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Editorial Comment

EDITORIAL COMMENT

Should we continue to use renin–angiotensin–aldosterone system blockers in patients with COVID-19?

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ABSTRACT

Patients with chronic kidney disease, chronic heart failure and hypertension have an increased risk of coronavirus disease 2019 (COVID-19)-related death. Renin–angiotensin–aldosterone system (RAS) blockers are commonly prescribed to decrease morbidity and mortality in these conditions. Following the pre-clinical demonstration of COVID-19 viral entry into cells via angiotensin-converting enzyme-2, the use of RAS blockers was questioned in infected individuals. Theodorakopoulou *et al*. extensively review the pathophysiology behind that hypothesis and observational or clinical trials on RAS blockers and COVID-19. Despite being a scientific hot spot of an ongoing debate, discontinuation of RAS blockers is not associated with improved clinical outcomes in COVID-19 and may have potential harmful effects, including exacerbation of the underlying disease.

Keywords: chronic kidney disease, COVID-19, hypertension, renin angiotensin system

Hypothetical detrimental effects of renin–angiotensin–aldosterone system (RAS) blockers have been among the highly debated topics during the coronavirus disease 2019 (COVID-19) pandemic based on pre-clinical studies demonstrating viral entry through binding of the spike protein to angiotensin-converting enzyme (ACE)-2 on the cell surface, as ACE-2 may be upregulated by treatment with RAS blockers. Theodorakopoulou *et al*. [1] reviewed the latest developments by exploring the pathophysiological framework behind this hypothesis and assessing the observational and interventional clinical studies conducted so far. Use of RAS blockers has been associated with the downregulation of soluble ACE-2, a molecule which may limit severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection by acting as a decoy receptor, and the upregulation of cell membrane ACE-2, which acts as a viral receptor and entry site. Nevertheless, this would be a considerable underestimation of the complexity of the RAS, as viral particles aggregated by soluble ACE-2 may be uptaken into cells via receptor-mediated endocytosis through angiotensin-1 receptor (AT1R) or arginine vasopressin receptor-1B, while some RAS components, such as angiotensin (1–7), may have tissue-protective properties. Although studies investigating the effects of RAS blockers on the severity of COVID-19 are limited, observational and interventional studies have not demonstrated any association between the use of RAS blockers and COVID-19 severity assessed as mortality, hospitalization, duration of hospital stay, need for mechanical ventilation or need for intensive care unit admission. Therefore, Theodorakopoulou *et al*. concluded that the use or discontinuation of RAS blockers has not yet been linked to the

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severity of COVID-19 in clinical studies, although the results of various ongoing trials are awaited.

RAS blockers, including ACE inhibitors and angiotensin receptor blockers (ARBs), are among the most commonly prescribed medications worldwide as they are indicated in the treatment of common conditions such as hypertension, chronic heart failure and chronic kidney disease, all of which have a combined prevalence of over 50% in the US adult population [2, 3]. Patients with such comorbidities constitute the most vulnerable population to COVID-19 in terms of hospitalization, intensive care unit admission, length of hospital stay and mortality rates [4]. In addition, COVID-19 has direct and indirect effects on the cardiovascular and renal systems during the acute phase of the infection as well as in the post-infectious period [5–7]. Therefore, proper management of such patients with appropriate pharmacotherapy is a useful key to improving outcomes. Discontinuation of RAS blockers has been proposed in COVID-19, but no benefit has yet been demonstrated in clinical studies. Moreover, discontinuation or switch of RAS blockers may have harmful effects on the control of hypertension, kidney injury (e.g. proteinuria) and cardiovascular functions, which may even worsen the clinical outcomes during the acute and chronic phases of COVID-19 [8–10]. In addition to their potential protective effects against inflammatory responses seen during the acute phase of COVID-19 through the angiotensin (1–7)–AT2R or angiotensin (1–7)–MasR pathways, both of which are anti-inflammatory, anti-proliferative and anti-fibrotic, discontinuation of RAS blockers therapy may worsen the prognosis via exacerbation of acute heart failure or hypertension or worsening of kidney damage [11, 12].

One of the major limitations of clinical studies assessed in this review is the exclusion of patients with contraindications to discontinuing RAS blocker therapy, including high-risk patients for acute heart failure exacerbation. Even though the exclusion of such patients is reasonable in the study design, it is important to emphasize that it reduces the generalizability of the results as mentioned by the authors. Another important limitation of these studies is the small number of clinical trials, especially randomized clinical trials, compared with the ongoing trials that may potentially lead to results that may contradict earlier findings from smaller studies. Similarly, studies so far have a low number of participants with respect to one of the most commonly prescribed medication groups, which may result in a larger margin of error and a lower level of confidence for the clinical outcome. An alternative hypothesis (i.e. potential tissue protection by RAS blockade) has led to alternative trial designs in which RAS blocker therapy is added to the therapeutic regimen of COVID-19 patients instead of being discontinued. Additionally, most studies have not evaluated the individual effects of ACE inhibitors and ARB separately despite the hypothesis that they may behave differently [e.g. ARBs will bind to AT1R, recently shown to be a pathway for viral entry into cells, and increase angiotensin 2 availability and, thus, substrate availability for ACE-2, potentially facilitating the generation of tissue protective angiotensin (1–7)]. In this regard, analysis of each drug group separately leads to a further decline in sample size and level of confidence in each study.

To conclude, RAS blockers are an essential part of the treatment of chronic kidney disease, chronic heart failure and hypertension. Their use has been investigated regarding potential detrimental and favourable effects during the acute and chronic phases of COVID-19 infection. As stated by Theodorakopoulou *et al*., discontinuation of RAS blocker therapy has not yet been associated with a better clinical outcome in COVID-19 patients, despite hypotheses derived from pre-clinical studies. However, there are multiple ongoing clinical trials investigating the potential therapeutic effects of RAS blocker discontinuation or soluble ACE-2 receptors. These studies may further clarify the issue and influence therapeutic guidelines regarding the management of COVID-19.

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CONFLICT OF INTEREST STATEMENT

M.K. is a member of the *CKJ* editorial board. All the other authors declare that they have no conflict of interest.

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