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Renin-angiotensin system inhibitors in COVID-19

Updated May 2, 2020

■ ABSTRACT

Concerns have been raised about the potential for renin-angiotensin system (RAS) inhibitors to upregulate expression of angiotensin-converting enzyme 2 (ACE2) and thus increase susceptibility to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) entry. Currently, there is no evidence that even if RAS inhibitors increase expression and activity of ACE2, that they would increase the risk of SARS-CoV-2 infection by facilitating greater viral entry or worsen outcomes in patients with COVID-19. At this time, there is no clinical evidence to suggest that treatment with RAS inhibitors should be discontinued in stable patients with COVID-19. In hospitalized patients with severe COVID-19, decisions about these medications should be based on clinical condition, including hemodynamic status and renal function.

■ WHAT DO WE KNOW ABOUT THE RENIN-ANGIOTENSIN SYSTEM?

The renin-angiotensin system (RAS) is a complex pathway with a crucial role in regulation of vascular physiology. There are 2 main components that should be considered for purposes of this discussion.

The classical pathway begins with the cleavage of angiotensinogen by renin to angiotensin I, and its subsequent conversion to angiotensin II by action of the angiotensin-converting enzyme (ACE). Angiotensin II mediates vasoconstriction and inflammation by binding to the angiotensin II type I receptor (AT1R).

The counter-regulatory pathway involves angiotensin-converting enzyme 2 (ACE2), which cleaves angiotensin I to form angiotensin (1-9) and also cleaves angiotensin II to form angiotensin (1-7). This serves to decrease angiotensin II, and angiotensin

(1-7) further affects vasodilation by binding to the Mas receptor. Thus, the ACE2/antiotensin (1-7)/Mas vasodilatory axis counterbalances the angiotensin II/AT1R vasoconstrictor axis.

ACE inhibitors block conversion of angiotensin I to angiotensin II, and angiotensin receptor blockers (ARB) block binding of angiotensin II to AT1R. By virtue of their beneficial hemodynamic and anti-inflammatory effects, these RAS inhibitors are a cornerstone of therapy in hypertension, proteinuric kidney disease, and heart failure.

■ WHAT IS THE RELATIONSHIP BETWEEN SARS-COV-2 AND ACE2?

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes COVID-19, gains entry into host cells via ACE2 in a way that is similar to SARS-CoV, which caused SARS in 2003, but with a much higher affinity.[1,2] This is a multistep process that includes binding of the spike (S) protein of the virus to ACE2, proteolytic cleavage of ACE2 by transmembrane serine protease 2 (TMPRSS2), and internalization of this complex, followed by viral replication and cell-to-cell transmission.

ACE2 is highly expressed in the alveolar epithelial cells in the lung (one of the major sites of viral injury), heart, kidneys, and gastrointestinal system.

■ IS THERE HARM WITH RAS INHIBITORS IN COVID-19?

Concerns have been raised about the potential for RAS inhibitors to upregulate expression of ACE2 and thus increase susceptibility for viral entry[3]—essentially, the speculation is that there may be more docking sites for the virus on the cell membrane leading to more viral entry.

While experimental animal models have indicated increased gene expression and activity of ACE2 in cardiac and renal tissue (particularly with ARB),[4,5] there are conflicting data regarding the effects of ACE inhibitors and ARB on ACE2 in human stud-

ies.[6–8] Additionally, data on lung specific effects of RAS inhibitors on ACE2 expression or activity are lacking.

Even if RAS inhibitors increase expression and activity of ACE2, there is no evidence at this time that they would increase the risk of SARS-CoV-2 infection by facilitating greater viral entry or worsen outcomes in patients with COVID-19.

Three observational studies now report data that show no evidence of harm with use of ACE inhibitors or ARBs. Mehra et al report data from 8,910 patients in 11 countries, and neither ACE inhibitors nor ARBs were associated with increased mortality; a secondary analysis restricted to patients with a history of hypertension also did not show any harm with these medications.[9] Mancia et al report data from 6,272 patients in Italy, compared to 30,759 matched controls, and neither ACE inhibitors nor ARBs were associated with the likelihood of SARS-CoV-2 infection; an additional analysis of severe infections also did not find any association with these medications.[10] Reynolds et al report data from 5,894 patients in New York with propensity score matching analysis among all patients and in those with hypertension, examining 5 different antihypertensive medication classes (ACE inhibitors, ARBs, beta blockers, calcium channel blockers, and thiazide diuretics)—no association was found for any these medication classes with likelihood of infection or risk of severe infection.[11]

Taken together, these studies support the recommendations from professional societies to continue ACE inhibitors and ARBs, and are reassuring to patients and health care providers to allay possible concerns about increased risk for infection with these medications.

■ IS THERE BENEFIT WITH RAS INHIBITORS IN COVID-19?

It is hypothesized that the binding of SARS-CoV-2 to ACE2 and its subsequent internalization would downregulate ACE2 expression, and thereby the ACE2/Angiotensin (1-7)/Mas axis, leading to unopposed local angiotensin II/ AT1R activity that mediates increased inflammation in the lung. Thus, RAS inhibitors may exert a protective anti-inflammatory effect by virtue of decreasing angiotensin II/ AT1R activity. Administration of ARBs also prevents ACE2 internalization,[12] which may enhance the ACE2/ angiotensin (1-7)/ Mas axis and attenuate inflammation. The possibility of using ARBs as tentative therapy for COVID-19 prior to the development of acute respiratory distress syndrome has been suggested.[13]

Experimental animal models have shown attenuation of lung injury induced by SARS-CoV (which caused SARS in 2003) with ARBs.[14] A small study in 12 COVID-19 patients reported higher circulating angiotensin II levels compared with healthy controls, and the higher angiotensin II levels correlated with high viral load and degree of lung injury; however, ACE2 levels were not determined in this study.[15]

It remains unknown at this time whether decreasing angiotensin II/AT1R activity or prevention of ACE2 internalization by use of RAS inhibitors would be effective in attenuating development of severe outcomes in COVID-19.

Descriptive data from a case series in the New York City area reported about 8% of patients taking ACE inhibitor and 11% taking ARB at home. About 48% of patients who were on ACE inhibitor and 50% of patients who were on ARB continued these medications in hospital. Mortality rates for patients with hypertension not taking ACE inhibitor or ARB, taking ACE inhibitor and taking ARB were 26.7%, 32.7%, and 30.6% respectively. These results are unadjusted for potential confounders and comorbidities, and cannot answer the question of risks versus benefits of these medications in COVID-19.[16]

A report from China described 174 hypertensive COVID-19 patients on ACE inhibitor or ARB matched to 348 patients with hypertension not on ACE inhibitor or ARB. In this propensity score matched analysis, use of ACE inhibitor or ARB was associated with a lower risk of mortality (adjusted HR 0.37, 95% CI 0.15–0.89, P = .03).The authors conclude that there is likely to be residual confounding, but it is unlikely that in-hospital use of these medications was associated with increased mortality.[17]

■ WHAT SHOULD I DO FOR PATIENT CARE?

At this time, there is no clinical evidence to suggest that treatment with RAS inhibitors should be discontinued in stable patients with COVID-19. These medications have been shown to have clear cardiovascular and renal benefits, and inappropriately stopping them is not advised based purely on a theoretical propensity for increased risk or severity of COVID-19 infection. Multiple specialty societies, including the European Society of Hypertension and the American Heart Association, have advised continuing these medications according to established guidelines and standard-of-care practices.[18,19] Healthcare providers should be available to discuss concerns with patients, particularly considering the rapid spread of information (and misinformation) on social media. Any

changes to medications should be made only after careful consideration of individual risks and benefits, and close follow-up is essential.

In hospitalized patients with severe COVID-19, decisions about these medications should be based on clinical condition, including hemodynamic status and renal function.

More data are awaited from analysis of COVID-19 patient registries regarding baseline use of RAS inhibitors prior to diagnosis, as well as comorbidities and patient outcomes. Additional evidence from clinical trials in COVID-19 patients will also provide further clarity. At the time of this writing, there are 3 registered clinical trials studying losartan (NCT04335123, NCT04312009, NCT04311177), 1 clinical trial randomizing patients on ACE inhibitors or ARBs to continue these medications vs switching to a thiazide diuretic or calcium channel blocker (NCT04330300), and 1 clinical trial randomizing patients on ACE inhibitors or ARBs to continue these medications vs discontinue them (NCT04338009). There is also an urgent need to better understand the pathogenetic mechanisms and the complex interplay of the components of the RAS system and viral interaction, and therapeutics targeting these mechanisms would benefit current and future treatment approaches.

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