JAMA Network Open

Invited Commentary | Infectious Diseases

Colchicine for the Treatment of Myocardial Injury in Patients With Coronavirus Disease 2019 (COVID-19)—An Old Drug With New Life?

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has infected more than 6 million individuals worldwide, leading to the ongoing coronavirus disease 2019 (COVID-19) pandemic and significant morbidity and mortality. Patients with active myocardial injury (ie, elevated troponin levels) are at a very high risk, with mortality rates reaching as high as 40%.[1,2] In particular, the subset of patients with evidence of myocardial injury and underlying cardiovascular disease are at exceedingly high risk, with mortality rates of nearly 70%.[1,2] While several mechanisms have been postulated for how SARS-CoV-2 may damage the lungs, heart, and other organs, indirect damage from innate, cellular, and/or humoral immune responses, including a severe cytokine storm, is a leading hypothesis supported by numerous studies reporting significantly elevated inflammatory biomarkers in patients with COVID-19.

Despite global efforts to identify effective therapies to combat COVID-19, to date there remain limited options supported by randomized clinical trial (RCT) data. In addition to antiviral agents, many novel anti-inflammatory agents, including interleukins 1 and 6, granulocyte macrophage colony stimulating factor, and C-C motif chemokine receptor 5 inhibitors, are being investigated in patients with COVID-19. However, many of these agents require intravenous administration in a hospital, are very expensive, do not have proven safety profiles, and are not widely available. Colchicine is an old anti-inflammatory drug derived from *Colchicum autumnale* that was used for joint swelling as early as 2000 BC and was first used to treat gout in the sixth century. It was initially approved by the US Food and Drug Administration in October 2009 for the treatment of gout and familial Mediterranean fever. Colchicine is a microtubule polymerization inhibitor and an inhibitor of interleukins 1 and 6, granulocyte macrophage colony stimulating factor, and the nucleotide-binding oligomerization leucine-rich repeat and pyrin domain (NLRP3) inflammasome, making it a potent anti-inflammatory agent.[3] More recently, colchicine's use in various cardiovascular conditions has been reported, including in the treatment of acute and recurrent pericarditis and postcardiotomy syndrome and for the reduction of major adverse cardiovascular events after acute myocardial infarction.[4-6] Although dose adjustments are required for certain comorbidities and concomitant drugs, colchicine is well established, safe, cost-effective, widely available, and orally administered, making it an attractive potential therapeutic option for patients with COVID-19. Indeed, colchicine would be an important addition to the frontline therapeutic COVID-19 resources accessible to patients even in resource-poor regions where costly and/or experimental treatments may not be available.

The study by Deftereos et al[7] provides intriguing initial data on the effect of colchicine on clinical outcomes in patients with COVID-19. The GRECCO-19 trial was an open-label RCT with 1:1 randomization comparing optimal medical treatment plus colchicine with optimal medical treatment alone (control group) among 105 patients from 16 Greek medical centers. Importantly, this open-label design allowed patients in either treatment group to be coenrolled in other RCTs and to receive investigational drugs. Inclusion criteria included a SARS-CoV-2 infection confirmed with polymerase chain reaction testing and 2 additional indicators of clinical infection. Study end point analysis was performed in 2 phases—the primary end point of the early biochemical phase was the difference in peak high-sensitivity troponin levels between the 2 groups, while the primary end point for the later clinical phase was clinical deterioration using the 7-point World Health Organization R&D Blueprint Ordinal Clinical Scale (defined as a 2-grade increase on the scale during the index hospitalization or

within 3 weeks of enrollment). The authors found that although biochemical evidence of myocardial injury between the 2 groups was similar, patients who received colchicine had significantly less clinical deterioration (1 patient [1.8%] vs 7 patients [14.0%]; odds ratio; 0.11; 95% CI, 0.01-0,96; *P* = .02). This deterioration in the control group was driven mainly by the need for mechanical ventilation. Additional findings included no between-group differences in C-reactive protein levels but significantly lower dimerized plasma fragment D levels in the colchicine group, suggesting colchicine-induced attenuation of the prothrombotic milieu. Notably, there were no significant differences in adverse events between the 2 groups.

The authors should be commended for conducting a well-designed, multicenter RCT in such a short period. Trial enrollment in the study was unfortunately limited by a dramatic reduction in the number of COVID-19 cases presenting in Greece, resulting in a small sample size and rendering the data hypothesis generating. Interestingly, the authors did not see a significant reduction in troponin levels with colchicine. This finding can be partly explained by the trial's inclusion criteria, which did not require an elevated troponin level. Furthermore, the median troponin levels were quite low and not clinically meaningful; this coupled with the trial's low event rate and very low mortality rate (ie, 5 of 105 patients [4.8%]) reflect a reasonably healthy study population in which troponin levels are likely to be in the reference range. However, they did observe a significant reduction in dimerized plasma fragment D levels in the colchicine group. This is an important and novel finding given that it suggests colchicine's mechanism of action to treat COVID-19 may be antithrombotic as well as anti-inflammatory. Deftereos et al[7] provide several intriguing hypotheses regarding how colchicine may be effective, from disrupting viral endocytosis to blunting the inflammatory cascade mediated by the NLRP3 inflammasome complex and other cytokines. Their work suggests that although an elevated troponin level may be a marker of poor outcomes, other processes, including thrombosis, may also be important determinants of outcomes. Future studies are needed to address the role of colchicine in patients with COVID-19 who present specifically with myocardial injury to assess whether there is a cardioprotective effect and, if so, the mechanisms by which it provides that effect.

A few limitations must be considered when interpreting the GRECCO-19 trial. First, as previously described, the study allowed for cotreatment with other investigational agents; nearly all patients received hydroxychloroquine and azithromycin (103 [98.1%]), one-third received lopinavir or ritonavir (34 [32.4%]), one-half received anticoagulation therapy (57 [54.3%]), and none received remdesivir. Although no significant differences were observed between the 2 groups in the use of these treatments, this extensive cotreatment makes the study less generalizable. Second, as mentioned earlier, the trial's small sample size combined with the low event rate make these data underpowered and hypothesis generating. Nonetheless, the results of the GRECCO-19 trial suggest that colchicine is safe and may improve outcomes in patients with COVID-19. These data will need to be corroborated with larger, longer-term studies. To that end, there are 12 ongoing trials listed on ClinicalTrials.gov that are actively recruiting patients with COVID-19 to evaluate the role of colchicine. These include the large outpatient Colchicine Coronavirus SARS-CoV-2 (COLCORONA) trial and the smaller inpatient Colchicine for the Treatment of Cardiac Injury in Hospitalized Patients with COVID-19 (COLHEART-19) trial, which will specifically evaluate the role of colchicine in patients with cardiac manifestations of disease. For now, we congratulate Deftereos et al[7] for adding to our growing scientific understanding of COVID-19 and showing us that an old drug may still have new life.

ARTICLE INFORMATION

Published: June 24, 2020. doi:10.1001/jamanetworkopen.2020.13556

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Conflict of Interest Disclosures: None reported.

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