Does the direct renin inhibitor have a role to play in attenuating severity of the outbreak coronavirus disease 2019 (COVID-19)?

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Dear Editor

The ongoing outbreak of coronavirus disease 2019 (COVID-2019) was caused by the novel 2019 coronavirus (2019-nCoV), which shares a similar genome sequence with the SARS coronavirus (SARS-CoV).[1,2] Like SARS-CoV, reports demonstrate that angiotensin-converting enzyme 2 (ACE2) could act as the receptor for 2019-nCoV.[1,3] Moreover, studies have shown that 2019-nCoV binds ACE2 with a higher affinity than the original SARS virus strain.[4]

Renin angiotensin system (RAS) activity regulates the human homeostatic state, and is intrinsically high in the lungs, which is rich in ACE and ACE2 and therefore a major site of systemic angiotensin II synthesis.[5] ACE2 functions in the RAS as a carboxypeptidase, cleaving angiotensin I to generate angiotensin 1-9, and cleaving angiotensin II to generate angiotensin 1-7.[6,7] Pulmonary ACE2 appears to play a role in regulating the balance of circulating angiotensin II/angiotensin 1-7 levels. When responding to hypoxia, angiotensin II induces pulmonary vasoconstriction to prevent shunting in patients with pneumonia or lung injury; nevertheless, the increased production of angiotensin II in the lungs under hypoxia also enhances pulmonary vascular permeability and accelerates subsequent pulmonary edema.[5] In acute respiratory distress syndrome (ARDS), the RAS also plays a major role in maintaining oxygenation. According to ARDS animal models, ACE2 knockout mice presented more severe symptoms compared with wildtype mice, supporting the view that overexpression of ACE2 appears protective.[8]

ACE2 is a crucial receptor for SARS-CoV and 2019-nCoV, and binding to ACE2 by CoV spike protein downregulates ACE2 expression. The loss of ACE2 expression results in severe acute respiratory failure.[9,10] AT1 receptor (AT1R) mediates angiotensin II-induced vascular permeability and severe acute lung injury. Therefore, CoV spike-mediated lung failure is suspected of being rescued by inhibition of AT1R from a RAS blockade, such as angiotensin II receptor block or angiotensin-converting enzyme inhibitor.[9,11] On the other hand, blockade of AT1R, with consequent elevation of both angiotensin I and angiotensin II, stimulates ACE2 activity.[6,11] A dilemma is that the RAS blockade could attenuate the severe lung injury induced by CoV infection *via* inhibition of AT1R, but also increase ACE2 expression and therefore provide more targets for virus binding and replicating. Taking both into account, we hypothesized that a higher-level blockade of RAS might resolve this dilemma. The optimal choice may be the direct renin inhibitor, which could decrease the original renin activity and, consequently, lower angiotensin I and II.[10] ACE2 expression would decrease because of low angiotensin I and II activity. Less ACE2 expression may prevent the body being attacked by 2019-nCoV because of fewer targets for the virus, while the AT1R is still inhibited by low renin activity, with adequate lung protection regardless of low ACE2 expression.

For data reported on 2 March 2020 by the World Health Organization (WHO), globally registered COVID-19 cases were 88,948, of which there were 80,174 cases in China, and other cases had spread to 64 countries reporting a total of 2069 cases. Very surprisingly, Africa had confirmed only two cases. According to the epidemiology, we also speculate whether the low infection rate in Africa is associated with the essentially low renin activity in the population of Africa.[12] As we know, the RAS blockade was less effective for hypertension control in the population of Africa

because of their low renin physiology. Additionally, higher mortality rates from COVID-19 are noted in aged (14.8% in ⩾80 years old) and male (2.8% in male and 1.7% in female, respectively) patients.[13] Regarding RAS activity, aging is associated with activation of RAS,[14] and testosterone in males is thought to increase renin levels.[15]

In conclusion, we hypothesize that the direct renin inhibitor may have a potential role in both attenuating the disease severity of COVID-19 infection *via* the blockade of RAS and lessening the target for the virus by downregulating ACE2 expression. Certainly, this speculation needs further precise investigation to be validated.

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Author contributions

Cheng-Wei Lin: Conceptualization; Visualization; Writing-original draft.

Yu-Yao Huang: Conceptualization; Supervision; Writing-review & editing.

Conflict of interest statement

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