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Brief report

Aerosolized type II transmembrane serine protease 2 inhibitor to combat COVID-19: a proposal

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ABSTRACT

Type II transmembrane serine protease (TMPRSS2) is expressed at the cell surface with COVID-19 infection. And COVID-19 infection misuse TMPRSS2 to advance their spread, making this protease potential focuses for intervention in COVID-19 infection. TMPRSS2 blocker may be the appropriate option to arrest cellular entry of COVID-19 by deregulating spike priming. Therefore a trial may be intended to watch the adequacy of aerosolized spraying of TMPRSS2 inhibitors to break the viral entry to the objective cells that empower to break the COVID-19 transmission. Targeting TMPRSS2 through aerosolized TMPRSS2 inhibitor is important to examine a possibly viable remedial technique in the treatment of COVID-19.

Keywords: COVID-19, TMPRSS2 inhibitor, Aerosolized treatment

Medication repurposing is a rising technique to the medication redeploying from existing medicines that can give the snappiest conceivable progress from seat to bedside to battle hard- to-treat ailments. Considering a quickly raising and fatal pandemic of COVID-19 disease, new medicines are direly required for the treatment or counteraction COVID-19.

COVID-19 which belongs to the beta coronavirus 2B lineage virus, initiates human cell entry after the spike protein (S-protein) present on the envelope composed of a lipid bilayer and envelope proteins, binds to a cell membrane receptor angiotensin-converting enzyme 2 (ACE-2).[1] There's a wealth of this receptor in cells in the lungs especially in type-2 pneumocytes, which may clarify the high frequency of pneumonia and bronchitis in those with serious COVID-19 disease. ACE-2 has a double role proceeding first to viral entry, at that point progression of the malady by deactivation of ACE-2. The protein-protein interactions are the mainstay event of the first entry of the COVID-19 virus inside the host cell. The expression of ACE-2 in differing tissues builds the danger of COVID-19 disease. The receptor-binding domain (RBD) of the S1 part of S-protein ties to ACE-2 and S2 part is cleaved by a type II transmembrane serine protease (TMPRSS2), resulting in fusion of membrane. TMPRSS2 is expressed at the cell surface and is in this manner obviously situated to control cell–cell and cell–matrix collaborations. Controlled proteolysis of cell factors is crucial to tissue homeostasis, though uncontrolled proteolytic action is connected to the disease. COVID-19 infection misuse TMPRSS2 to advance their spread, making this protease potential focuses for intervention in COVID-19 infection. S-proteins are synthesized and maintained in precursor intermediate folding states, and proteolysis allows the refolding and energy discharge required to make stable virus-cell linkages and membrane coalescence. Biochemical interaction studies and crystal structure analysis showed that S-protein, like a ligand, has a strong binding affinity to human ACE-2.[2] TMPRSS2 is essential for S-protein priming.[3] It was also reported that SARS-CoV-2 infection might down-regulate the ACE-2 expression in the lung. The central role of ACE-2 appears to counter ACE activity by reducing angiotensin-2

bioavailability and increasing angiotensin- (1–7) formation. The emerging concept is that an imbalance in ACE-2/angiotensin-(1–7) and ACE/Angiotensin-2 axes are critical in the development of cardiovascular diseases. The potential approach is to targeting ACE-2-mediated COVID-19 viral entry to decrease the viral spread and to protect the lung from injury. The use of an ACE-2 receptor inhibitor may not be a suitable option considering the negative effect on cardiac health. TMPRSS2 blocker may be the appropriate option to arrest cellular entry of COVID-19 by deregulating spike priming.

Trials concentrate on murine models after SARS-CoV and MERS-CoV infection impact our understandings that the absence of TMPRSS2 in the airways diminishes the seriousness of lung pathology.[4]

Two TMPRSS2 inhibitors named nafamostat mesylate (NM) and camostat mesylate (CM) were developed in Japan to treat inflammatory-related diseases. A number of studies highlighted the effects of protease inhibitors on the multicycle replications of various orthomyxoviruses and paramyxoviruses. It is reported that NM effectively inhibits MERS-CoV S- protein-initiated membrane fusion. NM can inhibit the membrane fusion at a concentration less than one-tenth that of CM, which is recently identified by a German group as an inhibitor of COVID-19 infection.[3] The inhibition of TMPRSS2 by the non-specific serine protease inhibitor camostat caused a 10-fold decrease in infection of calu-3 cells by SARS-CoV.[5] In another investigation, topical airway administration of CM attenuates epithelial sodium channel function and enhances mucociliary clearance[6]. This extra adequacy may contribute remedial advantage in COVID-19.

The remedial capability of aerosolized treatment relies upon fast retention and disposes of the pre-systemic metabolism of the drug through the oral route. The utilization of aerosol therapy to furnish high local drug concentrations with negligible systemic side effects makes this route an alluring alternative. Until now, there is not really discovered any proof of aerosolized treatment with TMPRSS2 blocker aside from one investigation on animals.[5] The specialized developments must go on and join aerosolized TMPRSS2 blockers. An unlabeled use of nebulized medications is gaining popularity as a treatment elective, and numerous medications are utilized unlabeled in a nebulized form. Aerosol drug delivery can provide many advantages over conventional therapy.[7] A suitable formulation and inhalation device design are waiting for better service. We can propose to nebulize TMPRSS2 blocker with suitable doses in selected cases on a trial basis to combat COVID-19.

Therefore a trial may be intended to watch the adequacy of aerosolized spraying of TMPRSS2 inhibitors to break the viral entry to the objective cells that empower to break the COVID-19 transmission. Targeting TMPRSS2 through aerosolized TMPRSS2 inhibitor is important to examine a possibly viable remedial technique in the treatment of COVID-19.

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