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LETTER TO THE EDITOR

Effect of angiotensin II blockers on the prognosis of COVID-19: a toxicological view

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Sir,

At the time of writing this letter (March 25, 2020), COVID-19 is spreading around the world, and unfortunately, our information as to its mechanism of action, prognostic factors, and management is limited. However, it is assumed that using receptor-mediated endocytosis, SARS-CoV-2 enters pulmonary alveolar epithelial cells via its entry receptor, that is, the angiotensin-converting enzyme 2 (ACE2) [1]. The virus creates an essential binding to the membrane-bound form of ACE2 and causes an internalization of the complex by the host cell [2].

Clinical presentations of symptomatic COVID-19 patients consist of fever, cough, nasal congestion, fatigue, and other signs of respiratory tract infection, typically presenting within 1 week following exposure to the virus. In approximately 75% of COVID-19 patients, the infection leads to acute illness with dyspnea and severe pneumonia, as observed in computed tomography (CT) scan on admission [1].

Angiotensin II receptor (AT1R) blockers, like losartan, valsartan, or telmisartan, are widely used for the management of hypertension [3]. Clinical experience with these drugs has shown that they are well-tolerated with a favorable safety profile. Sommerstein (2020) documented ACE inhibitors as a potential risk factor for fatal COVID-19 [4]. Parsa et al. evaluated the potential of ACE inhibitors to cause toxicity in adults and children and found that these drugs are generally safe. Also, they discovered that patients who ingested five-fold or a higher dose of these drugs might experience minor toxicity [3]. Therefore, from a toxicological perspective, this category of drugs is considered relatively safe. In this letter, we are raising a simple question: should we consider the use of angiotensin II receptor antagonists as an adjuvant treatment to manage hospitalized COVID-19 patients and patients experiencing respiratory symptoms clinically or by radiograph to halt the spread of the virus in healthy tissues?

Sun et al. [5] and Phadke et al. [6] proposed that due to the dysregulation of the renin-angiotensin system by SARS-CoV-2, these patients may benefit from the administration of AT2R blockers [3, 5]. They offered these suggestions based on the observation that ACE2 is the receptor-binding domain of SARS-CoV-2 spike protein [7]. Also, Vaduganathan (2020) highlighted the beneficial effects of ACE2 rather than its harmful effects in patients with known or suspected COVID-19 [8]. ACE2 metabolizes Ang II to Ang I-VII. ACE2 augments the bioactive peptide Ang I-VII that opposes the ANG II/ANG II Type 1 (AT1) receptor axis through its anti-inflammatory and antifibrotic activity in the lung and other tissues. The loss of ACE2 can intensify Ang II harmful activities and decrease the useful impact of Ang I–VII as a mechanism of SARS-CoV-2 [2, 9].

Two of the AT1R antagonists, namely, valsartan and telmisartan, have PPAR-ɣ agonistic activities. It has been shown that the activation of PPAR through synthetic and nutritional compounds could represent an efficient management plan to overcome the cytokine storm and to prevent the detrimental inflammatory impacts after coronavirus infection [10].

Hypertensive or diabetic patients who are on chronic angiotensin receptor blockers (ARB) or ACE inhibitor therapy may have upregulated AT1R receptors. Some authors believe that the increased expression of ACE2 would facilitate COVID-19 infection and suggest that diabetes and hypertension treatment with ACE2-stimulating drugs increases the risk of developing severe and fatal COVID-19 [11]. However, even in this situation, continued blocking of these receptors

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(which represent opening the door for viral entry) may prove to be more beneficial to the patient versus discontinuing/replacing these drugs with other antihypertensive drugs. Eliminating this proposed protective mechanism may worsen the scenario since the virus can enter cells without any disruption. In fact, the withdrawal of renin-angiotensin-aldosterone system inhibitors may be harmful in high-risk patients with COVID-19 diagnosis [12].

It should be noted that the expression of ACE2 is not a phenomenon of all or nothing. AT1R antagonists may enhance the expression of ACE2 in humans (although scattered evidence exists regarding the lungs), but there is a significant baseline amount of ACE2 that can bind and internalize the virus. Also, the role of angiotensin II, as a new vasopressor in the management of shock following COVID-19 and protector against SARS-CoV-2 in patients with or without shock, is unknown and must be studied at this time of international crisis.

In general, angiotensin II receptor antagonists are generally safe; we encourage healthcare providers to test and consider this drug in their management protocol, especially for young hospitalized patients without a history of chronic diseases. We also believe that the advantage of these drugs may outweigh its disadvantages. However, further studies are needed to investigate the efficacy of this treatment.

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