Patients taking angiotensin-converting enzyme inhibitors/angiotensin II type I receptor blockers: higher risks of severe acute respiratory syndrome coronavirus 2 infection but milder clinical manifestations?

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Recently, there has been an unprecedented interest in the topic of angiotensin converting enzyme 2 (ACE2)-associated drugs administration, such as angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin II type I receptor blockers (ARBs), in COVID-19 patients. A recent article put forward the concern that patients taking ACEIs/ARBs were under higher risk of COVID-19 infection.[1] They revealed that expression of ACE2, the receptor for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) to enter host cells, is up-regulated, thus facilitating the initial viral attachment step of SARS-CoV-2 in these patients.[2]

Right now, we have more questions than answers on the topic of ACEIs/ARBs and COVID-19. Firstly, can ACEIs/ARBs actually up-regulate ACE2 levels? How will they affect the two forms (cell membrane-bound and soluble) of ACE2? The latter form could be cleaved from the cell surface, but the biological significance of soluble ACE2 remains unclear. Theoretically, if membrane-bound ACE2 is predominantly elevated, it may lead to susceptibility to SARS-CoV-2. On contrary, if soluble ACE2 is dominantly elevated, it may potentially protect against viral infection through acting as a competitive interceptor of SARS-CoV-2 and other coronaviruses by preventing binding of the viral particle to the membrane-bound, full-length ACE2. Several animal studies suggested that ACEIs/ARBs could increase ACE2 levels.[3,4] For instance, Ferrario *et al*[5] found lisinopril or losartan alone induced increases in cardiac ACE2 gene expression and cardiac ACE2 activity, whereas the combination of these two drugs was associated with elevated cardiac ACE2 activity but not the level of expression. The levels of membrane-bound ACE2 in these animal models have been shown to increase under the administration of ACEIs/ARBs. However, the given doses were much greater than those in clinical practice, rendering the observed effects not extrapolatable to humans. Additionally, no direct clinical data identify the effects of ACEIs/ARBs on human tissue ACE2 expression or activity. In this regard, whether ACEIs/ARBs could increase the expression of membrane-bound ACE2 to increase the risk of COVID-19 infection still needs to be clarified.

Would ACEIs/ARBs contribute to the "milder symptoms" in COVID-19 patients? As a cellular entry receptor, ACE2, capable of facilitating the replication of the SARS-CoV-2,[6] is detected to degrade after binding to the virus.[7-9] ACE2 downregulation could lead to the angiotensin II/angiotensin II type 1 receptor (AT1R)-induced aggravation of lung injury or acute lung failure according to several animal findings of virus infection (severe acute respiratory syndrome coronavirus/H5N1).[8-10] ACEIs/ARBs have been shown to regulate the downstream signal of ACE2 (angiotensin II) and the inflammatory cascades, which may be related with better outcomes of the virus-associated lung injury.[11-14] In brief, ACEIs could inhibit angiotensin II production, and ARBs could block the binding of angiotensin II to the AT1R, both of which contribute to alleviate the angiotensin II-mediated inflammatory response and the acute lung injury. Taking the evidence together, ACEIs/ARBs treatment seems likely to provide better clinical outcomes through regulating ACE2 downstream inflammatory pathways. The following hypothesis has been raised based on the underlying mechanism of SARS-CoV-2-

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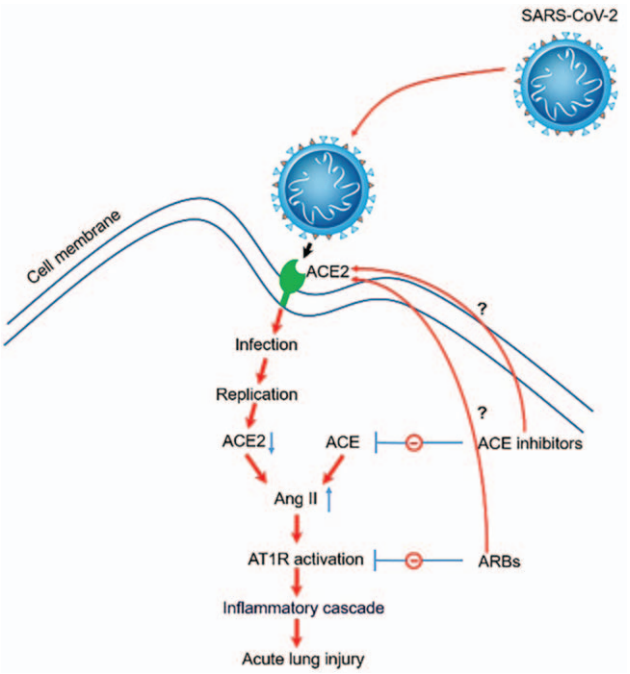

Figure 1: The speculated relationships among SARS-CoV-2, ACE2, ACEIs/ARBs, and lung injury. SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; ACE2: Angiotensin converting enzyme 2; ACE: Angiotensin converting enzyme; Ang II: Angiotensin II; AT1R: Angiotensin II type 1 receptor; ARBs: Angiotensin II type I receptor blockers.

induced lung injury mediated by ACE2 and the its association with ACEIs/ARBs [Figure 1].

Back to clinical practice, it is still too early to say ACEIs/ARBs treatment should be ceased or not. The vast majority of professional societies, including the European Society of Cardiology and American Heart Association, have suggested that patients should continue treatment with ACEIs/ARBs unless advised by their physicians, due to lack of convincing evidence that these drugs will increase the risks.

Below, two recently published cohort or cross-sectional studies are summarized, which are of higher quality and larger scale. Among hospitalized COVID-19 patients with hypertension, Zhang *et al*[15] found that inpatient use of ACEIs/ARBs was associated with lower all-cause mortality compared to non-users. However, there were no significant differences in the blood pressure between the two groups, which indicated that ACEIs/ARBs contributed to a better clinical outcome of COVID-19 independent of blood pressure control. Reynolds *et al*[16] conducted a propensity score-matched analysis to determine if prior use of ACEIs/ARBs was associated with the likelihood of SARS-CoV-2 infection or severe illness. The median difference in the likelihood of testing positive or having severe disease was not significant between ACEIs/ARBs users and non-users. Besides these controllable factors, genetic predisposition is also associated with an increased risk of SARS-CoV-2 infection. There have been several studies showing human ACE2 polymorphisms could predict SARS-CoV-2 susceptibility and outcome,[17-19] which may affect the clinical results of studies investigating the COVID-19 patients with ACEIs/ARBs treatment. In summary, extensive animal studies and large-scale optimized clinical studies are still warranted to explore the role of ACEIs/ARBs in COVID-19 patients.

Conflicts of interest

None.

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