AUTHOR REPLY
Therapeutics and Prevention

Reply to Siniorakis et al., "COVID-19 Interference with Renin-Angiotensin System in the Context of Heart Failure"

David S. Fedson,[a] Steven M. Opal,[b] Ole Martin Rordam[c]

[a]57, chemin du Lavoir, Sergy Haut, France
[b]Department of Medicine, Alpert Medical School of Brown University, Providence, Rhode Island, USA
[c]Fyordgata 59, Trondheim, Norway

KEYWORDS angiotensin receptor blockers, COVID-19, statins, angiotensin converting enzyme inhibitors, neprilysin inhibitors

We thank Eftychios Siniorakis and colleagues for their thoughtful letter on how repurposing statins and angiotensin receptor blockers (ARBs) for coronavirus disease 2019 (COVID-19) treatment might affect patients with heart failure (1). Our understanding of the pathophysiology of COVID-19 disease has advanced rapidly in the past few months. The immunological dysregulation associated with the disease and the cardiovascular effects of infection (and especially the role of angiotensin converting enzyme 2 [ACE2]) have been comprehensively reviewed (2–7). Some patients who develop acute respiratory distress syndrome (ARDS) can be severely hypoxic and yet show relatively normal pulmonary compliance (8). Endothelial dysfunction and intense inflammation seem to be important contributors to their distress (9). In addition, pulmonary microvascular coagulopathy, sometimes associated with pulmonary or systemic embolization, has added a new dimension to clinical care (10–12). Many physicians have added anticoagulation to their treatments (13). Recently, van de Veerdonk and colleagues called attention to the contribution of the kallikrein-kinin system to COVID-19-induced ARDS (14, 15). Although much attention has been focused on the relationship between the renin-angiotensin system (RAS) and COVID-19 (5–7), there is considerable cross talk between the RAS and kallikrein-kinin systems (14–16). Experimentally, a reduction in ACE2 activity can impair inactivation of the B1 bradykinin receptor and this can be associated with an increase in inflammation-induced acute lung injury (17).

This is the backdrop for the concern raised by Siniorakis et al.: some COVID-19 patients might have heart failure and be receiving combination treatment with an angiotensin receptor blocker (ARB)/angiotensin receptor neprilysin inhibitor (ARNI). Neprilysin is known to degrade bradykinin, and ARB treatment can increase bradykinin levels (18). Thus, if bradykinin is involved in the genesis of the intense inflammation and microvascular coagulopathy seen in many COVID-19 patients (11, 14, 15), the increase in bradykinin levels that accompanies ARB and neprilyin inhibitor treatment might be harmful. (Angiotensin converting enzyme inhibitors [ACEIs] also upregulate bradykinin, and they are more commonly associated with acute episodes of angioedema than are ARBs.) To our knowledge, there have been no reports of COVID-19 patients who were treated with both ARNIs and ARBs or ACEIs.

We believe that physicians should consider combination statin/ARB treatment of severely ill COVID-19 patients (19). Both drugs have beneficial effects on inflammation, coagulation abnormalities, and endothelial dysfunction. Recently published observational studies suggested that ACEIs, ARBs, and statins are associated with improved outcomes in COVID-19 patients (20, 21), although not all studies have shown this (22). Whether ARNI treatment of COVID-19 patients would be harmful remains to be

Citation Fedson DS, Opal SM, Rordam OM. 2020. Reply to Siniorakis et al., "COVID-19 interference with renin-angiotensin system in the context of heart failure." mBio 11:e01243-20. https://doi.org/10.1128/mBio.01243-20.

Address correspondence to David S. Fedson, davidsfedson@gmail.com.

This is a response to a letter by Siniorakis et al. (https://doi.org/10.1128/mBio.00946-20).

Published 29 May 2020

determined, although it has been shown to improve endothelial dysfunction in hypertensive rats (23). The great advantage of ACEIs, ARBs, and statins is that they are widely available as inexpensive generics in resource-poor countries where lockdowns and social distancing would be difficult to implement. The same cannot be said for virtually all of the other COVID-19 treatments now being tested in clinical trials.

REFERENCES

1. Siniorakis E, Arvanitakis S, Nikolopoulos I, Elkouris M. 2020. COVID-19 interference with renin-angiotensin system in the context of heart failure. mBio 11:e00946-20. https://doi.org/10.1128/mBio.00946-20.
2. Giamarellos-Bourboulis EJ, Netea MG, Rovina N, Akinosoglou K, Antoniadou A, Antonakos N, Damoraki G, Gkavogianni T, Adami ME, Katsaounou P, Ntaganou M, Kyriakopoulou M, Dimopoulos G, Koutsodimitropoulos I, Velissaris D, Koufargyris P, Karageorgos A, Katrini K, Lekakis V, Lupse M, Kotsaki A, Renieris G, Theodoulou D, Panou V, Koukaki E, Koulouris N, Gogos C, Koutsoukou A. 17 April 2020, posting date. Complex immune dysregulation in COVID-19 patients with severe respiratory failure. Cell Host Microbe https://doi.org/10.1016/j.chom.2020.04.009.
3. Chen G, Wu D, Guo W, Cao Y, Huang D, Wang H, Wang T, Zhang X, Chen H, Yu H, Zhang X, Zhang M, Wu S, Song J, Chen T, Han M, Li S, Luo X, Zhao J, Ning Q. 2020. Clinical and immunological features of severe and moderate coronavirus disease 2019. J Clin Invest 130:2620–2629. https://doi.org/10.1172/JCI137244.
4. Vabret N, Britton GJ, Gruber C, Hegde S, Kim J, Kuksin M, Levantovsky R, Malle L, Moreira A, Park MD, Pia L, Risson E, Saffern M, Salomé B, Selvan ME, Spindler MP, Tan J, van der Heide V, Gregory JK, Alexandropoulos K, Bhardwaj N, Brown BD, Greenbaum B, Gümüş ZH, Homann D, Horowitz A, Kamphorst AO, Curotto de Lafaille MA, Mehandru S, Merad M, Samstein RM, The Sinai Immunology Review Project. 6 May 2020, posting date. Immunology of COVID-19: current state of the science. Immunity https://doi.org/10.1016/j.immuni.2020.05.002.
5. South AM, Diz DI, Chappell MC. 2020. COVID-19, ACE2, and the cardiovascular consequences. Am J Physiol Heart Circ Physiol 318:H1084–H1090. https://doi.org/10.1152/ajpheart.00217.2020.
6. Gheblawi M, Wang K, Viveiros A, Nguyen Q, Zhong JC, Turner AJ, Raizada MK, Grant MB, Oudit GY. 2020. Angiotensin converting enzyme 2: SARS-CoV-2 receptor and regulator of the renin-angiotensin system: celebrating the 20th anniversary of the discovery of ACE2. Circ Res 126:1456–1474. https://doi.org/10.1161/CIRCRESAHA.120.317015.
7. Ingraham NE, Barakat AG, Reilkoff R, Bezdicek T, Schacker T, Chipman JG, Tignanelli CJ, Puskarich MA. 27 April 2020, posting date. Understanding the renin-angiotensin-aldosterone-SARS-CoV-axis: a comprehensive review. Eur Respir J https://doi.org/10.1183/13993003.00912-2020.
8. Gattinoni L, Coppola S, Cressoni M, Busana M, Rossi S, Chiumello D. 2020. COVID-19 does not lead to a "typical" acute respiratory distress syndrome. Am J Respir Crit Care Med 201:1299–1300. https://doi.org/10.1164/rccm.202003-0817LE.
9. Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, Mehra MR, Schuepbach RA, Ruschitzka F, Moch H. 21 April 2020, posting date. Endothelial cell infection and endotheliitis in COVID-19. Lancet https://doi.org/10.1016/S0140-6736(20)30937-5.
10. McGonagle D, Sharif K, O'Regan A, Bridgewood C. 2020. The role of cytokines including interleukin-6 in COVID-19 induced pneumonia and macrophage activation syndrome-like disease. Autoimmun Rev 19:102537. https://doi.org/10.1016/j.autrev.2020.102537.
11. McGonagle DM, O'Donnell JS, Sharif K, Emery P, Bridgewood C. 7 May 2020, posting date. Immune mechanisms of pulmonary coagulopathy in COVID-19 pneumonia. Lancet Rheumatol https://doi.org/10.1016/S2665-9913(20)30121-1.
12. Klok FA, Kruip M, van der Meer NJM, Arbous MS, Gommers D, Kant KM, Kaptein FHJ, van Paassen J, Stals MAM, Huisman MV, Endeman H. 10 April 2020, posting date. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res https://doi.org/10.1016/j.thromres.2020.04.013.
13. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. 2020. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost 18:1094–1099. https://doi.org/10.1111/jth.14817.
14. van de Veerdonk F, Netea MG, van Deuren M, van der Meer JW, de Mast Q, Brüggemann RJ, van der Hoeven H. 3 April 2020, posting date. Kinins and cytokines in COVID-19: a comprehensive pathophysiological approach. Cell https://doi.org/10.20944/preprints202004.0023.v1.
15. van de Veerdonk FL, Netea MG, van Deuren M, van der Meer JW, de Mast Q, Brüggemann RJ, van der Hoeven H. 2020. Kallikrein-kinin blockade in patients with COVID-19 to prevent acute respiratory distress syndrome. Elife 9:e57555. https://doi.org/10.7554/eLife.57555.
16. Su JB. 2014. Different cross-talk sites between the renin-angiotensin and the kallikrein-kinin systems. J Renin Angiotensin Aldosterone Syst 15:319–328. https://doi.org/10.1177/1470320312474854.
17. Sodhi CP, Wohlford-Lenane C, Yamaguchi Y, Prindle T, Fulton WB, Wang S, McCray PB, Jr, Chappell M, Hackam DJ, Jia H. 2018. Attenuation of pulmonary ACE2 activity impairs inactivation of des-Arg^{9}bradykinin/BKB1R axis and facilitates LPS-induced neutrophil infiltration. Am J Physiol Lung Cell Mol Physiol 314:L17–L31. https://doi.org/10.1152/ajplung.00498.2016.
18. Campbell DJ. 2018. Neprilysin inhibitors and bradykinin. Front Med (Lausanne) 5:257. https://doi.org/10.3389/fmed.2018.00257.
19. Fedson DS, Opal SM, Rordam OM. 2020. Hiding in plain sight: an approach to treating patients with severe COVID-19 infection. mBio 11:e00398-20. https://doi.org/10.1128/mBio.00398-20.
20. Zhang P, Zhu L, Cai J, Lei F, Qin JJ, Xie J, Liu YM, Zhao YC, Huang X, Lin L, Xia M, Chen MM, Cheng X, Zhang X, Guo D, Peng Y, Ji YX, Chen J, She ZG, Wang Y, Xu Q, Tan R, Wang H, Lin J, Luo P, Fu S, Cai H, Ye P, Mao XB, Liu W, Yan L, Liu Y, Chen M, Zhang M, Wang XJ, Touyz X, Xia RM, Zhang J, Huang BH, Yuan X, Rohit Y, Liu PP, Li H. 17 April 2020, posting date. 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 https://doi.org/10.1161/CIRCRESAHA.120.317134.
21. Mehra MR, Desai SS, Kuy S, Henry TD, Patel AN. 1 May 2020, posting date. Cardiovascular disease, drug therapy, and mortality in Covid-19. N Engl J Med https://doi.org/10.1056/NEJMoa2007621.
22. Li J, Wang X, Chen J, Zhang H, Deng A. 23 April 2020, posting date. 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 https://doi.org/10.1001/jamacardio.2020.1624.
23. Seki T, Goto K, Kansui Y, Ohtsubo T, Matsumura K, Kitazono T. 2017. Angiotensin II receptor-neprilysin inhibitor sacubitril/valsartan improves endothelial dysfunction in spontaneously hypertensive rats. J Am Heart Assoc 6:e006617. https://doi.org/10.1161/JAHA.117.006617.