sciendo

ACEI/ARB drug therapy in COVID-19 patients: Yes or no?

Jin Gong[1,3], Yingxian Sun[2], Liangdi Xie[1,3]

[1]Department of Geriatrics, the First Affiliated Hospital, Fujian Medical University, Fuzhou, Fujian Province, China;
[2]Department of Cardiology, the First Affiliated Hospital of Chinese Medical University, Shenyang, Liaoning Province, China;
[3]Fujian Hypertension Research Institute, the First Affiliated Hospital, Fujian Medical University, Fuzhou, Fujian Province, China

Address for Correspondence:
Dr. Liangdi Xie, Department of Geriatrics, the First Affiliated Hospital, Fujian Medical University, Fuzhou, Fujian Province, China.
E-mail: ldxield@163.com

Access this article online

Website: www.intern-med.com

DOI: 10.2478/jtim-2021-0011

Quick Response Code:

The recent outbreak of corona virus disease 2019(COVID-19), caused by a new virus, has spread to most countries around the world, which is now a global pandemic and public threat.[1, 2] Although COVID-19 has been controlled in China, the number of new infections is still rapidly increasing in many countries and leads to a high mortality. Some studies have found that old age, as well as the comorbidities, including hypertension, diabetes mellitus, and other cardiovascular diseases, lead to a high mortality rates after infection.[3, 4] COVID-19 belongs to the same family as viruses that cause severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS).[5, 6] Generally, although the onset of patients who infected with COVID-19 is not as dangerous as those infected with SARS, and the symptoms are even mild, the disease will accelerate suddenly in the later stage after infection, even leading to multiple organ failure, which may be related to the initiation of inflammatory storm induced by imbalance of the immune response.[7]

COVID-19 AND RAAS

COVID-19 is a single-stranded RNA virus belongs to the β-group of coronavirus, which is transmitted by intermediate host or infected person through droplets.[2] Previous studies revealed that COVID-19 virus penetrated into host cell, especially type 2 alveoli epithelial cells mainly through angiotensin converting enzyme 2(ACE2) as the SARS virus.[8, 9] After contacting with S-protein (spike protein) of COVID-19 virus, the complete molecular structure or transmembrane region of ACE2 enters the cells together with virus through endocytosis. After penetrating into cells, the S-protein gets activated by trypsin or furin, and after the membrane fusion, viral RNA is released into the cytoplasm, and then, the virus infects the cells. Although the physiological function of ACE2 has not yet been fully elucidated, several studies have demonstrated that ACE2 is related to the virus penetrated into cells and its replication.[5] Previous studies showed that, the expression level of ACE2 in cells is positively related with the susceptibility of S-protein of COVID-19. The expression level of ACE2 in cells was reduced significantly after COVID-19 infection, which leads to the increased level of angiotensin II (Ang II) and the activation of renin-angiotensin-aldosterone system (RAAS), thereby overactivating the Ang II type 1 receptor (AT1R) of lung cells to induce and aggravate lung injury.[10, 11] In addition, decrease in myocardial contractility and impairing of kidney after COVID-19 infection maybe related with ACE2.[11, 12]

Previous studies have revealed that the plasma Ang II levels of COVID-19 infections were significantly higher than those of healthy persons, and the levels of Ang II were positively correlated with virus titers and the severity of lungs injury, which showed that the infection of COVID-19 maybe induce the imbalance of RAAS of infections.[13] In addition, some studies also demonstrated that the lungs injury after infection is caused by severe inflammatory response, also known as cytokine storm, occurred at 2–4 weeks after COVID-19

infection, which induce the worsening of lung function, even to respiratory distress syndrome and respiratory – circulatory failure.[7, 14] Nevertheless, the activation and maintaining of inflammatory storm is activated by the activation and overexcitation of RAAS.[15]

RAAS AND LUNG INJURY

RAAS is an important endocrine system that regulates the physiological functions of the lungs and cardiovascular system and is involved in the initiation as well as progression of several diseases such as SARS, acute lung injury, hypertension, chronic kidney disease, heart failure, *etc*.[11, 16-18] ACE2 and angiotensin-converting enzyme (ACE) are two important parts of RAAS and maintain the balance of function as well as structures of blood vessels. On the one hand, ACE catalyzes angiotensin I (Ang I) into Ang II, which is related to vasoconstriction, aldosterone secretion, and the vascular remodeling under pathological conditions. The main receptor of Ang II is AT1R. On another hand, ACE2 could cleave Ang I into angiotensin 1-9 (Ang 1-9), which could transform into angiotensin 1-7 (Ang 1-7) through ACE2-dependent or ACE2-independent pathways. Ang 1-7 plays an important role in the vasodilation, anti-inflammatory, anti-fibrosis and inhibits the proliferation of vessel smooth muscle cells by activation of Mas receptors.[11, 19, 20]

Some previous studies have revealed the vital role of RAAS in acute lung injury in SARS or other influenza virus infections and showed that ACE2 associated a reduction of the pulmonary fibrosis and lungs injury caused by the overactivation of RAAS to a certain extent, which maybe related with the anti-inflammatory storm effects induced by ACE2.[10, 21] Basu *et al.* [22] also reported that the plasma ACE2 levels and Ang 1-7 in patients who suffered from hypertension combined with acute or chronic heart failure were significantly decreased and the levels of Ang II increased, while the treatment with recombinant human ACE2 could significantly induce a decline in the levels of Ang II as well as the increase in Ang 1-7 levels, which confirmed the vital role of ACE2 in the regulation of Ang 1-7/Ang II metabolic balance in the therapy of hypertension and heart and lung damage.

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS / ANGIOTENSIN RECEPTOR BLOCKERS (ACEI/ARBS) AND COVID-19

According to the differences in clinical manifestations, imaging presentation, as well as some other complication conditions, the disease status could be grouped into four types, including mild type, with slight clinical symptoms, but no imaging presentation of pneumonia; common type, with fever, respiratory tract and other symptoms, imaging findings of pneumonia; severe type, with any of the following conditions: respiratory distress and respiratory frequency ≥30 times/min, finger oxygen saturation at rest ≤93%, oxygenation index (PaO2/FiO2) ≤300 mm Hg (1 mm Hg = 0.133 kPa), or the clinical symptoms were progressively aggravated and the lungs lesion in imaging developed >50% within 24–48 hours; critical type, with any of the following conditions: respiratory failure requires mechanical ventilation, shock, combined with organ failures need to be treated in intensive care unit.[23] Most patients have mild or moderate symptoms after COVID-19 infection, which have the similar clinical manifestations to interstitial pneumonia.[23] Some researchers hypothesized that for the differences in severity of COVID-19, the impact of ACEI/ARBs use on patients were differ. A referral center cohort study in Northeast of France enrolled 149 patients with severe COVID-19 showed that there was a deleterious effect of long-term therapy with ACEI/ARBs among patients with severe COVID-19 with regard to their risk of developing acute kidney injury and acute respiratory failure.[24] However, Yang *et al.*[25] found that the ACEI/ARBs treatment could result in a marginally lower death rate and less critical cases in patients with COVID-19 and hypertension, which supported the use of ACEI/ARBs in COVID-19 patients with hypertension. In addition, Di *et al.*[26] found that there was no association between the use of ACEI/ARBs and COVID-19 severity or in-hospital mortality in COVID-19 patients. Zhang *et al.*[27] revealed the same results with Di, showed that ACEI/ARBs therapy was not associated with a higher risk of having severe infection, but associated with a lower risk of mortality in hypertensive.

Zhang *et al.*[4] have analyzed the epidemiological characteristics of COVID-19 in China and demonstrated that the infections in those who were with hypertension, diabetes mellitus, or other cardiovascular diseases and aged over 80 years old were more likely to be at highest risk of death. And, the infections in those aged over 80 years old have the highest mortality rate among all subgroups, followed by those who with cardiovascular diseases. For ACEI/ARBs are the first-line medications for blood pressure control recommended by guidelines over the world, continuous use of ACEI/ARBs in hypertensives with COVID-19 was still controversial. Several studies showed that the use of ACEI/ARBs was associated with a better prognosis, especially in hypertensives, while other studies revealed that there is no significantly correlation between ACEI/ARBs therapy and mortality of patients with COVID-19.[28-32] Meng *et al.* [33] demonstrated that ACEI/ARBs therapy could attenuate the inflammatory

response and improve the clinical outcomes of COVID-19 patients with hypertension. Zhang *et al.*[27] also showed continue used ACEI/ARBs in hypertensives with COVID-19 could reduce the mortality compared with those without ACEI/ARBs therapy. Furthermore, a meta-analysis demonstrated a lower mortality in hypertensives with COVID-19 with ACEI/ARBs therapy.[34] In addition, a meta-analysis enrolled 21,440 patients with pneumonia have revealed that compared with patients who were treated with placebo, the mortality reduced by 27% in those treated with ACEI, especially in Asian and post-stroke patients.[35] However, several studies in both China and some western countries found no association between the use of ACEI/ARBs and mortality of COVID-19 patients with hypertension.[30, 32, 36, 37] Studies showed that the use of ACEI/ARBs could not only alleviate the target organs damage of the underlying diseases like hypertension, diabetes mellitus, but also attenuate lungs injury by inhibiting the production or activation of Ang II.[38, 39] In addition, some studies have demonstrated that ACEI/ARBs could upregulate the expression of ACE2 mRNA and protein in some tissues in several animal models.[38] [39] And, the use of ACEI could attenuate lungs injury by upregulating the ACE2 levels in lungs injury models.[10, 40]

Furthermore, studies have revealed that ACE2 is equivalent to natural ACEI/ARBs. The reduction of ACE2 levels would lead to lungs injury and initiate inflammatory storm by making the balance of RAAS to ACE/Ang II/AT1R axis, while the increase of ACE2 levels would play a protective effects on cardiopulmonary by making the balance to Ang 1-7/Mas axis.[16, 41] Thus, whether it is the activation of ACE2 or the upregulation of ACE2 caused by the intake of ACEI/ARBs drugs, it may perform an anti-inflammatory protection effect against lung injury caused by COVID-19.

BRACE-CORONA study, the latest clinical trials published in ESC 2020 on September 01, 2020, has showed that the proportion of survived and discharged from hospital was 91.8% and 95%, respectively, in COVID-19 patients who discontinued the use of ACEI/ARBs drugs and those continued the use of ACEI/ARBs treatment, and the mean survival days as well as days of discharge are 25 days in both groups, which revealed that the use of ACEI/ARBs drugs has no effect on the survival rate of COVID-19 infections.[42, 43]

COVID-19 is now a major challenge to the global public health. Although the vaccines against COVID-19 undergoing clinical trials have been proved effective, the epidemiological characteristics, pathogenicity of virus, and the pathophysiological changes after infection were still unclear. And, further study to investigate specific clinical treatments is urgently needed. Whether the use of ACEI/ARBs in COVID-19 infection would aggravate the risk of death remains controversial. All in all, in patients with hypertension or other cardiovascular diseases who could effectively control blood pressure or reduce the incidence of complication by taking ACEI/ARBs drugs should continue the ACEI/ARBs treatment. Sudden discontinuation or dressing change will inevitably increase other risks. Strengthen family self-monitoring of blood pressure, and continuing the ACEI/ARBs treatment under the guidance of physicians is the best choice under COVID-19 threat.

Conflict of Interest

The authors declared no conflicts of interest.

REFERENCE

1. Wu F, Zhao S, Yu B, Chen YM, Wang W, Song ZG, *et al.* A new coronavirus associated with human respiratory disease in China. Nature 2020; 579: 265-9.
2. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, *et al.* A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 2020; 579: 270-3.
3. Seclén SN, Nuñez-Robles E, Yovera-Aldana M, Arias Chumpitaz A. Incidence of COVID-19 infection and prevalence of diabetes, obesity and hypertension according to altitude in peruvian population. Diabetes Res Clin Pract 2020: 108463.
4. Epidemiology Working Group for NCIP Epidemic Response Chinese Center for Disease Control and Prevention. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases(COVID-19) in China. Chin J Epidemiol 2020; 2: 145-51.
5. Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor recognition by the novel coronavirus from Wuhan: An analysis based on decade-long structural studies of sars coronavirus. J Virol 2020, 94: e00127-20.
6. Liu J, Zheng X, Tong Q, Li W, Wang B, Sutter K, *et al.* Overlapping and discrete aspects of the pathology and pathogenesis of the emerging human pathogenic coronaviruses SARS-CoV, MERS-CoV, and 2019-nCoV. J Med Virol 2020; 92: 491-4.
7. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: Consider cytokine storm syndromes and immunosuppression. Lancet, 2020, 395: 1033-4.
8. Zhao Y, Zhao Z, Wang Y, Zhou Y, Ma Y, Zuo W. Single-cell rna expression profiling of ACE2, the receptor of SARS-COV-2. Am J Respir Crit Care Med 2020, 202: 756-9.
9. Aguiar JA, Tremblay BJ, Mansfield MJ, Woody O, Lobb B, Banerjee A, *et al.* Gene expression and in situ protein profiling of candidate SARS-COV-2 receptors in human airway epithelial cells and lung tissue. Eur Respir J 2020, 56: 2001123.
10. Imai Y, Kuba K, Rao S, Huan Y, Guo F, Guan B, *et al.* Angiotensin-converting enzyme 2 protects from severe acute lung failure. Nature 2005, 436: 112-6.
11. Kuba K, Imai Y, Ohto-Nakanishi T, Penninger JM. Trilogy of ACE2: a peptidase in the renin-angiotensin system, a SARS receptor, and a partner for amino acid transporters. Pharmacol Ther 2010; 128: 119-28.
12. Patel VB, Zhong JC, Grant MB, Oudit GY. Role of the ACE2/Angiotensin 1-7 Axis of the Renin-Angiotensin System in Heart Failure. Circ Res 2016; 118: 1313-26.
13. Liu Y, Yang Y, Zhang C, Huang F, Wang F, Yuan J, *et al.* Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral

loads and lung injury. Sci China Life Sci 2020; 63: 364-74.
14. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, *et al*. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395: 497-506.
15. Boskabadi J, Askari VR, Hosseini M, Boskabady MH. Immunomodulatory properties of captopril, an ace inhibitor, on lps-induced lung inflammation and fibrosis as well as oxidative stress. Inflammopharmacology, 2019, 27: 639-47.
16. Tan WSD, Liao W, Zhou S, Mei D, Wong WF. Targeting the renin-angiotensin system as novel therapeutic strategy for pulmonary diseases. Curr Opin Pharmacol 2018, 40: 9-17.
17. Arendse LB, Danser AHJ, Poglitsch M, Touyz RM, Burnett JC, Jr., Llorens-Cortes C, *et al*. Novel therapeutic approaches targeting the renin-angiotensin system and associated peptides in hypertension and heart failure. Pharmacol Rev 2019, 71: 539-70.
18. Wang T, Lian G, Cai X, Lin Z, Xie L. Effect of prehypertensive losartan therapy on at1r and atrap methylation of adipose tissue in the later life of highfatfed spontaneously hypertensive rats. Mol Med Rep 2018; 17: 1753-61.
19. Te Riet L, van Esch J, Roks A, van den Meiracker A, Danser A. Hypertension: Renin-angiotensin-aldosterone system alterations. Circ Res 2015; 116: 960-75.
20. Zhou Z, Qiu YM, Liu YY, Tao J. Advances of COVID-19 and ACEI/ARB drug therapy. Chin J Hypertension 2020; 28: 204-9.
21. Kuba K, Imai Y, Rao S, Gao H, Guo F, Guan B, *et al*. A crucial role of angiotensin converting enzyme 2 (ACE2) in sars coronavirus-induced lung injury. Nat Med 2005; 11: 875-9.
22. Basu R, Poglitsch M, Yogasundaram H, Thomas J, Rowe BH, Oudit GY. Roles of angiotensin peptides and recombinant human ACE2 in heart failure. J Am Coll Cardiol 2017; 69: 805-19.
23. National Health Commission of China. Guideline on diagnosis and treatment of coronavirus disease 2019 in China (Interim 8th Edition). Infect Dis Inf 2020; 4: 289-96.
24. Oussalah A, Gleye S, Clerc Urmes I, Laugel E, Callet J, Barbe F, *et al*. Long-Term ACE Inhibitor/ARB Use Is Associated with Severe Renal Dysfunction and Acute Kidney Injury in Patients with severe COVID-19: Results from a Referral Center Cohort in the North East of France. Clin Infect Dis, 2020: ciaa677.
25. Yang G, Tan Z, Zhou L, Yang M, Peng L, Liu J, *et al*. Effects of angiotensin ii receptor blockers and ace (angiotensin-converting enzyme) inhibitors on virus infection, inflammatory status, and clinical outcomes in patients with covid-19 and hypertension: A single-center retrospective study. Hypertension 2020; 76: 51-8.
26. Di Castelnuovo A, Costanzo S, Antinori A, Berselli N, Blandi L, Bonaccio M, *et al*. Raas inhibitors are not associated with mortality in covid-19 patients: Findings from an observational multicenter study in italy and a meta-analysis of 19 studies. Vascul Pharmacol 2020; 106805.
27. Zhang X, Yu J, Pan LY, Jiang HY. ACEI/ARB use and risk of infection or severity or mortality of covid-19: A systematic review and meta-analysis. Pharmacol Res 2020, 158: 104927
28. Mehra MR, Desai SS, Kuy S, Henry TD, Patel AN. Cardiovascular disease, drug therapy, and mortality in COVID-19. N Engl J Med 2020; 382: e102.
29. Zhang P, Zhu L, Cai J, Lei F, Qin JJ, Xie J, *et al*. Association of Inpatient Use of Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers With Mortality Among Patients With Hypertension Hospitalized With COVID-19. Circ Res 2020; 126: 1671-81.
30. Li J, Wang X, Chen J, Zhang H, Deng A. Association of Renin-Angiotensin System Inhibitors With Severity or Risk of Death in Patients With Hypertension Hospitalized for Coronavirus Disease 2019 (COVID-19) Infection in Wuhan, China. JAMA Cardiol 2020; 5: 825-30.
31. Yang Q, Zhou Y, Wang X, Gao S, Xiao Y, Zhang W, *et al*. Effect of hypertension on outcomes of adult inpatients with COVID-19 in wuhan, china: A propensity score-matching analysis. Respir Res 2020; 21: 172.
32. Mancia G, Rea F, Ludergnani M, Apolone G, Corrao G. Renin-angiotensin-aldosterone system blockers and the risk of COVID-19. N Engl J Med 2020; 382: 2431-40.
33. Meng J, Xiao G, Zhang J, He X, Ou M, Bi J, *et al*. Renin-angiotensin system inhibitors improve the clinical outcomes of COVID-19 patients with hypertension. Emerg Microbes Infect 2020; 9: 757-60.
34. Liu X, Long C, Xiong Q, Chen C, Ma J, Su Y, *et al*. Association of angiotensin converting enzyme inhibitors and angiotensin II receptor blockers with risk of COVID-19, inflammation level, severity, and death in patients with COVID-19: A rapid systematic review and meta-analysis. Clin Cardiol 2020; 10.1002/clc.23421.
35. Caldeira D, Alarcão J, Vaz-Carneiro A, Costa J. Risk of pneumonia associated with use of angiotensin converting enzyme inhibitors and angiotensin receptor blockers: Systematic review and meta-analysis. BMJ 2012; 345: e4260.
36. Wang Z, Zhang D, Wang S, Jin Y, Huan J, Wu Y, *et al*. A Retrospective Study from 2 Centers in China on the Effects of Continued Use of Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers in Patients with Hypertension and COVID-19. Med Sci Monit 2020, 26: e926651.
37. Hu J, Zhang X, Zhang X, Zhao H, Lian J, Hao S, *et al*. COVID-19 is more severe in patients with hypertension; ACEI/ARB treatment does not influence clinical severity and outcome. J Infect 2020: S0163-4453(20)30334-0.
38. Li Y, Zeng Z, Li Y, Huang W, Zhou M, Zhang X, *et al*. Angiotensin-converting enzyme inhibition attenuates lipopolysaccharide-induced lung injury by regulating the balance between angiotensin-converting enzyme and angiotensin-converting enzyme 2 and inhibiting mitogen-activated protein kinase activation. Shock 2015; 43: 395-404.
39. Awwad ZM, El-Ganainy SO, ElMallah AI, Khattab MM, El-Khatib AS. Telmisartan and captopril ameliorate pregabalin-induced heart failure in rats. Toxicology 2019; 428: 152310
40. Wösten-van Asperen RM, Lutter R, Specht PA, Moll GN, van Woensel JB, van der Loos CM, *et al*. Acute respiratory distress syndrome leads to reduced ratio of ACE/ACE2 activities and is prevented by angiotensin-(1-7) or an angiotensin ii receptor antagonist. J Pathol 2011; 225: 618-27.
41. Wang W, McKinnie SM, Farhan M, Paul M, McDonald T, McLean B, *et al*. Angiotensin-converting enzyme 2 metabolizes and partially inactivates pyr-apelin-13 and apelin-17: Physiological effects in the cardiovascular system. Hypertension 2016; 68: 365-77.
42. Lopes RD, Macedo AVS, de Barros ESPGM, Moll-Bernardes RJ, Feldman A, D'Andréa Saba Arruda G, *et al*. Continuing versus suspending angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: Impact on adverse outcomes in hospitalized patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)--The BRACE CORONA Trial. Am Heart J 2020; 226: 49-59.
43. Lopes RD, Macedo AVS, de Barros ESPGM, Moll-Bernardes RJ, Feldman A, D'Andréa Saba Arruda G, *et al*. First randmized trial reassures on ACEIs, ARBs in COVID-19. ESC 2020.

How to cite this article: Gong J, Sun Y, Xie L. ACEI/ARB drug therapy in COVID-19 patients: Yes or no?. J Transl Intern Med 2021; 9: 8-11.