

Letter to the Editor

Interleukin-1 Receptor Antagonist in the Treatment of COVID-19 Induced Cytokine Storm

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Dear Editor

From late 2019 which Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first diagnosed to now, about 31 million people have been diagnosed by coronavirus disease 2019 (COVID-19) and more than ninety-thousands people have been died, globally. Many antiviral medications have been evaluated for their effect on the virus life-cycle and some have been approved to be used in emergencies (1). To date, no effective agent has shown a definite effect in the pharmacotherapy of COVID-19.

Although the optimal goal in this battle is to manufacture the vaccine, different aspects of the disease are now under investigation. Critical conditions due to ARDS and hyperinflammatory state play an important role in COVID-19 pathogenesis and it was shown in previous studies that mortality is increased in these patients (2). Hyperinflammation state in COVID-19, which leads to tissue damage and organ dysfunction, is caused by releasing a huge number of inflammatory mediators and is known as cytokine storm (3). The inhibitors of the immune-mediated pathways are being strongly investigated due to their potential effect in the treatment of cytokine storm in severe COVID-19.

Interleukin-1(IL-1) family contains 11 members with almost similar inflammatory activity (4). IL-1 pathway, as a regulator cytokine in inflammation control other cytokines in innate immune response (5). IL-1 acts as a leukocytic pyrogen and induces fever and also enhances the acute phase response and increase the level of lymphocyte activation (6). Receptor and direct IL-1 inhibitors here are two main different types of IL-1 pathway blockers. Anakinra, the first approved agent, an IL-1 receptor antagonist which produce by recombinant technology and was first identified in urine samples of febrile patients and used to treat some immune-mediated diseases (7). It has been used safely in the treatment of inflammation related to septic shock syndromes such as acute respiratory distress syndrome (ARDS), subsequent hemophagocytic lymphohistiocytosis (HLH), and macrophage-activating syndrome (MAS) and showed survival advantages (8). Based on clinical data on COVID-19, some clinical features of severe states are similar to HLH and MAS, but no in full similarity. In COVID-19 hyper inflammation state, MAS due to persistent INF- γ elevation which is an excessive inflammatory response is responsible for severe cytokine storm. There is some evidence for MAS/sHLH in COVID-19 which is supported by the abnormal laboratory parameters. An increase in C-reactive protein and

hyperferritinaemia which both have been recorded in COVID-19 patients are two key parameters in MAS/HLD diagnosis. Hyperactivation of immune activity is more confined to the pulmonary parenchyma and is associated with the development of ARDS. An increase in IL-1 serum levels in cytokine panel in patients with severe COVID-19 which resemble MAS/HLH has been noted (9). In this manner by inhibiting IL-1 pathway upregulation of multiple cytokines which is mediated by NF- κ B reduced.

From limited human study results on anakinra applicability in the treatment of moderate to severe COVID-19 patients with the hyperinflammatory state, some lights have been flashed. A cohort study in Milan, Italy confirmed COVID-19 patients with evidence of cytokine storm received different doses of anakinra by subcutaneous injection as an add-on therapy to hydroxychloroquine and lopinavir/ritonavir combination. Patients were followed to assess clinical outcomes on day 21. In this study treatment with high dose anakinra (5mg/kg) was associated with clinical improvement in 72% of the patients (10).

Safety outcomes in the administration of immunomodulators to severe COVID-19 are so important. By inhibiting innate immune response, it could be possible that the rate of other co-infection and also, viremia due to SARS-CoV-2 increase. In previous studies, the safety profile of anakinra has been evaluated in a different situation. Anakinra showed a reliable safety profile and even in patients with sepsis could affect the mortality rate and high dose anakinra administration in moderate to severe non-ICU admitted patients have been used safely (10). Besides needed precautions due to the increase in infection risk or decrease in the neutrophil count by utilization of anakinra, others such as hypersensitivity reactions, drug accumulation in renal failure, and drug-drug interaction should be considered.

Considering all the pros and cons of consuming anakinra as an IL-1 receptor blocker it may have an important role in decreasing the mortality or morbidity

related to cytokine storm in SARS-CoV-2 infection. Currently, several trials have been conducted to assess the efficacy and safety of different doses of anakinra in COVID-19 (NCT04318366, NCT04364009) and by the results of these studies, more insight will be gained about the effect of IL-1 receptors blockers in the treatment of hyperinflammatory status related to COVID-19.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

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