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COVID-19 and colchicine - Can we weather the storm?

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Abstract

We read with interest the study published by Cavalli et al. which showed that blocking interleukin-1 (IL-1) with high-dose of anakinra was safe and resulted in clinical improvement in 72% of patients with ARDS managed with non-invasive ventilation outside the intensive care unit [1]. Anakinra is a recombinant human IL-1 receptor antagonist that binds to the IL-1 receptor and block signal transduction. It is approved by FDA for rheumatoid arthritis and autoinflammatory syndromes treatment.

Commentary

In our recent publication, a narrative review on immunopathogenesis of severe forms of COVID-19, we highlighted the role of IL-1β release as a consequence of pyroptosis. Alveolar pneumocytes pyroptosis is an inflammatory cell death mechanism that lead to activation of the NLRP3 inflammasome and consequent release of IL-1β. This cytokine plays a major role in the development of the cytokine storm [2].

The recognition of a clinical hyperinflammatory syndrome, combined with high levels of cytokine in the sera of COVID-19 patients, pointed to immunomodulatory therapy as a possible treatment strategy. Although, the disappointing preliminary report of IL-6 inhibition trial - COVACTA highlighted the complexity of cytokine interplay in disease development [3].

There is important overlap among proinflammatory cytokine effects. Besides that, their interactions create a positive effect-loop enhancing its production. In this way, the success of immunomodulatory therapy may be driven by targeting early step of cytokine storm. Thus, the benefit of inhibiting IL-1β over IL-6 can be explained by the triggering role of IL-1β in the COVID-19 hyperinflammatory syndrome.

Cytokine targeted therapies are expensive and are not widely available. However, there are other strategies to block the activation of NLRP3 inflammasome, IL-1β release and NF-kB activation. Due to the urgency to find an effective treatment, repurposing drugs with known safety and tolerability profile is an interesting strategy. In this way, colchicine, an old anti-inflammatory drug used in gout arthritis, Behçet syndrome and familial Mediterranean fever may be an interesting therapeutic agent. Colchicine also reduced cardiovascular events among post-myocardium infarct patients [4].

The main anti-inflammatory effects of colchicine are caused by the disrupting of microtubule polymerization leading to impairment of NLRP3 inflammasome assembly and IL-1β production. It also interferes with neutrophil recruitment and adhesion to inflamed tissues by decreasing neutrophil selectin expression [5].

Up to best of our knowledge, the safety of colchicine could be demonstrated in the randomized double-blind clinical trial GRECCO-19. This study showed statistically significantly improved time to clinical deterioration with the use of colchicine [6] . However, due to the small sample size and low incidence of events, the study was underpowered to prove efficacy.

Several clinical trials are being conducted to access efficacy and safety of colchicine in COVID-19 patients. Among then, we point up COLCORONA (NCT04322682), which is a phase III multicenter randomized double blinded controlled trial that aims to enroll approximately 6000 patients to evaluate if short-term treatment with colchicine reduces the rate of death and lung complications related to COVID-19. We look forward to the results of this study, that we believe will provide strong evidence about the role of colchicine in COVID-19.

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