EDITORIAL

Anti-cytokine Therapy in Hospitalized Patients with COVID-19: The Jury is Out

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Received on: 10 September 2022; *Accepted on:* 12 September 2022; *Published on:* 30 September 2022

Keywords: Anakinra, Anti-cytokine therapy, Anti-inflammatory therapy, Corona virus-2019, Cytokine storm, Interleukin 1, Interleukin receptor antagonist, Interleukin 6 receptor antagonists, Inflammatory biomarker, Tocilizumab.

Indian Journal of Critical Care Medicine (2022): 10.5005/jp-journals-10071-24336

The biggest pandemic in the last 100 years, corona virus-2019 (COVID-19), is a new disease that challenged the medical research community in an unprecedented manner but equally amazing was the response of researchers in pursuit to treat the disease and control the pandemic. A whole lot of medications were given to patients during the early pandemic based on proven or unproven theories including repurposed drugs. More specific therapies were underway while the medical research community was trying to understand the disease and its pathophysiology.

Most of the patients were mildly symptomatic and responded with symptomatic therapy at home. Due to the sheer number of all infected cases, the proportion of severe and critically ill patients was also very high, and it overwhelmed the healthcare system throughout the world. The most severe and lethal form of COVID-19 has been linked to different and possibly combined pathophysiological processes, including severe acute diffuse alveolar damage, vascular thrombosis, and a hyperinflammatory response caused by the overproduction of pro-inflammatory cytokines.[1] Critically ill COVID-19 patients display higher plasma concentrations of pro-inflammatory cytokines than mild cases suggesting a relationship between inflammation and disease severity.[2]

Corticosteroid, which non-selectively inhibits inflammation were evaluated in the massive randomized evaluation of COVID-19 therapy (RECOVERY) trial, and "dexamethasone" was the first immune modulator to show a clear survival benefit. It was found to reduce mortality compared to usual care alone. Thus, after July 2020, dexamethasone was incorporated into the standard of care for patients admitted to the hospital with COVID-19. Subsequently, multiple randomized trials also indicated that systemic corticosteroid therapy improves clinical outcomes and reduces mortality in hospitalized patients with COVID-19 who require supplemental oxygen, presumably by mitigating the COVID-19-induced systemic inflammatory response that can lead to lung injury and multisystem organ dysfunction. However, it was not shown to be beneficial for COVID-19 patients who do not require oxygen.[3,4]

With the positive outcome benefits of corticosteroids, the search for more specific and targeted anticytokine therapy was an obvious path as some patients with severe COVID-19 develop a hyperinflammatory phenotype known as a cytokine storm.[1] The common cytokines responsible for this life-threatening inflammatory condition include interleukin 1 (IL-1) and IL-6, IL-8, interferon-γ (IFNγ), GM-CSF, and tumor necrosis factor (TNF).[1] Since corticosteroids became the standard of care for all patients who were hospitalized and required oxygen, the search for targeted and effective anti-cytokine therapy was conducted with ongoing steroid therapy. The questions which were under investigation included whether combining anti-cytokine therapy over and above the standard of care steroid therapy is beneficial or not and if so, which therapy, in which patient population, and when during illness.

Interleukin 6 is a proinflammatory cytokine. Drugs acting against IL-6 soon became the area of research for patients of COVID-19 with hyperinflammation. Tocilizumab and sarilumab both are recombinant humanized anti-IL-6 receptor monoclonal antibodies. The results of the RECOVERY and REMAP-CAP, a randomized, embedded, multifactorial adaptive platform trial for community-acquired pneumonia provided consistent evidence that tocilizumab, when co-administered with corticosteroids, offers a modest mortality benefit in certain patients with COVID-19 who are severely ill, who are rapidly deteriorating and have increased oxygen needs, and who have a significant inflammatory response.[5,6] If tocilizumab is not available, sarilumab may be used as an alternative because it has demonstrated a similar clinical benefit in improving survival and reducing the duration of organ support in the REMAP-CAP trial.[7] Tocilizumab and sarilumab should only be given in combination with a course of dexamethasone (or an alternative corticosteroid at a dose that is equivalent to dexamethasone 6 mg). In contrast to the REMAP-CAP and RECOVERY trials, the REMDACTA trial, a randomized double-blind placebo controlled trial which assessed tocilizumab and remdesivir in hospitalised patients with severe COVID-19 did not find a mortality benefit of tocilizumab. The trial randomized hospitalized COVID-19 patients, most of whom required NIV or high-flow oxygen support,

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How to cite this article: Garg SK. Anti-cytokine Therapy in Hospitalized Patients with COVID-19: The Jury is Out. Indian J Crit Care Med 2022;26(10):1069–1071.

Source of support: Nil

Conflict of interest: None

to receive tocilizumab or a placebo. All the participants received remdesivir and most received corticosteroids. Tocilizumab use did not reduce 28-day mortality (18% in the tocilizumab arm and 20% in the placebo arm).[8]

Another proinflammatory cytokine, IL-1 is also elevated in patients with COVID-19. Drugs that block the IL-1 receptor or drugs that block IL-1 signaling can potentially interrupt this autoinflammatory loop. Interleukin 1 is located upstream of IL-6 in the inflammation cascade; therefore, it was hypothesized that targeting IL-1 will be more efficient in hyperinflammatory forms of COVID-19 than IL-6 inhibition, which has already provided encouraging results in randomized controlled trials of patients with severe COVID-19 admitted to the intensive care unit when administered to patients admitted to hospital with COVID-19 in need of oxygen supplementation in the RECOVERY trial.[1]

Anakinra is a recombinant human IL-1 receptor antagonist. In the SAVE-MORE a pivotal, confirmatory, phase III randomized clinical trial, 594 hospitalized patients who had moderate or severe COVID-19 pneumonia and plasma-soluble urokinase plasminogen activator receptor (suPAR – an unspecific inflammatory biomarker) levels above or equal to 6 ng/mL were randomized to receive either anakinra or placebo. The study found that patients who received anakinra had a lower risk of clinical progression of COVID-19 than those who received a placebo.[9] Moreover, CORIMUNO-ANA-1, a randomized controlled trial that compared the use of anakinra to usual care in 116 hospitalized patients who were hypoxemic but did not require high-flow oxygen or ventilation, was stopped early for futility.[10] Furthermore, REMAP-CAP, an open-label, adaptive platform, randomized controlled trial that evaluated several immunomodulators in patients with COVID-19 who required organ support, found that anakinra was not effective in reducing the combined endpoint of in-hospital mortality and days of organ support.[7] Although the SAVE-MORE study suggests that suPAR levels could be used in risk stratification to identify populations that could benefit from IL-1 inhibition, the laboratory assay that is used to assess suPAR levels is not currently available in the larger part of the world. Also, CAN-COVID, a Phase III, multicenter, double-blind, randomized placebo-controlled trial that evaluated canakinumab, another IL-1 inhibitor that blocks the IL-1 signaling, in hospitalized patients with COVID-19 who were hypoxemic but did not require ventilatory support, reported that the use of canakinumab did not improve the likelihood of survival without invasive mechanical ventilation.[11]

Furthermore, granulocyte-macrophage colony-stimulating factor (GM-CSF) is believed to be a key driver of lung inflammation in severe and critical COVID-19 pneumonia, operating upstream of other pro-inflammatory cytokines and chemokines. Anti-GM-CSF monoclonal antibodies may mitigate inflammation by inhibiting this signaling. Drugs targeting GM-CSF directly by neutralizing the biological function of GM-CSF were studied. Clinical data are lacking to definitively establish the potential benefits and risks associated with the use of GM-CSF inhibitors in patients with COVID-19. None of these agents are currently FDA-approved for any indication.[3]

In yet another study published in *The Indian Journal of Critical Care Medicine* on a total of 90 patients, the researcher compared anakinra and tocilizumab in the treatment of COVID-19. They concluded that in terms of early improvement including the requirement of a mechanical ventilator, tocilizumab is better than anakinra or standard therapy, but anti-cytokine therapy does not affect overall survival. The study was limited by its small sample size and retrospective nature.[12] A pooled data from the 3 observational studies in at a total of 237 subjects with documented COVID-19 infection showed that anakinra is superior to tocilizumab in terms of COVID-19 death prevention, by decreasing the corresponding risk by 40%.[13–15]

The COVID-19 treatment guidelines by the National Institutes of Health (NIH), USA recommend the use of IL-6 inhibitors (e.g., sarilumab, tocilizumab) in hospitalized patients who require supplemental oxygen, high-flow oxygen, non-invasive ventilation (NIV), or mechanical ventilation but guidelines do not recommend either for or against the use of anakinra for the treatment of COVID-19.[3] Similarly, guidelines from the European Respiratory Society recommending IL-6 receptor antagonist monoclonal antibody therapy to hospitalized patients with COVID-19 requiring oxygen or non-invasive ventilatory support in addition to systemic corticosteroids. The guideline also suggests against the use of IL-1 receptor antagonist monoclonal antibodies for hospitalized patients with COVID-19.[16]

We need to have more randomized controlled trials to clear the air with defined inclusion criteria, exclusion criteria, and primary and secondary outcomes. Is there any role of both IL-1 and IL-6 inhibitors in combination with steroids, or IL-1 inhibitors should be given if the IL-6 inhibitor is not effective or *vice versa* or can we avoid steroids altogether and one of the anti-cytokine therapies is adequate? Many questions remain unanswered. The way number of COVID-19 cases have been decreasing globally and more importantly, as the severity of COVID-19 illness has reduced significantly, the use of these medications in the management of COVID-19 will also likely to reduce significantly. Therefore, it is possible that we may not get the answer to these still unresolved questions.

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