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

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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–T cell (CAR–T cell) therapy results in syndromes of hyperinflammation. These syndromes are characterized by the overproduction of cytokines and other secreted proinflammatory molecules. Emerging evidence suggests that a subset of patients with COVID-19 develops a cytokine storm syndrome (CSS) that is associated with elevation of proinflammatory cytokines, including IL-6, IL-2R, IL-8, TNF-α, and G-CSF (2, 4-8), similar to the excessive cytokine production by lung-infiltrating monocytes/macrophages and pneumocytes observed in SARS-CoV-1 and Middle East respiratory syndrome–CoV (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 […]

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

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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–T cell (CAR-T cell) therapy results in syndromes of hyperinflammation. These syndromes are characterized by the overproduction of cytokines and other secreted proinflammatory molecules. Emerging evidence suggests that a subset of patients with COVID-19 develops a cytokine storm syndrome (CSS) that is associated with elevation of proinflammatory cytokines, including IL-6, IL-2R, IL-8, TNF-α, and G-CSF (2, 4–8), similar to the excessive cytokine production by lung-infiltrating monocytes/macrophages and pneumocytes observed in SARS-CoV-1 and Middle East respiratory syndrome–CoV (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 nonsurvivors 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 suggest that inhibiting the IL-6 signaling axis may reduce patient morbidity and the need for mechanical ventilation (24) but may fail to treat very advanced disease (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 cell, 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 α-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 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 CSS 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 α₁-AR antagonist utility in preventing—not treating—COVID-19–CSS. We emphasize that the extensive experience with 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 α₁-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.

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22. Cohort multiple randomized controlled trials


