

## BRIEF REVIEW

## Treating Cytokine Storm in Patients with COVID-19

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Cytokine storm is a dangerous sequela of SARS-CoV-2. It is a dysregulated response that causes overactivation of immune cells with massive production of inflammatory cytokines. This can lead to acute pulmonary injury, multiorgan failure, and potential death.[1]

Early recognition of COVID-19-induced cytokine storm syndrome has prognostic and therapeutic implications.[2] Although elevated cytokine levels occur in such patients, the severity of the condition might not correlate with serum cytokine concentrations due to their short half-life and diurnal variation.[3] The plasma neutrophil-to-lymphocyte ratio is an accepted intensity marker of systemic inflammation and is predictive of disease severity [4, 5] and mortality.[6]

Many immunomodulating drugs have been utilized to treat COVID-19-induced cytokine storm. Administering glucocorticoids, interleukin (IL)-6 inhibitors (tocilizumab), Janus kinase inhibitors (baricitinib), and IL-1 inhibitors (anakinra) can attenuate the illness. Plasma exchange therapy is another intervention that had been attempted [7], as well as vasoactive intestinal peptide (aviptadil).[8]

In the Randomized Evaluation of COVID-19 Therapy trial (RECOVERY), dexamethasone resulted in a lower 28-day mortality among those who received invasive mechanical ventilation or oxygen at baseline. However, it only helped those requiring respiratory support.[9]

Glucocorticoids with or without tocilizumab (group 1) versus supportive care (group 2) were compared in subjects with COVID-19-associated cytokine storm. Group 1 patients evidenced a 79% higher likelihood of clinical improvement (hazard ratio [HR] 1.8 [95% CI 1.2–2.7]), 65% lower mortality risk (HR 0.35 [95% CI 0.19–0.65]), and 71% lower risk of invasive mechanical ventilation (HR 0.29 [95% CI 0.14–0.65]).[10] There was no separate group receiving only glucocorticoids or tocilizumab; thus, it was not possible in this study to assess the im-

pact of each medication individually.

Drugs targeting IL-1 or IL-6 separately did not benefit patients with COVID-19 in terms of time to clinical improvement. They also had no impact on baseline mortality risk, hypoxic respiratory failure rate, or sequential organ failure assessment (SOFA) score.[11]

A meta-analysis of randomized controlled trials indicated that baricitinib decreased 28-day mortality in hospitalized adults with COVID-19. Patients requiring respiratory support at baseline benefited the most.[12]

A systematic review of 18 studies, including 14 case series, two case-control studies, one propensity score-matched study, and one randomized controlled trial, comprised 384 subjects with severe COVID-19. Amongst them, 220 received therapeutic plasma exchanges with improvement in PaO<sub>2</sub>/FiO<sub>2</sub> ratio and decrease in biomarkers of inflammation. However, despite clinical progress, the effect on mortality was not statistically significant.[13]

The synthetic vasoactive intestinal peptide (aviptadil) is another medication currently under investigation in six clinical trials as an inhalation and intravenous therapy for patients with respiratory failure during COVID-19. A randomized, placebo-controlled trial with 196 subjects evidenced a 2.0-fold increased odds of survival (95% CI 1.05–3.88;  $P < .035$ ) among aviptadil-treated patients.[14]

The reviewed data are in concordance with the current guidelines for COVID-19 treatment recommended by the National Institutes of Health.[15] Corticosteroids (dexamethasone), interleukin-6 inhibitors (tocilizumab or sarilumab), and/or Janus kinase (JAK) inhibitors (baricitinib or tofacitinib) are recommended immunomodulators for hospitalized patients with COVID-19, according to their disease severity. IL-1 inhibitors (e.g., anakinra) have insufficient evidence to support their use in these cases.

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