



Colchicine

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Colchicine is an anti-inflammatory drug that is used to treat a variety of conditions, including gout, recurrent pericarditis, and familial Mediterranean fever.¹ Recently, the drug has been shown to potentially reduce the risk of cardiovascular events in those with coronary artery disease.² 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.³ 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: Nonhospitalized Patients

COLCORONA, a large, placebo-controlled, randomized trial that evaluated colchicine in outpatients with COVID-19, did not reach its primary efficacy endpoint of reducing hospitalizations and death.⁴ However, in the subset of patients whose diagnosis was confirmed by a positive SARS-CoV-2 polymerase chain reaction (PCR) result from a nasopharyngeal swab, a slight reduction in hospitalizations was observed among those who received colchicine.

PRINCIPLE, an open-label, adaptive-platform, randomized trial that evaluated colchicine versus usual care, was stopped for futility when no significant difference was found between the colchicine and usual care recipients for the outcome of time to first self-reported recovery from COVID-19.⁵

The PRINCIPLE trial showed no benefit for 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 for 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**).

Rationale: Hospitalized Patients

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.⁶ 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

COLCORONA Trial: Nonhospitalized Patients

The COLCORONA trial was a double-blind, placebo-controlled, randomized trial in outpatients who

received a diagnosis of COVID-19 within 24 hours of enrollment.⁴ Participants were aged ≥ 70 years or aged ≥ 40 years with at least 1 of the following criteria: body mass index ≥ 30 , diabetes mellitus, uncontrolled hypertension, known respiratory disease, heart failure or coronary disease, fever $\geq 38.4^{\circ}\text{C}$ within the past 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 placebo or colchicine 0.5 mg twice daily for 3 days, then once daily for 27 days. 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.

Results

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

Limitations

- The trial stopped at approximately 75% of the target enrollment, which may have limited the study's power to detect differences for the primary outcome.
- Some patient-reported clinical outcomes potentially were misclassified.

PRINCIPLE Trial: Nonhospitalized Patients

PRINCIPLE was a randomized, open-label, platform trial that evaluated colchicine in symptomatic, nonhospitalized patients with COVID-19.⁵ Included participants had symptoms for ≤ 14 days and were aged ≥ 65 years or aged ≥ 18 years with comorbidities or shortness of breath. 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. Futility was defined as not reaching a clinically meaningful benefit (i.e., a hazard ratio ≥ 1.2 , corresponding to about 1.5 days of faster recovery in the colchicine arm) for the endpoint of time to first self-reported recovery.

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 a positive test for SARS-CoV-2 (156 participants in the colchicine arm; 1,145 in the usual care arm; and 1,454 in the other treatments

arm).

- The trial stopped early because of futility; 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 showed no significant differences between the colchicine and usual care arms for self-reported time to recovery and for hospitalizations or death due to COVID-19.
- There were no statistically significant differences between the colchicine and usual care arms for the secondary outcomes in both the primary analysis population and in the subgroups, including the subgroups based on symptom duration, baseline disease severity, age, and comorbidities.
- The occurrence of adverse events was similar in the colchicine and usual care arms.

Limitations

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

RECOVERY Trial: Hospitalized Patients

In the RECOVERY trial, hospitalized patients with COVID-19 were randomized 1:1 to receive colchicine (1 mg followed by 0.5 mg 12 hours later, 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, 94% of participants were receiving corticosteroids.
- In both arms, the primary endpoint of all-cause mortality at Day 28 occurred in 21% of participants (rate ratio 1.01; 95% CI, 0.93–1.10; $P = 0.77$).
- There were no statistically significant differences between the arms for the endpoints of median time to discharge 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 1 case of rhabdomyolysis.

Limitation

- The study had an open-label design.

COLCOVID Trial: Hospitalized Patients

COLCOVID was a multicenter, open-label, randomized trial in hospitalized adults with confirmed or suspected SARS-CoV-2.⁷ Patients were assigned 1:1 to receive either colchicine (1.5 mg followed by 0.5 mg orally within 2 hours of initial dose, then twice daily for 14 days or until hospital discharge) plus usual care or usual care alone.

Results

- The study enrolled 1,279 participants.
- There were no statistically significant differences between the colchicine and usual care arms for either of the coprimary outcomes, which were mortality by Day 28 (HR 0.88; 95% CI, 0.70–1.12) and mechanical ventilation or mortality by Day 28 (HR 0.83; 95% CI, 0.67–1.02).
- More individuals in the colchicine arm than in the usual care arm experienced diarrhea (11.3% vs.

4.5%).

Limitation

- The study had an open-label design.

GRECCO-19 Trial: Hospitalized Patients

GRECCO-19 was a prospective, open-label, randomized clinical trial that included patients with COVID-19 from 16 hospitals in Greece.⁸ Participants were assigned 1:1 to receive colchicine (1.5 mg followed by 0.5 mg after 60 minutes, then 0.5 mg twice daily for up to 3 weeks or until hospital discharge, whichever comes first) plus the standard of care or the standard of care alone.

Results

- The study enrolled 105 participants.
- Fewer participants in the colchicine arm (1 of 55 participants) than in the standard of care arm (7 of 50 participants) reached the primary clinical endpoint of clinical status deterioration 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 arm were significantly more likely to experience diarrhea than those in the standard of care arm (45.5% vs. 18.0%; $P = 0.003$).

Limitations

- The study had an open-label design.
- The sample size and number of clinical events were small.

The results of several small, randomized trials and retrospective cohort studies that evaluated various doses and durations of colchicine in hospitalized patients with COVID-19 have been published in peer-reviewed journals or been made available as preliminary, non-peer-reviewed reports.^{9–12} Some of those studies showed 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 reported higher discharge rates or fewer deaths among patients who received colchicine than among those who received comparator drugs or placebos. However, the findings from these studies are difficult to interpret due to significant design or methodological limitations, including small sample sizes, open-label designs, differences in the clinical and demographic characteristics of participants, and differences in the cotreatments (e.g., remdesivir, corticosteroids) permitted 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. Colchicine clearance is decreased in patients with impaired renal function and may require dose reduction along with increased monitoring for adverse effects. Significant increases in colchicine plasma levels may occur when colchicine is coadministered with drugs that inhibit cytochrome P450 (CYP) 3A4 or P-glycoprotein (P-gp), increasing the risk of colchicine-induced adverse effects. The risk of myopathy may be increased with 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.^{13,14} 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 antimetabolic 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.^{13,15}

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).

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