-19 and neutrophilia in airways (Funk *et al*., 2020). The role of leukotrienes in NF- kB activation has been presented in Figure 2.

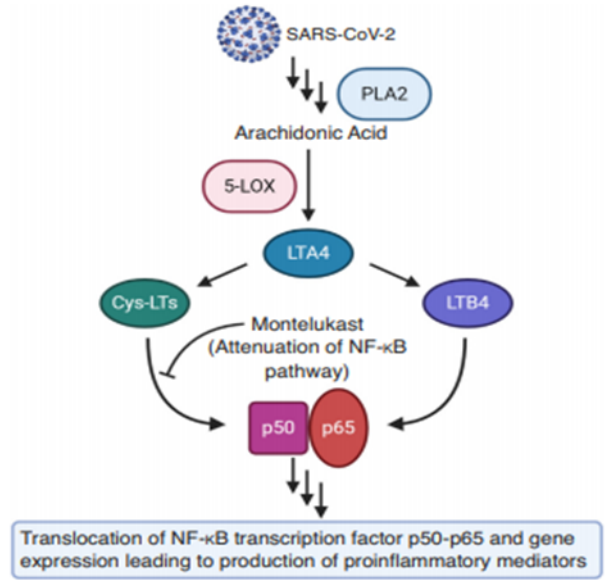


Figure 2: Role of leukotrienes in NF- kB activation, leading to increased proinflammatory mediators.

A potential therapeutic: Montelukast

A drug with a good safety profile-Montelukast is a leukotriene receptor antagonist (LTRA). This drug is widely used in asthmatic patients. It interferes in immune modulation by inhibiting pro-inflammatory mediators which causes bronchoconstriction and endothelial cell permeability, thereby improving lung function. Also, a study reported that montelukast prevents collagen deposition in lung and fibrotic response in animal models, this suggests that LTRAs might be useful in pulmonary fibrosis (Topaloglu *et al*., 2018). Studies show that Montelukast inhibited NF-kB signaling in a dose-dependent manner in a human acute monocytic leukemia cell line (THP-1). This indicates that it affects controlling the cascade of cytokine release (Topaloglu *et al*., 2018). Montelukast blocks the CysT1 receptor and prevents the inflammatory cascade resulting in anaphylactic, oedematous, and pro-inflammatory actions (Suceveanu *et al*., 2020). It reduces leukotriene-mediated cytokine release thereby potentiates moderating background inflammation in obesity and the body's inflammatory response to SARS-COV-2 infection (Almerie *et al*., 2020). CysLT1 receptor antagonism is the primary mechanism of therapeutic activity of Montelukast (Anderson *et al*., 2009).

Antiviral activity of montelukast

In addition to functions such as immune modulation and improvement of lung injury, Montelukast has a potential anti-viral activity as it's shown to disrupt the virion's integrity to release the viral genomic RNA and irreversibly

inhibit viral infectivity. SARS-CoV-2 virus propagation requires the main protease Mpro, which is processing and cleaving the viral polypeptides (Aigner *et al*., 2020). Montelukast may also have a direct antiviral effect on the SARS-CoV-2 main protease enzyme thus acting as a potential Mpro inhibitor. Studies suggest that montelukast binds to the active pocket of the main protease enzyme with high affinity (Downing *et al*., 2020). Hence Montelukast has a dual role as - a leukotriene antagonist and a protease inhibitor.

Anti-fibrotic effets of montelukast

The anti-fibrotic action of montelukast has been confirmed in an animal model of pulmonary fibrosis. It has been shown that montelukast limits the residual extent of COVID-19 sequelae of pulmonary fibrosis and has the potential to regulate the extracellular remodeling matrix, thus inhibiting the fibrosis.

Alleviation of vascular damage

Important events triggered by SARS – COV – 2 include platelet aggregation and thrombosis. So we can expect a high number of activated platelets in COVID – 19 patients, which release multiple inflammatory molecules. Platelet function is influenced by CysLTs in airway inflammation and also platelets express CysLT1R and CysLT2R. The above mechanisms suggest that CysLTs might be involved in platelet activation thus using CysLT1R antagonists such as montelukast is advantageous in the treatment of inflammatory states, particularly in combination with antiplatelet drugs (Aigner *et al*., 2020).

Extrapulmonary effects of montelukast

Apart from affecting the lungs, SARS-COV-2 affects multiple other organs.

CNS& Ocular

ACE2 receptor is expressed on cells of the central nervous tissue, namely neurons and glial cells, this makes them potential target cells of this virus in the CNS. Also, there are shreds of evidence showing that ACE-2 and Type-II Transmembrane Serine Protease [TMPRSS2] are located on the conjunctival epithelium of adult humans, making the outer ocular surface susceptible to SARS-COV-2 infection. Experimental studies demonstrated that: montelukast helps in CNS repair and regeneration in animal models of aging, chronic neurodegenerative disease, and acute CNS lesions (Aigner *et al*., 2020). Montelukast acts in a protective and regenerative mode in various cells and could have the potential to protect and repair SARS-COV-2-induced damages in the brain. The same applies to retinal damages also, as montelukast has been shown to prevent degeneration of capillaries in the retina in an animal model.

Renal

SARS-COV-2 infection is also associated with Acute Kidney Injury (AKI) through direct binding to renal ACE-2. Activation of the LT pathway [5-Lipoxygenase & Cys-LTs] is evident and mediates nephrotoxicity through induction of inflammation and apoptosis. Studies have shown that NF-kB pathway activation is associated with AKI, thereby inhibition of this pathway may attenuate AKI. Through suppression of NF-kB signaling, montelukast provides potent anti-inflammatory effects, being able to alleviate kidney injury.

Gastro-intestinal Tract

Since the virus can be transmitted by feces by inhalation of the infected droplet, gastrointestinal symptoms that are more common in Covid-19 are diarrhea, nausea, vomiting, and abdominal pain. It has been reported that Cys-LT antagonists have anti-inflammatory and anti-emetic effects (Al-Kuraishy *et al*., 2021; Aigner *et al*., 2020). 5-LO and Cys-LT play a vital role in the pathophysiology of intestinal ischemic reperfusion injury, therefore montelukast and other Cys-LT inhibitors attenuate intestinal ischemic reperfusion injury and also the gastric mucosal damage.

ACE-2 expression is not only limited to the lung, and so the extrapulmonary spread of SARS-COV-2 is observed (Downing *et al*., 2020; Hoffmann *et al*., 2020). Montelukast ameliorates extra-pulmonary manifestations of Covid-19 either directly through Cys-LTRs blockage in different organs or indirectly through NF-kB signaling pathway inhibition (Lima-Morales *et al*., 2021).

Delivering the drug – Montelukast

The available and recommended daily dose of Montelukast is 10 mg tablet. The absorption of montelukast into the blood is relatively slow and inconsistent, the reason for this is - montelukast is freely soluble in water, and its solubility is markedly increased above pH value of 7.5 and significantly reduced under acidic conditions which are normally found in the gastrointestinal tract. Since most of the COVID-19 patients are elderly and in critical care alternative drug delivery method is required (Scaife *et al*., 2013). A buccal mucoadhesive film formulation of montelukast is in a recent Phase I study that showed good safety and tolerability profile in healthy subjects. And also provides a reduction in first-pass-effect and a 52 % higher bioavailability compared to montelukast tablets (Aigner *et al*., 2020). Some studies detected a reduction in SARS-COV-2 infection among elderly patients with asthma when treated with Montelukast (Chams *et al*., 2020; Raymond *et al*., 2020). Its main role is that it inhibits activation of NF-kB in a human monocyte/macrophage cell and suppression of IL-8 in a monocyte/macrophage cell line pre-treated with TNF (Merad *et al*., 2020; Maeba *et al*., 2005).

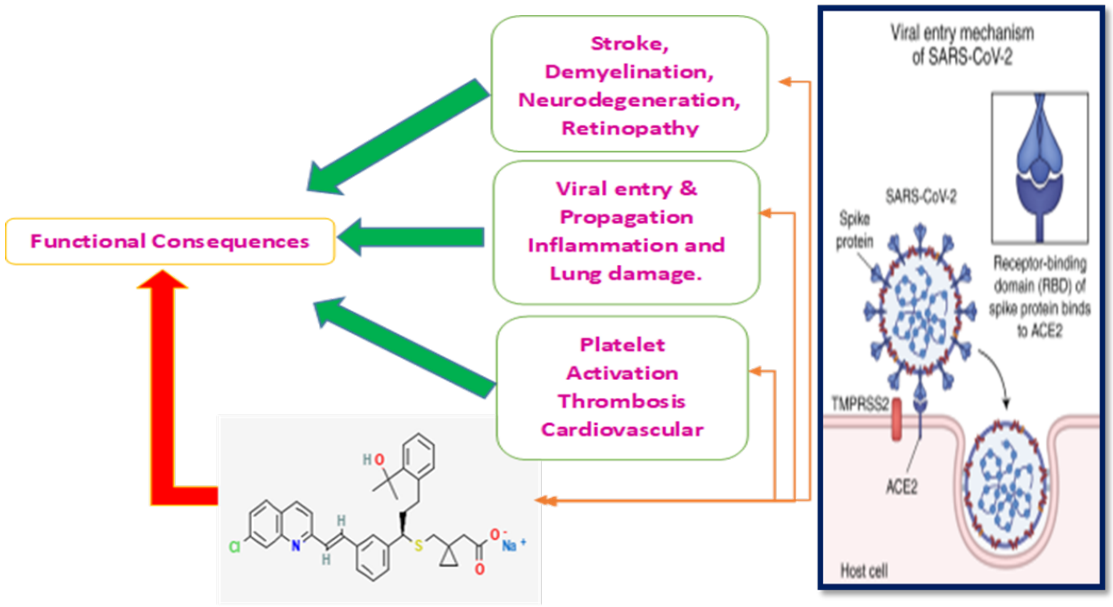


Figure 3: Effectiveness of montelukast in addressing various detrimental processes and promotion of functional recovery.

Randomized trial

Various studies and trials are being conducted to confirm the efficacy of montelukast. One such trial is a randomized, controlled open-labeled trial with 160 covid – 19 confirmed patients. After getting informed consent from the hospitalized individual, patients were randomly allocated by computer-generated methods without the researcher's knowledge (Tavares *et al*., 2021). Two groups were assigned, out of which one group received 10 mg of oral montelukast in addition to standard care, whereas the second group received only standard care. Screening of the individual happened in the first 72 hours and on the 14th day. Data recording was done on case records and registered in an electronic database, validated finally by a staff. The primary outcome of this trial aimed to assess the time to recovery by day-29, and the secondary outcome analysis is to look out for changes in the laboratory values. Apart from assessing these two outcomes, safety outcomes were assessed based on adverse effects during treatment. This trial was considered essential to improve clinical outcomes related to Covid. This trial came up with the conclusion that the addition of montelukast to the standard care reduced the hospitalization period and diminish the cost burden and resulted in a better prognosis (Tavares *et al*., 2021).

Conclusion

Till date, we do not have an effective treatment for SARS-COV-2. The major cause of disease severity and death in patients with COVID-19 is an excessive inflammatory response to SARS-COV-2. Cytokine storm syndrome and increased IL-6 levels have been noted in patients with severe SARS-COV-2 infection. Levels of IL-6 were 2.9 folds higher in complicated SARS-COV-2 infections in comparison with mild diseases. As Leukotrienes are considered to be involved in the pathology of COVID-19, LT receptor antagonist montelukast might provide antiviral activity through modulation of the Mpro inhibitor site. Montelukast modulates the production of IL-6, TNF-alpha, and MCP-1 through inhibition of NF-Kb activation. Apart from the alleviation of the pathology, Montelukast promotes structural and functional recovery. Montelukast is a potential drug with two most important actions on this infection: by improving lung inflammation or by acting on the virus, thus limiting its replication in the host. To conclude, reduction in the pro-inflammatory mediators by Montelukast results in mitigation of COVID-19 symptoms, and thus serves as a therapeutic for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections, and alleviates severe complications of the infection such as ARDS and cytokine storm syndrome.

Authors' contributions

Dr. Thurka contributed to writing the manuscript, Ms. Sravani Marpaka planned & designed the concept of the manuscript, supported in writing the manuscript, and collected the reference articles, and Dr. Chakradhar T and Dr. Swati Negi reviewed the article.

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Conflict of Interest

There is no conflict of interest.

Funding source

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