

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

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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 SARS-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 (IFN) 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.

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