Should Colchicine be used in the treatment of COVID-19?

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This rapid review summarizes the available evidence on the efficacy and safety of Colchicine in treating patients with COVID-19. This may change as new evidence emerges.

KEY FINDINGS

There is insufficient evidence to conclude on the effectiveness of colchicine in the management of COVID-19. Currently, there are 13 ongoing clinical trials.

- Colchicine is an anti-inflammatory agent currently being used for gout, familial Mediterranean fever, Behcet's syndrome as well as pericarditis.
- Its powerful anti-inflammatory properties may have the potential to prevent the development of COVID-19 complications.
- The GRECCO-19 randomized controlled trial showed that participants who received colchicine on top of standard treatment had a statistically significant improvement in time to clinical deterioration compared to those who did not receive colchicine (OR 0.11 (95% CI 0.01, 0.96)). The results however must be interpreted with caution.
- There are still 13 ongoing studies that may be released from the period of July 2020 to December 2020.
- Common adverse events include gastrointestinal effects such as diarrhea but does not exhibit serious and life-threatening adverse events.
- There is no mention of colchicine in the WHO Interim Guidance or US CDC Clinical Interim Guidelines for COVID-19 management at this time.

BACKGROUND

Colchicine has a unique anti-inflammatory property with a prolonged anti-inflammatory effect even after discontinuation.[1] According to a study by Leung (2015), the mechanisms of action of colchicine on the immune system includes inhibition of neutrophil chemotaxis, adhesion and mobilization, and superoxide production as well as inhibition of NACHT-LRRPYD-containing protein 3 (NALP3) inflammasomes and interleukin (IL) 1β processing and release.[3] It's primary mechanism is tubulin disruption leading to subsequent down regulation of multiple inflammatory pathways and modulation of innate immunity.[3] It is this inflammatory mechanism that may potentially have an effect on the clinical course of the patient with COVID-19 in terms of developing pneumonia and other cardiac complications.

RESULTS

The first to release its results was the GRECCO-19 randomized controlled trial.[4] This trial recruited 105 hospitalized adult patients diagnosed with SARS-CoV-2 infection by polymerase chain reaction–reverse transcriptase testing. Eligibility is confirmed if with fever and 2 or more additional symptoms that included cough, sustained sore throat, anosmia and/or ageusia, fatigue and arterial oxygen partial pressure lower than 95mmHg. The eligible patients were allocated to either standard medical treatment or colchicine on top of standard medical treatment. The colchicine was given as a loading dose of 1.5 mg followed after 60 minutes by 0.5 mg. The 0.5 mg was then given twice a day for 21 days or until discharged.

The primary endpoints included a biochemical phase and a clinical phase. In the early biochemical phase they looked at the maximum high-sensitivity cardiac troponin level and time for C-reactive protein to reach more than 3 times the upper reference limit. The clinical phase looked at time from baseline to clinical deterioration by 2 points on a 7-grade clinical status scale ranging from able to resume normal activities to death. Secondary endpoints were percentage of patients requiring mechanical ventilation, mortality, and serious adverse events.

The GRECCO-19 study was not explicit in its allocation methods, it is an open label study where colchicine with standard care was compared to standard care alone opening it to potential risk of bias. Baseline characteristics were comparable and the outcome measurements were standard and objective. Analysis was by intent-to-treat and there were no drop-outs. Overall risk of bias for this study was deemed to be moderate because of the issues presented. The conclusions can still change as more studies or evidence are released.

This study did not show significant differences in the biochemical phase in terms of high-sensitivity cardiac troponin or C-reactive protein levels. However, it showed a statistically significant improvement in time to clinical deterioration with an odds ratio of 0.11 (95% CI 0.01, 0.96) favoring colchicine, but only by a very narrow margin. Furthermore, the event rates are quite low (Colchicine = 1/50, Placebo = 7/55) that compromises the robustness of the statistical analysis. We computed for the RR which showed no effect RR 0.16 (0.02 to 1.23) with a very wide confidence interval. Cumulative event free 10-day survival was 83% in the control group compared to 97% in the colchicine group (p=0.03).[4]

There were similar adverse events in the 2 groups except for diarrhea as this was more frequent in the colchicine group (25 patients) than in the control group (9 patients) that would give an odds ratio of 3.79 (95% CI 1.55, 9.2).[4] However, this was reported as generally self-limiting.

All 13 ongoing trials are randomized controlled trials recruiting from as little as 70 patients to as high as 6000. Five (5) of these trials are phase 3 while the rest are phase 2 trials. Countries involved in these trials include Argentina, Canada, Greece, Iran, Italy, Mexico, Russia (Moscow), Spain, and USA. The details of the ongoing trials are in Table 1.

Recommendations from Other Guidelines

There are currently no specific recommendations for the use of colchicine for COVID-19 patients in the WHO Interim Guidance, US-NIH COVID-19 treatment Guidelines, PSMID guidelines at this time.[5-7]

CONCLUSION

Hospitalized patients with COVID-19 showed an improved time to clinical deterioration with colchicine compared to no colchicine. Because this observed difference was very small with wide confidence interval, the use of colchicine must still be approached with caution, taking into consideration the adverse events that can manifest with its use. Evidence can still change as more studies are completed.

Declaration of Conflict of Interest

No conflict of interest.

CONCLUSION

Presently, there is insufficient evidence regarding the use of BCG vaccine as prophylaxis to COVID-19. The results of ongoing clinical trials are needed.

Declaration of Conflict of Interest

No conflict of interest

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Table 1. Characteristics of included studies

No.	Clinical Trial ID / Title	Status	Primary Completion / Study Completion Date	Phase & Study design	Locations	Target Sample Size & Population	Intervention Group(s)	Comparison Group(s)	Outcomes
1	Colchicine Coronavirus SARS-CoV2 Trial (COLCORONA)	Recruiting	Sept 2020 / Sept 2020	Phase 3 RCT Single blind (participant)	Canada USA Spain	6000 Adults 40 years and older; with COVID-19 infection within the last 24 hours; Outpatient setting (not hospitalized); Must possess at least 1 high-risk criteria	Colchicine 0.5mg twice daily for first 3 days and then once daily for the last 27 days	Placebo twice daily for the first 3 days and then once daily for the last 27 days	- Number of participants who die or require hospitalization due to COVID-19 infection - Number of participants who die - Number of participants requiring hospitalization due to COVID-19 infection - Number of participants requiring mechanical ventilation
2	Colchicine in Moderate-Severe Hospitalized Patient Before ARDS to Treat COVID-19	Recruiting	May 2020 / June 2020	Phase 2 RCT Open label	USA	70 Adults 18 years and older; hospitalized and requiring care for COVID-19	Colchicine starting dose of 1.2 mg followed by 0.6mg after 2 hours if they do not have significant gastrointestinal symptoms, on day 1. After that, they will take colchicine 0.6mg twice a day for 14 days or until discharged or release from the hospital.	Usual care	- Percentage of patients requiring supplemental oxygen beyond 8L nasal cannula - Percentage of patients who will require mechanical ventilation - Hospital length of stay - Mortality - Maximum CRP - Maximum Troponin Elevation
3	Preemptive Therapy with Colchicine in Patients Older than 70 years with High Risk of Severe Pnuemoniae due to Coronavirus	Recruiting	Sept 2020 / Dec 2020	Phase 3 RCT Open label	Spain	1028 Adults 70 years and older; diagnosis of COVID-19 infection within the last 24 hours, confirmed by PCR test; Outpatient setting or in a nursing home.	Colchicine 0.5 mg orally (PO) twice daily for the first 3 days and then once daily for the last 18 days plus symptomatic treatment	Symptomatic treatment (paracetamol or best symptomatic treatment based on doctor recommendations)	- Number of participants who die due to COVID-19 infection - Number of participants who require hospitalization due to COVID-19 infection
4	Colchicine Counteracting Inflammation in COVID-19 Pneumonia (ColCOVID-19)	Recruiting	June 2020 / July 2020	Phase 2 RCT Open label	Italy	310 Adults 18 years and older; positive nasopharyngeal swab for COVID-19, asymptomatic or paucisymptomatic; and/or with clinical risk factors for poor outcome (clinically relevant chronic lung disease, diabetes and/or heart disease) or symptomatic with	Colchicine 1mg (or 0.5 mg in CKD)/day + standard of care for COVID-19 pneumonia	Standard of care for COVID-19 pneumonia	- Clinical improvement - Hospital discharge - Death - Clinical status - Mechanical ventilation - Hospitalizaiton - Time from treatment initiation to death - Time to negativization from COVID-19 - Fever

						respiratory or systemic symptoms			
5	Colchicine in COVID-19: A Pilot Study	Recruiting	June 2020 / Oct 2020	Phase 2 RCT Open Label	Italy	308 18 years and older; virological diagnosis of SARS-CoV-2 infection (real-time PCR); Hospitalized due to clinical/instrumental diagnosis of pneumonia; Oxygen saturation at rest in ambient air ≤94%	Colchicine 0.5 mg three times a day if weight is less than 100 kg; 1 mg twice a day if weight is more than 100 kg for 30 days or up to discharge plus current care	Current care alone	- Rate of entering the critical stage - Trend of White blood cell count - Change of the "Sequential Organ failure Assessment" (SOFA) - Rate of biochemical criterion (CK, ALT, ferritin) recovery - Rate of disease remission - Toxicity of Colchicine
6	Colchicine Plus Phenolic Monoterpenes to Treat COVID-19	Recruiting	June 2020 / Oct 2020	Phase 1, 2 RCT Double blind	Iran	200 10 years or older defined cases of COVID-19 based on laboratory and/or radiological and clinical manifestation	Colchicine plus a Herbal extraction containing a Phenolic Monoterpene Fractions will be added to standard treatment in patients with COVID-19	Standard Treatment for COVID-19 based on National Recommendations	- Mortality rate - Change in patients clinical manifestation - Length of hospitalization - C-reactive protein - lymphocyte count - serum lactate dehydrogenase - serum Interleukin-6 - erythrocyte sedimentation rate
7	Colchicine Twice Daily During 10 Days as an Option for the Treatment of Symptoms Induced by Inflammation in Patients With Mild and Severe Coronavirus Disease (ColchiVID)	Recruiting	April 2021 / April 2021	Phase 2 RCT Quadruple blind	Mexico	174 18 years and older; diagnosed with COVID-19; hospitalized	Colchicine 1mg, 1 ½ pill in day 1 and ½ pill BID during 10 days in both mild and severe COVID-19	Placebo, 1 ½ pill in day 1 and ½ pill BID during 10 days in both mild and severe COVID-19	- Number of patients with improvement in body temperature, myalgia, arthralgia, total lymphocyte count, D-dimer, fibrinogen and ferritin levels - Progression to severe disease
8	Colchicine to Reduce Cardiac Injury in COVID-19 (COLHEART-19)	Recruiting	April 2021 / April 2021	Phase 2 RCT Open Label	USA	150 18 years and older; Confirmed COVID-19 infection by polymerase chain reaction Cardiac injury	Colchicine 0.6 mg po BID x 30 days plus current care per UCLA treating physicians	Current care per UCLA physicians alone	- Composite of all-cause mortality, need for mechanical ventilation, or need for mechanical circulatory support (MCS) - Delta (peak minus baseline) troponin level - Delta (baseline to peak) brain natriuretic peptide (BNP) level - Change in left ventricular ejection fraction (LVEF) on echo - Delta (peak minus baseline) C-Reactive protein (CRP) inflammatory biomarker level - Delta (peak minus baseline) DDimer inflammatory biomarker level

									- Time (days) to primary endpoint - Number of participants requiring mechanical ventilation - Number of participants requiring MCS - Re-hospitalization at 90 days - All-cause mortality
9	The Effects of Standard Protocol With or Without Colchicine i n Covid-19 Infection	Recruiting	May 2020 / May 2020	Phase 2 RCT Double blind	Iran	80 >18 years old with nasopharyngeal swab confirmed COVID-19 PCR, CT involvement compatible with COVID, Fever and Dyspnea without hypoxemia	Colchicine 1.5 mg loading then 0.5 mg BID P.O. plus standard treatment	Standard treatment	- CRPxN/R ratio change - Clinical deterioration by the WHO definition - PCR Viral Load - CT severity involvement index - LDH change
10	Trial to Study the Benefit of Colchicine in Patients With COVID-19 (COL-COVID)	Recruiting	Oct 2020 / Nov 2020	Phase 3 RCT Open label	Spain	102 Adults 18 years and older; SARS-CoV-2 infection confirmed by PCR. Admitted in the hospital in the previous 48 hours, with clinical status 3, 4 or 5 of WHO classification	Colchicine initial dose of 1.5 mg (1 mg and 0.5 mg two hours after), followed by 0.5 mg every 12 hours during the next 7 days and 0.5 mg every 24 hours until the completion of 28 days of total treatment plus standard therapy	Standard therapy	- Changes in the patients' clinical status through the 7 points ordinal scale WHO R&D Blueprint expert group - Changes in IL-6 concentrations - Improvement in the clinical status - Changes in the score for the Sequential Organ Failure Assessment (SOFA score) - Changes in the punctuation in the National Early Warning Score - Number of days with invasive mechanical ventilation - Number of days with high flow oxygen therapy - Changes in other inflammatory markers - Changes in severity markers - Changes in myocardial damage
11	The ECLA PHRI COLCOVID Trial. Effects of Colchicine on Moderate/High-risk Hospitalized COVID -19 Patients. (COLCOVID)	Recruiting	June 2020 / Aug 2020	Phase 3 RCT Open label	Argentina	2500 Adults (age ≥18 years) COVID-19 suspicious and admitted to hospital or already in hospital and fever (with or without at the time of randomization) and SARS (severe acute respiratory syndrome) shortness of breath - (dyspnea) or image of typical or atypical pneumonia or	Local standard care plus colchicine with specific dosage schedule. Patients not receiving Lopinavir/Ritonavir: Loading dose of 1.5 mg followed by 0.5 mg after two hours. The next day 0.5 mg bid for 14 days or unil discharge	Local standard of care for COVID-19 SARS moderate / high-risk patients	- All-cause mortality - Composite outcome: Composite of intubation for mechanical ventilation or death.

						oxygen desaturation (SpO2 ≤ 93)	Patients receiving Lopinavir/Ritonavir: Loading dose of 0.5 mg then after 72 hours from the loading dose, 0.5 mg every 72 hours for 14 days or until discharge Under treatment with colchicine that are starting with Lopinavir/Ritonavir: Dose of 0.5 mg 72 hours after starting Lopinavir/Ritonavir then continue with 0.5 mg every 72 hours for 14 days or until discharge		
12	COLchicine Versus Ruxolitinib and Secukinumab In Open Prospective Randomized Trial (COLORIT)	Recruiting	July 2020 / Aug 2020	Phase 2 RCT Open label	Russia (Moscow)	70 Adults 18 years and older; COVID 19 with the mild and severe course - positive polymerase chain reaction (PCR) and/or virus pneumonia in computer tomography; Lung exposure on CT more than 25%; Sp02 without supportive oxygen ≤ 93%; C-reactive protein > 60 mg/l or elevation of C reactive protein 3 times in 8-14 days after first symptoms	Colchicine 0.5mg twice a day per os during the first three days and then 0.5mg daily per os if weight < 86 kg or 0.5mg twice a day per os if weight > 85kg for seven days. Plus standard therapy for COVID 19	Standard Treatment	- Change from baseline in clinical assessment score COVID 19 (CAS COVID 19) Frame: baseline - Combine endpoint: Time to death or mechanical ventilation - C-reactive protein - D-dimer - EuroQol Group. EQ-5D™ - exposure area on lung CT
13	Anti-Coronavirus Therapies to Prevent Progression of Coronavirus Dise ase 2019 (COVID-19) Trial (ACT COVID19)	Recruiting	Dec 2020 / June 2021	Phase 3 RCT Open label	Canada	4000 Adults 18 years and older; Symptomatic and laboratory-confirmed diagnosis of COVID-19; High risk; Within 7 days (ideally 72 hours) of diagnosis, or worsening clinically	Outpatients: Colchicine 0.6 mg twice daily for 3 days, then 0.6 mg once daily for 25 days (total 28 days). Inpatients: Colchicine 1.2 mg followed by 0.6 mg 2 hours later, then 0.6	Usual Care	- Composite of hospitalization or death - Disease progression by 2 points on a 7-point scale

							mg twice daily for 28 days		