



## The rationale for the use of colchicine in COVID-19: comments on the letter by Cumhur Cure M et al.

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Dear Editor,

We read with great interest the letter by Cumhur Cure M et al., who raised several points of concern about the use of colchicine for the treatment of severe acute respiratory syndrome coronavirus 2 infection disease (COVID-19) [1]. However, by considering the experience with colchicine in clinical practice and its mechanisms of action, we respectfully disagree with their suggestion of discouraging the use of this drug in COVID-19 [2]. On the contrary, there may be a rationale for investigating its beneficial effects.

Recent observational studies underlined the effectiveness of blocking the COVID-19-mediated cytokine storm by targeting interleukin (IL)-1 and IL-6 in patients with hyperinflammatory syndrome [3]. High-dose intravenous anakinra was used in 29 patients with severe cytokine storm with 89% of survival rate [4]. One hundred patients with severe COVID-19 pneumonia and acute respiratory failure were treated with tocilizumab, with a rapid and sustained response in 77% of them [5].

Therefore, the management of COVID-19 should aim at early identification and treatment of hyperinflammation in or-

der to prevent the cytokine storm. In this view, colchicine may be a drug with potential effects in the early phase of COVID-19-mediated inflammation. In fact, colchicine can prevent and treat the flares of many autoinflammatory diseases characterized by aberrant IL-1/IL-6 pathway activation [6]. Notably, colchicine can block the activation of NACHT-LRRPYD-containing protein 3 (NLRP3) inflammasome, which was demonstrated to be directly induced by the viroporin-E of SARS-CoV [7]. The effectiveness of colchicine has been already reported in COVID-19 patients, even in the presence of hemodynamic complications, such as cardiac tamponade [8], and acute renal injury in a kidney transplant recipient [9].

Besides hyperinflammation, disseminated intravascular coagulation (DIC) and increased occurrence of cardiovascular events are complications of COVID-19 [3, 10]. These might be justified by the presence of endothelial cell infection and endothelitis [11]. Endothelial cell damage can be found also in Behçet's disease (BD), an autoinflammatory disease characterized by neutrophil activation, increased oxidative stress, and generation of a thrombophilic status [12]. Colchicine is largely used in BD, in which it may be useful also for inflammation-induced thrombosis [13]. Furthermore, colchicine was able to reduce the recurrence of secondary cardiovascular events after myocardial infarction, thanks to the inhibition of oxidative stress on the endothelium due to inflammatory cytokines [14]. These studies provide a rationale for a possible role of colchicine in the prevention of coagulation activation and thrombosis in COVID-19.

On the other hand, Cumhur Cure M et al. hypothesized that colchicine might emphasize SARS-CoV2 infection. This is in contrast with *in vitro* and animal studies in which colchicine-mediated cytoskeleton blockade was able to reduce cell-to-cell transfection during coronavirus infection, thus limiting the viral load [15]. They hypothesized also that colchicine toxic effects might increase the risk of DIC and acute respiratory distress, but in clinical practice this might be relevant only in

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very rare cases of drug hyperdosage, while virus-specific mechanisms are likely to be much more important. Indeed, it should be remarked that, despite its narrow therapeutic window, the risk of serious drug-related toxic effects is minimal for medium–low doses of colchicine (0.5–1 mg daily) [9, 16].

In conclusion, in our opinion, the risk–benefit ratio might be favorable for colchicine as a candidate drug for COVID-19. This assumption is supported by different experimental models and extensive clinical experience in autoinflammatory diseases, which did not raise any concern about the safety of this drug. Based on this rationale, several trials are ongoing in different countries to investigate the role of colchicine in the treatment of COVID-19 (Canada [ClinicalTrials.gov Identifier: NCT04322682]; Italy [NCT04375202 and NCT04322565]; Greece [NCT04326790]; Spain [NCT04350320]; Argentina [NCT04328480]; Iran [NCT04360980]; USA [NCT04355143 and NCT04363437]).

The manuscript does not contain clinical studies or patient data.

## Compliance with ethical standards

**Disclosures** None.

**Code availability** Not applicable.

**Ethics approval** Not applicable.

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