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Review Article

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SHOULD ACE INHIBITORS AND ARBS BE PRESCRIBED OR PROSCRIBED IN COVID-19?

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ABSTRACT

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which have been responsible for current pandemic COVID – 19 disease. This virus competes with the renin-angiotensin-aldosterone system (RAAS) through angiotensin-converting enzyme2 (ACE2), an enzyme that play an important role not only in activation of RAAS but also act as a receptor for virus entry point. This interaction between ACE2 and COVID-19 viruses has been considered as a potential factor in their infectivity, and it is a matter of great concerns about the use of ACEIs/ARBs that might alter ACE2 and may be responsible for vivid outcomes in ongoing COVID-19 pandemic.

KEYWORDS: SARS-CoV-2 – severe acute respiratory syndrome coronavirus 2; COVID-19 – coronavirus disease-19; ACE2 - angiotensin-converting enzyme2; RAAS – renin-angiotensin aldosterone system; ACEIs - angiotensin converting enzyme inhibitors; ARBs – angiotensin receptor blockers.

INTRODUCTION

In renin-angiotensin-aldosterone system (RAAS), Angiotensin-converting enzyme or ACE, constitute the central component. ACE controls blood pressure (BP) by regulating the volume of fluids in the body by converting hormone angiotensin-I to the active vasoconstrictor angiotensin-II. In this way, ACE indirectly increases blood pressure by causing vasoconstriction of blood vessels. ACE inhibitors (ACEI) are widely used for treatment of cardiovascular diseases as pharmaceutical drugs. Leonard T. Skeggs Jr. in 1956[1] discovered angiotensin converting enzyme .They are principally found in the capillaries of lungs and also in endothelial and epithelial cells of kidneys,[2] heart, arteries, and intestines.[3,4] Other functions of ACE are in degradation of bradykinin and amyloid beta-protein but less known.

It lowers blood pressure (BP) by catalysing the hydrolysis of angiotensin II (a vasoconstrictor peptide) into angiotensin (1–7), a vasodilator and anti-inflammatory.[5] molecule. For some coronaviruses ACE2 serves as the entry point into the cells. hACE2 is the human version of the enzyme.[6]

Angiotensin-converting enzyme 2 (ACE2) is a single-pass type I membrane protein, its enzymatically active domain is exposed on the surface of cells (Fig.1). It is a zinc containing metalloenzyme; it contains a C-terminal collectrin renal amino acid transporter domain and an N-terminal peptidase domain. The extracellular domain of ACE2 is cleaved from the transmembrane domain by an enzyme known as sheddase, and this soluble protein is released into the blood stream and finally excreted through urine.

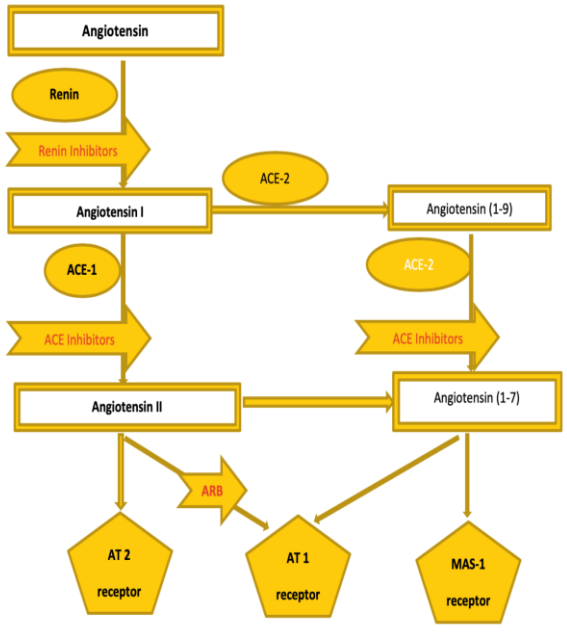

Figure 1: Showing renin angiotensin system. ACE-angiotensin converting enzyme, AT- angiotensin.

Location within the body (Table 1)

ACE2 is known to be present in most human organs (oral and nasal mucosa, nasopharynx, long, stomach, small intestine, colon, skin, lymph nodes, thymus, bone marrow, spleen, liver, kidney, and brain). ACE2 is attached to the cell membrane of mainly lung alveolar epithelial cells - type II alveolar cells, arterial and venous endothelial cells and arterial smooth muscle cells, and enterocytes of the small intestine in most organs. The expression of ACE2 mRNA is also found in the hypothalamus, cerebral cortex, striatum, and brainstem. Angiotensin-converting enzyme (ACE) located mainly in the capillaries of the lungs but can also be found in endothelial and kidney epithelial cells.

Table 1: Showing the effects of angiotensin receptor activation.

Organ	Actions
Blood vessels	Vasoconstriction, smooth muscle cell hypertrophy, superoxide generation endothelin secretion, monocyte activation inflammatory cytokines
Heart	Coronary vasoconstriction, proarrythmia, positive inotropy, myocyte apoptosis, myocardial fibrosis
Kidney	Sodium and water retention, efferent arteriolar vasoconstriction, glomerular and interstitial fibrosis
Adrenal gland	Aldosterone secretion
Brain	Sympathetic activation Vasopressin secretion

Angiotensin-converting enzyme or ACE Inhibitors

Angiotensin 1-7 (Ang-(1-7)) is a major active component of the RAS, which is produced from cleavage of Ang II by angiotensin-converting-enzyme type 2 (ACE2). Angiotensin 1-7 inhibits purified canine ACE activity (IC50=0.65 μM). It acts as a local synergistic modulator of kinin-induced vasodilation by inhibiting ACE and releasing nitric oxide. Angiotensin 1-7 shows antiangiogenic and growth-inhibitory effects on the endothelium by blocking Ang II-induced smooth muscle cell proliferation and hypertrophy. It also has anti-inflammatory activity.

Captopril is a potent, competitive inhibitor of ACE.

Perindopril erbumine (Perindopril tert-butylamine salt) – it is also a potent ACE inhibitor, which is used to treat high blood pressure, heart failure or stable coronary artery disease.

Enalapril (maleate), the active metabolite of enalapril, is an ACE inhibitor.

Trandolapril is a nonsulfhydryl prodrug that is hydrolysed to the active diacid Trandolaprilat that has been used in the treatment of hypertension and congestive heart failure (CHF), and after myocardial infarction (MI).

Other ACE inhibitors are Lisinopril dehydrate, Benazepril hydrochloride, Fosinopril sodium, Enalaprilat dehydrate, Quinapril hydrochloride, Ramipril etc.

Angiotensin Converting Enzyme Inhibitors (ACEIs) and Angiotensin Receptor Blockers (ARBs) – Improve or Worse Prognosis in Pandemic COVID-19 Hypertensive Patients ?

Entry point for Coronavirus: ACE2 as a transmembrane protein serves as the main entry point into the cells for some coronaviruses, including SARS-CoV (virus that causes SARS), HCoV-NL63 and SARS-CoV-2 (cause COVID-19)[7-9] More specifically, the binding of the SARS-CoV2 to the enzymatic domain of ACE2 on the surface of cells and the spike S1 protein of SARS-CoV result in endocytosis and translocation of both the virus and the enzyme into endosomes located within the cells.[10] The priming of the S protein by the host serine protease TMPRSS2 is also required for this entry process, the inhibition of which is under current investigation as a potential therapeutic.[11]

Thus it has to hypothesize that decreasing the levels of ACE2, in cells, might help in fighting the infection. On the other hand, ACE2 has been shown to have a protective effect against virus-induced lung injury by increasing the production of the vasodilator and anti-inflammatory angiotensin 1-7.[12] As the studies conducted on mice, the interaction of the ACE2 with spike protein of coronavirus induces a drop in the levels of ACE2 in cells through internalization and degradation of the protein and hence may help to cause lung damage.[12,13]

Both ACE inhibitors and ARBs that is used to treat high blood pressure, in rodent studies have been shown to upregulate ACE2 expression hence may affect the severity of coronavirus infections.[14] In a systematic review and meta-analysis published on July 11, 2012 it is found that "use of ACE inhibitors was associated with a significant 34% reduction in risk of pneumonia compared with controls." Moreover, "the risk of pneumonia was also reduced in patients treated with ACE inhibitors who were at higher risk of pneumonia, particularly those having stroke and heart failure. The use of ACE inhibitors was also associated with reduction in pneumonia related mortality, although the results were less robust than for overall risk of pneumonia."[15]

Patients having underlying health conditions like hypertension, heart failure, and chronic kidney disease are at increased risk of severe coronavirus disease 2019 (COVID-19). Many physicians, healthcare professionals, researchers, and patients are actively debating the potential influence of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) in patients during the COVID-19 outbreak. As one of the way, the virus enters through ACE2 in the body, the enzyme (ACE) that converts angiotensin I to angiotensin II in the lungs and other tissues and organs, suggesting that the drug may increase susceptibility to the virus and severity of the disease.

ACEI, ARBs and COVID-19

At the end of 2019, the current pandemic infection is Coronavirus disease 2019 (COVID-19) that is caused by a positive-sense RNA virus which is named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The older patients, particularly with comorbid conditions like pulmonary disease, cardiac disease, kidney disease, diabetes, and hypertension, are particularly susceptible populations and have been associated with even higher mortality and morbidity rates.

The mortality and morbidity of COVID-19 patients with hypertension is increased and an association has been observed in a number of initial epidemiological studies outlining the characteristics of the COVID-19 epidemic in China. Wu et al[16] found in 201 patients with COVID-19, that hypertension had a hazard ratio of 1.70 for death and 1.82 for acute respiratory distress syndrome. Zhou et al[17] in 191 patients with COVID-19 found that hypertension had a hazard ratio of 3.05 for in-hospital mortality.

ACEIs and ARBs and COVID-19 are linked, because of the known association between angiotensin-converting enzyme2 (ACE2) and SARS-CoV-2. For viral entry ACE2 has been shown to be a co-receptor for SARS-CoV-2 with increasing evidence that it has a protracted role in the pathogenesis of COVID-19. In human body ACE2 has a broad expression pattern with strong expression noted in the heart, gastrointestinal system, and kidney with more recent data identifying expression of ACE2 in type II alveolar cells in the lungs. The use of ACEIs and ARBs increase expression of ACE2 and it also increase patient susceptibility to viral host cell entry and propagation. However, there is very limited evidence showing changes in serum or pulmonary ACE2 levels. More relevant, in the pathogenesis and mortality, the significance of ACE2 expression on COVID-19 is not specifically known.

Many patients and clinicians are aware of the recently publicized interplay between RAS and COVID-19 illness. Patients concerned about susceptibility to Corona virus whether to continue taking ACEIs and ARBs and patients who test positive for the virus likely will have the same concern about their prescribed ACE inhibitors and ARBs. For this experts have postulated both potentially harmful and beneficial effects of these drugs on the natural history of COVID-19.[18] For the entry of SARS-Co-2 into human cells the membrane bound ACE2 participates and animal studies show that ACEIs and ARBs upregulate ACE2 expression and this effect could increase risk for or severity of COVID-19. In contrast to this, some researchers contemplate that ACEIs and ARBs could benefit patients with COVID-19 through various mechanisms e.g. ACE2 converts angiotensin II to angiotensin-(1-7), that has potentially beneficial vasodilatory and anti-inflammatory properties; upregulating ACE2 (with ACEIs or ARBs) could enhance this process, but observational studies have not yielded compelling data on whether COVID-19 patients who take these drugs fare better or worse than otherwise similar patients.

For these uncertainties, professional societies have navigated by recommending that patients receiving ACEIs and ARBs should continue taking them. The American College of Cardiology and American Herat Association (ACC/AHA) gave a statement that “there are no experimental or clinical data demonstrating beneficial or adverse outcomes with background use of ACE inhibitors or ARBs”[19] The statement recommends continuing these drugs if they are being prescribed for valid cardiovascular indications and advises clinicians not to add or remove them “beyond actions based on standard clinical practice”.

After an in-depth review of more than 60 published studies, Dr. Sanchis-Gomar and his co-authors conclude that, till now no studies have reported an increase in circulating ACE2 levels or expression thus far, and increased expression would not necessarily imply an increased risk of infection or disease severity. Their research included studies that suggest that elevated levels of angiotensin II, the target of renin-angiotensin-aldosterone system (RAAS) inhibitors such as ACEIs and ARBs, may foster acute respiratory distress syndrome (ARDS) in COVID-19 patients. Other research suggests that RAAS inhibitors may have a role to play in the treatment of COVID-19. The authors note, however, that much more research and evidence are needed.

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