Serine protease inhibitors could be of benefit in the treatment of COVID-19 disease

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Introduction

With the advent of the coronavirus disease 2019 (COVID-19) pandemic, a disease associated with severe acute respiratory distress syndrome confronts the world's health systems.[1] Resource-constrained countries are worse hit, though with lower mortality records largely because of limited screening opportunities. The world is experiencing a second wave, which has been reported to be more lethal. According to the World Health Organisation (WHO), latest figures of the infection stand at over 100 million confirmed cases and over 2 million deaths. Rates differ from one region to another.[2] The impact on the world's economy and population dynamics is huge and needs to be ameliorated within the shortest possible time.

Search for treatment

While the search for vaccines is ongoing, with hints of success, drugs for acute treatment have remained a challenge. A flurry of activities in drug re-purposing is ongoing, as earlier ones touted as useful have turned out to have limited success. That is the fate of hydroxychloroquine, with widespread reports of adverse reactions and potential harms of its use.[3] Ivermectin, a cheap anti-parasitic drug that was recently re-purposed for treatment of COVID-19 disease, ran into controversy soon after initial recommendation.[4] Notwithstanding these initial set-backs, the development of new drugs or re-purposing of available drugs remains a viable option.[5] Following recent observations and better understanding of disease pathology and treatment, there seems to be promise in the utilisation of serine protease inhibitors as part of current therapy for COVID-19.

Disease pathophysiology

Currently, a hyper-coagulable state as a result of hyper-inflammation is considered a critical mechanism driving mortality in the disease state. This implicated pathway includes thrombo-inflammation propagated by angiotensin converting enzyme 2 (ACE 2) receptor-mediated pulmonary and vascular endothelial injury. Accompanying this is a hypofibrinolytic state in the alveolar space created by elevation of plasminogen activator inhibitor-1 (PAI-1) derived from pulmonary cells of the epithelium and endothelium.[6] As posited by Al-Samakri *et al.*,[7] this appears to be the key mechanistic pathway resulting in multi-organ failure and death; with autopsies showing extensive fibrin thrombi in the small vessels and capillaries. Histologically, lung tissues from COVID-19 disease patients show florid capillary endothelial injury as well as micro-thrombi formation in alveolar capillaries and small calibre pulmonary vasculature.[8]

Generally speaking, when individuals are infected, a host inflammatory response is triggered as part of innate immunity. This involves cells of the leucocyte line (monocytes and macrophages) that are mobilised early in infection to protect cells from further pathogen attack. This results in increased production of pro-inflammatory cytokines, which have pleiotropic effects, including but not limited to activation of the coagulation cascade and generation of thrombin.[9] These cytokines include interleukin 1b, interleukin 6 and tumour necrosis alpha, which affect normal cells and tissues of victims in what has been called a cytokine storm. This occurs later in the infection when adaptive immune response becomes prominent. These cytokines in high levels encountered in cytokine storms suppress oxygen utilisation in the body, leading to multiple organ failure and ultimately death. The COVID-19 infection-induced cytokine storm activates the coagulation cascade on the one hand but, on the other, suppresses the fibrinolytic system.[1] The outcome of this perturbation in the naturally balanced coagulation and fibrinolysis is

fibrin deposition. The fact that, in clinically ill COVID-19 patients, thrombosis occurs in the lung vessels and other organ systems with no obvious primary embolic source, gives credence to local thrombosis as a putative mechanism.[10] Some patients appear to have a more severe cytokine storm in response to COVID-19 infection, implying greater perturbation of the coagulation cascade. The cytokines and other inflammatory factors released cause inflammation in the vascular endothelium, resulting in microvascular endothelial injury and clots in the microvasculature. This affects gaseous exchange in the lung with the clinically observed hypoxia and desaturation. With this, a vicious cycle of endothelial injury is set up, with worsening micro-thromboembolism. As posited by Connors and Levy,[11] this sets the scene for benefit from venous thromboembolism prophylaxis. Concordance with this comes from the work of Piazza *et al.*,[12] who indicated that, unless contra-indicated, thromboprophylaxis should be available to all hospitalised COVID-19 patients.

Potential benefit of serine protease inhibitors

PAI-1 is ubiquitous, being produced by many cells in the body. Inflammation is one of the situations in the body that upregulates it.[13] PAI-1, levels of which are raised in COVID-19 infection alongside tissue plasminogen activator (t-PA), has been found to be elevated in patients with severe COVID-19 infection.[14] Whereas t-PA converts plasminogen to plasmin, which lyses insoluble fibrin to soluble fibrin degradation products, the co-existence of PAI-1 does not permit this action. This is the reason for t-PA alone not being a good candidate drug for therapy.[15] PAI-1 on its own is known to suppress fibrinolysis, allowing pathological fibrin deposition and tissue damage. This fibrinolytic shutdown is known to occur in infection-driven inflammation and is characterised by increased PAI-1 activity.[16] Derived from the foregoing, any agent that can inhibit PAI-1 activity or inactivate it would be of benefit in the treatment of COVID-19. Once it is depleted or inactivated, t-PA levels will increase and, by converting plasminogen to plasmin, cause lysis of fibrin and thrombi to soluble fibrin degradation products.[17] This is where the promise of serine protease inhibitors arise. They inactivate PAI-1 and permit degradation of fibrin and thrombi effect of t-PA. With these being shown to be the cause of morbidity and mortality in COVID-19 infections, serine protease inhibitors will ameliorate disease severity and improve outcomes.

Conclusion

Some workers are already calling for the use of serine protease inhibitors for COVID-19 infection for reasons adduced above, as well as their ability to block entry of the virus through the ACE-2 receptors,[18] since it also needs the serine protease transmembrane serine protease 2 for cell entry.[19] The viruses utilise their spike protein to attach to the ACE-2 receptors on the respiratory epithelial cells and the serine protease transmembrane protein to assemble and multiply the viruses intracellularly. This initiates and sustains inflammation. They therefore act beneficially in preventing establishment of infection by blocking the ACE-2 receptors through which the virus enters the cells of the respiratory epithelium. Where the infection is already in place, the cytokine storm following adaptive immunity causes elevation of PAI-1 and t-PA that perturbs the coagulation and fibrinolytic cascade – the accepted pathogenetic mechanism of morbidity and mortality. Serine protease inhibitors block production of PAI-1 from cells undergoing inflammation, thus permitting t-PA to rise and degrade fibrin and thrombi. These should encourage a therapeutic trial to clearly define and characterise these benefits pending the debut of an effective and widely accepted vaccine that will nudge up herd immunity in the population.

Conflict of interest statement

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