Updates on renin-angiotensin system blockers in hypertensive patients with COVID-19

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Since the beginning of the current coronavirus disease 2019 (COVID-19) pandemic, there have been numerous discussions about whether angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB) should be continued or discontinued during the course of COVID-19. ACE2, first discovered as a homologue of ACE in 2000,[1,2] is now known to have multiple physiological functions, including its role as a negative regulator of the renin-angiotensin system (RAS), in amino acid transport, and as a cell entry receptor for SARS-CoV and SARS-CoV-2, the pathogens that cause severe acute respiratory syndrome (SARS) and COVID-19, respectively. Because the role of ACE2 as the SARS-CoV-2 receptor provides a possible mechanistic link between COVID-19 and RAS, and because older people who are particularly vulnerable to COVID-19 are frequently prescribed RAS blockers due to multiple comorbidities such as hypertension, cardiovascular disorders, and kidney diseases, the possible roles of RAS blockers in COVID-19 (either favorable, harmful, or neutral) have been widely debated. Discussions have further been fueled because of several experimental observations showing increased ACE2 abundance in response to RAS blockers in animal models. However, ACE2 overexpression is certainly not a universal finding that follows the administration of these agents.[3] In addition, there is little evidence that therapeutic doses of RAS blockers in humans influence tissue ACE2 abundance, especially at the cell surface.[4,5]

In alveolar epithelial type II cells, nasal epithelia, and other cells that co-express ACE2 and transmembrane protease serine 2 (TMPRSS2),[6] the binding of the spike protein of SARS-CoV-2 to ACE2 is followed by the proteolytic cleavage of the spike protein by TMPRSS2, which allows cell membrane fusion and endocytosis of SARS-CoV-2.[7] Besides the role of ACE2 as the receptor for SARS-CoV-2, this protein negatively regulates tissue angiotensin II levels by cleaving it into angiotensin 1-7.[5] Angiotensin 1-7 then binds to Mas receptor, which also suppresses tissue inflammation and fibrosis induced by angiotensin II. The antagonizing effects of ACE2 on angiotensin II signaling can potentially attenuate acute lung injury. Indeed, experimental studies have shown

that lung inflammation induced by acid aspiration or sepsis is attenuated by RAS inhibition but is aggravated by the genetic ablation of ACE2.[8] Therefore, modulation of membrane-bound ACE2 levels in the target tissues can in theory alter the susceptibility and severity of SARS-CoV-2 infection.

In the early phase of the COVID-19 pandemic, several observational studies were performed to address this issue in several countries, including China, Spain, Italy, and the United States.[9-12] As reviewed previously,[13] these studies consistently showed that ACE inhibitors or ARBs did not aggravate the disease severity of COVID-19. Although the above-mentioned observational studies were well conducted and endorsed the recommendation of the scientific journals and medical societies for the continued use of RAS blockers,[14] randomized controlled trials are needed because retrospective analysis could potentially be confounded by unmeasured biases.

Earlier this year, two randomized controlled trials, the REPLACE COVID trial [15] and the BRACE CORONA trial,[16] tested the possible influence of RAS blockers during the clinical course of patients with COVID-19. The REPLACE COVID trial was a prospective, randomized, open-label trial conducted in 20 hospitals in seven countries (USA, Canada, Mexico, Sweden, Peru, Bolivia, and Argentina).[15] In this study, 152 hospitalized patients with COVID-19 who were prescribed ACE inhibitors or ARB therapy before hospital admission were randomly assigned to the continuation or discontinuation of RAS blockers (mean age, 62 years). The authors found that the primary outcome, which was a global rank score incorporating time to death, duration of mechanical ventilation, time on renal replacement therapy or inotrope, and the area under the curve of the modified Sequential Organ Failure Assessment (SOFA) score, did not differ between the two groups. The BRACE CORONA trial was conducted in Brazil and included 659 patients hospitalized with mild to moderate COVID-19 who were taking ACE inhibitors or ARBs prior to hospitalization (median age, 55 years).[16] The authors

exmined the effect of continuing or discontinuing RAS blockers on the number of days alive and out of the hospital for 30 days from randomization. This study again found no difference in the primary outcome (discontinuation group 21.9 ± 8 days vs continuation group 22.9 ± 7.1 days).

More recently, the results of the ACEI-COVID trial have been published.[17] In this trial conducted in 35 centers in Austria and Germany, 204 patients with symptomatic SARS-CoV-2 infection who were on chronic ACE inhibitors or ARB treatment were randomly assigned to the continuation or discontinuation of RAS blockers for 30 days (median age, 75 years). Consistent with previous studies, the primary endpoint, which was the maximal SOFA score within 30 days, was not significantly different between the two groups. However, this study found that secondary endpoints such as the area under the SOFA score and mean SOFA score, were significantly lower in the discontinuation group than in the continuation group. Nonetheless, the primary result of the study was considered to be neutral because there was no significant difference in the primary endpoint.[17]

In the current of the American Journal of Hypertension, Bahrini et al. provided additional evidence on this problem, by performing a prospective, blinded, randomized clinical trial in Iran. The study included 64 admitted patients with COVID-19, who were previously diagnosed as having essential hypertension and were on ACE inhibitor or ARB treatment (mean age, 66.3 ± 9.9 years). Study participants were randomly allocated to the continuation of RAS blockers or substitution with a calcium channel blocker (amlodipine) for 14 days. The main outcome, which was the length of stay in the hospital and in the intensive care unit, was not different between the two groups, while blood pressure levels were maintained at similar levels in both groups. As acknowledged by the authors, the study had several limitations, such as a short follow-up period and relatively small sample size compared with the above-mentioned clinical trials. However, there were also some notable points.

First, treatment allocation was blinded to the participants and study investigators by over-encapsulation of the antihypertensive medications. Second, the study included moderate to severe cases, with a mortality rate of approximately 15%, which was higher than that of the BRACE CORONA trial and was comparable to the REPLACE COVID trial. Third, the effects of RAS blockers on the course of COVID-19 were tested in different population groups from those included in the previous studies. This is particularly important given that the disease burden and severity of COVID-19 vary from country to country.

In summary, these results support the general recommendations that RAS blockers be maintained during COVID-19 hospitalization in patients with hypertension, since RAS blockers do not promote worse outcomes. Besides the trials that have compared continuation versus discontinuation of ACE inhibitors or ARBs in patients with COVID-19, the results of several studies that have addressed the possible beneficial effects of adding RAS blockers during COVID-19 have recently been reported.[18,19] These studies included 100–160 patients with COVID-19 who were not on ACE inhibitor or ARB treatment and the participants were randomized to ARB group or standard care (or placebo) group when they were diagnosed with SARS-CoV-2 infection. One study found a significant reduction in inflammatory markers by RAS inhibitor treatment,[19] whereas another trial was terminated early

partly because of the low likelihood of treatment effect.[18] In addition to these studies, there are several ongoing trials that are addressing this issue. For example, the Ramipril for the Treatment of COVID-19 (RAMIC) trial is investigating the potential benefits of ramipril (2.5 mg) compared with that of a placebo in improving survival, reducing intensive care unit admissions, and the use of mechanical ventilation support in 560 patients hospitalized for severe COVID-19 (NCT04366050). Moreover, two other trials are investigating the effects of losartan (NCT04312009) and spironolactone (NCT04345887) in patients hospitalized for COVID-19. Hopefully, these ongoing clinical trials, as well as the prospective meta-analysis of randomized trials,[20] will elucidate the optimal use of RAS blockers in patients with COVID-19.

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