QJM: An International Journal of Medicine, 2020, 1–2

doi: 10.1093/qjmed/hcaa103
Advance Access Publication Date: 27 March 2020
Correspondence

CORRESPONDENCE

Are certain drugs associated with enhanced mortality in COVID-19?

M.R. Goldstein[1]*, G.A. Poland[2] and C.W. Graeber[3]

From the [1]NCH Physician Group, Center for Healthy Living, 132 Moorings Park Drive, Naples, FL 34105, USA, [2]Mayo Vaccine Research Group, Mayo Clinic and Foundation, 611C Guggenheim Building, Rochester, MN 55905, USA and [3]Mayo Clinic College of Medicine and Science, University of Central Florida, College of Medicine, NCH Healthcare System Internal Medicine Residency, Affiliate of the Mayo Clinic School of Medicine and Science, Naples, FL 34102, USA

*Address correspondence to Mark R. Goldstein, NCH Physician Group, Center for Healthy Living, 132 Moorings Park Drive, Naples, FL 34105, USA. email: markrgoldstein@comcast.net

Prevalent comorbidities for the development of severe pneumonia requiring intensive care unit treatment, acute respiratory distress syndrome (ARDS), and death from Coronavirus disease 2019 (COVID-19) include hypertension, diabetes, and cardiovascular disease.[1,2] We posit that drugs commonly used in the treatment of those comorbidities may actually increase the risk of severe pneumonia, ARDS, and mortality in the setting of COVID-19; the drugs of primary concern include angiotensin receptor blockers (ARBs) used for blood pressure lowering and statins used for cholesterol lowering.

Notably, angiotensin-converting enzyme 2 (ACE2) is the functional receptor for cell entry of the severe acute respiratory syndrome–coronavirus 2 (SARS–CoV-2) and is abundantly expressed by alveolar type II epithelial cells.[3] Importantly, ARBs increase the expression of the ACE2 receptor; however, ACE-inhibitors do not change the expression of that receptor.[4] Therefore, it is possible that ARBs facilitate viral entry into alveolar epithelial cells resulting in a greater pathogenic pulmonary response.

Disturbingly, statins might also promote the activation of the inflammasome pathway in ARDS resulting in increased levels of the proinflammatory cytokine, interleukin-18 (IL-18),[5] and, as a result, more severe disease due to an IL-18 induction of an interferon γ-biased cytokine storm.[6] In support of this possibility, a retrospective analysis of a multicenter randomized, placebo-controlled trial testing the statin, rosuvastatin, for the treatment of infection-related ARDS, yielded concerning results.[5] Baseline IL-18 levels were positively associated with subsequent morbidity and mortality. Moreover, subjects randomized to rosuvastatin 20 mg daily for the 28-day trial were more likely to exhibit a rise in IL-18 levels and that rise was significantly associated with increased mortality.[5] Furthermore, subjects treated with systemic corticosteroid therapy were less apt to have a rise in IL-18 levels[5]; this might explain why methylprednisolone treatment decreased mortality in those with COVID-19 pneumonia associated ARDS from Wuhan, China.[2]

In conclusion, both ARBs and statins are the standard of care and commonly used in the chronic treatment of the comorbidities associated with severe COVID-19 pneumonia, ARDS, and death. Through their mechanism of action, by ARBs increasing viral entry and statins increasing IL-18 levels, these drugs might synergistically promote severe pneumonia, ARDS, and death in the setting of COVID-19, particularly in older individuals who are more likely to be taking these drugs. Investigators reporting on COVID-19 clinical trials or retrospective studies should also include what drugs the subjects are taking at baseline and throughout the illness so the medical community can determine if indeed ARB or statin treatments portend a worse outcome with COVID-19. This is vitally important in a spreading pandemic, potentially victimizing an older population. In the meantime, clinicians need to decide on an individual basis if an ACE-inhibitor should be substituted for an ARB for blood pressure control and if statin treatment should be halted during the pandemic, particularly if statins are being used for the primary prevention of cardiovascular disease. Attention to this might save countless lives.

Conflict of interest: None declared.

References

1. Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, *et al*.; for the China Medical Treatment Expert Group for Covid-19. Clinical characteristics of Coronavirus Disease 2019 in China. *N Engl J Med* 2020; doi:10.1056/NEJMoa2002032.
2. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, *et al*. Risk factors associated with acute respiratory distress syndrome and death in patients with Coronavirus Disease 2019 Pneumonia in Wuhan, China. *JAMA Intern Med* 2020; doi: 10.1001/jamainternmed.2020.0994.
3. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrier T, Erichsen S, *et al*. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell* 2020; **181**:1–10.
4. Hilal-Dandan R. Renin and angiotensin. In: Brunton LL, ed. *Goodman & Gilman's the Pharmacological Basis of Therapeutics*, Thirteenth Edition. New York, McGraw Hill Education, 2018, 471–88.
5. Rogers A, Guan J, Trtchounian A, Hunninghake G, Kaimal R, Desai M, *et al*. Association of elevated plasma interleukin-18 level with increased mortality in a clinical trial of statin treatment for acute respiratory distress syndrome. *Crit Care Med* 2019; **47**:1089–96.
6. Kaplanski G. Interleukin-18: biological properties and role in disease pathogenesis. *Immunol Rev* 2018; **281**:138–53.