Letter to the Editor

Colchicine for COVID-19: Hype or hope?

We appreciate the efforts of Schattner [1] to summarize the evidence from randomized controlled trials regarding the efficacy and safety of colchicine for various emerging indications, which included coronavirus disease 2019 (COVID-19). The four randomized controlled trials [2–5] summarized by Schattner [1] which investigated the use of colchicine in patients with COVID-19 strongly suggesting a beneficial effect of the use of colchicine. Nevertheless, Schattner might have overlooked the recently published RECOVERY trial [6] investigating the use of colchicine in patients with COVID-19 (available as a preprint during the time of his literature search), which is by far the largest randomized trial ($n = 11,340$) to report the effects of colchicine in patients with COVID-19. According to the RECOVERY trial [6], the use of colchicine in patients with COVID-19 was not associated with reduction in 28-day mortality (rate ratio = 1•01; 95% confidence interval 0•93–1•10). In fact, the findings of the RECOVERY trial [6] on colchicine had dampened the enthusiasm of further investigating the effects of colchicine in patients with COVID-19.

The NLRP3 inflammasome, a multiprotein complex in macrophages, dendritic cells, and other non-immune cells, is a vital part of the innate immune system for antiviral host defenses. The aberrant activation of the NLRP3 inflammasome during the course of COVID-19 leads to the production of interleukin-1β, facilitating the formation of cytokine storms and the subsequent multiorgan injury. This is the rationale where colchicine, a well-known NLRP3 inhibitor, has been repurposed for the treatment of COVID-19. Nevertheless, such beneficial effects of colchicine did not appear to translate into mortality benefits. It is likely that the proportion of enrolled patients with concurrent obesity and/or diabetes in the existing trials, who would have more pronounced activation of the NLRP3 inflammasome, was too low to allow detection of mortality benefits [7,8]. In the trial by Tardif et al. [2] in which the findings have been summarized by Schattner [1], the participants had a median body mass index of 30.0 kg/m^2. There was a significant reduction in the odds for a composite of death or hospitalization due to COVID-19 in colchicine users compared to non-colchicine users (odds ratio = 0.75; 95% confidence interval: 0.57–0.99). Besides, the pre-specified subgroup analysis reported that the odds for a composite of death or hospitalization due to COVID-19 was trended towards a significant effect in patients with concurrent diabetes receiving colchicine (odds ratio = 0.37; 95% confidence interval: 0.37–1.01).

Besides the purported anti-inflammatory action of colchicine which has been discussed by Schattner [1], colchicine could also suppress the formation of neutrophil extracellular traps (NETs) [9]. Colchicine stabilizes the cytoskeleton, thereby attenuating chromatin swelling and subsequent NET release from neutrophils. Interestingly, NETs have been found to contribute to immunothrombosis in patients with COVID-19, especially those with severe course of illness. Therefore, colchicine, being one of the anti-NETs therapeutics, could also be useful as an adjunct to anticoagulants for thromboprophylaxis in this patient population. Noteworthily, a recent systematic review and meta-analysis [10], which aimed to determine the effects of colchicine on several inflammatory hematological biomarker levels among patients with COVID-19 noted that the use of colchicine relative to control treatment led to statistically significantly lower mean D-dimer level (standardized mean difference = −0.9; 95% confidence interval −1.22−−0.57), which is a sensitive marker of thrombosis.

With the wisdom of hindsight, future randomized trials aiming to determine the effects of colchicine in patients with COVID-19 should focus on the population of patients with COVID-19 with concurrent obesity and/or diabetes, and preferably at the early (mild) stage of illness, in order to elicit its efficacy to prevent mortality and clinical deterioration. In addition, apart from evaluating its mortality benefits, there should be a concurrent evaluation of its efficacy for thromboprophylaxis (as an adjunct to anticoagulants) among patients with COVID-19. These trials should also be designed in a way that the treatment duration of colchicine is long enough (21 days or until discharge) to establish its therapeutic efficacy.

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Declaration of Competing Interest

The authors report no conflict of interest.

Reference

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