



Review Article

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Coronavirus Disease-2019 and Angiotensin Converting Enzyme Inhibitors- What is The Dilemma?

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Abstract

Severe acute respiratory syndrome coronavirus – 2 (SARS-CoV-2) is the causative agent of Coronavirus Disease-2019 (COVID-19). SARS-CoV-2 attacks the target cells via Angiotensin converting enzyme (ACE)2 receptor. Some preclinical studies have suggested that the renin-angiotensin-aldosterone system antagonists can increase ACE2 expression and as ACE2 is the receptor for the cellular entry for SARS-CoV-2, concerns raised about safety of these agents in patients with COVID-19. Concerns have been raised regarding the hypothesis that the use of ACE inhibitors may be associated with severe symptoms of COVID-19. So far, no clear studies or investigations have shown any evidence of this hypothetical theoretical risk between the use of renin-angiotensin-aldosterone system antagonists and COVID-19. At present, there is not enough evidence to discontinue the use of ACE inhibitors. All the major professional societies on hypertension and cardiovascular disease have recommended against discontinuing ACE inhibitors to prevent or decrease COVID-19 transmission until newer contrary evidence is available.

Keywords: SARS-CoV-2, ACE inhibitors, Cardiovascular disease, Renin angiotensin aldosterone system antagonists, COVID-19.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a major pandemic of worldwide importance in the current times. Diabetes mellitus, hypertension, cardiovascular disease, advanced age have been noted as important associated comorbidities with COVID-19 [1]. Patients with pre-existing cardiovascular diseases appear to be at increased risk for COVID-19. These patients with pre-existing cardiac diseases and diabetes mellitus are also the patient group who benefit from the use of Angiotensin converting enzyme (ACE) inhibitors raising concerns regarding any association between the use of ACE inhibitors and severity of COVID-19 [1,2,3]. There seems to be some hypothetical link between ACE inhibitors and COVID-19 however, the epidemiological association between the two has yet to be investigated further [3,4].

Pathophysiology

COVID-19 is caused by Severe acute respiratory syndrome coronavirus – 2 (SARS-CoV-2). The causative viral agent enters the target host cells via ACE2 (Angiotensin converting enzyme 2) which serves as the port of entry to the virus [3,4,5]. ACE2 enzyme is abundantly found in type II alveolar cells of the lungs, and COVID-19 commonly involves lungs. COVID-19 also leads to gastrointestinal symptoms and ACE2 is also abundantly found in the gastroduodenal epithelial lining [5,6,7]. The severity of COVID-19 correlates with the density of the ACE2 in the involved tissues and there have been hypotheses that the reduction of ACE2 levels may be protective against the disease. The contrary hypothesis is that the use of ACE inhibitors leading to elevated ACE2 activity may be protective. Neither of these hypotheses have been investigated or tested [3,5,6,8].

Hypotheses and controversies on the link between the COVID-19 and ACE

ACE2 is a transmembrane protein and acts as the port of entry for SARS-CoV-2. Transmembrane protease, serine 2 (TMPRSS2) is the essential primer for cellular entry of SARS-CoV-2 into the target host cells [3,5,8,9]. COVID-19 caused by SARS-CoV-2 was declared a pandemic by the World Health Organization on March 11, 2020. COVID-19 continues to be an ongoing pandemic and contagious in humans [2,5,10,11].

Is there a hypothetical possibility that ACE2 receptor expression on the cells is increased by the use of ACE inhibitors and whether it leads to severe symptoms of COVID-19? Is a connection between these even a possibility?

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ACE2 is down regulated in the cells which are SARS- CoV- 2 infected in the animal studies indicating that lower levels of ACE2 might contribute to lung injury [9,12,13,14].

ACE was discovered several decades ago and ACE2 was discovered relatively later. ACE converts angiotensin I into angiotensin II. ACE2 converts angiotensin II into angiotensin I. Angiotensin II is a potent vasoconstrictor whereas angiotensin I as a potent vasodilator [10,11,14].

ANGIOTENSIN I

↓ACE

ANGIOTENSIN II

↓

Vasoconstriction

ANGIOTENSIN II

↓ACE2

ANGIOTENSIN I

↓

Vasodilation

It is known that ACE levels increase in bronchoalveolar fluid in patients with acute respiratory distress syndrome [7,12]. There has been some evidence of the link between the renin-angiotensin-aldosterone system activation and acute lung injury. Some animal studies have shown that ACE inhibitors may delay the onset of acute respiratory distress syndrome. ACE2 may protect against lung injury, opposite to the effect of ACE on the lung injury [7,10,12,14,15].

Because SARS-CoV-2 binds to ACE2, does it downregulate ACE2 leading to angiotensin II mediated worsening of lung injury and pulmonary edema?

The hypothetical possibility that ACE inhibitors may increase the severity of COVID-19 and possible increased vulnerability to infection remains controversial as there is no real clinical data available to support these hypotheses [12-15,16]. Further investigation and research are required to identify if there is, if any, real association between renin-angiotensin-aldosterone system and SARS-CoV-2 infection.

Despite the theoretical concerns on safety of ACE inhibitors, there is not enough evidence to discontinue use of these drugs [17,18].

The ACC, AHA, HFSA recommended continuation of renin angiotensin aldosterone system antagonists for the conditions where these agents have proven beneficial effect and individualized treatment decisions in patients with COVID-19 on March 17, 2020. So far, all the professional societies on hypertension and cardiovascular disease have recommended to continue taking ACE inhibitors and/or angiotensin receptor blockers until any new contrary evidence is available [2,14,16]. The use of ACE inhibitors and/ or angiotensin receptor blockers should not be discontinued to prevent or decrease COVID-19 transmission per the most recent guidelines by all professional societies on hypertension and cardiovascular diseases [14-16,18].

CONCLUSION

Hypertension and cardiovascular disease are common chronic conditions and maybe risk factors for COVID-19. SARS- CoV-2 uses the ACE 2 receptor to gain entry inside the target cells. TMPRSS2 is a

protease required to prime the SARS-CoV-2 for gaining intracellular entry. SARS-CoV-2 has the unique ability to bind the ACE2 on human cells. There has been hypothetical concerns that ACE inhibitors may be linked to severity of COVID-19. Currently, all the major professional societies have recommended against adding or discontinuing renin angiotensin aldosterone antagonists- ACE inhibitors/angiotensin receptor blockers for prevention or reduction of transmission of COVID-19 due to the lack of clear evidence of potential benefit or harm of these drugs.

Conflict of interest

The authors declare no conflict of interest.

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