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Enalpril in Covid 19: A Possible Role Beyond Hypertension

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Abstract

The sequence similarities the between SARS-CoV-2 and SARS-CoV, indicates that SARS-CoV-2 utilizes ACE-2 as a cellular entry receptor. SARS-CoV-2 could utilize ACE-2 from humans. ACE inhibitors are designed to prevent the conversion of angiotensin I to angiotensin II, and ACE2 further converts angiotensin 2 to angiotensin 1-7, acting as a counterbalance for the proinflammatory angiotensin 2. When the virus occupies all the ACE2 receptors on host cells, there is more angiotensin 2 free-flowing in the system to activate the RAS pathway, which leads to Covid-19 complications . If the conversion of angiotensin 1 to angiotensin 2 is blocked by ACE inhibitors, the Covid-19 complications will be prevented. Considering this point, the Enalpril drug used as antihypertensive was hypothesized to act as repurposing drug in the treatment of SARS-CoV-2.

Keywords: enalpril; covid 19; sars cov-2; drug repurposing; hypertension

Hypothesis

1. Enalpril : Historical re-purposing and pleiotropy

Enalapril is used to treat the patients suffering from hypertension, symptomatic heart failure, and asymptomatic left ventricular dysfunction [1]. It also helps to protect the kidneys function in hypertension, heart failure, and diabetes, and may be used in the absence of hypertension for its kidney protective effects [3]. It is mostly used in chronic kidney failure [2]. Enalapril is an emerging treatment for psychogenic polydipsia. It was observed in a double-blind, placebo-controlled trial that when used, enalapril decreased consumption of water (determined by urine output and osmolality) in 60% of patients [4]. The many Pleiotropic effects of enalpril and its wide spread utility in medicine made us to explore its utility in the treatment of Covid 19.

2. ACE and Enalpril Mechanism of action

Angiotensin-I converting enzyme (ACE), also called peptidyldipeptidase A, mainly belongs to the type-I membrane-anchored dipeptidylcarboxypeptidase family and it is involved in controlling of blood pressure through renin angiotensin system by regulating electrolyte homeostasis [5]. ACE is a zinc metallopeptidase, has a little sequence homology with the remaining members in the peptide family [5]. Human ACE has main two functional domains (N and C), each of which has active site with zinc ion binding site [6]. Both domains have differences in their substrate specificities, physiological forms, and inhibitors [7]. The N and C domains catalyze the hydrolysis of substrates with similar efficiencies. Inhibition of the N domain of ACE has no impact on blood pressure regulation [7,8]. C domain targeting was found to be more sufficient for controlling blood pressure, and all inhibitors target this site. The important catalytic component of ACE is Zinc [5,9,10].

ACE, or kininase II, causes cleavage of the C-terminal dipeptide from Ang I and bradykinin that lack a penultimate proline residue. ACE is strategically poised to regulate the balance between the Renin Angiotensin Aldosterone system (RAS) and the kallikrein-kinin system. The RAS plays a major role in the blood pressure regulation. Reduction in sodium delivery at the macula densa, decreased renal perfusion pressure, and sympathetic activation all stimulate secretion of renin by the juxtaglomerular cell, the major source of renin in the circulating RAS [11,12,13]. Renin cleaves the inactive decapeptide Ang I from the prohormone angiotensinogen, a noninhibiting member of

the serpin superfamily of serine protease inhibitors [14]. Ang II is then cleaved from Ang I by the action of ACE [15]. Ang II is a potent vasoconstrictor, acting directly on vascular smooth muscle cells [16]. Ang II causes volume expansion through sodium retention (via Aldosterone [17] and renal vasoconstriction) and fluid retention (via antidiuretic hormone).[18] At the cellular level, Ang II promotes migration, proliferation, and hypertrophy.[19-23] Most of these effects of Ang II appear to be mediated through the AT1 receptor, although recent studies are defining roles for the AT2 and AT4 subtype receptors. As mentioned earlier, in addition [24] to catalyzing the formation of Ang II, ACE (or kininase II) catalyzes the degradation of bradykinin.

Enalaprilat, the active metabolite of enalapril, inhibits ACE. Inhibition of ACE decreases levels of angiotensin II, leading to less vasoconstriction and decreased blood pressure[25].

3. ACE-2 is an gateway Entry Receptor for SARS-CoV-2

During 2003, the virus that caused the newly severe acute respiratory syndrome (SARS) spread rapidly from China causing almost 800 deaths and disrupting travel, economics and even scientific conventions. Perhaps as a result of public health measures, the disease faded away only to re-emerge in China this year. Within months it had been identified as a positive strand RNA virus, classified as a member of the coronavirus family (SARS-CoV); its genome was sequenced [26,27]. Like other coronaviruses, it is the N-terminal portion (S1 domain) of the viral spike (S) glycoprotein that mediates the initial high-affinity binding to a receptor on the surface of susceptible cells. The spike sits in the viral envelope and projects outwards to give a 'corona'-like appearance to the virus, hence its name.

It was identified [28] that, the S1 domain of the SARS-CoV S protein bound to the African Green monkey kidney cell line Vero E6, which is permissive for viral replication. Then co-immunoprecipitated the protein responsible for the viral binding and entry. This SARS-CoV receptor, a glycoprotein was identified by mass spectrometry as ACE2. When ACE2 was over expressed in human cells non-permissive for viral infection, SARS-CoV entry and replication were facilitated and this entire process was blocked by an ACE2 antibody 28.

The ACE2 tissue distribution also appears to exhibit some correlation with SARS-CoV infection sites and disease pathology. It was later [29] confirmed that ACE2 was a SARS-CoV receptor and showed that the receptor-binding domain was probably located between residues 272 and 537 of the spike glycoprotein. A crucial aspartic acid in this region was essential for binding with ACE2. Modelling of the ACE2 structure based on the known structure of ACE has provided another approach to predicting potential binding contacts between ACE2 and the SARS-CoV S protein [30].

COVID-19 virus identification and sequencing indicated that it shared 88% sequence identity with two bat-derived SARS-like CoV, indicating that it was originated in bats.[31] The genome of coronavirus contains structural proteins like spike (S) protein, nucleocapsid (N) protein, membrane (M) protein, and the envelope (E) protein.[32] Among this , the S protein is responsible for facilitating entry of the CoV into the target cell. It is composed of a short intracellular tail, a transmembrane anchor, and a large ectodomain that consists of a receptor binding S1 subunit and a membrane-fusing S2 subunit.33The analysis of the receptor binding motif (RBM) in the S protein showed that most of the amino acid residues important for receptor binding were conserved between SARS-CoV and SARS-CoV-2, indicating that the 2 CoV strains use the same host receptor for cell entry.[34] The receptor utilized by SARS-CoV for entry is Angiotensin-Converting Enzyme 2 (ACE-2) [35] . The sequence similarities the between SARS-CoV-2 and SARS-CoV, may indicate that SARS-CoV-2 also utilizes ACE-2 as a cellular entry receptor. SARS-CoV-2 could utilize ACE-2 from humans, Chinese horseshoe bats, civet cats, and pigs to get entry into ACE-2-expressing HeLa cells[36].

4. Targeting ACE2's role in facilitating viral entry

ACE inhibitors are designed to prevent the conversion of angiotensin 1 to angiotensin 2, and ACE2 further converts angiotensin 2 to angiotensin 1-7, acting as a counterbalance for the proinflammatory angiotensin 2. When the virus occupies all the ACE2 receptors on host cells, there is more angiotensin 2 free-flowing in the system to activate the RAS pathway, which leads to Covid-19 complications. If the conversion of angiotensin 1 to angiotensin 2 is blocked by ACE inhibitors, the Covid-19 complications will be prevented.

5. Repurposing of ACEI, Enalpril against SARS COVID 2:

Most patients with cardiovascular comorbidities qualify for angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB) therapy.[37] Of note, Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 uses the receptor angiotensin-converting enzyme (ACE) 2 for entry into target cells.[38] Ferrario et al reported that both ACEI and ARB could significantly increase mRNA expression of cardiac ACE2.[39] On the basis of these thoughts, we generated the hypothesis that these drugs might play a role in the severe course of COVID-19 cases.[40] More importantly, no clinical-epidemiological data have been put forward and it is unknown whether the hypothesized mechanism plays a pivotal role in COVID-19.

Conflict of interest

The authors **K.Ravishankar, GVN Kiranmayi** were at the time of writing are employees of Aditya College of Pharmacy, Suramplem, India. The authors confirm that this article content has no conflict of interest.

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