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Review Article

Aliskiren as a Promising Interim Prophylaxis and Early Stage Treatment in Ambulatory Hypertensive Patients Who are at High Risk for Covid-19 Infection

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Abstract: The new coronavirus disease (COVID-19) resulted in a pandemic in 2019 and encouraged researches worldwide to look for a treatment or a cure for this disease. As the risk of COVID-19 infection increases in people with concomitant comorbidities leading to the higher possibility to death due to the infection and increases the burden, it is essential to provide prophylaxis for patients who aren't yet diagnosed and have a high risk of the infection especially in the early stages, as this is substantial in decreasing the onus on governments, health care system, and people who are at high risk especially hypertension and heart failure patients, because they are already on medications which might make the scenario worse One of the suggested promising medications is the renin inhibitor, Aliskiren, which was approved in 2007 for the treatment of hypertension. Several studies pointed out that Aliskiren can be used to prevent the virus from entering the host cells or at least prevent the disease from progressing into ARDS. Aliskiren inhibits renin and this will eventually result in the disruption of the renin-angiotensin system pathway that is suggested to be an entry point for the COVID-19. Some studies showed that this medication showed high affinity to the viral protease M pro which can be a target to terminate the replication of the virus in the host cells. This review article will highlight the suggested role of Aliskiren as a promising prophylactic and early stage treatment in ambulatory hypertensive patients who are at high risk for COVID-19.

Keywords: Aliskiren; ACE2; Anti-Hypertensive agents; Coronavirus; COVID-19; Viral entry inhibitors; SARS-CoV-2; Pandemic viral; RAS; Renin inhibitor.

INTRODUCTION

The coronavirus disease (COVID-19) originated in December, 2019 in Wuhan, China and the outbreak has been declared by the WHO as a pandemic on 11 March 2020. According to the latest data published by the WHO, COVID-19 affected 213 countries, areas, or territories. COVID-19 has many distinctive features than other viral infections, as its rate of spreading is exponential as many statistical analysts have concluded, as of 20th of April 2020 number of cases are approaching 2.5 million human being.("Coronavirus is growing exponentially – here's what that really means," n.d.),(Worldometer, 2020). there is no currently available or approved treatment or vaccine to treat coronavirus disease. Thus, it is extremely important to find out a medication to end this current pandemic.

According to (Wang *et al*., 2008), the entry point of the SARS coronavirus that spread in 2003 is angiotensin converting enzyme 2 (ACE2). Since COVID-19 is a member in the same family of SARS-CoV, It is postulated that Coronaviruses enter the host cells that they infect by interacting with spike protein and angiotensin-converting enzyme 2 (ACE2) receptor, which is known as COVID-19 specific cellular receptor (Wu *et al*., 2020) . After entry of COVID-19 to the body cells its led to inactivation of these receptor and inhibits them from exhibiting their protective functions in the lung and CV system, as it binds to ACE-2 receptors via its spike crown like glycoproteins as S, the S glycoprotein has 2 forms, first the S1 unit which facilitates the attachment of the virus to the cellular ACE-2 receptor and compromises cellular

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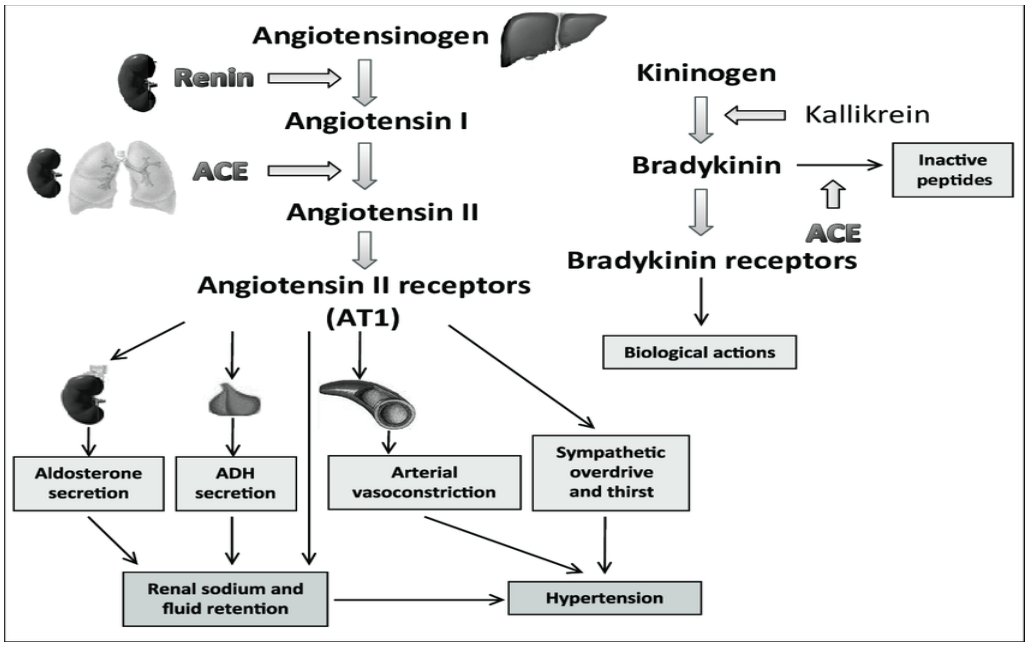
glycans to bind and results in improper proteins folding , in turn this attachment will drive target host cells to release proteases as serine protease (TMPRSS2) which are the key for producing the second form S2 prime that allows for viral infusion with the cell membrane of the host (Hoffmann *et al*., 2020),(Mcmurray, Pfeffer, Ph, & Solomon, 2020). It was observed that the binding of the SARS-CoV protein S to ACE2 receptor downregulated ACE2, and produced angiotensin on a large scale. This, in turn, results in the production pro-inflammatory and pro-oxidant agents which can result in complications such as lung injury (Zhang *et al*., 2020). There is emerging evidence that suggests the role of the RAS pathway in the pathogenesis of the human coronavirus and its negative impact on the lung injury that occurs during SARS-CoV infection (Wevers & Hoek, 2010) targeting the RAS pathway by administering the renin inhibitor [**Aliskiren**] might be a promising method in finding a treatment for the currently fast - spreading disease (Kouhpayeh *et al*. (2020). Aliskiren is an orally bioavailable potent direct renin inhibitor, it is the first drug discovered to act on shutting the whole pathway of renin degradation, it use as antihypertension agent. This review article will highlight the suggested role of the antihypertensive agent and renin inhibitor, Aliskiren, (Sanoski, 2009) as a promising prophylactic and early stage treatment in ambulatory hypertensive patients who are at high risk for COVID-19.

DISCUSSION

The RAAS plays a vital role in human physiology as it is concerned with the regulation of blood pressure, electrolytes balance, fluid volume, and vascular resistance. the mechanism of renin secretion from the kidney specifically from juxtaglomerular apparatus includes (outer cortex, midcortex, juxtamedullary) , and is controlled by various stimulus, as decrease in NaCl level reached to the to the kidney, hypo-perfusion to the kidney detected by baroreceptors, and epinephrine and norepinephrine sympathetic stimulation of the cells in the kidney. The cells of juxtaglomerular produce pro-renin which then cleaved to produce the active renin, renin stimulate liver to release angiotensinogen, also its release depends on many contributors for example inflammation, the cleavage of angiotensinogen to the decapeptide angiotensin I is mediated by renin stimulation of enzymatic cleavage of terminal amino acid from angiotensinogen, the next step is the conversion of angiotensin I to the octapeptide angiotensin II by ACE-1 enzyme that removes the 2 terminal amino acids (Leucine and Histadine).

Furthermore, it is noted that angiotensin II bind to its receptor AT1, angiotensin II promotes several activities through its binding to AT1, for instance neural effects as stimulation of ADH release, cardiovascular effects as vasoconstriction, adrenal effects as stimulation of Aldosterone release, and renal effects as increasing Na reabsorption.(Junior Lima Santos, Krieger, & Pereira, 2012),(Durante *et al*., 2012),("The Renin-Angiotensin-Aldosterone-System - Renin Release - Angiotensin II Production - TeachMePhysiologyTeachMePhysiology," n.d.)



ACE-2 was found to be expressed not only in the renal system but also in other tissues as lungs in larger amounts than in renal, vascular endothelium, brain, and adrenal gland. That explains the ability of COVID-19 to affect all of the previously mentioned tissues due to the presence of ACE-2 receptors, as COVID-19 acts as a ligand to these receptors. Not only these but the high density of ACE-2 receptors that occupy the surface of the lung as it is the major site of SARS-Corona virus that contributes to the development and deterioration in acute respiratory distress syndrome. Also well differentiated epithelial cells have suffered from major attack of SARS-coronavirus, there for imbalance in the secretion of pro-inflammatory mediators and further activation of macrophages that worsen the scenario according to the "cytokine storm hyper-inflammatory" theory in COVID-19.(Jia *et al*., 2005),(Mills, Davies, & Devalia, 1999) The release of pro-inflammatory molecules will result in dysregulated immune responses in the body and this in turn can potentially lead to organ failure and lung damage which is occurs in patients with COVID-19 infection (Zhang *et al*., 2020

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Aliskiren reduce the amount of plasma renin activity, unlike other anti-hypertensive agents as ARBs and ACE-I, Aliskiren is accompanied by decrease in the levels of Angiotensin I & II without risk of compensatory increasing Angiotensin I & II levels via negative feedback as like as in cases of ACE-Is and ARBs administration, respectively (Vaidyanathan, Jarugula, Dieterich, Howard, & Dole, 2008),(Vaidyanathan, Camenisch, t al., 2008)). Edele Mancini and Jonas Fürst suggested a hypothesis based on the finding that highly elevated angiotensin II levels were observed in COVID-19 patients, and this elevation correlated to severity of disease and viral load (QIN *et al*., 2020). Elevated angiotensin II levels, that correlate with the viral load and the insight that ACE2 is upregulated by angiotensin II, can be explained as follows: the virus will make use of ACE2 in severe cases and leads to lung tissue infection. Unfortunately, the elevated levels of ACE2 will facilitate the entry of the virus to the cells. In this case, the internalised ACE2 receptor will not be able degrade angiotensin II. The increase in ACE2 via the increased angiotensin II will result in further lung infection and that is opposite of what we desire. So at high rate the virus will be able to enter the cells and invade more easily. It is worth to mention that infected patients with previous lung conditions will hardly benefit from AT1 receptor blocking and simply blocking AT1 receptors with ARBs could be harmful in some patients .So using ARBs might worsen the scenario due to compensatory mechanism and increase the number of ACE-2 receptors, we suggest hypertensive patients to switch to a safer drug that will not worsen the case of COVID-19 infection as Aliskiren.

Pharmacokinetically, Aliskiren reaches the peak plasma concentration after 1-3 hours after oral administration, although it is eliminated via the liver then excreted mostly unchanged in the bile, a small part of it predicted by 5% is metabolized via CYP450 3A4, clinical studies have demonstrated that the drug-drug interactions of Aliskiren are almost negligible, and the co-administration of it with other drugs that are metabolized by CYP 3A4 will not affect its plasma concentrations. It is a substrate for p-glycoprotein, and it has no interaction with drugs that are also a substrate of p-glycoprotein. regarding to hepatic and renal impairment, the degree of hepatic impairment either mild, moderate or severe according to child-Pugh score doesn't need dosage adjustment from healthy individuals, although the portion of the drug that is eliminated via the kidney is minimal, administration of Aliskiren has shown increase in area under the curve and maximum concentration in patients with renal impairment aside from the degree of failure, despite this Aliskiren starting dose needs no adjustment but caution should be warranted. Its elimination half-life is estimated in a range of 34-41 hours, which allows for once daily administration of 150 mg or 300 mg according to BP readings for treatment of hypertensive patients as monotherapy or in combination with other drugs. It is also fair to mention the side-effects that Aliskiren might cause GIT disturbances as diarrhea 2%, skin rash 1%, increased SCr <7%, increase creatinine phosphokinase in the muscles 1%, and cough 1%.("aliskiren - UpToDate," n.d.)

Mendoza-Martinez C and Rodriguez-Lezama (Mendoza *et al*., 2020) have recently made use of computer-aided drug design methodologies to search for a possible treatment for COVID-19. They selected the top-scored compounds from the docking calculations to nominate candidate ligands for SARS-CoV-2 main protease. Their results showed that Aliskiren was positively ranked as a SARS-CoV-2 main protease inhibitor, this suggests that Aliskiren can potentially inhibit virus replication. According to a recent molecular docking research conducted by Aly, O. (Aly, 2020) Aliskiren showed the highest binding energy in comparison with the other tested compounds with COVID-19 main protease M pro, a potential target for medications to treat COVID-19 (Chen, Liu and Guo, 2020). This is an added benefit to its already known activity which is inhibiting renin and reducing ACE2 expression (Mourad & Levy, 2020). we can conclude

that the using the renin inhibitor, Aliskiren, will be dysregulation of RAAS pathway and this consequently will make the virus entry much harder (Sommerstein, Kochen, Messerli and Gräni, 2020).

CONCLUSION

Aliskiren would be an appealing agent to target two different diseases at the same time: hypertension and coronavirus disease. The complications of these two diseases are usually seen in elderly patients and thus this supports the use of this agent.The positive role that Aliskiren is showing could make it a possible prophylactic and treating agent in hypertensive patients who are at risk of COVID-19 complications. Clinical trials should be conducted on any theoretically promising agent before it is approved by the FDA. Therefore, the authors are looking forward to conduct clinical trials soon to assess the safety and the efficacy of the proposed agent in the actual clinical practice.

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