Montelukast - Its Immunomodulatory and Antiviral Action in COVID-19

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Coronavirus disease-19 (COVID-19) is the deadliest pandemic that the whole world is facing today. COVID-19 is different from normal flu by its two lethal manifestations which includes deadly pneumonia which may lead to acute respiratory distress syndrome (ARDS) due to hyper-inflammation of alveolar tissues and pulmonary intravascular coagulopathy (PIC).[1,2] It is noteworthy here to mention that both these lethal manifestations of COVID-19 are due to abnormally high levels of pro-inflammatory cytokines like interleukin (IL) - 1β, IL - 6, and tumour necrosis factor (TNF) - α, termed as "cytokine storm."[3,4]

There is a certain link between pro-inflammatory cytokines like IL - 1β, IL - 6, and TNF - α and its pro-coagulatory influence on coagulation pathway mediated by tissue factor that binds and activate factor VII, leading to formation of tissue factor – VII a complexes which results in the activation of clotting factor X and IX.[4] Recently the researchers in China and some European countries have found raised level of pro-inflammatory cytokines particularly IL - 6 in severe cases of COVID-19. They also found raised D-dimer, fibrinogen levels and prothrombin time in moderate to severe COVID-19 cases.[5,6]

Both of these lethal manifestations of COVID-19 – ARDS and PIC are linked to raised levels of pro-inflammatory cytokines, particularly, IL - 6. It is not very clear that the pro-inflammatory action of cytokines is mediated through leukotrienes as the biochemical assay for leukotrienes are not widely available but possibility of this probable mechanism cannot be ruled out. Hence, development of any molecule with ability to inhibit pro-inflammatory cytokines, particularly IL-6 may be able to tame the lethal nature of COVID-19, and may ultimately reduce the mortality of this deadly pandemic.

Montelukast sodium is such molecule which has capacity to inhibit pro-inflammatory cytokines such as IL - 1β, IL - 6, and TNF - α.[7] Montelukast sodium is leukotriene receptor antagonist that inhibits the cysteinyl leukotriene type-1 receptor. Leukotrienes modulate the production of pro-inflammatory cytokines.[8] Its antagonist action on leukotriene receptors can inhibit the production of these pro-inflammatory cytokines.

Even recent in silico study by Jacobson at Oak Ridge National Lab, was found that excess bradykinin production may be responsible for pulmonary, cardiac, neurological and nephrological lethal manifestations of COVID-19.[9] Crimi et al.[10] already found that Montelukast is effective to control bradykinin induced bronchoconstriction. Thus, theoretically, montelukast seems to be best molecule to deal with deadly manifestation of COVID-19 even if we go by cytokine storm hypothesis or bradykinin hypothesis.

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DOI: 10.18410/jebmh/2021/327

How to Cite This Article:
Chakkarwar PR. Montelukast - its immuno-modulatory and antiviral action in COVID-19. J Evid Based Med Healthc 2021;8(21):1731-1732. DOI: 10.18410/jebmh/2021/327

Submission 05-02-2021,
Peer Review 14-02-2021,
Acceptance 06-04-2021,
Published 24-05-2020.

In addition, in silico study has demonstrated a high binding affinity of montelukast molecule to the terminal site of virus's main protease enzyme which is needed for virus RNA synthesis and replication.[11] Even few studies show that montelukast have antiviral activity against Zika and few more viruses.[12] Besides this, montelukast can be better option than dexamethasone on two reasons - firstly, it can be used at preventive level itself and secondly, montelukast possesses broad spectrum of anti-inflammatory properties, which can target corticosteroid insensitive neutrophils besides its action on eosinophils and monocytes.[13]

It is notable to mention here that Virginia medical school in its study found that montelukast sodium can prevent deadly pneumonia due to cytokine storm of viral infections which further supports our hypothesis.[14] Besides this, one of the important side effects of montelukast sodium is increased bleeding tendency i.e., it negatively influences the normal coagulation pathway. This is supportive to our proposed hypothesis that montelukast sodium can prevent the PIC.

A few case reports across the world also directly support our view that montelukast can successfully help in treatment of COVID-19.[16,17]

Hence, there is an urgent need to seriously look into this cost-effective, generic, easily available, a potential game changer molecule which may save many innocent lives from across the world from this deadly pandemic of COVID-19.

Financial or other competing interests: None.
Disclosure forms provided by the authors are available with the full text of this article at jemds.com.

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