Preventing cytokine storm syndrome in COVID-19 using alpha-1 adrenergic receptor antagonists

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Conflict of interest:
The Johns Hopkins University (JHU) filed a patent application on the use of various drugs to prevent cytokine release syndromes, on which VS, RB, NP, BV, KWK, and SZ are listed as inventors. JHU will not assert patent rights from this filing for treatment related to COVID-19. MFK received personal fees from Bristol-Myers Squibb and Celltrion. BV, KWK, & NP are founders of and hold equity in Thrive Earlier Detection. KWK & NP are consultants to and are on the Board of Directors of Thrive Earlier Detection. BV, KWK, NP & SZ are founders of, hold equity in, and serve as consultants to Personal Genome Diagnostics. SZ holds equity in Thrive Earlier Detection, and has a research agreement with BioMed Valley Discoveries, Inc. KWK & BV are consultants to Sysmex, Eisai, and CAGE Pharma and hold equity in CAGE Pharma. NP is an advisor to and holds equity in Cage Pharma. BV is also a consultant to Nexus, and KWK, BV, SZ, and NP are consultants to and hold equity in NeoPhore. CB is a consultant to Deupy-Synthes and Bionaut Pharmaceuticals. CB, BV, KWK, SZ, and NP are inventors on some of these technologies. Licenses to these technologies are or will be associated with equity or royalty payments to the inventors as well as to Johns Hopkins University. The terms of all these arrangements are being managed by Johns Hopkins University in accordance with its conflict of interest policies. SA is an advisor and holds an equity stake in two private companies, Prealize (Palo Alto, CA) and Dr. Consulta (Brazil). Prealize is a health care analytics company and Dr. Consulta operates a chain of low-cost medical clinics in Brazil.
Dysregulated host immune responses drive mortality in pneumonia and acute respiratory distress syndrome (ARDS) caused by a wide range of infections. In Coronavirus disease 2019 (COVID-19), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) elicits an exuberant local or systemic immune response (hyperinflammation) in the lung and other sites of viral replication, compromising organ function and leading to high morbidity and mortality (1–4).

**Cytokine storm syndrome in COVID-19**

Physiologic immune responses are coordinated and self-resolving, whereas uncontrolled immune activation in some patients with infection, autoimmune rheumatic disease, or chimeric antigen receptor (CAR)-T cell therapy results in syndromes of hyperinflammation. These syndromes are characterized by the over-production of cytokines and other secreted pro-inflammatory molecules. Emerging evidence suggests that a subset of patients with COVID-19 develops a cytokine storm syndrome (CSS) that 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 (2, 4–8), similar to the excessive cytokine production by lung-infiltrating monocytes/macrophages and pneumocytes observed in SARS-CoV-1 and MERS-CoV infection (9). Alveolar inflammation and diffuse alveolar damage impair the infected lungs’ ability to participate in gas exchange, culminating in ARDS and necessitating mechanical ventilation (10). ARDS is the main driver of mortality of COVID-19, so preventing the hyperinflammation is critical for avoiding this progression.

**Treating cytokine storm in COVID-19**

One potential therapeutic target is the IL-6 signaling pathway. IL-6 levels diverge profoundly between survivors and non-survivors in the third week after symptom onset and predict COVID-19 severity and in-hospital mortality (1, 8, 11). Tocilizumab and sarilumab, monoclonal antibodies targeting the IL-6 receptor, and siltuximab, a chimeric antibody targeting IL-6, are currently being investigated for the treatment of patients with COVID-19-CSS (12–23). Pending data from randomized controlled trials,
retrospective data from 21 patients with severe or critical COVID-19 treated with tocilizumab suggests that inhibiting the IL-6 signaling axis may reduce patient morbidity and the need for mechanical ventilation (24), if administered early enough in the disease course (25). However, given the cost, immunosuppression, and potential adverse reactions of tocilizumab, this strategy will likely be restricted to select patients in developed countries.

**Preventing cytokine storm by targeting the catecholamine-cytokine axis**

We have shown that CSS, observed with bacterial infections, CAR-T cells, and other T cell-activating therapies, is accompanied by a surge in catecholamines (26). 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 (α₁-AR) signaling (26). 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 hyperinflammatory stimulus was observed with the well-tolerated α₁-AR antagonist, prazosin, (but not beta-adrenergic receptor [β-AR] antagonists) demonstrating that this class of drugs can also prevent cytokine storm (26).

Preliminary results from a recent retrospective clinical study revealed that for hospitalized patients diagnosed with pneumonia or acute respiratory distress, the likelihood of requiring mechanical ventilation and dying was significantly lower if patients were taking α₁-AR antagonists during the year preceding hospitalization (27).

**Need for clinical trials**

These findings offer a rationale for studying α1-AR antagonists to prevent cytokine storm syndrome and its dire consequences in people who are at risk for developing severe COVID-19. This population includes people who are recently infected with SARS-CoV-2 and people who are not yet infected but are at high risk for exposure. Prazosin is inexpensive and safe, as documented by long-term
treatment of millions of patients with benign prostatic hyperplasia, hypertension, and other conditions. However, all drugs can have unanticipated side effects in different clinical contexts, and the incompletely understood relationship between hypertension and COVID-19 suggests caution in using any agent that affects blood pressure (28). Prospective clinical trials in high risk patients are needed to assess $\alpha_1$-AR antagonist utility in preventing—not treating—COVID-19-CSS. 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 or infected with SARS-CoV-2. Such trials could be expeditiously implemented in areas suffering from high infection rates that are overwhelming hospital capacity. To that end, we are actively pursuing clinical trials at multiple institutions and will make our protocols available on http://clinicaltrials.gov/ when approved by the Johns Hopkins Internal Review Board. The potential therapeutic benefit of $\alpha_1$-AR antagonism may extend beyond COVID-19. The potential utility of prazosin prophylaxis and early abortive therapy in the prevention of morbidity and mortality in ARDS, pneumonia, (CAR)-T cell therapy, and autoimmune rheumatic disease deserves dedicated study.

**Acknowledgments:** Dr. Konig was supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases of the National Institutes of Health under Award no. T32AR048522. Allison Koenecke was supported by the National Science Foundation Graduate Research Fellowship under Grant no. DGE 1656518. Any opinion, findings, and conclusions or recommendations expressed in this material are those of the authors and do not necessarily reflect the views of the National Science Foundation. Joshua Vogelstein and Susan Athey were partially supported by funding from Microsoft Research. Dr. Bettegowda was supported by the Burroughs Wellcome Career Award for Medical Scientists. This work was further supported by The Virginia and D.K. Ludwig Fund for Cancer Research, The Lustgarten Foundation for Pancreatic Cancer Research, and the BKI Cancer Genetics and Genomics Research Program.
References:


7. Pedersen SF, Ho Y-C. SARS-CoV-2: A Storm is Raging [Internet]. *Journal of Clinical Investigation* [published online ahead of print: March 27, 2020]; doi:10.1172/JCI137647


11. Liu T et al. *The potential role of IL-6 in monitoring severe case of coronavirus disease 2019 [Internet]*. Infectious Diseases (except HIV/AIDS); 2020:


