Supplemental Text 1: IL-6 in COVID-19 Infection

The review by Leisman et al (2020) demonstrated IL-6 concentrations in other conditions associated with markedly elevated cytokine levels (i.e., sepsis, CAR-T-associated cytokine release syndrome, and non-COVID-19 ARDS) were anywhere from 12 to 100 times higher than the IL-6 concentrations associated with severe or critical COVID-19 infection. The authors suggest that cytokine storm may not play as pivotal a role in COVID-19-induced end-organ dysfunction as previously thought. However, it is important to consider that these other hyperinflammatory conditions analyzed in the aforementioned have differing pathophysiology and biology compared to COVID-19, and as such a head-to-head comparison of IL-6 levels may not be entirely appropriate in evaluating the role of the cytokine response in COVID-19. In fact, studies have shown that elevated IL-6 levels in COVID-19 are associated with higher SARS-CoV-2 viral load and poorer prognosis, thus supporting the central role of a heightened inflammatory response in COVID-19 (1,2). This observation does not preclude the possibility that other cytokines associated with the release syndrome (e.g., IL-1β, which is more directly regulated by colchicine than IL6)) may be equally or more important than IL-6 in COVID-19 responses.

Since the start of the COVID-19 pandemic, significant resources have been allocated to investigate the therapeutic efficacy of anti-IL-6 therapies with respect to severe COVID-19 infection. Thus far, the results of these studies have been equivocal at best. In a meta-analysis by Lan et al, although patients treated with tocilizumab were found to have lower all-cause mortality compared to the placebo group, the results did not achieve statistical significance, with risk of ICU admission and the need for mechanical ventilation similar between the two groups (3). None of the included studies were randomized controlled trials, however, and in many of them baseline characteristics/illness severity of patients were not matched. Larger-scale randomized trials have shown similar results, with trials of both tocilizumab and sarilumab failing to meet their primary endpoint (4,5). Furthermore, some studies have demonstrated that the immunosuppressive effects of anti-IL-6 therapies may actually contribute to adverse effects in COVID-19 patients due to secondary bacterial or, less commonly, fungal infections (3,6). Despite these overall
disappointing results, ongoing studies continue to investigate anti-IL-6 agents with respect to combination therapies, and alternative dosing regimens that may hold promise for COVID-19 infection.

Although colchicine has been shown to inhibit IL-6 secretion, it has multiple additional mechanisms of action that may potentially temper the COVID-19-induced hyperinflammatory response. Additionally, colchicine is not immunosuppressive compared to its anti-IL-6 counterparts, and thus may be a more suitable COVID-19 treatment. Finally, most studies of colchicine have aimed to dampen inflammation at an early stage, whereas most studies of anti-IL-6 therapeutics have been directed at treating the COVID-19 inflammatory response at a very advance stage of the infection, when targeting a single cytokine may simply be too little, too late.

References


