

Angiotensin-Converting Enzyme Inhibitors May Increase Risk of Severe COVID-19 Infection

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Abstract

Coronavirus is a pathogen that has been known to medicine for a long time with 39 different genotypes, which fall under the broad realm of Riboviria, which mainly target the human respiratory system. The novel coronavirus disease 2019 is caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). This virus has an enveloped single-stranded positive strand RNA structure and it uses the spike projection as a key to enter cells, the S protein has great significance because of its function in receptor binding. This new coronavirus belongs to the beta-genus coronavirus, it has been reported that coronavirus disease 2019 has 79.5% homologousity with SARS-CoV, and their receptors are angiotensin converting enzyme 2 (ACE2). Furthermore, several countries have started to treat coronavirus-infected patients with repurposed therapeutics such as HIV protease inhibitors (Ritonavir) and Kaletra, because clinical trials are taking a long time and there is no effective targeted treatment to cure the patient with the disease. This review article is questioning the role of Angiotensin converting enzyme inhibitors in COVID-19 infection severity and treatment.

Keywords

Coronavirus, acute respiratory syndrome, , Spikeprotein, angiotensin-converting enzyme 2, protease inhibitors.

Introduction

Constant epidemic cluster of pneumonia cases associated with a novel coronavirus, called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was described in Wuhan, Hubei Province, China in December 2019 (Zu, 2020; Lai *et al.*, 2020).

The virus had rapidly spread across China and many other countries (Khan *et al.*, 2020). Moreover, on 11th, February 2020, the World Health Organization (WHO) officially announced a new name of this epidemic disease as coronavirus disease (COVID-19). The new coronavirus belongs to the beta-genus coronavirus (Jiang, *et al.*, 2020) and it has been reported that COVID-19 has 79.5% homologousity with SARS-CoV as well as its receptors are angiotensin-converting enzyme 2 (ACE2) (Ni, *et al.*, 2020). As of the 19th, May 2021, a total of 165,376,099 cases of new coronavirus infection have been reported all over the world, including 16,293,880 active cases, 100,064 cases of critical illness and 3,427,066 deaths. The proportion of severe and critical illness was as high as 5.19% and the fatality rate was as high as 18% (Worldmeters, 2021). Furthermore, several countries have started to treat COVID-19 patients with repurposed therapeutics such as HIV protease inhibitors (Ritonavir) and Kaletra, because clinical trials are taking a long time and there is no effective targeted treatment to cure the patient with the disease (Kumar *et al.*, 2020). This review article is

questioning the role of Angiotensin converting enzyme inhibitors in COVID-19 infection severity and treatment.

COVID-19 Symptoms

COVID-19 symptoms usually appear after incubation period of 5-6 days with the common symptoms at onset of infection are cough, fatigue and fever. Also, the chest CT scan would reveal pneumonia and acute respiratory distress syndrome (ARDS) which can lead to a life-threatening condition and in need for life-support to sustain patient's life (Wang *et al.*, 2020).

Patients with the novel Coronavirus (COVID-19) who had severe symptoms were those having comorbidities such as hypertension and diabetes mellitus. Many of these cases were treated with angiotensin-converting enzyme 2 (ACE2) inhibitors (Bourgonjeet *al.*, 2020)..

Role of Angiotensin-converting enzyme 2 in COVID-19 infection

Angiotensin-converting enzyme 2 (ACE2) serves as the entry point into cells for some coronaviruses such as COVID-19. These viruses bind to their target cells (Zemlin & Wiese, 2020) through angiotensin-converting enzyme 2 which acts as a functional receptor for the spike glycoprotein of human coronavirus HCoV-NL63, d human severe acute respiratory syndrome coronavirus SARS-CoV and Coronavirus (COVID-19) (Zhuang *et al.*, 2020)..

The respiratory tract is the main site of disease in patients with COVID-19, this viral infection causes viral pneumonia and, in some cases, leads to death because of fatal respiratory failure after 10-14 days of getting the virus (Lax *et al.*, 2020).

Molecular mechanisms and ACE2

A recent study found that COVID-19 is composed of few structural proteins; nucleocapsid, spike and envelope proteins, among them, S protein which is placed at the external of the pathogen and its role is attaching the virus to human receptor with a subsequent fusion and entry into host cell (Ishola *et al.*, 2021).

The spike glycoprotein goes through the membrane; forms homotrimers that emerge out from the viral surface (Patil *et al.*, 2021). Moreover, each spike (S) glycoprotein is composed of two functional subunits, namely, S1 and S2 subunits. Furthermore, the S1 subunit is responsible for binding to the host cell receptor and the S2 subunit causes fusion of the viral and cellular membranes (Huang *et al.*, 2020).

ACE2 is an important part of the renin-angiotensin system (RAS). The latter is known to play an important role in regulating electrolytes balance and blood pressure (Zhao *et al.*, 2020). Moreover, after producing angiotensin by the liver, it is secreted in the blood, then renal juxtaglomerular complex secretes the enzyme renin which converts angiotensin to angiotensin I (Ang I). The latter is also converted through angiotensin converting enzyme into vascularly active angiotensin II (Octapeptide) (Cushman & Cheung, 1971) which then performs its biological effects by Angiotensin type 1 and type 2 Receptors (AT₁R and AT₂R). This will mediate release of catecholamines, causing vasoconstriction, bronchial smooth muscles contraction, activation of NF- κ B to produce inflammatory mediators (Gao *et al.*, 2008), activation of the NADH/NADPH oxidase that produces ROS products, activation of Toll-like receptor 4 causing apoptosis (Alkuraishy *et al.*, 2017), and causing pulmonary fibroblasts

proliferation (Nguyen et al., 2013). In contrast to AT₁R, AT₂R is coupled with the G_i protein and promotes growth inhibition by activating a variety of phosphatases (e.g. tyrosine phosphatase, SH2-domain phosphatase 1, serine/ threonine protein phosphatase 2A) (Gallo-Payet & Battista, 2011).

Moreover, ACE is also responsible for the degradation of phosphorylated peptides and substance P, two local pro-inflammatory peptides that trigger the release of prostaglandins and cause dry cough (Overlack, 1996). As a result, adverse reactions to ACE inhibitors (ACEIs) are often characterized by persistent dry cough. Currently, ACEIs and AT₁R antagonists are widely used to treat hypertension, diabetic nephropathy and congestive heart failure (Steckelings *et al.*, 2001).

Studies were conducted to investigate whether ACE2 can be a cellular entry receptor for COVID-19 using HeLa cells that express ACE2 proteins from humans, Chinese horseshoe bats, civets, pigs and mice. The results showed that COVID-19 was able to use all these ACE2 proteins as a cellular entry receptor. These results indicated that ACE2 is possibly the cell receptor that COVID-19 uses to enter humans' cells (Hirano & Murakami, 2020).

ACE2 is an enzyme that is attached to the outer surface of many organs such as kidney, vascular endothelium, epithelia of the small intestine, and lungs, this could explain the multi organ dysfunction showed in many cases of COVID-19 infection (Yan, Xiao, & Lin, 2020). Moreover, The zinc ion is essential for the activity of the ACE zinc metalloenzyme because of the participation in the catalysis of peptide hydrolysis. This activity leads to inhibition of angiotensin-converting enzyme (ACE) by metal-chelating agents (Acharya *et al.*, 2003).

Furthermore, ACE2 tends to be upregulated in Type 1 and Type 2 diabetic patients, therefore; they would get ACEIs or AT₁R antagonists to minimise the subsequent effects of increased amount of ACE2. Also, those patients will have increased number of receptors compared to patients who take alternative medications. These increased numbers of receptors in the lungs will allure more coronavirus Spike to bind and, therefore; they will be at more risk of getting severe COVID-19 infection (Shereen *et al.*, 2020). Interestingly, thiazolidinedione's and ibuprofen can increase the amount of ACE2 in diabetic patients (Sridharan, *et al.*, 2020).

Potential therapeutic approaches for COVID-19 infection

The use of affinity-purification mass spectrometry (APMS) was significant in identifying the proteins associated between human and COVID-19 by studying their protein-protein interactions (PPIs). These studies demonstrated that there is a total of 332 COVID-19-human PPIs (Add Reference).

As a result of this interaction, possible treatments are used as potential therapeutics to address ACE2-mediated COVID-19 following SARS-CoV-2 infection. For the current time, drugs that were already approved, such as HIV protease inhibitors (Ritonavir) and Kaletra, are employed as repurposed therapeutics to treat COVID-19 because clinical trials are taking a long time (Kumar *et al.*, 2020).

In addition, there are no specific therapies or vaccines approved to treat COVID-19 infection, however; many drugs are currently used under clinical trials as treatments for this disease, but these trials are still in their early stages. Examples of these potential drugs are

Remdesivir, Chloroquine, Hydroxychloroquine, Lopinavir, Ritonavir and Favipiravir (Khan, *et al.*, 2020).

Nonetheless, it was stated by the World Health Organization (WHO), the Centers for Disease Control and Prevention (CDC) and The US Food and Drug Administration (FDA) that there are currently no medications or vaccines proven to be effective for the treatment or prevention of COVID-19 infection (Moore, *et al.*, 2020).

Targeting ACE2 and Potential Therapy

The renin-angiotensin system (RAS) may be an important choice for new coronavirus pneumonia COVID-19 as it has the same virus receptor, ACE2, as SARS-CoV. ACE2 is highly expressed in the human lung tissue, gastrointestinal tract and a wide range of vascular endothelial cells and arterial smooth muscle cells. In addition, the skin, nasal cavity and oral mucosa base cells have ACE2 expression.

Organs that express ACE2 in high amounts may be the target organs for COVID-19. The results showed that in addition to the widespread changes in the lungs, patients infected with SARS also developed systemic vasculitis and inflammation of various organs such as heart, kidneys, liver and adrenal glands.

Moreover, the patients develop extensive necrosis of spleen lymphatic tissue. The researchers believe that the lungs, immune organs and small blood vessels throughout the body are the main targets for SARS virus attacks, whereas respiratory distress and/or reduced immune function is the main cause of death.

At present, patients with mild illness of COVID-19, who are clinically infected, have symptoms like nasal congestion, runny nose, sore throat and diarrhoea. On the other hand, severe cases quickly developed pneumonia, septic shock and even clotting dysfunction and other complications. Some patients presented with digestive tract symptoms as the main clinical manifestations, which may be related to the distribution of ACE2 in the human body.

How to effectively improve the clinical symptoms of patients and reduce patient's body damage, is an important treatment strategy. Activating ACE 2/Ang (1-Ang)/Mas signalling pathways or inhibiting ACE/Ang II/AT₁R pathways may be important treatments for new coronavirus pneumonia (Chen, *et al.*, 2010).

ACE2 deficiency causes a significant reduction in the severity of infection caused by the virus of SARS in the lungs. Increasing exogenous ACE2 is not the preferred treatment strategy against pneumonia, but increasing the exogenous Ang (1-7) or activating Mas receptors, or ACE/Ang II/AT₁R pathway inhibitors such as ACEI preparations, such as Captopril and Ramipril, and AT₁R inhibitors, such as candesartan (Michaud, *et al.*, 2020).

Although animal experiments showed that the expression of ACE2 was reversed in the treatment of hypertension or vascular damage with Olmesartan or telmisartan, it did not exceed normal expression of ACE2 in the body (Igase *et al.*, 2005). This suggests that the recovery of ACE2 expression after administration may be related to the decline of cell inflammation and functional recovery. ACE2 is significantly higher in children and young people than in the elderly (Dhockak *et al.*, 2020). However, the expression in older women is higher than that in older men. The patients with SARS-CoV infection were mainly middle-

aged and young patients, while those with severe COVID-19 infection were mainly elderly patients, especially older male patients (Dhockaket *et al.*, 2020).

Therefore, the high or low expression of ACE2 does not determine severity of COVID-19 infection, yet the immune response of the body and the amount of viral infection may affect severity of COVID-19 infection.

Conclusion

ACE2 can play a significant role in the outcome of COVID-19 infection in older age people. In addition, if patients with diabetes and hypertension are treated with ACE2 stimulating drugs and/ or ACEI drugs, they will be at an increased risk of getting severe COVID-19 infection.

There are vaccines approved to prevent COVID-19 infection, however; many therapeutics currently in use are under clinical trials, yet they are still in their early stages. Examples on the latter include Remdesivir, Chloroquine, Hydroxychloroquine, Lopinavir; Ritonavir and Favipiravir.

We suggest that patients with diseases such as heart disease, hypertension, or diabetes, who take drugs that increase ACE2 as treatment, may encounter a severe type of COVID-19 infection, so it would be important for drugs such as ACE inhibitors or AT₁R blockers to be monitored and there are alternative therapeutics to treat hypertension. For example; antihypertensive calcium channel blockers can be used as a suitable treatment as no study showed any evidence to suggest that these drugs can increase ACE2 expression or activity in humans (Bourgonje, *et al.*, 2020).

These considerations can provide further knowledge to the investigation of the role of ACE2 in the therapeutic approaches linked to ACE2 receptor activity.

Conflict of interest statement

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