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Letter to the Editor

# Colchicine as a Potential Treatment Choice for COVID-19 Patients in Developing Countries: COVID-19 and Colchicine

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COVID-19 has affected the global population since 2019. In developing countries, people suffer, livelihoods are endangered, the economies crash due to disease control-related restrictions and lockdown measures. In addition, people may be denied medical attention due to a lack of medical facilities, inadequate healthcare providers, a shortage of vaccines, and the unavailability of affordable and effective medicines.

The National Institutes of Health (NIH) has issued treatment guidelines for COVID-19 patients. Many of the suggested drugs, such as dexamethasone and tocilizumab, are immunomodulators. However, immunomodulators are generally contraindicated in patients with infection because they suppress the immune response. Therefore, it is necessary to consider whether COVID-19 is a simple result of SARS-CoV-2 infection. We hypothesize that SARS-CoV-2 is an unusual virus that can cause a greater inflammatory response than most other viruses. Clinical characteristics similar to rheumatic disease [1] and fibrotic-like lung changes [2] may persist after recovery from SARS-CoV-2 infection. In addition, the pathophysiology of moderate and severe COVID-19 fits a proposed model of antibody-dependent enhancement and antibody-dependent infection of macrophages as the critical step in the progression to severe disease, contributing to dysregulated immune responses [3]. Considering this, mild COVID-19 is a simple viral infection, but severe COVID-19 involves hyperinflammation induced by SARS-CoV-2 infection that may be important in the pathogenesis. Therefore, preventing hyperinflammation could lead to more COVID-19 patients experiencing only mild respiratory symptoms, reducing the number of patients requiring oxygen therapy, and improving the prognosis, thus reducing the burden on the healthcare system.

Hydroxychloroquine, an antirheumatic drug that received significant attention during the pandemic as pre-exposure or post-exposure prophylaxis to prevent COVID-19, did not show a decreased risk of SARS-CoV-2 infection [4]. However, small randomized control trials (RCTs) and retrospective studies have demonstrated that colchicine effectively treats COVID-19 and significantly improves the prognosis [5-7]. The COLCORONA trial was a large RCT of 4488 outpatients diagnosed with mild COVID-19 diagnosed by polymerase chain reaction (PCR) testing or clinical criteria [8]. The COLCORONA trial showed that colchicine had no statistically significant effect on the composite endpoint of death or hospital admission for COVID-19 (odds ratio [OR] 0.79; 95% confidence interval [CI] 0.61～1.03, p=0.081). However, of all 4,488 patients, PCR-confirmed COVID-19 patients were 4,159 (92.7%), and subgroup analysis for these patients showed significantly lower mortality and hospital admission rates than the placebo group (OR 0.75; 95% CI 0.57～0.99, p=0.042). The NIH guidelines suggested that colchicine and other immunomodulators could be considered but stopped recommending them because of insufficient evidence of their effectiveness. This study had limitations that challenged to provide targeted results. Contrary to the initial plan, the COLCORONA trial included only 75% of eligible patients due to various circumstances (substantial logistical, personal, and financial problems maintaining the central study call cen-

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ter continuously operating 24 hours a day). Thus, the study showed that the p-value for the primary composite endpoint of 0.081. In addition, colchicine was initially administered twice daily and decreased to once daily after three days. This management differs from the continued twice daily administration in other previous studies where significant effects were observed [5-7]. Colchicine bioavailability widely varies (from 24% to 88% of the administered dose) [9]. Therefore, once daily administration may not be effective in patients who require twice daily administration to suppress inflammation. Gastrointestinal side effects are more likely if colchicine is administered twice daily and with higher doses. To reduce the possibility of side effects, decreasing the dose from twice daily to once daily, or reducing the dose by half if the side effect persists after reducing the frequency to once daily administration, may help. Thus, using a flexible dosing strategy can further improve the prognosis of COVID-19 patients due to greater inhibition of inflammation.

Colchicine has a different mechanism of action against COVID-19; combining it with NIH-recommended drugs, such as bamlanivimab plus etesevimab, casirivimab plus imdevimab, and remdesivir, may enhance its effectiveness in treating COVID-19 patients. In addition, unlike glucocorticoids that inhibit various inflammatory cells such as lymphocytes, which are essential for antiviral immunity [10], colchicine acts primarily on neutrophils and macrophages associated with hyperinflammation and cytokine storm [11]. Therefore, hyperinflammation and cytokine storm can be suppressed while minimizing lymphocyte inhibition, which is vital for viral immunity, thereby minimizing the effect of SARS-CoV-2 infection or secondary bacterial infection.

Colchicine is inexpensive and is administered orally; therefore, it is a viable drug suitable for use in developing countries for treating COVID-19. However, further research is needed to clarify the therapeutic effect of colchicine in COVID-19 patients who do not require dexamethasone or tocilizumab treatment.

## CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

## AUTHOR CONTRIBUTIONS

Writing-original draft: B.G. Writing-review & editing: B.G. and J.K.

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