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Renin–Angiotensin–Aldosterone System Inhibitors in Patients with COVID-19: General Considerations and Clinical Implications

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ABSTRACT

Initially reported in China at the end of 2019, the coronavirus pandemic has now reached an international scale with more than 1.5 million cases worldwide and more than 80,000 deaths by April 8th of this year. Recent studies have shown that the virus invades host cells by the angiotensin-converting enzyme 2 receptor, making it essential to viral transmission. Concerns have been raised about possible benefits and harms associated with the use of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptors blockers in these patients. However, there is lack of evidence to recommend even temporarily discontinuing renin-angiotensin system inhibitors/blockers in patients infected with the SARS-CoV-2.

KEYWORDS: Coronavirus; Pandemics; Renin–angiotensin system; Angiotensin-converting enzyme inhibitors; COVID-19.

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INTRODUCTION

Initially reported in China at the end of 2019, the coronavirus pandemic has now reached an international scale with more than 1.5 million cases worldwide and more than 80,000 deaths by April 8th of this year[1]. Most patients who end up in the intensive care unit (ICU) have significant lung deterioration and require mechanical ventilation. However, cardiac complications including myocardial ischemia, myocarditis and cardiac dysfunction have also been described and can substantially increase the mortality rate[2].

Recent studies showed that COVID-19 virus invades host cells by the angiotensin-converting enzyme 2 (ACE2) receptor, making it essential to viral transmission[3]. The virus uses the ACE2 receptor, downregulating the renin-angiotensin-aldosterone system (RAS) and thus, the modulation of this process could have implications in disease progression[4].

COVID-19, SARS and ACE2

ACE2 is present in multiple organs and is directly associated with heart function and the development of diabetes and hypertension[5]. As is known from classic previous studies, ACE inhibitors (ACEIs) have an important role in the treatment of cardiovascular disease, significantly reducing morbidity and mortality in patients with heart failure[6–9], for which the same is seen with the use of renin–angiotensin system (RAS) antagonist medications[10,11].

Because of this association of COVID-19 with the ACE2 receptor, there are concerns of possible benefits and harms associated with the use of ACE inhibitors and angiotensin receptors blockers (ARBs) in infected patients.

Since the first outbreak of SARS-related coronavirus in 2003, the ACE2 protein was known as a receptor for the SARS-CoV virus[12]. Due to this association, when scientists initially isolated the new virus (SARS-CoV-2) and published the genome sequence collected from the first five patients in Wuhan, China, the hypothesis of ACE2 being a cellular entry receptor was formulated. The results confirmed that only cells expressing ACE2 receptor could be infected[13]. Given this mechanism, a concern about the use of RAS antagonists, which can potentially increase the expression of ACE2 leading to an increased virus infection, was raised in the medical community. The correlation between elevated plasma levels of ACE2 and the severity of lung injury in COVID-19 infected patients[14] also corroborated this concern. Despite the existence of a feasible and plausible mechanism, there is no evidence to support this potential effect in humans. Many studies have investigated elevated ACE2 levels in patients with cardiovascular diseases including poor biventricular performance[15], left atrium remodeling[16] and myocardial fibrosis among patients with severe aortic stenosis[17], yet, none were able to demonstrate that ACEI/ARB use had any influence. Only one study assessed the long-term effect of ACEIs/ARBs on the treatment of patients with hypertension: Olmesartan is the only drug found to have an increased ACE2 level in the urine[18].

All this data was produced using animal experiments, preclinical observation studies and trials of patients not infected with the new SARS-CoV-2. Nearly four months after the first cases described in December 2019, and the worldwide spread of the virus, initial retrospective cohorts show a high prevalence of hypertension from 13% in nonsevere patients[19] up to 30% among hospitalized patients[20,21]. Based on this, a considerable number of patients are expected to be taking ACEIs and ARBs. Meng and colleagues retrospectively analyzed 42 patients (17 of them on ACEIs or ARBs) admitted to a single center in China for which both groups had an equal number of severe disease presentations and baseline characteristics. Considering the limitations of a small retrospective analysis, the RAS group had better clinical and laboratorial outcomes than the non-RAS group[13]. Another retrospective analysis of 112 patients with SARS-CoV-2 performed in Wuhan found that the use of ACEIs or ARBs had no effect on mortality and morbidity[22]. These findings reinforce the idea presented by Liu et al. who proposed that in patients infected with the COVID-19, angiotensin II plasma levels are directly correlated with viral load and lung injury – suggesting the use of ARBs as a potential treatment for these patients[14].

ACEIs/ARBs and GUIDELINES

ACEIs and ARBs have been widely used worldwide for decades. Their benefits in heart disease, hypertension and kidney disease are well known.

ACEIs have shown decreasing mortality, morbidity and hospitalizations regardless of the etiology and severity of the heart failure with reduced ejection fraction (HFrEF)[23,24]. The American Heart Association (AHA), American College of Cardiology (ACC), European Society of Cardiology (ESC) and Brazilian Society of Cardiology (SBC) recommend ACEIs for all patients with HFrEF unless contraindicated[25–27]. ACEIs should be started as soon as the patient is diagnosed with HFrEF and should not be discontinued even if left ventricle function improves[28]. Therefore, in times of pandemic, when access to the healthcare system is limited, changing ACEI long term treatment is risky and can be fatal in patients with HFrEF.

ACEIs and ARBs are the most frequently used medications for hypertension (HTN), especially in patients with diabetes, microalbuminuria and heart disease. ACC/AHA, ESC and SBC recommend their use as a first line medication – independently, or combined with diuretics and/or calcium channel blockers[29–31]. Even for patients with hypertension without target organ damage, the regimen change is possible but still requires strict outpatient follow up. At this point, when the number of COVID-19 cases continues to increase and the demand of certified healthcare professionals and medical supplies rises, avoiding unnecessary visits is mandatory in order to reduce possible virus exposures and to further avoid overwhelming the health system.

ACEIs and ARBs are also indicated for patients with chronic kidney disease with or without diabetes in the presence of elevated urinary albumin excretion[32]. The risk of temporarily discontinuing these medications in this population could appear low in the short term; however, as far as is known, there are no studies to validate this suspicion.

Despite current experimental studies showing the potential of ACEIs increasing the risks of complicated SARS-Cov-2, there are no robust human studies validating this harm to date (April 8th of 2020). Furthermore, the dangers of discontinuing ACEIs on large scale could be tremendous. A recent AHA/ACC statement advises against discontinuing ACEIs/ARBs in patients with COVID-19 unless there is a separate contraindication. A statement by the SBC recommends individually evaluating the cardiovascular risks of discontinuing these medications in patients with COVID-19.

CONCLUSION

In summary, based on the evidence presented by current studies up until April 8th of 2020, there is lack of evidence to recommend even temporarily discontinuing RAS antagonists in patients infected with the SARS-CoV-2 as well as to prescribe them for all patients. The use of this class of drugs as potential treatment to modulate plasma ACE2 levels is not yet clearly elucidated and requires further clinical trials for before such conclusions can be made.

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