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COVID 19 - Myths and Facts of ACEIs and ARBs – An Evidenced Based Approach

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ABSTRACT

As angiotensin-converting enzyme 2 (ACE2) is identified as a functional receptor for SARS-CoV-2, which leads to COVID-19, it has raised the question that is it necessary to discontinue ACE2 to elderly patients, who are affected with COVID-19.

INTRODUCTION

In the 21st century, coronaviruses (CoVs) caused three major epidemics of respiratory distress[1] syndrome, which include severe acute respiratory syndrome coronavirus (SARS‐CoV) in 2003 with epicenter in Guangdong, China,[2] Middle East respiratory syndrome coronavirus (MERS‐CoV) in 2012 in Saudi Arabia,[3] and the third epidemic of respiratory coronavirus is the 2019‐novel coronavirus (2019‐nCoV) or coronavirus disease (COVID‐19) which is mainly centered in Wuhan province, China.[4]

The renin-angiotensin system (RAS) is a pivotal mediator in the development of hypertension and associated cardiovascular diseases. While the ACE/Ang-II/AT1R is a well-established axis of the RAS leading to vasoconstrictive and proliferative effects, the ACE2 linking to angiotensin(1-7) [Ang(1-7)] and its G-protein coupled protein receptor Mas, provides a vasoprotective anti-proliferative mechanism, resulting in counter-regulation of RAS[5].

Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers

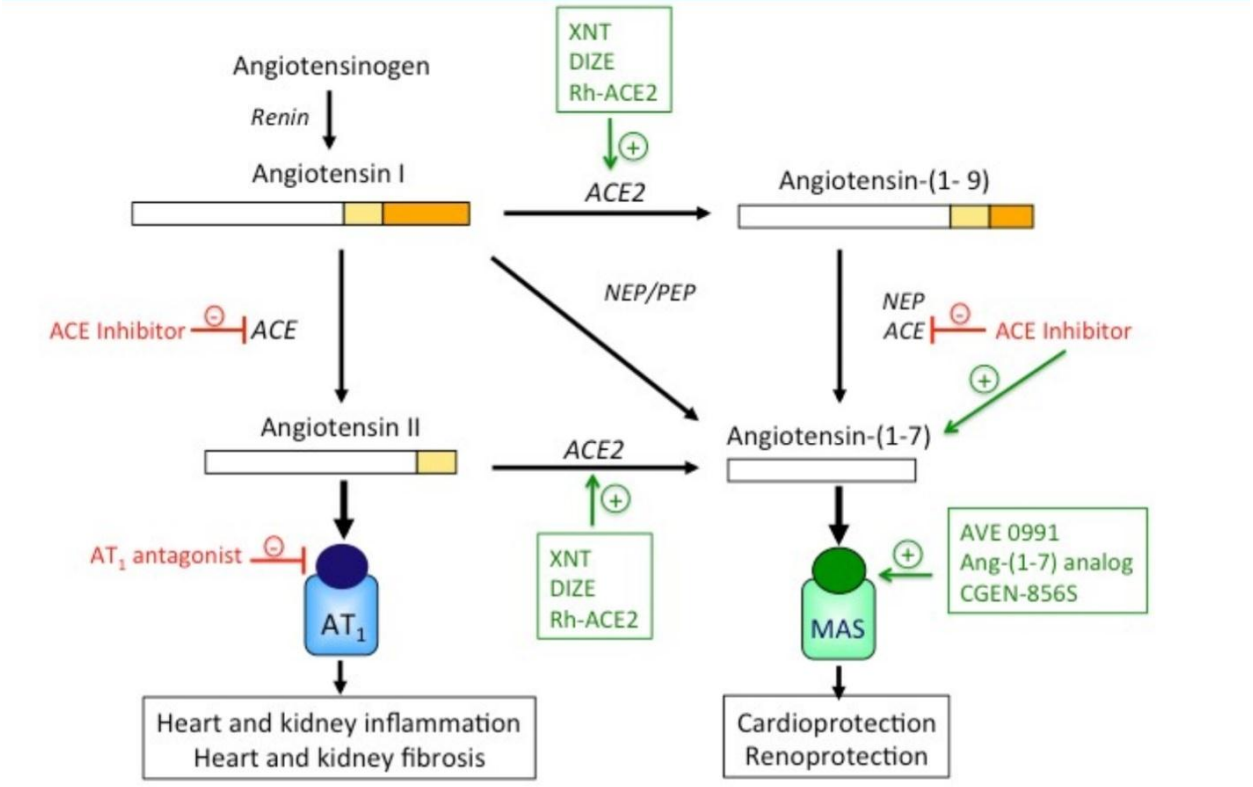
(ARBs) are important therapeutic agents for the treatment of CVD in elderly patients. Chronic use of ACE inhibitors and ARBs upregulates ACE2 expression. ACE2 receptors serve as binding sites for SARS-CoV-2 virions in the lungs. Patients who take ACEIs and ARBS may be at increased risk of severe disease outcomes due to SARS-CoV-2 infections. This has led to concerns of a theoretical risk with the use of ACE-I or ARBs. At present, no clinical data are indicating an increased risk of severe disease among individuals receiving either agent.

The Renin Angiotensin System

For years, the Renin-Angiotensin System (RAS) is a pivotal physiological regulator of heart and kidney homeostasis, but also, it plays an important role in the pathophysiology of heart and kidney diseases. According to the traditional view, angiotensinogen produced by the liver is converted into Angiotensin (Ang) I through the action of renin, an enzyme synthesized by cells of the juxtaglomerular apparatus of the kidney.[6] Subsequently, Ang, I is cleaved by Angiotensin-Converting Enzyme (ACE) generating Ang II, which exerts its effects by binding to two G-protein coupled receptors named angiotensin receptor type 1 (AT1) and type 2 (AT2).[7]

Recently, new components of the RAS have been discovered, including angiotensin-converting enzyme 2 (ACE2), Angiotensin (Ang)-(1-7), Mas receptor, Ang-(1-9) and Alamandine which counteract the effects of Ang II. In experimental models of the heart and renal diseases, Ang-(1-7), Ang-(1-9) and Alamandine produced vasodilation, inhibition of cell growth, anti-thrombotic, anti-inflammatory and anti-fibrotic effects.[8]

Graphical abstract



Legend: ACE – angiotensin-converting enzyme; ACE2- angiotensin-converting enzyme 2; AT1 – angiotensin receptor type 1; AVE0991- nonpeptide agonist of Mas receptor; CGEN-8565 - peptide agonist of Mas receptor; DIZE - diminazene aceturate; MAS – Mas receptor, G-coupled protein receptor of Angiotensin-(1-7); NEP – neutral endopeptidase; PEP – prolyl endopeptidase; Rh-ACE2 – human recombinant angiotensin-converting enzyme 2; XNT - xanthenone

Evidence to up-regulation of ACE2:

Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are highly recommended medications for patients with cardiovascular diseases, such as refractory hypertension, heart failure, coronary artery disease, and post-myocardial infarction status[9, 10], and in patients with diabetes and renal insufficiency.[11] ACE inhibitors increase levels of Ang I, which can then be converted to Ang-(1-9) by ACE2 or to Ang-(1-7) by other endopeptidases, while ARAs increase the availability of Ang II to be converted into Ang-(1-7).[12] Patients taking ACEIs or ARBs chronically for cardiovascular diseases are assumed to have an increased number of ACE2 receptors throughout their cardiopulmonary circulations as observed in experimental animal models.[13] But this mechanism of the increased number of ACE2 receptor is still controversial. Also, it was shown that both the treatments increased the ACE2 activity in the heart and kidneys of normotensive and hypertensive rats and rats with myocardial infarction.[14,15] Earlier demonstrations showed that ACE2 is insensitive to ACE inhibitors which prompted us to evaluate the effect of ACE inhibitors on ACE2 expression. Expression of ACE2 mRNA, protein, and Mas mRNA was markedly upregulated in both CCl4-injured rat liver and AngII-treated HSC. ACE inhibitors can upregulate ACE2 in case of liver injury both in vivo and in vitro.[16] Ferrario CM et al found that intravenous infusions of ACEIs and ARBs in experimental animals increased the number of angiotensins converting enzyme 2 (ACE2) receptors in the cardiopulmonary circulation.[15]

Fernandes L et al. pioneering work in experimental models of hypertension proved that the administration of the Mas receptor antagonist, A-779, attenuated the effects of ACE inhibitors and ARBs.[17,18] In Lewis rats model, the administration of Losartan enhanced plasma and urinary concentrations of Ang-(1-7) and renal activity of ACE2, without altering the expression of ACE and of Mas and AT1 receptors.[19] Igase et al. in a model of hypertensive nephropathy showed that olmesartan treatment increases plasma levels of Ang-(1-7) leading to cardio and renoprotective effects.[20] Zong WN et al. did not alter Mas receptor expression in an animal model but elevated the plasma levels of Ang-(1-7) and decreased the expression of AT1 receptors in heart tissue.[21] In experimental autoimmune myocarditis, the treatment with telmisartan increased myocardial protein levels of ACE2 and Mas receptor.[22,23] Kocks et al. reported that healthy individuals receiving ACE inhibitors

combined with low sodium diet exhibit an elevation in plasma levels of Ang-(1-7) without changing Ang II concentration.[24]

Interactions between classical RAS inhibitors and COVID-19:

Severe acute respiratory syndrome (SARS) is an emerging infectious disease caused by a novel coronavirus (SARS-CoV). SARS-CoV spike (S) protein, a type I membrane-bound protein, is essential for the viral attachment to the host cell receptor angiotensin-converting enzyme 2 (ACE2). The phylogenetically related beta coronavirus, SARS-Cov-2, causes the novel coronavirus disease (nCoV-2019) or COVID-19. S proteins anchor both beta coronaviruses to ACE2 receptors in the lower respiratory tract of infected patients to gain entry into the lungs. Viral pneumonia and potentially fatal respiratory failure may result in susceptible persons after 10-14 days.[25]

The aforementioned studies have strongly supported that the use of AEIs and ARBs increase the expression of ACE2 in alveolar epithelial type II cells (AECII). Elderly patients with comorbidities treated with AEIs and ARBs are at greater risk of contracting symptomatic and even fatal COVID-19 infections. This warning is supported by a recent descriptive analysis of 1,099 patients with laboratory-confirmed COVID-19 infections treated in China during the reporting period, December 11, 2019, to January 29, 2020, Guan et al. reported more severe disease outcomes in patients with hypertension, coronary artery disease, diabetes, and chronic renal disease. The results of this study proved that patients with COVID-19 infections, treated with ACEIs or ARBs, suffered severe disease outcomes.[26]

SUMMARY

In the face of the worldwide coronavirus (COVID-19) pandemic, The European Society of Cardiology (ESC), the American College of Cardiology (ACC), American Heart Association (AHA), and Heart Failure Society of America (HFSA) are advising patients who are undergoing treatment with ACE inhibitors (ACE-i) and angiotensin receptor blockers (ARBs), that they should not be discontinuing the treatment unless it is recommended by their physician. But there is no evidence to support the use or discontinuation of these agents either for the treatment or for the prevention of COVID-19. Patients treated with ACEIs and ARBs should avoid crowds, mass events, ocean cruises, prolonged air travel, and all other people with respiratory illnesses especially during the COVID-19 outbreak to reduce the risk of infection.

For elderly patients with comorbidities, treatment of hypertension and other cardiovascular disorders with ACEIs or ARBs appears to be a risk factor that could result in severe outcomes like mechanical ventilation, ICU admission, and death, in patients with COVID-19 infections. This conclusion is supported by a recent study in China of over 1,000 patients with COVID-19 infections stated that severe outcomes resulted in patients with hypertension, coronary artery disease, diabetes, and chronic renal disease.

CONCLUSION

The results of the recent study suggest that ACE inhibitors and ARBs can upregulate ACE2 expression in the lungs which is helpful in the treatment of lung diseases and also produce vasodilation, inhibition of cell growth, anti-thrombotic, anti-inflammatory and anti-fibrotic effects. Hence the sudden withdrawal of ACEIs or ARBs in patients contract COVID-19 may lead to mild to severe cardiovascular outcomes. Other than the recent study in China, none of the clinical data or recent guidelines have suggested the withdrawal of ACEIs or ARBs in patients with COVID-19 infection. As far as possible, based on the patient's age and other comorbidities, clinicians may switch over to another type of antihypertensive drugs, in which the existing guidelines for discontinuation should be followed. Future case-control studies in patients with COVID-19 infections are recommended to foresee the risk factor associated with ACEIs or ARBs and then the treatment can be undertaken accordingly.

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