Should COVID-19 Patients Use Angiotensin-Converting Enzyme Inhibitors?

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Abstract

As the search for the appropriate pharmaceutical intervention in the treatment and management of coronavirus disease 2019 continues, researches have been investigating the role of angiotensin-converting enzyme 2 inhibitors. The utilization of angiotensin-converting enzyme 2 inhibitors through the course of the infection of coronavirus disease 2019, has been described as being two-fold. Though the exact mechanism of action of angiotensin-converting enzyme 2 inhibitors in coronavirus positive patients is unknown. It has been postulated that hypertensive patients, or other patients taking angiotensin-converting enzyme 2 inhibitor medication, should continue administering the medication as before the infection. However, research has hypothesized that in using the medication, there is concern that the medication will cause the upregulation of the angiotensin-converting enzyme 2 receptors. The fear of the upregulation stems from the notion that the receptors prove to be the entry origin of the cell in the alveolar epithelium. The upregulation has been postulated to cause an increase in the viral load and, thus, may cause an exponential progression in the presentation of symptoms; this further may cause a patient to experience complications of the viral disease that is noted to be faster than in a prior healthy, individual that may be infected.

Keywords: ACE Inhibitor; COVID-19; SARS-CoV-2; ARB Inhibitor

For the third time in a decade, the coronavirus family has been associated with a global pandemic. The need to solidify a treatment of coronavirus disease 2019 (COVID-19) is imperative. While social distancing is being emphasized, the transmission of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is of high risk. The clinical manifestations of COVID-19, in addition to constitutional symptoms, are primarily respiratory; ranging from cough, shortness of breath and chest pain in mild cases; to quickly deteriorating into acute respiratory distress syndrome (ARDS), respiratory failure, or even multiple organ dysfunction in severe cases. The mechanism of entrance of the virus is through the spike (S) glycoprotein that is present on its cell surface. The glycoprotein has high affinity for the angiotensin converting enzyme 2 (ACE2) receptor [1]. The virus attaches to the ACE2 receptor on type II pneumocytes. Because of the utilization of the ACE2 receptor, a dilemma persists in attempting to understand what the role of angiotensin converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs), is in SARS-CoV-2 patients. ACEIs i.e. lisinopril, captopril, enalapril; are the second most frequently prescribed medications for aterial hypertension; in addition to that, they are implemented for other chronic cardiovascular diseases i.e. heart failure, post-myocardial infarction, as well as in diabetic nephropathy and chronic kidney disease. ACE2 receptors have a broad expression pattern in the human body with strong expression noted in the gastrointestinal system, heart, and kidney, with more recent data identifying expression of ACE2 in type II alveolar cells in the lungs [2]. One suggestion is that ACE inhibitors (ACEIs) could directly inhibit ACE2; however, ACE2 functions as a carboxypeptidase and is not inhibited by clinically prescribed ACEIs [3]. In addition, there is also concern that the use of ACEIs will increase the expression of ACE2 and increase patient susceptibility to viral host cell

entry and propagation [2]. The two-fold nature surrounding the concern of administering ACEIs in COVID-19 positive patients demands for further research to determine whether ACEIs increases the susceptibility or decreases the viral load.

ACEIs and ARBs are used in hypertensive patients to disrupt the renin-angiotensin-aldosterone system (RAAS). RAAS is a complex system that is responsible for regulating blood pressure. Kidneys initiate RAAS by releasing renin in response to low blood volume, low sodium levels, or high potassium levels [4]. Renin converts circulating angiotensinogen to angiotensin I. Angiotensin I converts to angiotensin II by angiotensin-converting enzyme 2. Angiotensin II causes contraction of the muscles surrounding blood vessels, compressing the vessels and thus, increasing blood pressure. Angiotensin II also stimulates the release of aldosterone that plays an imperative role in increasing water and sodium reabsorption, thereby, increasing both blood volume and pressure. ACEIs will block the conversion of angiotensin I to angiotensin II. Inhibiting the production of angiotensin II, stimulates the dilation of the blood vessels, causing a decrease in the blood pressure. ACEIs inhibit the breakdown of bradykinin, a vasodilator, thus dilating blood vessels. Furthermore, inhibition of angiotensin I to angiotensin II will cause an increased excretion of sodium and water; also leading to decrease blood volume and pressure.

A study by Liu., et al. showed that serum angiotensin II levels in patients with COVID-19 pneumonia was significantly higher compared with healthy individuals and were linearly associated with viral load and lung injury [5,6]. Based on this, it can be postulated that SARS-CoV-2 binding to ACE2 may attenuate residual ACE2 activity, skewing the ACE/ACE2 balance to a state of heightened angiotensin II activity, leading to pulmonary vasoconstriction and inflammatory and oxidative organ damage, increasing the risk for acute lung injury (ALI) [5]. It has also been postulated that increased levels of soluble form of ACE2 may act as a competitive interceptor of SARS-CoV-2 and slow virus entry into the cells, thus protecting from ALI [7]. In a meta-analysis of 37 studies, ACEIs and ARBs were associated with reduced risk of pneumonia and pneumonia-related mortality compared with control treatment [8]. The cause for lung injury in COVID-19 positive patients is hyperinflammation and a cytokine storm; both cause acute respiratory failure from acute respiratory distress syndrome (ARDS). Cytokines such as, interleukin-1 (IL-1), interleukin-6 (IL-6), and tissue necrosis factor alpha (TNFα) are released as the newly replicated virus buds off of the epithelial cells [1]. These cytokines cause hyperinflammation in the lungs and wreak havoc as they enter the bloodstream causing smooth muscle dilation along with contraction of blood vessel endothelial cells, increasing capillary permeability [1,5]. It is important to note that although many theories have been postulated, what drives such intense hyperinflammation is not yet known; however, upregulation of ACE2, ACEIs, and ARBs can exert anti-inflammatory and antioxidative effects that may be beneficial in preventing ALI and ARDS [5]. Based on the pathophysiology of SARS-CoV-2 and on the mechanism of action of ACEIs and ARBs, these agents may possess a role in management of select patients with severe COVID-19.

Despite the possible up-regulation of ACE2 by RAAS inhibition and the theoretically associated risk of a higher susceptibility to infection, there is currently no data proving a causal relationship between ACE2 activity and SARS-CoV-2 mortality [9]. Studies state that patients who have been on ACEI or ARB therapy prior to the pandemic should continue to take them during active infection [10], to prevent rapid deterioration of health. The rapid deterioration can be associated with the upregulation of ACE2 receptors that is said to be caused by ACEIs and ARBs. Due to the SARS-CoV-2 gaining entrance into the alveolar cells through the ACE2 receptors, increased receptors allow for an increase in the viral entry into the alveolar cells. Increasing the viral load is postulated to increase severity of the symptoms seen in COVID-19 positive patients. Due to this hypothesis, it is imperative that the ACEI and ARB therapy in hypertensive patients continues prior to active infection. Whether or not continuing the medication is detrimental to COVID-19 positive patients, has yet to be determined.

Conflict of Interests

The authors declare that they have no competing interests.

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AH proposed the project and drafted the letter; SSMT edited and revised the letter. All authors read and approved the final manuscript.

Bibliography