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Endotheliitis, endothelin, and endothelin receptor blockers in COVID-19

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ABSTRACT

We summarize the role of endothelin as a potent vasoconstrictor, pro-inflammatory, pro-oxidative agent in the pathophysiologic effects and end-organ dysfunction of coronavirus disease 2019 (COVID-19). Endotheliitis is an under-recognized pathophysiologic process that causes various types of dysfunction in end organs, including heart, lung, kidney, and brain. Endothelin receptor blockers, such as bosentan and sitaxentan, can pave a path ahead in the realm of COVID-19 therapies. These agents have a potential role against COVID-19 and should be studied in research trials to determine their efficacy in treatment of this severe disease.

Introduction

From the beginning of the coronavirus disease 2019 (COVID-19) pandemic, multiple studies had been underway to formulate a cure and treatment protocols. Initially, empirical ideologies were used, which eventually were disproved in clinical trials. Case fatality rates still range from 1% to 7%, but these numbers deserve scrutiny on the basis of data acquisition.[1]

A gross limitation has been mentioned in identification of the exact causes of death in populations affected by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.[2] Although the infection may be present in a patient who is considered seropositive for the virus, the primary cause of the patient's death could be the worsening of a concurrent comorbidity, lack of hospital supplies and equipment, and/or a noninclusive cause regardless of the virus[2].

Background:

With careful introspection of the pathogenesis of SARS-CoV-2, we came across a wide variation in pathophysiologic mechanisms that show its virulence and mortality rate. Be it the Spanish flu of 1918 or COVID-19, the main cause of death was respiratory disease.[3] Initial findings showed that non-survivors had an early increased neutrophil to lymphocyte ratio, relatively low lymphocyte counts, and increased C-reactive protein and D-dimer levels[2,4] with use of the prediction model calculator in that paper[4] (http://118.126.104.170). These findings were nonconclusive of the mechanisms of death. Recently, a cardiovascular component has been considered causative of the downward spiral in the health status of a patient who dies of COVID-19.

Rationale

The entry mode of SARS-CoV-2 was identified to be through the angiotensin-converting enzyme (ACE) 2 receptor, expressed in such organs as heart, liver, kidney, lung, and gastrointestinal tract. All these organs have depicted symptoms among patients infected by the virus: carditis, pneumonitis, pneumonia, acute kidney injury, and multiorgan failure. The same receptor also is expressed on endothelial cells.[5] Blood vessel endothelia pose a high risk of infection and viral entry, thus causing cardiovascular deterioration that includes myocardial injury and acute myocardial infarction, myocarditis,[6,7] heart failure, dysrhythmias, and thrombotic events including stroke. Monteil et al. [8] demonstrated entry of SARS-CoV-2 into in vitro endothelial cells. Case reports mentioned by Varga et al. [9] show that the histologic picture of COVID-19 involves endotheliitis and lymphocytic endotheliitis in such organs as lung, heart, kidney, and liver.

More importantly, these infected organs form large networked beds of endothelium. Further, the presence of groupings of apoptotic bodies was the hallmark finding of patients who died of COVID-19. Undoubtedly, endothelial dysfunction would span the vasculature and evolve

Abbreviations: ACE, angiotensin-converting enzyme; COVID-19, coronavirus disease 2019; ET-A, endothelin receptor A; ET-B, endothelin receptor B; ET-1, endothelian-1; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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into the critical condition of the patient. Endothelial dysfunction has been associated with an increase in endothelin, the hormone that regulates vascular tone and coagulative tendencies.[10] The hypothesis of endothelial dysfunction raises the question about whether endothelin is implicated in the pathogenesis of endothelial disruption and inflammation. Bottomline is that, the string that connects all these organs are endotheliitis and subsequent elevation of ET-1 in plasma.

Evaluation and justification:

In the Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial at the University of Oxford, investigators have shown that dexamethasone decreased the risk of death from 40% to 28%.[11] Earlier, dexamethasone had been shown to lessen the development of progressive pulmonary arterial hypertension in rats.[12] It also has been shown to block hypoxia-induced endothelial dysfunction.[13] Interestingly, the study of glucocorticoids (which also are involved in leukocyte endothelial adhesion),[14] vascular endothelial growth factor,[15] and the nontranscriptional activation of endothelial nitric oxide synthase [15] raises the question about whether other pathways are involved. These pathways can be modulated effectively with endothelin receptor blockers, anti-inflammatory drugs, ACE inhibitors, angiotensin receptor blockers, and endothelial stabilizers (eg, statins).

On comparison of patients with higher risks of death (eg, because of prior heart disease, coronary artery disease, diabetes mellitus, renal insufficiency, hypertension),[16] an observed common pathophysiologic thread to connect all these disease presentations is the prevalence of increased endothelin levels in blood and the ACE pathways.[17] Given a higher mortality risk among patients with elevated endothelin levels, it is prudent to investigate the association of endothelin receptor blockers as a potential therapy to reduce the severity and mortality rate of COVID-19.

Discussion

Endothelin is a potent vasoconstrictor, proinflammatory, proliferative, and pro-oxidative molecule. This hormone acts on the G protein–coupled transmembrane endothelin receptor A (ET-A) and endothelin receptor B (ET-B). Endothelins have different subtypes, and endothelian-1 (ET-1), endothelian-2, and endothelian-3 have various functions based on receptor binding. In general, ET-A modulates vasoconstriction; ET-B generally modulates vasodilation, excluding an opposite effect during venous circulation.

Patients with heart failure have increased ET-$1_{(1\text{-}31)}$ levels.[18] Patients with essential hypertension have an elevated ET-1 level at the vasculature walls. Hyperglycemia of persons with diabetes is also an inducer for ET-1 production. Studies of heart failure, hypertension, and diabetes show evidence that upholds a reduction in morbidity and death with use of endothelin receptor antagonists. Endothelin receptor blockers such as bosentan and sitaxentan must be involved in clinical studies for combating the COVID-19 pandemic with this pathophysiologic foundation.[19] In addition, an area of cardiovascular overlap occurs where the ET-1 increase is reduced with use of ACE inhibitor drugs.[20]

With more than 78.7 million confirmed COVID-19 cases globally and more than 1.73 million lives lost to COVID-19 thus far, scientists and physicians must combine efforts to fundamentally and continually decipher the pathophysiology behind the disease and the endothelial system and its interrelated molecular pathways, which are essential in the severe cases that require intensive care.

Ethics Approval and Consent to Participate

Not applicable.

Consent for Publication

All authors have approved the contents of this paper for publication.

Availability of Data and Material

Not applicable.

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Authors' contributions

D.K.S. and A.T. conceived the presented idea. D.K.S., A.T., T.R.C., and W.D.F. contributed to the manuscript writing equally.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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