Perspective   *Görüş*

COVID-19 and RAAS blockers: Could Aliskiren be an appropriate option?
COVID-19 ve RAAS blokerleri: Aliskiren uygun bir seçenek olabilir mi?

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The world was recently confronted with a new global health problem caused by a novel coronavirus: severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes the infectious disease called coronavirus disease 2019 (COVID-19). Control of the disease and research of new treatment options are crucial. At present, there are no specific therapeutic agents for the illness. In addition to an association with increasing age, it has been observed that the mortality rate increases in patients with comorbid conditions. According to the World Health Organization-China Joint Mission on Coronavirus Disease 2019 report, cardiovascular disease, diabetes, and hypertension present the greatest risk among comorbid conditions.[1]

The potential role of the renin-angiotensin-aldosterone system (RAAS) in coronavirus infection is primarily based on the activity of angiotensin-converting enzyme 2 (ACE2), which is the SARS-CoV-2 receptor-binding domain. A comparison with an earlier form of the virus, SARS-CoV, revealed that the ACE2 affinity of the new SARS-CoV-2 is higher.[2] The physiological role and mechanism of action of ACE2 contrast with those of the broadly known homologue, ACE, which is inhibited by a major class of antihypertensive drugs known as ACE inhibitors.[3] The primary action of the ACE enzyme is converting angiotensin I to angiotensin II, the most potent mediator of the RAAS. Binding to the AT1 receptor leads to vasoconstriction, cardiovascular remodeling, catecholamine release, and many other effects. Therefore, angiotensin II has a pivotal role in blood pressure regulation and atherosclerosis. ACE2 deactivates angiotensin II by converting it to angiotensin 1–7, which is one of the largely pleiotropic bioactive metabolites of the RAAS. Angiotensin 1–7 is a potent vasodilator and its effect occurs via binding to the Mas receptor, which is coded by Mas proto-oncogenes and couples with G proteins. The effect of angiotensin 1–7 via the Mas receptor has been demonstrated to be the complete opposite of angiotensin II's effect on the AT1 receptor.[4]

COVID-19 and the potential effects of RAAS-blocking antihypertensive drugs

The major organs expressing ACE2 are the heart and lungs.[5] In addition to its many protective effects by generating angiotensin 1–7, it is now known that ACE2 also has a critical role as a binding site for the spike protein of SARS-CoV-2. As a result of their mechanism of action, ACE inhibitors and angiotensin receptor blockers (ARBs) can increase the level of ACE2. With this in mind, there may be a concern about the transmission risk of the virus with the use of ACE inhibitors and ARBs in patients with COVID-19.[6] However, the data on ACE2 expression with the administration of ACE inhibitors and ARBs are controversial.[7] The evidence is not yet sufficient. Accord-

Abbreviations:

ACE2	*Angiotensin-converting enzyme 2*
ARB	*Angiotensin receptor blocker*
COVID-19	*Coronavirus disease 2019*
RAAS	*Renin-angiotensin-aldosterone system*
SARS-CoV-2	*Severe acute respiratory syndrome coronavirus 2*

ing to guidelines,[8] we can easily conclude that ACE inhibitors and ARBs remain the cornerstone of pharmacological antihypertensive therapy in patients with cardiovascular disease and diabetes.

Patients with cardiovascular disease, diabetes, or hypertension have a higher mortality rate and many of these patients are treated with ACE inhibitors or ARBs. Although there may be an increased risk for the transmission of the virus, there is still uncertainty as to whether patients receiving ACE inhibitor or ARB therapy have a poorer prognosis among all patients receiving antihypertensive medication since patients with cardiovascular diseases already have a higher mortality rate without the presence of COVID-19 infection. Experience with earlier members of the coronavirus family (namely SARS-CoV and the Middle East respiratory syndrome coronavirus) has demonstrated that the effects of coronavirus are not limited to the lungs; there are also important impacts on the cardiovascular system, including acute and chronic cardiac injury.[6] In this sense, cardiac protection, which is mainly provided by RAAS blockers, is extremely important.

The transmissibility of the virus and the underlying pathophysiology of lung injury induced by the virus should be taken into consideration. It has been demonstrated that ACE2 expression at a cellular site was conversely down-regulated by SARS-CoV after receptor binding. Interestingly, the increase in expression of ACE2 notably preserves the lungs from injury, whereas stimulation of AT1 receptors by angiotensin II increases the risk of pulmonary pathology.[3,9,10] The therapeutic potential of ARBs is highlighted in patients with COVID-19 pneumonia and lung injury, given the effects of AT1 receptor blocking and increasing the ACE2 level.[3] There are registered pilot studies of recombinant human ACE2 as a treatment for COVID-19-induced pneumonia. If new studies show promising results and find evidence that would support this pathophysiological pathway, the drug repositioning of existing RAAS blockers that increase the ACE2 level may be considered for COVID-19 treatment. It would be faster and less expensive than the research and development of a new biotechnological drug.

Could a direct renin inhibitor, aliskiren, be an appropriate option for treatment?

The role and effect of the ACE2 level on COVID-19 is relevant in 2 main areas of concern, the pathophys-

iology of lung injury and the transmissibility of the virus. The role of ACE2 as a binding spike protein for the virus leads to concerns about the use of ARBs and ACE inhibitors because an increased ACE2 level may increase transmissibility. However, the evidence at this time remains inadequate. In addition to considering the mortality rate, the prevalence of COVID-19 among hypertensive patients who receive various antihypertensive medications should be thoroughly evaluated to prove this hypothesis. If the use of ACE inhibitors and ARBs is identified as a risk factor for the transmission of SARS-CoV-2, there will be subsequent discussion on switching to other antihypertensive medications. This would not be an easy decision for physicians, since RAAS blocking is critical in the treatment of several cardiovascular diseases. In this scenario, another choice would be direct renin inhibitors that provide RAAS blocking without increasing the ACE2 level. The only renin inhibitor currently approved by health authorities is aliskiren, which has a similar efficacy and safety profile to ACE inhibitors and ARBs. Aliskiren inhibits the RAAS system at its rate-limiting step and decreases plasma renin activity differently than ACE inhibitors and ARBs. Although clinical trials have demonstrated that aliskiren is as effective and safe as other antihypertensive drugs, its use did not become widespread due to certain challenges related to the development of new drugs when effective treatment is available with existing drugs. It is not ethically possible to perform a head-to-head comparison between aliskiren and existing RAAS blockers in conditions such as heart failure, myocardial infarction, and so on because optimal treatment can be achieved with ACE inhibitors or ARBs for the vast majority of cardiovascular diseases. The lack of successful studies of aliskiren with hard endpoints and as an add-on treatment, lack of evidence of providing additional benefit without any harm compared with available optimal treatment are the main reasons it is not more commonly used.[11] If new evidence of risk related to ACE inhibitors and ARBs and COVID-19 infection should appear, aliskiren may be an alternative to provide the necessary RAAS blockade and cardiovascular protection without increasing the ACE2 level. A possible reduction in ACE2 expression with aliskiren treatment and the need for further investigation was highlighted in a very recent publication.[12] Although not tested in preclinical or clinical settings, the high binding energy of aliskiren, which may lead

to viral protease inhibition, was also demonstrated in an interesting molecular docking study preprint publication.[13] Additionally, in an analysis of 4 patients with hypertension hospitalized due to respiratory symptoms of COVID-19, (only 3 of which were later confirmed by nucleic acid and antibody detection), after discontinuation of ACE inhibitors and ARBs and starting treatment with aliskiren (1 patient with heart failure was treated with aliskiren plus diuretic, 3 patients were treated with aliskiren plus calcium channel blocker), it was reported that the condition of all of the patients improved and they were discharged without any aliskiren-related adverse events.[14] This study deserves to be discussed more comprehensively; however, only the abstract of this article by Guo et al.[14] was available in English and it was not possible to evaluate the entirety of the study.

Conclusion

COVID-19 is a worldwide health problem. It is now very well-known that the populations with the greatest mortality risk are elderly patients and those with cardiovascular diseases. In this sense, both cardioprotection and the treatment of these patients are critically important. Every day we continue to learn new details and gain new insights related to COVID-19 infection. Healthcare providers must think about all scenarios, reconsider all antihypertensive/cardiovascular treatment options, and stay updated on scientific knowledge in order to make the best decisions based on new evidence and complex circumstances. For example, patients who use antihypertensive drugs that increase ACE2 expression might have a higher risk, yet increased ACE2 expression is suggested as a new treatment option for lung injury. Therefore, both the possible preventive effects of the increase in ACE2 level for lung injury and the role of an increased ACE2 level on virus transmission risk should be thoroughly investigated. All possibilities should be kept in mind to select the most appropriate treatment for each patient. Aliskiren may be a treatment option to be considered, but there is a need for further investigation to reach a more definitive conclusion. There are also other antihypertensive treatment options. Calcium channel blockers and diuretics that do not have a direct effect on the RAAS and beta blockers selected only for patients with specific conditions are not of the same class as RAAS blocker drugs. These may be alternatives for appropriate patients. Lastly,

as an add-on treatment option, neprilysin inhibitors, which act through a different pathway and probably decrease the ACE2 level, may provide additional benefit. In conclusion, several relevant medical societies and associations have declared that patients should continue their antihypertensive treatment. It has been established that the vast majority of patients with COVID-19 have a very mild infection and recover. Unnecessary cardiovascular treatment adjustments may cause more serious problems. Additionally, international societies have underlined the benefits of ACE inhibitors and ARBs in cardiac patients and the lack of evidence of harm in COVID-19 patients.[15]

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