Letter to the editor

More evidence is urgently needed to confirm the relation between angiotensin-converting enzyme inhibitors and COVID-19

Dear Editor,

The Corona Virus Disease 2019 (COVID-19) outbreak caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been announced as a pandemic by the World Health Organization (WHO). As of March 25, 2020, there are 81,896 confirmed cases of COVID-19 in China and additional 293,602 cases in 195 other countries, areas or territories.

The SARS-CoV-2 infection requires binding to the receptors expressed in human tissues. Several studies have demonstrated that SARS-CoV-2 invades host cells through acting with angiotensin-converting enzyme 2 (ACE2). Zhou *et al* confirmed that SARS-CoV-2 interacts with same cell entry receptor, ACE2, as the SARS-CoV [1]. Vincent Munster *et al* established a method to quickly screen the receptor-binding domain of SARS-CoV-2, and further proved ACE2 as the receptor for SARS-CoV-2 infection [2]. Another recent study also showed that similar to SARS-CoV, SARS-CoV-2 employs ACE2 as the entry receptor depending on serine protease TMPRSS2 [3]. Now, the structure of dimeric full-length human ACE2 as well as the interaction site between CoV spike (S) glycoprotein of SARS-CoV-2 and ACE2 has been indentified. The affinity of S protein to ACE2 is 10 to 20 times higher than that of SARS-CoV [4,5]. All these findings suggested that ACE2 may serve as the "gate" from where SARS-CoV-2 initially enters the infect host cells.

As an isoenzyme of ACE, ACE2 reduces angiotensin II level, and promotes generation of angiotensin 1–7 (Ang1–7) to exert several protective effects such as vasodilation, anti-inflammation, anti-proliferation and anti-fibrosis [6]. ACE2 is mainly expressed in the lung, testis, kidney, cardiovascular and gastrointestinal system. A recent study showed that ACE2 expression is enriched in a small population of type II alveolar cells according to the public database and the state-of-the-art single-cell RNA-Seq technique [7]. It suggests that alveolar cells may be the target cell of coronavirus infection to cause serious pneumonia.

It is noted that some patients with COVID-19 also suffer form hypertension. Angiotensin-converting enzyme inhibitors (ACEI), as one of the most common antihypertensive drugs, are widely used in clinic. There is a speculation that long-term ACEI administration might increase ACE2 level due to the feedback mechanisms. Elevated expression of ACE2 can potentially enhance the binding of SARS-CoV-2 to S protein, accelerate coronavirus replication, and aggravate the symptoms of pneumonia. However, the recommendation to discontinue the use of ACEI in COVID-19 patients is not well grounded due to the lack of evidence in clinical settings. From our own prospective, more evidence is urgently needed to further support this.

First, data is required to indicate that long-term ACEI administration can increase the level of ACE2. The difference of ACE2 level and activity in normotensive individuals and hypertensive individuals with or without long-term ACEI treatment should be analyzed. It is better to do autopsy to look into the ACE2 expression in the lung tissues of patients who died of COVID-19 with or without a medication history of ACEI, which can provide a first-hand evidence to confirm the relation between ACEI treatment and ACE2 expression. Second, the hypothesis that ACEI promotes SARS-CoV-2 infection should be further verified, using hypertensive animals with ACEI administration for a long time or with ACE2 over-expression, such as hACE2 transgenic mice or ACE2 conditional knock-in mice to see whether they become more susceptible to SARS-CoV-2 infection or more likely to have severe symptoms, excessive virus copies and aggravated pulmonary injury. On the other hand, such susceptibility may be attenuated in ACE2 knock-out animals. More importantly, clinical evidence is indispensable. A retrospective multi-center cohort study regarding COVID-19 patients with hypertension is desired. It is to be elucidated whether long-term ACEI administration is a risk factor for the development to severe or critical COVID-19. It is noteworthy that several cases relapse after the COVID-19 patients have been cured in clinic, which suggests that the coronaviruses may still be latent in the body. Thus, discharged patients should also be regularly followed up to determine whether there is a statistical difference on recurrence rate with or without long-term ACEI treatment.

In summary, more evidence is urgently needed to confirm the relation between ACEI and COVID-19, which could guide the clinical applications of anti-hypertension medication in COVID-19 patients.

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