Official Title: Colchicine in moderate severity hospitalized patients before ARDS to treat COVID-19 (the COMBAT-COVID-19 Pilot Study)

NCT Number: NCT04363437

Protocol ID: 2020-04-12

Date of Document: April 24, 2020

COlchicine in Moderate severity hospitalized patients Before ARDS to Treat COVID-19

(the COMBAT-COVID-19 Pilot Study)

PROTOCOL

TITLE Colchicine in moderate severity hospitalized patients before ARDS to treat COVID-19 (the COMBAT-COVID-19 Pilot Study)

INTRODUCTION

The most prevalent complication of COVID-19 infection is respiratory failure from severe acute respiratory syndrome (SARS), the leading cause of mortality. There is increasing indication that the decompensation in severe COVD-19 infection may be due to a cytokine storm syndrome. This hyperinflammatory syndrome results in a fulminant and fatal hypercytokinemia and multiorgan failure. There are a number of trials currently underway testing Remdesivir, Lopinavir/Ritonavir, Interferon, Hydroxychloroquine or Chloroquine, Tociluzimab, and Sarilumab however there is a concern that treatment in the late stages of COVID-19 infection may still yield poor outcomes. Approximately 15% of patients with COVID-19 infection are hospitalized and 20-30% of these hospitalized patients require ICU care and/or mechanical ventilation.[1] [2] Overall mortality in hospitalized patients is approximately 20-25%. There is significant interest in therapies that can be given upstream to reduce the rate of mechanical ventilation and thus mortality.

BACKGROUND AND SIGNIFICANCE

Cytokine storm and the inflammatory cascade activation is believed to be associated with significant rises in IL1B, IL6, IL12, IFNgamma, TNFalpha, IL15, IL17 and others. Several research studies are currently evaluating powerful anti-inflammatory drugs for COVID-19 including, steroids, IL1 inhibitors, and IL6 inhibitors. Colchicine is a strong anti-inflammatory medication approved for the

[1] The Incubation Period of Coronavirus Disease 2019 (COVID-19) From Publicly Reported Confirmed Cases: Estimation and Application. Lauer SA et al. Ann Intern Med. 2020 Mar 10.
[2] Viral dynaics in mild and severe cases of COVID-19. Yang Liu et al. The Lancet, March 19, 2020.

treatment of Familial Mediterranean Fever and gout, in doses ranging from 0.3 to 2.4mg daily. Its mechanism of action is through the inhibition of tubulin polymerization, as well as through potential effects on cellular adhesion molecules and inflammatory chemokines. It might also have direct anti-inflammatory effects by inhibiting key inflammatory signalling networks known as inflammasome and pro-inflammatory cytokines. Additionally, evidence suggests that colchicine exerts a direct anti-inflammatory effect by inhibiting the synthesis of tumor necrosis factor alpha and IL-6, monocyte migration, and the secretion of matrix metalloproteinase-9. Through the disruption of the cytoskeleton, colchicine is believed to suppress secretion of cytokines and chemokines as well as in vitro platelet aggregation. All these are potentially beneficial effects that might diminish or ameliorate the COVID-19 inflammatory storm associated with severe forms of the disease.

Regarding COVID-19, there have been reports that myocardial injury is frequently present. Cardiac biomarker elevation was found to be an independent predictor of the need for mechanical support.[3] Additionally, 33% of the patients had myocarditis and circulatory failure in one study from Wuhan.[4]

Experimental models have demonstrated that NLRP3 has a significant role in the development of ARDS.[5] [6] Structural dry-lab models have shown that the new SARS-CoV-2 proteins such as viroporins E, 3a and 8a play a significant role in viral

[3] Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. March 2020. doi:10.1016/s0140-6736(20)30566-3
[4] Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med. March 2020. doi:10.1007/s00134-020-05991-x
[5] Grailer JJ, Canning BA, Kalbitz M, et al. Critical Role for the NLRP3 Inflammasome during Acute Lung Injury. J Immunol. 2014;192(12):5974-5983. doi:10.4049/jimmunol.1400368
[6] Jones HD, Crother TR, Gonzalez-Villalobos RA, et al. The NLRP3 inflammasome is required for the development of hypoxemia in LPS/mechanical ventilation acute lung injury. Am J Respir Cell Mol Biol. 2014;50(2):270-280. doi:10.1165/rcmb.2013-0087OC

replication and pathogenetic injury[7] and that these proteins provoke activation of inflammasome NLP3.[8] [9] [10]
Colchicine is a non-selective inhibitor of NLRP3 inflammasome .

Colchicine, after oral administration, is absorbed after 1-2 hours and reaches peak anti-inflammatory effect within 24-48 hours. This is the time required for drug to accumulate in granulocytes (neutrophils, eosinophils, basophils) and monocytes (macrophages). Patients generally present to the hospital after a week after inoculation and 3-4 days of symptoms. Progression into florid ARDS frequently occurs rapidly a few days after hospitalization. Initiation of anti-inflammatory therapy may be best utilized early in the hospital course, to deter a potential cytokine storm and clinical deterioration.

Colchicine has been demonstrated to be well tolerated in an acute population recently. Low-dose colchicine administered to patients who survived from acute coronary syndrome resulted in a statistically significant reduction of cardiovascular complications. Markers of inflammation including IL1b, IL18 and IL6 were also demonstrated to be reduced by colchicine in ACS.[11] [12] Our proposed trial seeks to

---

[7] Castano-Rodriguez C, Honrubia JM, Gutierrez-Alvarez J, et al. Role of Severe Acute Respiratory Syndrome Coronavirus Viroporins E, 3a and 8a in Replication and Pathogenesis. MBio. 2018;9(3). doi:10..1128/mBio.02325-17.
[8] Nieto-Torres JL, Verdiá-Báguena C, Jimenez-Guardeño JM, et al. Severe acute respiratory syndrome coronavirus E protein transports calcium ions and activates the NLRP3 inflammasome. Virology. 2015;485:330-339. doi:10.1016/j.virol.2015.08.010
[9] Shi C-S, Nabar NR, Huang N-N, Kehrl JH. SARS-Coronavirus Open Reading Frame- 8b triggers intracellular stress pathways and activates NLRP3 inflammasomes. Cell death Discov. 2019;5(1):101. doi:10.1038/s41420-019-0181-7
[10] Chen I-Y, Moriyama M, Chang M-F, Ichinohe T. Severe Acute Respiratory Syndrome Coronavirus Viroporin 3a Activates the NLRP3 Inflammasome. Front Microbiol. 2019;10(JAN):50. doi:10.3389/fmicb.2019.00050
[11] Martínez GJ, Robertson S, Barraclough J, et al. Colchicine Acutely Suppresses Local Cardiac Production of Inflammatory Cytokines in Patients With an Acute Coronary Syndrome. J Am Heart Assoc. 2015;4(8):e002128. doi:10.1161/JAHA.115.002128
[12] Robertson S, Martínez GJ, Payet CA, et al. Colchicine therapy in acute coronary syndrome patients acts on caspase-1 to suppress NLRP3 inflammasome monocyte activation. Clin Sci (Lond). 2016;130(14):1237-1246. doi:10.1042/CS20160090

randomize patients to test the hypothesis that colchicine reduces the incidence and progression of cytokine storm to reduce oxygen requirements and mortality in patients with COVID-19 infection.

Regarding the safety and tolerability of colchicine, the drug has been safely used in the outpatient setting for gout in the doses utilized for this trial. Additionally as mentioned, the medication has been given in patients with acute myocardial infarctions with favorable outcomes. The side effect of GI upset and diarrhea, while not uncommon, can be attenuated with dose reduction and if necessary cessation of the medication.

STUDY OBJECTIVES

To demonstrate that Colchicine in moderate/high-risk COVID patients:

1) Reduces the need for oxygen supplementation beyond 8L nasal cannula
2) Reduces the need for mechanical ventilation
3) Reduces max troponin elevations
4) Reduces inflammatory markers
5) Reduces length of hospitalization
6) Reduces mortality

HYPOTHESIS

We hypothesize that treatment with colchicine in COVID-19 moderate/high-risk patients may decrease the risk of progression into ARDS requiring increased oxygen requirements, mechanical ventilation, and mortality.

STUDY DESIGN

Prospective, completely randomized, open labeled, controlled study. Patients will be randomized into two groups (A and B). Patients of group A will be treated under what is considered current standard of care at Maimonides Medical Center while group B patients will receive colchicine in addition to standard of care.

Treatment arm

In addition to the local standard of care for COVID 19 patients, the patient will receive colchicine PO as such:

- Loading dose of 1.2 mg followed by 0.6mg after 2 hours if without significant gastrointestinal symptoms (day 1)
- The next day 0.6mg bid for 14 days or until discharge

Patients who are on HMG-Co A Reductase Inhibitors (atorvastatin, fluvastatin, pravastatin, simvastatin), fibrates, genfibrozil, amiodarone, dronedarone or digoxin should have the colchicine dosage reduced to a loading dose of 0.6mg followed by 0.3mg after two hours (day 1) followed by 0.3mg BID for 14 days or until discharge.

If patients have significant gastrointestinal symptoms after loading, the dosage may be reduced to 0.3mg BID for the rest of the 14 day course or until discharge. If gastrointestinal symptoms continue, the medication should then be discontinued. Patients who experience sensory motor neuropathy, or symptoms and laboratory findings consistent with rhabdomyolysis should prompt immediate discontinuation of the drug. If renal function deteriorates during the treatment course and CrCl <30ml/min, colchicine should also be discontinued.

Control arm
Usual medical therapy (can include medications such as hydroxychloroquine, azithromycin)

Patients should NOT receive Steroids (IV/PO), Remdesivir, IL-6 inhibitors (Tociluzimab, Sarilumab), JAK inhibitors, IL-1 inhibitors, or other immunomodulators for COVID-19 after randomization while *not* intubated. Since the primary clinical endpoint is progression of disease, if the patient requires mechanical ventilation, the primary clinical endpoint is met and the above experimental salvage medications will be permitted. To rephrase, the patient *will be allowed* steroids, Remdesivir, IL-6 inhibitors and other immunomodulators *only after* intubation if deemed medically necessary by the treating physician.

Subjects:

Eligibility Criteria:
Inclusion criteria:
- Males and females >=18 years of age
- Willing and able to provide written informed consent prior to performing study procedures
- Currently hospitalized and requiring medical care for COVID-19
- Patient must have a positive COVID-19 PCR result
- Peripheral capillary oxygen saturation <94% on room air at screening

Exclusion criteria:

- Requirement of oxygen supplementation >8L nasal cannula
- Pregnancy
- Known hypersensitivity to colchicine
- Patient currently in shock or with hemodynamic instability requiring pressors
- History of cirrhosis
- Alanine Aminotransferase (ALT) or aspartate aminotransferase (AST) > 5X upper limit of normal (ULN)
- Patients with severe renal disease, CrCl <30ml/min
- Patients requiring invasive mechanical ventilation at screening or Clinical estimation that the patient will require mechanical respiratory support within 24 hours
- Patient is currently taking colchicine for other indications (gout or Familial Mediterranean Fever)
- Patient received IV or PO steroids during the hospitalization
- Patient received Remdesivir, Sarilumab, Tociluzimab, Lopinavir/Ritonavir or other immunomodulator given for COVID-19 treatment (Note: convaslescent plasma infusion is NOT an exclusion)
- Patient is on (and cannot discontinue) a strong CYP3A4 inhibitor (eg clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, atazanavir), a moderate CYP3A4 inhbitor (eg diltiazem, verapamil, fluconazole, amprenavir, aprepitant, fosamprenavir) or a P-gp Inhibitor (eg cyclosporine, ranolazine)
- Patient is undergoing chemotherapy for cancer
- Patient is considered by the investigator, for any reason, to be unsuitable candidate for the study

Design: The pilot study is a prospective randomized study involving colchicine in the experimental arm. The study will be performed in the inpatient wards at Maimonides Medical Center.

Data Collection Procedures: Data will be collected from Sunrise Clinical Manager Electronic records at Maimonides Medical Center.

Patients with COVID-19 infection are usually assessed with laboratory tests to determine their inflammatory state. Markers such as CRP, troponin, LDH and Ferritin, and IL6 level are used routinely during the patient's hospitalization. These markers are also frequently repeated during hospitalization to gauge a patient's clinical status. At the time of study randomization, a set of these markers will be obtained if not already obtained in the prior 24 hours. We recommend clinical follow up of these markers as medically indicated by the treating physician. We recommend ascertainment of a peak troponin elevation during the hospitalization and peak CRP as would be expected in standard medical care.

Biochemical end points

- Maximum troponin elevation
- Maximum CRP; Time (days) from colchicine initiation to achieve CRP <1

Clinical end points

- PRIMARY:
    - Percentage of patients who require escalation of supplemental oxygen beyond low-flow nasal cannula (>8L/min)
- SECONDARY:
    - Percentage of patients who will require mechanical ventilation
    - Hospital length of stay
    - Mortality

Safety Monitoring

We anticipate colchicine to have an excellent safety profile given the medication's widespread use in the outpatient and inpatient setting. However, given the medication's widespread use in the outpatient and inpatient setting. However outcome data at each 20 patients will be evaluated to ensure there are no adverse events which would would necessitate pausing or discontinuation of the study. A signal for adverse events will be discussed internally with the investigators and reported to the IRB. Serious adverse events will be reported within 24 hours to the IRB.

Data Analysis:

All continuous variables will be summarized with mean and SD, where applicable, and median and IQR where necessary. All categorical variables will be summarized using frequency and percentage.

Primary endpoint analysis of patients who require an escalation of supplemental oxygen beyond low-flow nasal cannula will be performed using Fisher's exact test. Percentage of patients requiring mechanical ventilation and mortality will also be examined using Fisher's exact test. Student's t-test, Mann-Whitney's U, and Mood's Medial test will be utilized to examine maximum troponin elevation, maximum CRP and time from admission to achieve CRP<1, and hospital length of stay, depending on which statistical assumptions are met.

All analyses will be performed using SAS version 9.4.

Sample Size:
We will collect 70 patients, 35 in each arm, for this pilot study. Results of this pilot study will be utilized to power a larger study.

Expected Outcomes: We hope to demonstrate that colchicine reduces the percentage of patients who will require increased oxygen requirements, mechanical ventilation during hospitalization and reduce mortality. We hope to also demonstrate a lower peak serum CRP and troponin in the patients who receive colchicine. Decreased peak troponin may translate to improved cardiac outcomes.

Timetable: We estimate enrollment to be completed in 1 month and follow up to be completed in approximately 2 weeks following enrollment. We hope to have data analyzed and results ready to submit for publication in 2 months from start date.