

Targeting the catecholamine-cytokine axis to prevent SARS-CoV-2 cytokine storm syndrome

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) encompasses a phylogenetically defined group of evolving viral strains that have caused an ongoing pandemic. Coronavirus disease 2019 (COVID-19) refers to the clinical syndrome of SARS-CoV-2 infection which disproportionately affects older adults with underlying hypertension and heart disease¹. The mortality of severe COVID-19 appears

to be driven by acute respiratory distress syndrome (ARDS) and a dysregulated immune response to SARS-CoV-2²⁻⁴.

Emerging evidence suggests that a subset of COVID-19 is characterized by the development of a cytokine storm syndrome (CSS) that resembles cytokine release syndrome (CRS) in chimeric antigen receptor (CAR)-T cell therapy^{2,4,5}. Hyper-inflammation in COVID-19 is associated with elevation of pro-inflammatory cytokines including interleukin (IL)-6, IL-2R, IL-8, tumor necrosis factor- α , and granulocyte-colony stimulating factor^{4,6}. This is similar to the exuberant cytokine production by lung-infiltrating monocytes/macrophages and pneumocytes observed in SARS-CoV and MERS-CoV infection⁷.

Targeting the hyper-inflammation in COVID-19 may be critical for reducing mortality. IL-6 levels diverge profoundly between non-survivors and survivors in the third week after symptom onset and are predictors of COVID-19 severity and in-hospital mortality^{1,8,9}. Tocilizumab, a monoclonal antibody targeting the IL-6 receptor, is currently being investigated for the treatment of patients with COVID-19-CSS (ChiCTR2000029765, NCT04306705, NCT04310228)¹⁰⁻¹². Pending data from randomized controlled trials, retrospective data from 21 patients with severe or critical COVID-19 treated with tocilizumab suggests that inhibition of the IL-6 signaling axis is highly effective¹³. However, given the cost, immunosuppression, and potential adverse reactions of tocilizumab, this strategy will likely be restricted to select patients in developed countries.

We have recently shown that CRS observed with bacterial infections, CAR-T cells, and other T cell-activating therapies is accompanied by a surge in catecholamines¹⁴. Catecholamines enhance inflammatory injury by augmenting the production of IL-6 and other cytokines through a self-amplifying feed-forward loop in immune cells that requires alpha-1 adrenergic receptor (α 1-AR) signaling¹⁴. Prophylactic inhibition of catecholamine synthesis with metyrosine, a tyrosine hydroxylase antagonist, reduced levels of catecholamines and cytokine responses and resulted in markedly increased survival following various inflammatory stimuli in mice. Similar protection against a hyper-inflammatory stimulus was observed with prazosin, demonstrating that α 1-AR antagonists can also prevent cytokine storm¹⁴.

To date, no controlled trials have examined the benefits of α 1-AR antagonism for the prevention of CSS and ARDS in human subjects. To investigate a potential role for α 1-AR antagonists in preventing poor outcomes in ARDS, we conducted a retrospective analysis of hospitalized patients diagnosed with ARDS. Using data from the Truven Health MarketScan Research Database (2010-2017), we identified 12,673 men (age 45-64) with “ARDS” as identified using International Classification of Diseases (ICD)-9 and ICD-10 diagnosis codes. Of these, 1,189 patients (9.4%) were prescribed α 1-AR antagonists in the previous year, 8.1% died in the hospital, and 15.6% received invasive mechanical ventilation. Logistic regression models were used to estimate adjusted odds ratios (AOR) and confidence intervals (CI) correlating receipt of α 1-AR antagonists (doxazosin, prazosin, silodosin, terazosin, and tamsulosin) in the previous year with these outcomes. Models were adjusted for comorbid conditions in the prior year as well as age and year of hospital admission.

We found that patients with prior use of α 1-AR antagonists had lower adjusted odds of the composite of invasive mechanical ventilation and mortality compared to non-users (AOR 0.80, 95% CI 0.69-0.94, $p=0.008$) (Figure 1). The unadjusted association was similar in magnitude (OR 0.80, 95% CI 0.68-0.94, $p=0.007$), as were results analyzing each component endpoint separately. Mirroring findings from pre-clinical models, these findings support a clinical rationale to study α 1-AR antagonists in the prophylaxis of ARDS and states of local and systemic immune dysregulation. Given the limitations of claims databases and retrospective analyses, our data on their own cannot establish causality or a therapeutic benefit of α 1-AR antagonists.

The findings discussed herein offer a rationale for studying α 1-AR antagonists in the prophylaxis of COVID-19-CSS. However, all drugs can have unanticipated side effects, and the incompletely understood relationship between hypertension and COVID-19 suggests caution in using any agent that impacts blood pressure¹⁵. Prospective, double-blinded clinical trials of α 1-AR antagonists in high-risk patients, when administered prior to symptom onset, will therefore be required to assess their utility in preventing COVID-19-CSS. Prazosin is inexpensive and safe, as has been documented by long-term

treatment of millions of patients with benign prostatic hyperplasia, hypertension, and other conditions. We emphasize that the extensive experience with using prazosin for other indications should prioritize - *not obviate* - rigorous, controlled clinical research rather than indiscriminate off-label use in patients exposed to SARS-CoV-2. Such trials could be expeditiously implemented in areas suffering from high infection rates that threaten to overwhelm hospital capacity. We encourage readers to recommend specific populations and trial designs to test the hypothesis proposed herein.

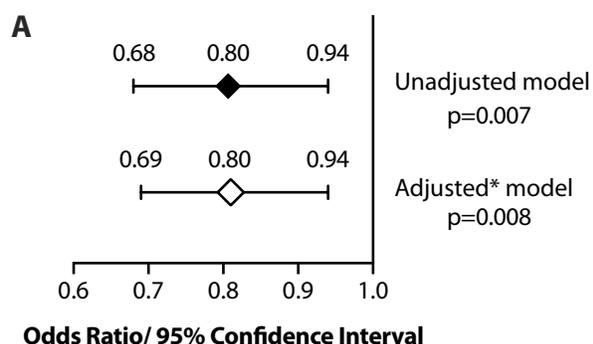


Figure 1. Logistic regression of the composite of invasive mechanical ventilation and in-hospital mortality in patients with ARDS who are on α 1-AR antagonists using data from MarketScan Research Database. *adjusted for comorbid hypertension, ischemic heart disease, acute myocardial infarction, heart failure, chronic obstructive pulmonary disease, diabetes mellitus, benign prostatic hyperplasia, and post-traumatic stress disorder identified from health care encounters in the prior year as well as age and year.

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COI: In 2017, Johns Hopkins University filed a patent application on the use of various drugs to prevent cytokine release syndromes, on which V.S., R.B., B.V., K.W.K., and S.Z. are listed as inventors.