

Renin–angiotensin system inhibition in COVID-19 patients: Friend or foe?

Host cell penetration of SARS-COV-2 is mediated by angiotensin-converting enzyme 2 (ACE2), which is expressed on the surface of epithelial cells lining the respiratory tract, cardiomyocytes, endothelial cells, and vascular smooth muscle cells (1). Animal experiments have revealed that expression and activity of ACE2 in various organs are increased with the administration of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) (2). Therefore, previous speculations suggested worse outcomes in patients with COVID-19 with the use of renin–angiotensin system (RAS) inhibitors (3). Although, there is no evidence that shows an association of ACEIs or ARBs with upregulation of ACE2 levels in human lung or cardiac tissues, higher urinary ACE2 levels documented in patients with hypertension treated with ARBs suggest that upregulation of ACE2 may also occur in humans (4, 5). These findings led to the hypothesis that RAS inhibition by means of ACEIs and ARBs may increase the risk of COVID-19 through upregulation of ACE2 and increase of viral load. ACE2 is a paralogue of ACE; however, they have opposite effects (6). ACE2 downregulates the RAS and acts as a deactivator of angiotensin II by converting it into angiotensin-(1–7) which has opposite properties to angiotensin II. Angiotensin II is an active peptide causing vasoconstriction, fibrosis, and inflammation by binding to angiotensin 1 receptor (AT1R). In contrast, angiotensin-(1–7) induces vasodilatation and shows antifibrotic and anti-inflammatory properties (7).

Although it is well recognized that ACE2 and its membrane expression and tissue activity play a key role in COVID-19 infection, the exact mechanisms are complex. ACE2 may facilitate virus entry into the cells; however, once the viral endocytosis occurs, the virus induces a decrease in the ACE2 tissue activity (8). Reduction of ACE2 activity results in angiotensin II accumulation which leads to aggravation of COVID-19-induced inflammation (9). Thus, high membrane levels of ACE2 may induce viral infection in the contamination phase acting as a receptor, nevertheless once patients are infected, high levels of ACE2 are probably beneficial in the inflammatory lesion phase due to its anti-inflammatory and anticoagulant features (6).

In the current issue of this journal, a scientific letter by Eroğlu et al. (10) addresses the hypothesis that unopposed AT2 levels secondary to suppressed ACE2 expression is the main driving mechanism behind the severe clinical consequences of patients

with COVID-19 (10). ACEIs and ARBs may be beneficial in management of patients with COVID-19 as a result of their counteracting role on the destructive effects of angiotensin II and AT1R. RAS modulation by ACEI and ARBs that leads to increased expression of ACE2 may help in mitigating the deleterious effects of angiotensin II, which is responsible for severe manifestations of COVID-19 (7). Therefore, in addition to use of ACEI/ARB, suppression of excess AT2 activity with the use of statins and heparin may also play a role in preventing COVID-19 related complications.

The study conducted by Şenkal et al. (11) investigated the consequences of chronic use of ACEIs and ARBs in hospitalized COVID-19 patients. Based on their clinical experience early in the outbreak and past evidence derived from animal studies demonstrating beneficial effects of ACEIs and ARBs in acute lung injury, the investigators hypothesized that patients with ACEIs as a part of their already existing antihypertensive regimen would be less likely to suffer severe disease compared to those on non-RAS inhibiting regimens (12). This study involving 611 COVID-19 patients revealed that ACEI exposure, but not ARB use, significantly reduced the risk of severe disease. ACEI exposure was also associated with milder infiltrations seen on baseline computed tomography, lower C-reactive protein and ferritin, higher monocytes, shorter hospitalization, and less requirement of specific empirical treatments. Although exposure to ARBs was not associated with improved outcomes, its use was also not related with an increased adverse event rate. Their findings are in accordance with several observational studies demonstrating that use of ACEI/ARBs was associated with lower risk of COVID-19 infection, serious complications, or deaths (13, 14). Although this study has a number of limitations, it has a significant value in confirming that there is no harm in using ACEIs/ARBs in an in-patient COVID-19 population.

The data regarding the role of ACEIs and ARBs in COVID-19 are derived from retrospective small-scale studies having a high risk of chance associations and from observational studies with high probability of confounding factors. Use of different diagnostic tests within one study and lack of information about the continuation of ACEI/ARB treatment during hospitalization are the limitations of these studies. The quality of studies published during the pandemic raises concerns among the scientific com-

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munity. Recently, a study investigating the effect of ACEI and ARBs in COVID-19 patients was retracted from one of the top medical journals (15). The scientific society is getting through an extraordinary and unfamiliar era. We are desperately in need of information; however, we have several constraints in collecting and processing of reliable data due to the devastating nature of the disease. Further, well-designed epidemiological studies and prospective trials are urgently required, in order to investigate the role of ACEIs and ARBs in the management of COVID-19 patients with and without additional indications for these drugs.

In summary, findings of Şenkal et al. (11) are in line with the recommendations of the scientific societies advocating continuation of ACEI/ARB in patients with COVID-19 unless cessation is clinically indicated (5). However, given the lack of solid evidence, initiation of these drugs merely with the goal of COVID-19 management without another clinical indication (hypertension, heart failure etc.) cannot be recommended.

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