Randomized, Open-Label, Controlled Trial of Colchicine to Reduce Cardiac Injury in Hospitalized COVID-19 Patients (COLHEART-19)

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9Colchicine for the Treatment of Cardiac Injury in Hospitalized Patients with COVID-19 (COLHEART-19)

Background:

SARS-CoV-2, a novel betacoronavirus that causes a new human disease referred to as COVID-19, has led to a worldwide pandemic affecting over a million people. Of those patients infected, up to 80% have only mild symptoms that resolve spontaneously. Patients that develop more severe symptoms are generally hospitalized and can experience acute respiratory distress, cardiac injury or shock, renal failure, and ultimately death. Patients with underlying cardiovascular disease and elevated cardiac biomarkers are particularly at risk with mortality reaching up to 70%. While several mechanisms have been postulated for how SARS-CoV-2 may damage the heart, it is plausible that the indirect damage from innate, cellular, or humoral immune response including 'cytokine storm' may play a pivotal role. We hypothesize that colchicine may attenuate the myocardial injury observed in later stages of COVID-19 through downregulation of the inflammatory and the host adaptive immune response.

Colchicine is a microtubule inhibitor and anti-inflammatory agent approved by the FDA for gout and familial Mediterranean fever. It has been suggested that the inhibition of the microtubule polymerization interferes with lipopolysaccharides resulting in the down-regulation of interleukin (IL) - 6, IL-1, GM-CSF, and the NLRP3 inflammasome. Several trials have also shown its benefit to prevent post-cardiotomy syndrome, treat acute and recurrent pericarditis, and reduce cardiovascular events after acute myocardial infarction. Recently the COLCORONA trial (NCT04322682) has been announced. Unlike the outpatient-based COLCORONA trial, we propose a pilot randomized controlled study (COLHEART-19) to evaluate whether Colchicine improves short-term outcomes in hospitalized patients. The possible addition of Colchicine to the limited COVID-19 armamentarium would be a pivotal shift in the management of this challenging patient population.

COLHEART-19 Protocol:

Eligible participants will include hospitalized patients ≥ 18 years-old with confirmed COVID-19 infection and objective evidence of cardiac injury (elevated troponin, elevated B-type natriuretic peptide [BNP], new ischemic or arrhythmogenic changes on ECG/telemetry, decrease in left ventricular ejection fraction [LVEF] or new pericardial effusion on echocardiogram). Exclusion criteria include: severe hematologic or neuromuscular disorders, severe renal impairment with concomitant hepatic impairment, co-administration of CYP3A4 and P-glycoprotein (P-gp) transport system inhibitors, concurrent use of strong CYP3A4 or P-gp inhibitors in patients with renal or hepatic impairment; pregnancy, breast feeding mothers, and women of childbearing age unable to take 2 forms of contraception. Enrollment will occur within 7 days of admission to the hospital and within 3 days of meeting eligibility criteria. Patients will be randomized in a 1:1 ratio to receive open-label Colchicine 0.6 mg po BID x 30 days plus current care per treating physicians versus current care per treating physicians alone (control arm). For patients unable to take medications by mouth, tablets will be crushed and administered in 10cc of water and placed in a nasogastric or enteral feeding tube. Our trial design allows for patients in either study arm to be co-enrolled in other investigational therapeutic trials for COVID-19.

The primary endpoint is the composite of all-cause mortality, need for mechanical ventilation, or need for mechanical circulatory support (MCS) at 90 days. Secondary endpoints include: time (days) to the primary endpoint, the individual components of the primary endpoint, re-hospitalization rates at 90 days, markers of cardiac injury (peak troponin, delta [peak minus baseline] troponin, peak and delta BNP levels, inflammatory biomarkers (peak and delta CRP and D-Dimer levels), and change in World Health Organization R&D Blueprint Ordinal Scale from baseline to 30 days.

We aim to enroll 150 total patients to address the following specific aims:

Specific Aims/Goals:

Aim 1. To determine if Colchicine improves short-term clinical outcomes in hospitalized COVID-19 patients with cardiac manifestations of disease

Hypothesis: Colchicine significantly reduces the composite endpoint of all-cause mortality, need for mechanical ventilation, and need for MCS at 90 days

Aim 2. To assess whether or not Colchicine reduces metrics of cardiac injury in patients hospitalized with COVID-19 with evidence of cardiac involvement and if it improves cardiac function

Hypothesis: Colchicine results in a significantly lower peak troponin/BNP

COLHEART-19 Trial Protocol:

Inclusion Criteria:

1. Age at least 18 years-old
2. Cardiac injury (**any of the following**)
    a. Elevated troponin
    b. Elevated BNP
    c. New ischemic or arrhythmogenic changes on ECG/telemetry
    d. New decrease in LVEF or new pericardial effusion on echocardiogram
3. Informed consent

Exclusion Criteria:

1. Pregnancy, breastfeeding mothers, and women of childbearing age who are unable to use adequate contraception, which includes:
    a. Intrauterine devices (IUD), contraceptive implants, or tubal sterilization
    b. Hormone method with a barrier method
    c. Two barrier methods
    d. If a partner's vasectomy is the chosen method of contraception, a hormone or barrier method must also be used in conjunction
2. Co-administration of CYPA3A4 and P-glycoprotein transport inhibitor
3. History of severe hematologic disease or neuromuscular disorder
4. Severe renal impairment with concomitant hepatic impairment
5. Concurrent use of colchicine and strong P-glycoprotein transport system inhibitors with renal or hepatic impairment

1. Informed consent obtained from the patient

2. Patients randomized 1:1 to Colchicine 0.6 mg po BID x 30 days plus current care per UCLA treating physicians vs. standard of care current care per UCLA treating physicians alone (control arm)
    a. Adaptive trial design allows for patients in either study arm to be co-enrolled in other COVID-19 investigational studies

3. Dosing for Colchicine
    a. 0.6 mg po BID x 30 days
    b. Dose reduction as follows:

i. 0.3-0.6 mg daily or every other day in setting of gastrointestinal intolerance (nausea, diarrhea, emesis, abdominal discomfort)
ii. 0.6 mg daily in setting of weak or moderate CYP3A4 inhibitor
iii. 0.3 mg daily in setting of strong CYP3A4, P-gp inhibitors, or protease inhibitors
iv. 0.3 mg daily in setting of CKD stage ≥ 4 (CrCl <30 ml/min) or liver failure (AST/ALT > 3x normal).
v. 0.6 mg every 14 days in patients with end stage renal disease or requiring dialysis

4. Adverse reactions to Colchicine
    a. Dose reduction secondary to drug intolerance as above
    b. All adverse reactions reported to the COLHEART-19 Trial Investigators
    c. Severe adverse reactions will be reported to the UCLA IRB and FDA

5. Labs/Imaging (in addition to labs/imaging obtained as part of clinical care per treating physicians):
    a. Day 1 (Baseline): Troponin/BNP/CRP/D-Dimer, ECG, and echocardiogram (if not ordered by the treating team)
    b. Days 3 and 7 (*only if patient remains hospitalized*): Troponin/BNP/CRP/D-Dimer

6. Phone and electronic chart follow-up at 30 and 90 days for clinical outcomes and re-hospitalization rates.

If you have any questions, please contact the one of the COLHEART-19 Trial Investigators:

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