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Angiotensin II, III, and IV may be important in the progression of COVID-19

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Dear Editor,

The long-term consequences of SARS-CoV-2 infection and treatment of novel coronavirus disease 2019 (COVID-19) are not yet known. Several drug studies have focused on the renin–angiotensin system (RAS) and angiotensin-converting enzyme 2 (ACE2). Angiotensin (Ang) II levels were found to be high in patients infected with SARS-CoV-2.[1,2] The virus enters the cell after it binds to ACE2, as an ACE2–virus complex. The virus may alter ACE2 function and render the enzyme dysfunctional.[2] Because the virus targets ACE2, treatments for COVID-19 may also need to target ACE2. In phase I and II studies and several case reports, recombinant ACE2 has been reported to improve the clinical course of patients with COVID-19 by increasing Ang II degradation.[3–5] Along with Ang II, Ang III, and Ang IV may be responsible for severe forms of COVID-19.

Ang II, a potent vasoconstrictor, triggers oxidative stress and inflammation. ACE2 converts Ang II to Ang 1–7 and Ang I to Ang 1–9.[6] Ang 1–9 is one of the major products of the ACE pathway and is converted to Ang 1–7 by ACE and neprilysin.[6,7] ACE inhibitors (ACEIs), angiotensin receptor blockers (ARBs), statins, and some oral antidiabetics cause ACE2 upregulation.[8] ACE2 upregulation increases the degradation of Ang II to Ang 1–7 and alamandine.[9] Alamandine is a vasodilator peptide with anti-inflammatory and antiproliferative effects.[9] ACE2 upregulation and an increase in Ang 1–7 and Ang 1–9 cause vasodilation and alleviate inflammation.[10–12] Thus, increasing ACE2 and Ang 1–7 may contribute to the treatment of hypertension and diabetes, two critical comorbidities of COVID-19.[13]

Although an increase in the degradation of Ang II occurs in patients using ACEIs, Ang II formation continues through secondary pathways. Cathepsin G and kallikrein enzymes produce Ang II independently of ACE.[14] ACE also breaks down bradykinin and, when ACE is blocked, bradykinin levels increase.[15] Bradykinin activates the chymase pathway in tissues such as the heart and lung,[15] allowing production of Ang II, Ang III, and Ang IV. The chymase pathway also generates Ang II from Ang 1–12.[14]

According to the results of a meta-analysis, ACEIs and ARBs do not adversely affect mortality rate and duration of hospital stay in patients with COVID-19.[16] The meta-analysis indicated that ACEIs have a protective effect against COVID-19, but ARBs do not.[16] However, in patients using ACEIs, Ang II formation continues through non-ACE pathways. The existence of alternative pathways for Ang II production and the increased Ang II levels even with blockage of the Ang type-1 receptor (AT1R) render the degradation steps of Ang II important. Ang II is converted to Ang III by aminopeptidase A and Ang III is converted to Ang IV by aminopeptidase N.[10–12] Ang III increases vasopressin release from the brain and aldosterone release from the kidney.[12] When Ang III binds to AT1R, it acts in a fashion similar to Ang II, causing vasoconstriction and inflammation.[17] Ang IV binds to the Ang type-4 receptor (AT4R) leading to vasodilation, natriuresis, and nitric oxide release.[10,11] However, Ang IV causes vasoconstriction by binding to AT1R and increases the risk of thrombosis by activating the plasminogen activator inhibitor (PAI).[11] Ang IV binding to AT4R also can cause release of PAI-1 and this may lead to thrombotic events.[18] Returning to Ang II, it may cause arteriolar thrombosis by several mechanisms independent of AT1R activation.[19] The Ang type-2 receptor plays a role in the first phases of Ang II-mediated thrombosis. AT4R plays a role in the cessation phases of Ang II-mediated thrombosis.[19] Also, T lymphocytes interact with Ang II, causing proinflammatory cytokine release and activating the platelets and the coagulation cascade. T lymphocytes mediate the acceleration of microvascular thrombosis.[20]

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Thrombotic events are common during COVID-19 and antithrombotic therapy has been shown to reduce mortality.[21] ACEIs and ARBs have antithrombotic effects mediated by Ang 1–7.[22] These effects may be lost when the virus disrupts ACE2 function and inhibits Ang 1–7 formation. ACEIs reduce Ang 1–7 degradation through the mechanisms mentioned above and can be protective against thrombosis triggered by SARS-CoV-2. However, ACE or AT1R blockage may not prevent thrombosis in patients using ACEIs or ARBs because, even with ACE or AT1R blockage, Ang II, Ang III, and Ang IV can cause detrimental effects in patients with COVID-19.

Inhibiting ACE or blocking AT1R may not eliminate the negative effects of SARS-CoV-2 infection and may not prevent thrombosis. Therefore, treatments based only on Ang II may not be sufficient in COVID-19 patients.

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