

COVID-19 and RAAS inhibitors: the controversy continues

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Abstract

Since the beginning of the recent SARS-COVID pandemic, renin-angiotensin-aldosterone system inhibitors (RAASIs) have been in the center of controversy. The virus interacts with angiotensin converting enzyme 2 (ACE2) receptors in the lungs at the initial step of its entry in to the body. Theoretically, therapeutic use of RAASIs may aggravate the severity of lung damage by increasing ACE2 expression in the lung tissues.

Given the widespread use of angiotensin converting enzyme inhibitors and angiotensin receptor blockers among patients with high blood pressure and other non-communicable diseases in Sri Lanka, some guidance on the use of these drugs in patients with Corona virus Disease 2019 (COVID-19) is needed. At present there isn't any credible evidence to support the withdrawals from those who are on regular treatment with these drugs. We present the available data on the subject while awaiting the results of the observational studies that is being conducted with RAAs in patients with COVID-19.

Key words: RAAS inhibitors, ACEIs, ARB, ACE2, COVID-19

Introduction

Currently the world is at the grips of a rapidly evolving pandemic caused by SARS-CoV-2, a novel coronavirus with clinical presentation somewhat similar to that of severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). Since it was first reported in Wuhan, China at the end of


2019 as the cause of a cluster of pneumonia, there were more than 3 090 445 confirmed cases and 217 769 deaths worldwide as of 30th April 2020¹.

SARS-CoV-2 utilises the ACE2 receptors to gain entry to human lung tissues, similar to SARS-CoV². Therefore, it is prudent to understand the inter-action between the virus and the ACE2 receptor. Most patients with cardiovascular disease qualify for treatment with angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) and Ferrario et al. (2005) has reported that both ACEIs and ARBs could significantly increase the expression of cardiac ACE2 mRNA³. Several Chinese studies have shown a high prevalence of cardiovascular disease among hospitalised COVID-19 patients with severe disease⁴. Based on these, Sommerstein and Gräni (2020) hypothesized that angiotensin-converting enzyme inhibitors (ACEIs) may act as a potential risk factor for COVID-19 by up-regulating ACE2⁵. Since then, series of articles have been published on this possible interaction.

ACEIs and ARBs are medicines widely used in the treatment of hypertension, heart failure, diabetes and coronary artery diseases. Mortality associated with COVID-19 is increased in those with these comorbid conditions and elderly⁶. The prevalence of non-communicable diseases in Sri Lanka is substantial⁷ and as such, a significant number of patients are also on regular, long term treatment with ACEIs/ARBs for coronary artery disease, hypertension and diabetes mellitus. Currently, there is a growing concern about the continued use of ACEIs/ARBs in those infected with or at risk of COVID-19 infection. Hence, we draw

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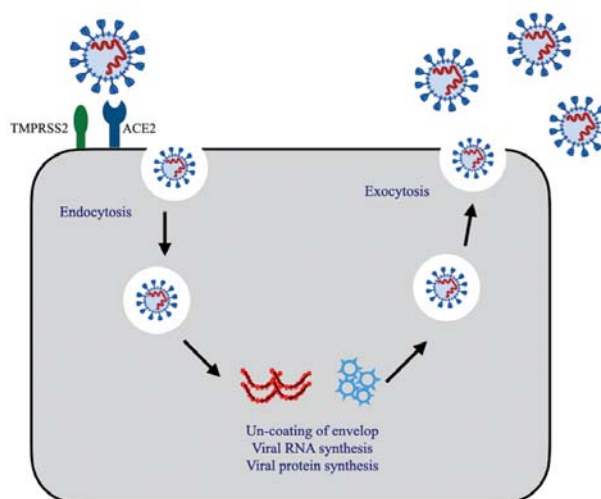
our focus on available data to analyse the relationship of SARS-CoV-2 and ACE2 receptors and the effects of COVID-19 on those treated with ACEIs/ARBs.

SARS-CoV-2 and ACE 2 receptors

The renin-angiotensin-aldosterone system (RAAS) is a classic endocrine system which plays a pivotal role in the development of hypertension and associated cardiovascular diseases⁸. Angiotensin II is the main active substrate of renin-angiotensin-aldosterone (RAA) pathway which by binding to type-1 receptors (ATR-1) causes a variety of effects, including vasoconstriction and vascular remodeling⁹.

ACE2 is a cellular transmembrane protein with an extra cellular receptor binding site¹⁰. It is the key counter regulatory enzyme of the RAAS which causes degradation of angiotensin II to angiotensin 1-7 (Ang 1-7)¹¹. In addition, ACE2 directly hydrolyses the angiotensin I to angiotensin 1-9 (Ang 1-9)¹¹. ACE2 is distributed in various organs of the human body, mainly in the epithelium of the airways, type II alveolar cells, enterocytes of the small intestine, endothelial cells of arteries and veins and brain¹⁰. The tissue distribution of ACE2 is organ specific and its expression is low in the lung. In normal human lung tissues, ACE2 expression in type I and II alveolar epithelial cells may get upregulated in certain clinical states¹⁰.

Corona viruses are a large family of enveloped single standard RNA viruses with potential to cause infection in broad range of vertebrates¹². The viral genome encodes four major structural proteins and the spike (S) protein, a surface glycoprotein which facilitates the virus entry into host cells¹³. Sequential analysis has shown only 75% similarity between the S protein of SARS-CoV-2 and SARS-CoV¹⁴. However, the amino acid residues on the receptor binding motif (RBM) in the S protein were conserved between these two virus strains, suggesting that SARS-CoV-2 also use the same receptor to enter humans as SARS-CoV¹⁵. The priming of S protein by the host serine protease TMPRSS2 is crucial for the virus to gain entry into the host and the subsequent spread within the host². The binding of virus S protein with the enzyme results in endocytosis of the virus and translocation of both virus and the enzyme into the endosomes¹⁶. New virus particles are produced inside the cell and viruses are released via exocytosis.



The role of ACE 2 receptors in the host cell entry of SARS-CoV-2

Effects of ACEIs/ARBs on ACE2 receptors

In-vivo animal studies show mixed findings with respect to the effect of ACEIs on ACE2 expression on various tissues. The effect of ARBs on ACE2 levels and its activity are inconsistent in experimental animal models where some studies have shown upregulation of ACE2 expression while others have shown no effect^{3,17,18}. Treatment with olmesartan has shown to cause a concomitant rise in plasma angiotensin concentrations and ACE2 mRNA expression in the myocardium¹⁹. Continuous administration of lisinopril has a 5-fold rise of the cardiac ACE2 mRNA expression while a 3-fold rise was observed with losartan¹⁷.

Human studies regarding the effects of RAAS inhibition on ACE2 expression and its activity are limited. In one study, intravenous administration of ACEIs did not affect the production of angiotensin 1-7 in patients with coronary artery disease²⁰. Few studies on plasma ACE2 activity in patients with coronary artery disease, heart failure and atrial fibrillation have shown no difference in patients on RAAS inhibitors compared to control groups^{21,22}. Despite the 42% structural homology between ACE 2 and ACE, their substrate specificity and enzymatic activity are quite different and therefore, the activity of ACE2 is not directly affected by the clinical use of ACEIs²³.

These seemingly conflicting data indicates a lack of correlation between the degree of ACE2 expression on tissues and its activity. While it is known that the effects of ARB and ACEIs therapy is mainly due to the

ACE2 expression on cardiac tissues, the effects on lung specific ACE2 mRNA expression in humans is not yet fully understood²⁴.

In contrast, another hypothesis argues that the RAAS inhibitors can be protective. It has shown that binding of corona virus to ACE2 can result in down regulation of ACE2 expression²⁵. This can result in excessive production of angiotensin II due to the ACE/ACE2 imbalance. Angiotensin II can increase pulmonary vascular permeability and lung damage. Hence, upregulation of ACE2 expression with long term treatment with ACE inhibitors and ARBS can theoretically mitigate the lung injury by two main mechanisms. First by degrading angiotensin II into angiotensin 1-7 and thereby reducing the angiotensin II mediated deleterious effects. Second by increasing production of angiotensin 1-7 which has been found to be protective in several lung injury models²⁶.

A study by Liu et al. (2020) 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 injury²⁷. It is therefore possible for those infected with SARS CoV-2 to have an increased risk of acute lung injury. Blocking the RAA system by ACEIs/ARBs and resultant increase in ACE2 might help to reduce these harmful effects²⁵.

Use of ACEI/ARBs in those with COVID-19

The limited data available on the use of ACEIs/ARBs in those with COVID-19, is conflicting. Analysis of data obtained via a symptom tracker app from a large but relatively young, community-based population of app users, has shown a modest increased risk of self-reported COVID-19 infection with classical symptoms in those taking ACEIs²⁸.

However, in a retrospective, multi-center study of adult patients with hypertension diagnosed with COVID-19, inpatient use of ACEI/ARB was associated with lower risk of all-cause mortality compared with ACEI/ARB non-users²⁹. The authors therefore concluded that in-hospital use of ACEI/ARB is unlikely to be associated with an increased mortality risk. Another study from Wuhan, China that evaluated hypertensives hospitalized with COVID-19, observed no difference in disease severity or death rate in patients taking ACE inhibitors or ARBs and those not taking such medications³⁰. A preliminary study from United Kingdom (not peer reviewed) also did not show

any evidence for ACEIs increasing the short-term severity of COVID-19 disease, but showed a reduced risk of rapidly deteriorating severe disease³¹. As the sample sizes of all these studies were small, large scale studies are needed for more conclusive evidence.

These studies provide a modest reassurance that the use of ACE inhibitors or ARBs in hypertensive patients with COVID-19 does not increase the risk of clinical deterioration or death. This is encouraging as there is established benefit of RAAS inhibitors in protecting myocardium and kidneys and the potential for harm related to the withdrawal of RAAS inhibitors in patients in otherwise stable condition. The issue is further complicated as COVID-19 is severe in those with underlying cardiac disease and that COVID-19 is also associated with myocardial injury^{6,32}.

Conclusions

The evidence for benefit and harm due to use of RAAS inhibitors in those with COVID-19 remains controversial at best. Limited studies conducted so far show that continuing RAAS inhibitors in those with COVID-19 is not associated with poor outcomes. In the absence of strong evidence, all published guidelines by the relevant professional associations worldwide, recommend against stopping RAASIs in those on regular therapy for clinical conditions for which proven benefit exists when infected with SARS-CoV-2³³.

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