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The possible management of hypertensive patients infected with COVID-19 through the use of Aliskiren

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Abstract

In late 2019, a novel corona virus (COVID-19) was identified in Wuhan, a city in the Hubei province of China. COVID-19 rapidly spread and led to an outbreak in China and then became a global health emergency. Human pathogenic coronavirus bind to their target cells through angiotensin-converting enzyme 2 (ACE2). The expression of ACE2 is substantially increased in hypertension patients and with type 1 or type 2 diabetes. Hypertension is also treated with ACE inhibitors and ARBs, which results in an upregulation of ACE2.We therefore hypothesis that hypertension and diabetes treatment with ACE2-stimulating drugs increases the risk of developing severe and fatal COVID-19. Therefore, we propose for COVID-19 patients to prevent ANG I and II formation by direct blockade of renin with the specific inhibitor called Aliskiren. The aliskiren acts as a renin inhibitor, which blocks the conversion of angiotensinogen to ANG I. Hence, blood pressure is reduce by decreasing the amount of ANG II to reach the AT1 receptor, thereby causing a decrease ACE2 released. Through the respective review, we hope to contribute to the treatment of patients infected with COVID-19, especially hypertensive patients.

Highlights

1. In late 2019, a novel coronavirus (SARS-CoV-2) which infected a lot of people in Wuhan, a city in the Hubei province of China.
2. Human pathogenic coronaviruses COVID-19 bind to their target cells through angiotensin-converting enzyme 2 (ACE2), which is express by epithelial cells of the lung, intestine, kidney, and blood vessels.
3. Them, the clinically used ACE1-inhibitors (Captopril, Enalapril) enhance renin activity and therefore ANG I and ANG-(1-7) and ACE2 levels.
4. Therefore, we propose for COVID-19 patients to prevent ANG I formation by direct blockade of renin with the specific inhibitor Aliskiren.

Introduction

In late 2019, a novel coronavirus (first: 2019-nCov, then: SARS-CoV-2) was identified as the cause of a cluster of pneumonia cases, which infected a lot of people in Wuhan, a city in the Hubei province of China [1]. SARS-CoV-2 (COVID-19) rapidly spread and led to an outbreak in China and then became a global health emergency. Although control measures and isolations have been applied for prevention, the infection has increased and caused a pandemic [2]. Although this virus belongs to a relatively well-known viral family, *Coronaviridae*, and is similar to viruses that caused severe acute respiratory syndrome (SARS), which had an outbreak in 2002, and Middle East respiratory syndrome (MERS), which had an outbreak in 2012. The COVID-19 in some characteristics, there are a lot of uncertainties and unknown specifications about this virus such as its origin and source of infection, its emergence, and its mechanism of action and transmission [3,4].

In terms of pre-existing medical conditions, cardiovascular diseases had the higher prevalence among diseases that put patients at higher risk of COVID-19 threats. Decreasing the pro-inflammatory cytokines, which leads to a weaker immune function may account for this condition [2,5]. It is worth noting that similar results found regarding MERS [6]. We also found that smokers are more susceptible to Coronavirus infections. According to the current analysis, hypertension, cardiovascular diseases, diabetes, kidney disease, smoking were among the most prevalent underlying diseases among hospitalized patients with COVID-19 [7].

Human pathogenic coronaviruses COVID-19 bind to their target cells through angiotensin-converting enzyme 2 (ACE2), which is express by epithelial cells of the lung, intestine, kidney, and blood vessels [8]. The expression of ACE2 is substantially increased, mainly, in hypertensive patients and with type 1 or type 2 diabetes, who are treated with ACE inhibitors and angiotensin II (ANG II) type-I receptor blockers (ARBs) [8,9]. Hypertension is also treated with ACE inhibitors and ARBs, which results in an upregulation of ACE2 [9]. These data suggest that ACE2 expression is increase in diabetes and treatment with ACE inhibitors and ARBs increases ACE2 expression. Consequently, the increase expression of ACE2 would facilitate infection with COVID-19. We therefore hypothesis that diabetes and hypertension treatment with ACE2-stimulating drugs increases the risk of developing severe and fatal COVID-19 [10].

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The renin-angiotensin-aldosterone system (RAAS) is a hormone system that regulates blood pressure and fluid balance [11]. When renal blood flow is reduced, the kidney converts prorenin to renin and secretes it directly into the circulation. Plasma renin then converts angiotensinogen released by the liver to ANG I. In its turn, ANG I is subsequently converted to angiotensin II (ANG II) by the angiotensin-converting enzyme (ACE) found in the lungs [11]. This causes blood vessels to constrict, resulting in increased blood pressure. The ANG II also stimulates the secretion of the hormone aldosterone from the adrenal cortex, which causes the tubules of the kidney to increase the reabsorption of sodium and water into the blood [11]. This increases the volume of the extracellular fluid in the body, which also increases blood pressure [11]. RAAS is an important target site for five distinctive antihypertensive drug classes: i) Beta-blockers; ii) Renin inhibitors, iii) Angiotensin-converting enzyme inhibitors (ACEIs); v) Angiotensin receptor blockers (ARBs) and vi) Aldosterone inhibitors [11].

Aliskiren, the renin inhibitor, lowered systolic and diastolic blood pressure (BP) compared to placebo in a dose-dependent manner. Musini, *et al.* in systematic review, suggest lowered BP by a magnitude that is similar to what has been determined with ACEIs and ARBs [11].

Main goal

The severity of the COVID-19 pandemic is more severe in patients with certain comorbidities, including hypertension, diabetes and respiratory disorders. A common point between coronavirus pathogenesis and hypertension is the presence and increased ACE2. The data compilation was based in use of the antihypertensive (low costs), RAAS cascade and Aliskiren use alternative. We reflected on the possibility of mitigation the hypertension patient risk and COVID-19 infection. Our proposal suggests the possible Aliskiren therapy, thus decreased ACE2 released and higher the hypertensive patient´s life quality and minor life risk.

Data set

The novel coronavirus showed a similar pattern of infection to other coronaviruses in humans, particularly SARS-nCoV, Bat SARS-like CoV, and MERS-nCoV. After comparing the infection patterns of other vertebrate coronavirus hosts, the infection patterns of minks was found to be most similar to those of the novel coronavirus [12,13]. By modelling the spike protein of the receptors for COVID-19, Xu and colleagues reported that ACE2 could be the receptor for this virus [14]. Similarly, ACE2 is also the receptor for SARS-nCoV and NL63 [15-17]. According to their model, the binding strength between COVID-19 and ACE2 is higher than the threshold required for virus infection, albeit being weaker than that between SARS-nCoV and ACE2. Zhou and colleagues conducted virus infectivity studies and showed that ACE2 is essential for COVID-19 to enter HeLa cells. These data indicated that ACE2 is likely to be the receptor for COVID-19 [18].

The RAAS hormonal cascade begins with the biosynthesis of renin by the juxtaglomerular cells (JG) that line the afferent (and occasionally efferent) arteriole of the renal glomerulus. Renin is synthesized as a preprohormone, and mature (active) renin [19]. Mature renin is stored in granules of the JG cells and is release into the renal and then the systemic circulation. In addition to this regulated pathway, it appears that the kidney also releases unprocessed prorenin via a constitutive pathway. In fact, prorenin accounts for about 70% to 90% of the immunoreactive renin in the human circulation [19,20]. Active renin secretion is regulate principally by interdependent factors: a) Renal baroreceptor mechanism in the afferent arteriole that senses changes in renal perfusion pressure; b) Changes in delivery of NaCl (sensed as changes in Cl-concentration) to the macula dense cells of the distal tubule; c) Sympathetic nerve stimulation via Beta-1 adrenergic receptors and d) Negative feedback by a direct action of ANG II on the JG cells [21].

Control of renin secretion is a key determinant of the activity of the RAAS. Renin regulates the initial, rate-limiting step of the RAAS by cleaving the N-terminal portion of a large molecular weight globulin, angiotensinogen [19]. Angiotensinogen is secreted constitutively by the liver, so plasma levels are generally stable and do not change acutely; however, both hepatic and extrahepatic synthesis have been shown to rise in response to glucocorticoids, estrogens and other sex steroids, thyroid hormone, inflammatory cytokines (e.g., interleukin-1 and tumor necrosis factor) to form the biologically inert ANG I or ANG-(1-10) and ANG II [22]. The inactive ANG I is hydrolyzed by ACE, which removes the C-terminal dipeptide to form the ANG II [ANG-(1-8)], a biologically active, potent vasoconstrictor. ACE is a membrane-bound exopeptidase and is localized on the plasma membranes of various cell types, including vascular endothelial cells, microvillar brush border epithelial cells (e.g., renal proximal tubule cells), and neuroepithelial cells. It is this membrane-bound ACE that is thought to be physiologically important [22]. Thus, functionally, the enzymatic actions of ACE potentially result in increased vasoconstriction and decreased vasodilation. For instance, it appears that in the brain, ANG IV increases blood pressure by cooperating with ANG II on angiotensin II type 1 (AT1)-receptor signalling, because its hemodynamic effects require the presence of both ANG II and functional AT1 receptors. ACE2 can also cleave a single amino acid from the C-terminus of ANG I to form ANG-(1-9), a peptide with no known function at this time [22,23]. As already noted, ANG II is the primary effector of a variety of RAAS-induced physiological and pathophysiological actions by four angiotensin receptor subtypes have been described [24]. The type 1 (AT1) receptor mediates most of the established physiological and pathophysiological effects of ANG II. These include actions on the cardiovascular system (vasoconstriction, increased blood pressure, increased cardiac contractility, vascular and cardiac hypertrophy), kidney (renal tubular sodium reabsorption, inhibition of renin release), sympathetic nervous system, and adrenal cortex (stimulation of aldosterone synthesis) [25]. There is some evidence that, despite low levels of expression in the adult, the type 2 (AT2) receptor AT2 receptor might mediate vasodilation and antiproliferative and apoptotic effects in vascular smooth muscle and inhibit growth and remodeling in the heart [24,25]. The type 4 (AT4) receptors are thought to mediate the release of plasminogen activator inhibitor 1 by ANG II and by the N-terminal truncated peptides (ANG III and IV), but the function of the type 3 (AT3) receptors is unknown [24]. In addition to receptors for the angiotensin peptides, very recent evidence suggests the existence of high-affinity cell surface receptors that bind both renin and prorenin in several tissues, including heart, brain, placenta, and kidney, with localization to glomerular mesangium and subendothelial vascular smooth muscle [26]. One receptor that has been carefully characterized has been reported to cause reversible activation of bound prorenin and to enhance the catalytic activity of bound renin, thus serving as a template for local ANG I generation [26]. As already noted, ANG II, via the AT1 receptor, also stimulates the production of aldosterone by the zona glomerulosa, the outermost zone of the adrenal cortex. Aldosterone is a major regulator of sodium and potassium balance and thus plays a major role in regulating extracellular volume [27].

In resume, the RAAS is an important regulator of blood pressure and fluid-electrolyte homeostasis [27,28]. Aliskiren is active in the

RAAS. Renin gets secreted by the kidney based on changes in blood volume and renal perfusion. Renin is responsible for the conversion of angiotensinogen to ANG I. ANG I is converted to ANG II by ACE2. ANG II binds to the AT1 receptor and works as a vasoconstrictor, causing the release of catecholamines and promoting aldosterone secretion and sodium reabsorption [28]. These effects together act to increase blood pressure. ANG II also can inhibit renin release, causing negative feedback to the RAAS [29]. Aliskiren is the first non-peptide orally active renin inhibitor approved by FDA and as ACE Inhibitors first step of the hypertension [30,31].

Target point

The most common drugs for the treatment of hypertension are: i) Losartan is a selective, competitive ANG II receptor type 1 (AT1) antagonist, reducing the end organ responses to ANG II. Losartan administration results in a decrease in total peripheral resistance (afterload) and cardiac venous return (preload). Reduction in blood pressure occurs independently of the status of the RAAS [32]. Because of losartan dosage, plasma renin activity increases due to removal of the ANG II feedback. However, renin is released from the kidneys when there is reduced renal arterial pressure, sympathetic activation, or increased sodium delivery to the distal renal tubule [32]. ii) Captopril blocks the conversion of ANG I to ANG II and prevents the degradation of vasodilatory prostaglandins, thereby inhibiting vasoconstriction and promoting systemic vasodilation [33]; iii) Moreover, ANG I is converted to ANG II by ACE. Moreover, ACE2 convert ANG II and constricts blood vessels, increasing blood pressure. The active metabolite of Enalapril, inhibits ACE. Inhibition of ACE decreases levels of ANG II, leading to less vasoconstriction and decreased blood pressure, but in the similar profile, plasma renin activity increases due to removal of the ANG II feedback [34].

The ACE2 [35] is an enzyme attached to the outer surface (cell membranes) of cells in the lungs, arteries, heart, kidney, and intestines [36,37]. ACE2 lowers blood pressure by catalysing the cleavage of ANG II (vasoconstrictor) into ANG (1–7) (vasodilator) [38,39]. Both ACE inhibitors and ARBs that are used to treat high blood pressure have been shown in rodent studies to upregulate ACE2 expression hence may affect the severity of coronavirus infections [40,41]. Curiously, multiple professional societies and regulatory have recommended continuing standard ACE inhibitor and ARB therapy [42- 44].

As a transmembrane protein, ACE2 serves as the main entry point into cells for some coronaviruses, including HCoV-NL6335, SARS-CoV (the virus that causes SARS) [45-47] and COVID-19 [48-50]. More specifically, the binding of the spike S1 protein of SARS-CoV and COVID-19 to the enzymatic domain of ACE2 on the surface of cells results in endocytosis and translocation of both the virus and the enzyme into endosomes located within cells [51,52].

This has led some to hypothesize that decreasing the levels of ACE2, in cells, might help in fighting the infection. Furthermore, according to experimental studies, the interaction of the spike protein of the coronavirus with ACE2 induces a drop in the levels of ACE2 in cells through internalization and degradation of the protein and hence may contribute to lung damage [53,54].

Therefore, we propose for COVID-19 patients to prevent ANG I formation by direct blockade of renin with the specific inhibitor Aliskiren. This avoids any harmfully increased angiotensin levels and takes care of hypertension [55].

Study proposal

The categories of the severity of COVID-19 infection are very different in two guidelines. The WHO guideline shows five levels of severity: mild, severe, acute respiratory distress, sepsis, and septic shock. In the septic shock for children, the criteria are based on the guideline of hemodynamic support of pediatric and neonatal Septic Shock from the American College of Critical Care Medicine [57].

Hypertensive patients infected with COVID-19 have a greater severity of symptoms, a higher rate of hospitalization and a greater possibility of progressing to death, especially when associated with comorbidities such as diabetes and pre-existing lung diseases. The medications used to treat hypertension, the most common and low cost for the population (in Brazil), in their mechanism of action can also aggravate the pathogenesis of COVID-19. Mainly, because the entry of the coronavirus in the human cells occurs through ACE2. The RAAS system, in its different stages, responsible for the elevation of pathological arterial pressure, is inhibited by drugs such as Losartan, Captopril and Enalapril in a way that does not inhibit ACE2 and at times can increase the expression of the respective enzyme.

Retrospective analysis of SARS-Coronavirus patients suggested that inhibition of the RAAS may reduce mortality [57]. It has also been demonstrated that the SARS-Coronavirus binds to the ACE2 to be internalized into the cells where it replicates. Then ACE2 expression on the cell surface is downregulated, decreased infection intensity [58]. Lung injury in SARS is specifically mediated by ACE2, and increased ANG II levels were measured in the lungs of SARS-challenged mice [59]. Several ANG peptides and receptors may contribute to this lung injury: Ang II via AT1 and AT2 receptors or ANG-(1-7) via the Mas receptor that forms a heterodimer ("sibling receptor") with the bradykinin BK2 receptor well known for causing angioedema including considerable vascular leakage. Signaling of the heterodimer is activated by both specific ligands i.e. by ANG-(1-7) for MasR and by bradykinin nonapeptide for BK2R [60].

Jacobs, *et al.* recommended Aliskiren use is available as 150 mg or 300 mg tablets. Patients usually initiate therapy on 150 mg daily and may be increased to 300 mg daily if necessary. Doses over 300 mg daily did not demonstrate any additional blood pressure lowering but did show an increased rate of diarrhea [29]. Aliskiren is also available as oral pellets for patients who cannot swallow tablets. The pellets are available as a 37.5 mg capsule. Aliskiren administration is oral. It should be taken daily at the same time. Patients may take Aliskiren with or without a meal, but the recommendation is for consistent administration with regard to meals [29].

Conclusion

Through the respective review, we hope to contribute to the treatment of patients infected with COVID-19, especially hypertensive patients. We suggest that of the use of Aliskiren, blocks renin, which in turn, reduce ANG conversion, consequently decreasing ACE2 expression and diminished arterial pressure and, maybe, COVID-19 infection gravity. Instead of the antihypertensive drugs commonly used, can be an important alternative with the aim of mitigating the severity of COVID-19 infection in hypertensive patients, minimizing the need for admission to the public health system and significantly reduce the death of these patients.

Disclosure statement

We declare there is no conflict of interest in the content of the article.

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