Colchicine is an anti-inflammatory drug that is used to treat a variety of conditions, including gout, recurrent pericarditis, and familial Mediterranean fever. Recently, the drug has been shown to potentially reduce the risk of cardiovascular events in those with coronary artery disease. Colchicine has several potential mechanisms of action, including reducing the chemotaxis of neutrophils, inhibiting inflammasome signaling, and decreasing the production of cytokines, such as interleukin-1 beta. When colchicine is administered early in the course of COVID-19, these mechanisms could potentially mitigate or prevent inflammation-associated manifestations of the disease. These anti-inflammatory properties coupled with the drug’s limited immunosuppressive potential, favorable safety profile, and widespread availability have prompted investigation of colchicine for the treatment of COVID-19.

**Recommendations**

- The COVID-19 Treatment Guidelines Panel (the Panel) **recommends against** the use of colchicine for the treatment of nonhospitalized patients with COVID-19, except in a clinical trial (BIIa).
- The Panel **recommends against** the use of colchicine for the treatment of hospitalized patients with COVID-19 (AI).

**Rationale**

**For Nonhospitalized Patients With COVID-19**

COLCORONA, a large randomized placebo-controlled trial that evaluated colchicine in outpatients with COVID-19, did not reach its primary efficacy endpoint of reducing hospitalizations and death. However, in the subset of patients whose diagnosis was confirmed by a positive SARS-CoV-2 polymerase chain reaction (PCR) result from a nasopharyngeal (NP) swab, a slight reduction in hospitalizations was observed among those who received colchicine.

PRINCIPLE, another randomized, open-label, adaptive-platform trial that evaluated colchicine versus usual care, was stopped for futility when no significant difference in time to first self-reported recovery from COVID-19 between the colchicine and usual care recipients was found.

The PRINCIPLE trial showed no benefit of colchicine, and the larger COLCORONA trial failed to reach its primary endpoint, found only a very modest effect of colchicine in the subgroup of patients with positive SARS-CoV-2 PCR results, and reported more gastrointestinal adverse events in those receiving colchicine. Therefore, the Panel **recommends against** the use of colchicine for the treatment of COVID-19 in nonhospitalized patients, except in a clinical trial (BIIa).

**For Hospitalized Patients With COVID-19**

In the RECOVERY trial, a large randomized trial in hospitalized patients with COVID-19, colchicine demonstrated no benefit with regard to 28-day mortality or any secondary outcomes. Based on the results from this large trial, the Panel **recommends against** the use of colchicine for the treatment of COVID-19 in hospitalized patients (AI).

**Clinical Data for COVID-19**

**Colchicine in Nonhospitalized Patients With COVID-19**

**The COLCORONA Trial**

The COLCORONA trial was a contactless, double-blind, placebo-controlled, randomized trial in...
outpatients who received a diagnosis of COVID-19 within 24 hours of enrollment. Participants were aged ≥70 years or aged ≥40 years with at least 1 of the following risk factors for COVID-19 complications: body mass index ≥30, diabetes mellitus, uncontrolled hypertension, known respiratory disease, heart failure or coronary disease, fever ≥38.4°C within the last 48 hours, dyspnea at presentation, bicytopenia, pancytopenia, or the combination of high neutrophil count and low lymphocyte count. Participants were randomized 1:1 to receive colchicine 0.5 mg twice daily for 3 days and then once daily for 27 days or placebo. The primary endpoint was a composite of death or hospitalization by Day 30; secondary endpoints included components of the primary endpoint, as well as the need for mechanical ventilation by Day 30. Participants reported by telephone the occurrence of any study endpoints at 15 and 30 days after randomization; in some cases, clinical data were confirmed or obtained by medical chart reviews.4

Results

• The study enrolled 4,488 participants.
• The primary endpoint occurred in 104 of 2,235 participants (4.7%) in the colchicine arm and 131 of 2,253 participants (5.8%) in the placebo arm (OR 0.79; 95% CI, 0.61–1.03; P = 0.08).
• There were no statistically significant differences in the secondary outcomes between the arms.
• In a prespecified analysis of 4,159 participants who had a SARS-CoV-2 diagnosis confirmed by PCR testing of an NP specimen (93% of those enrolled), those in the colchicine arm were less likely to reach the primary endpoint (96 of 2,075 participants [4.6%]) than those in the placebo arm (126 of 2,084 participants [6.0%]; OR 0.75; 95% CI, 0.57–0.99; P = 0.04). In this subgroup of patients with PCR-confirmed SARS-CoV-2 infection, there were fewer hospitalizations (a secondary outcome) in the colchicine arm (4.5% of patients) than in the placebo arm (5.9% of patients; OR 0.75; 95% CI, 0.57–0.99).
• More participants in the colchicine arm experienced gastrointestinal adverse events, including diarrhea which occurred in 13.7% of colchicine recipients versus 7.3% of placebo recipients (P < 0.0001). Unexpectedly, more pulmonary emboli were reported in the colchicine arm than in the placebo arm (11 events [0.5% of patients] vs. 2 events [0.1% of patients]; P = 0.01).

Limitations

• Due to logistical difficulties with staffing, the trial was stopped at approximately 75% of the target enrollment, which may have limited the study’s power to detect differences for the primary outcome.
• There was uncertainty as to the accuracy of COVID-19 diagnoses in presumptive cases.
• Some patient-reported clinical outcomes were potentially misclassified.

The PRINCIPLE Trial

PRINCIPLE is a randomized, open-label, platform trial that evaluated colchicine in symptomatic, nonhospitalized patients with COVID-19 who were aged ≥65 years or aged ≥18 years with comorbidities or shortness of breath, and who had symptoms for ≤14 days. Participants were randomized to receive colchicine 0.5 mg daily for 14 days or usual care. The coprimary endpoints, which included time to first self-reported recovery or hospitalization or death due to COVID-19 by Day 28, were analyzed using a Bayesian model. Participants were followed through symptom diaries that they completed online daily; those who did not complete the diaries were contacted by telephone on Days 7, 14, and 29. The investigators developed a prespecified criterion for futility, specifying a clinically meaningful benefit in time to first self-reported recovery as a hazard ratio ≥1.2, corresponding to about 1.5 days of faster recovery in the colchicine arm.

Results

• The study enrolled 4,997 participants: 212 participants were randomized to receive colchicine;
2,081 to receive usual care alone; and 2,704 to receive other treatments.

- The prespecified primary analysis included participants with SARS-CoV-2 positive test results (156 in the colchicine arm; 1,145 in the usual care arm; and 1,454 in the other treatments arm).
- The trial was stopped early because the criterion for futility was met; the median time to self-reported recovery was similar in the colchicine arm and the usual care arm (HR 0.92; 95% CrI, 0.72–1.16).
- Analyses of self-reported time to recovery and hospitalizations or death due to COVID-19 among concurrent controls also showed no significant differences between the colchicine and usual care arms.
- There were no statistically significant differences in the secondary outcomes between the colchicine and usual care arms in both the primary analysis population and in subgroups, including subgroups based on symptom duration, baseline disease severity, age, or comorbidities.
- The occurrence of adverse events was similar in the colchicine and usual care arms.

Limitations

- The design of the study was open-label treatment.
- The sample size of the colchicine arm was small.

Colchicine in Hospitalized Patients With COVID-19

The RECOVERY Trial

In the RECOVERY trial, hospitalized patients with COVID-19 were randomized to receive colchicine (1 mg loading dose, followed by 0.5 mg 12 hours later, and then 0.5 mg twice daily for 10 days or until discharge) or usual care.6

Results

- The study enrolled 11,340 participants.
- At randomization, 10,603 patients (94%) were receiving corticosteroids.
- The primary endpoint of all-cause mortality at Day 28 occurred in 1,173 of 5,610 participants (21%) in the colchicine arm and 1,190 of 5,730 participants (21%) in the placebo arm (rate ratio 1.01; 95% CI, 0.93–1.10; P = 0.77).
- There were no statistically significant differences between the arms for the secondary outcomes of median time to being discharged alive, discharge from the hospital within 28 days, and receipt of mechanical ventilation or death.
- The incidence of new cardiac arrhythmias, bleeding events, and thrombotic events was similar in the 2 arms. Two serious adverse events were attributed to colchicine: 1 case of severe acute kidney injury and one case of rhabdomyolysis.

Limitations

- The trial’s open-label design may have introduced bias for assessing some of the secondary endpoints.

The GRECCO-19 Trial

GRECCO-19 was a small, prospective, open-label randomized clinical trial in 105 patients hospitalized with COVID-19 across 16 hospitals in Greece. Patients were assigned 1:1 to receive standard of care with colchicine (1.5 mg loading dose, followed by 0.5 mg after 60 minutes and then 0.5 mg twice daily until hospital discharge or for up to 3 weeks) or standard of care alone.7
Results

• Fewer patients in the colchicine arm (1 of 55 patients) than in the standard of care arm (7 of 50 patients) reached the primary clinical endpoint of deterioration in clinical status from baseline by 2 points on a 7-point clinical status scale (OR 0.11; 95% CI, 0.01–0.96).
• Participants in the colchicine group were significantly more likely to experience diarrhea (occurred in 45.5% of participants in the colchicine arm vs. 18.0% in the standard of care arm; \( P = 0.003 \)).

Limitations

• The overall sample size and the number of clinical events reported were small.
• The study design was open-label treatment assignment.

The results of several small randomized trials and retrospective cohort studies that have evaluated various doses and durations of colchicine in hospitalized patients with COVID-19 have been published in peer-reviewed journals or made available as preliminary, non-peer-reviewed reports. Some have shown benefits of colchicine use, including less need for supplemental oxygen, improvements in clinical status on an ordinal clinical scale, and reductions in certain inflammatory markers. In addition, some studies have reported higher discharge rates or fewer deaths among patients who received colchicine than among those who received comparator drugs or placebo. However, the findings of these studies are difficult to interpret due to significant design or methodological limitations, including small sample sizes, open-label designs, and differences in the clinical and demographic characteristics of participants and permitted use of various cotreatments (e.g., remdesivir, corticosteroids) in the treatment arms.

Adverse Effects, Monitoring, and Drug-Drug Interactions

Common adverse effects of colchicine include diarrhea, nausea, vomiting, abdominal cramping and pain, bloating, and loss of appetite. In rare cases, colchicine is associated with serious adverse events, such as neuromyotoxicity and blood dyscrasias. Use of colchicine should be avoided in patients with severe renal insufficiency, and patients with moderate renal insufficiency who receive the drug should be monitored for adverse effects. Caution should be used when colchicine is coadministered with drugs that inhibit cytochrome P450 (CYP) 3A4 and/or P-glycoprotein (P-gp) because such use may increase the risk of colchicine-induced adverse effects due to significant increases in colchicine plasma levels. The risk of myopathy may be increased with the concomitant use of certain HMG-CoA reductase inhibitors (e.g., atorvastatin, lovastatin, simvastatin) due to potential competitive interactions mediated by CYP3A4 and P-gp pathways. Fatal colchicine toxicity has been reported in individuals with renal or hepatic impairment who received colchicine in conjunction with P-gp inhibitors or strong CYP3A4 inhibitors.

Considerations in Pregnancy

There are limited data on the use of colchicine in pregnancy. Fetal risk cannot be ruled out based on data from animal studies and the drug’s mechanism of action. Colchicine crosses the placenta and has antimitotic properties, which raises a theoretical concern for teratogenicity. However, a recent meta-analysis did not find that colchicine exposure during pregnancy increased the rates of miscarriage or major fetal malformations. There are no data for colchicine use in pregnant women with acute COVID-19. Risks of use should be balanced against potential benefits.

Considerations in Children

Colchicine is most commonly used in children to treat periodic fever syndromes and autoinflammatory conditions. Although colchicine is generally considered safe and well tolerated in children, there are no data on the use of the drug to treat pediatric acute COVID-19 or multisystem inflammatory syndrome in children (MIS-C).
References


12. Colchicine (Colcrys) [package insert]. Food and Drug Administration. 2012. Available at: [https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/022352s017lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/022352s017lbl.pdf).
