RAAS-Blockade in COVID-19: The Ace of Spades?

Dear Sir,

According to the World Health Organization, the first case of the novel coronavirus 2019 illness (COVID-19) was observed in the Wuhan City, China in December 2019. Since then, this disease has been declared a pandemic and, as of June 17, 2020, almost 8 million people have been infected. Early on, the cell entry receptor for the virus was identified as angiotensin converting enzyme 2 (ACE2).\[1\] This has led to significant controversy regarding the use of renin angiotensin aldosterone system (RAAS) inhibitors in infected patients. Largely in light of the nonhemodynamic roles of the angiotensin converting enzyme (ACE) system, evidence is building that RAAS-inhibitors could play an important role in mitigating COVID-19 disease.

Several initial reports from China and Italy described hypertension and diabetes as common comorbidities in patients with severe COVID-19 illness. These reports sparked concerns about the safety of RAAS-blockers including angiotensin converting enzyme inhibitors (ACE-Is) and angiotensin type 1 receptor blockers (ARBs) in potentiating SARS-CoV-2 infection. This concern was fueled by animal studies showing upregulation of ACE2 in response to RAAS-blockade and hence availability of more viral entry receptors.\[2\] While increased levels of ACE2 mRNA levels have been observed in enterocytes of patients treated with ACE-Is, similar data in lung tissue is lacking.\[3\] International societies have issued guidelines favoring continuation of ACE-Is and ARBs in patients taking these agents for their cardiovascular benefits. However, prescribing these agents anew to patients remains debatable. We summarize data suggesting potential immunological benefit of RAAS-blockade, along with its cardioprotective role.

In addition to its well-known role in the renin-angiotensin-aldosterone system, ACE upregulates inflammation and fibrosis pathways. ACE cleaves angiotensin I to angiotensin II (Ang II), which can induce production of inflammatory cytokines like TNF-alpha, IL-6, IL-1B, IFN-G, IL-23, and IL-17 by activating the angiotensin type 1 receptor (AT\textsubscript{1}R) on neutrophils and macrophages.\[4\] Ang II is also prothrombotic by increasing the release of plasminogen activator inhibitor (PAI-1) from human adipocytes.\[5\] Hence, blocking ACE and AT\textsubscript{1}R could negate both these proinflammatory and prothrombotic effects. This was demonstrated in an elegant mouse study by Imai et al. They concluded that ACE/AngII/AT\textsubscript{1}R axis promotes disease pathogenesis in a mouse sepsis lung injury model, and this was reversed by blocking the AT\textsubscript{1}R with losartan.\[6\]

Imai et al. further showed that ACE2 and AT\textsubscript{1}R (angiotensin type 2 receptor), on the other hand, protect mice from severe acute lung injury. ACE2 cleaves Ang II to Ang (1-7) and Ang I to Ang (1-9), both of which have anti-inflammatory effects via Mas receptor and AT\textsubscript{2}R, respectively. Therefore, upregulation of ACE2 in response to RAAS-blockade could further promote a state of immuno-resolution and decrease severe lung inflammation seen with COVID-19. This anti-inflammatory effect of RAAS-blockers can explain why ACE inhibitors conferred protection from pneumonia in a BMJ meta-analysis.\[7\]

Several observational studies have evaluated the association between RAAS-blockade and severity and mortality of COVID-19. One of the earliest studies divided 42 hypertensive patients into ACEI/ARB (n = 17) and non-ACEI/ARB (n = 25) groups. They found that patients on ACEI or ARB therapy had lower rates of severe disease, a lower level of IL-6, and decreased peak viral load as compared to patients on non-ACEI/ARB therapies.\[8\] Yang et al. evaluated 126 COVID-19 patients in Hubei, Wuhan and compared ACEI/ARB (n = 43) and non-ACEI/ARB (n = 83) groups. They concluded that the ACEI/ARB group had statistically lower concentrations of hs-CRP and procalcitonin and a non-statistically significant trend towards lower severity of illness as well as mortality.\[9\] While small and preliminary, these findings are consistent with a decreased inflammatory response due to blockade of the ACE/AngII/AT\textsubscript{1}R axis. On the other hand, observational studies from New York\[10\] and Korea\[11\] did not find any relationship between ACEI/ARB use and COVID-19 severity. More recently though Guo et al. conducted a meta-analysis of nine observational studies, including the ones described above. They found that ACE-I/ARB therapy decreased mortality in COVID-19 patients with hypertension (odds ratio 0.57, 0.38–0.84).\[12\]

In conclusion, overall data hints towards a potential immunological benefit of RAAS-blockade in COVID-19 illness. Contrary to earlier concerns, none of the published studies to date have shown increased morbidity or mortality with RAAS-inhibitors in these patients. Discontinuing these medications may potentially harm patients with heart failure and ischemic cardiomyopathy given their proven mortality benefits.\[13\] Hence, we not only agree with the various guidelines in favor of continuing RAAS-inhibitors but also encourage initiation of these agents in patients who are otherwise candidates due to cardiovascular indications. Delaying or deferring RAAS-blocker initiation due to the COVID-19 pandemic is not consistent with the available scientific evidence. In fact, RAAS-blockade may be our Ace of Spades!

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Conflicts of interest

There are no conflicts of interest.

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