NCT04349371

Title: Chloroquine (CQ) prophylaxis for Health Care Workers at risk for COVID
Short title: Saved by CQ
Clinical Phase: II
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Protocol Version: 3.0 (IRB approved 11/09/2020)

Primary Objective: The primary objective is to determine the clinical efficacy of CQ in health care workers with moderate to high risk of exposure to COVID-19 in preventing symptomatic COVID-19 infections.

Secondary Objectives: Secondary endpoints will explore the efficacy of CQ in preventing any infection as defined by seroconversion to positive anti-COVID antibody status.

Study Design: Double blind, placebo controlled, randomized study of CQ in health care workers with risk of COVID exposure. The primary objective is to determine the clinical efficacy of CQ in health care workers with moderate to high risk of exposure to COVID-19 in preventing symptomatic COVID-19 infections. Safety assessments include AEs, vital signs, ECGs, and physical examinations.

Stratification will be based and levels of exposure: -moderate risk: defined by patient facing work in outpatient/in-house clinic at least 2 days/week -high risk: ICU/ER/procedure rooms with aerosolized particles and high risk of contamination Stratification based on age: -Under 50 years of age -Older than 50 years of age

Sample size: 175 patients/group. Sample size based on a projection that 15% of healthcare workers will develop symptomatic COVID-19 illness and an anticipated 67% reduction in rate (i.e. 5%) among those treated with CQ. 175 patients per group, allowing for a 10% dropout rate, will permit detection of a difference of this magnitude or greater for the primary endpoint, assuming a two-tailed alpha and 80% power. The trial is not powered on any secondary outcomes or interim analyses.

Study Duration: -1 month accrual of patients with treatment duration of 2-3 months or until exposure levels become negligible - 2 month follow up visit, 3 month follow up visit

Treatment Description: 3 Patients will receive CQ 500 mg every day for one week, then 500 mg weekly for the duration of the exposure. A dose of 250 mg daily will be allowed for severe GI intolerance.

Primary Endpoint: Decrease by 67% in number of symptomatic illness in at risk healthcare workers; a decrease in symptomatic COVID infections from 15% to 5% in the treatment arm.

Co-primary Endpoint: Decrease by 70% in number of severe illness in at risk healthcare workers.

Secondary Endpoints: 1. Decrease by 67% in number of sero-conversions in at risk healthcare workers. 2. Percent of patients with adverse events NCI-CTCAE Grade 3 or higher. 3. Percent of patients with GI intolerance.

Inclusion Criteria: 1) Age ≥18 years, 2) Employment by New York Presbyterian Hospital 3) Clear assignment to areas of the hospital that involve patient contact and possible exposures for at least 2 days a week >/= 8 hours a day

Exclusion Criteria: 1) Individuals who are taking CQ for other indications 2) New use of NSAIDs 3) High risk background medications not limited to immunosuppressive regimens, steroids, anti-B cell therapies, anti-cytokine therapies, chemotherapies, JAK-inhibitors 4) Individuals with a history of retinopathy that would contraindicate the use of CQ 5) Known allergy to CQ or chloroquine 6) Known QT prolongation and torsades de point 7) Have screening electrocardiogram (ECG) abnormalities that, in the opinion of the investigator, are clinically significant and indicate an unacceptable risk for the patient's participation in the study. 8) Any individual with QTc over 500 msec will be excluded. 8) Individuals who have history of any cardiac disease. 9) Individuals with history of renal disease 10) Individuals who are taking any QT prolonging meds such as but limited to: • Antipsychotics: Haloperidol, Ziprasidone, Quetiapine, Thioridazine, Olanzapine, Risperidone • Antiarrhythmics: Amiodarone, Sotalol, Dofetilide, Procainamide, Quinidine, Flecainide • Antibiotics: Macrolides, Fluoroquinolones • Antidepressants: Amitriptyline, Imipramine, Citalopram, • Others: Methadone, Sumatriptan, Ondansetron, Cisapride

Study Stopping Rules

Study enrollment will be put on temporary hold and expedited reports will be prepared and reported to the DSMB for an ad hoc meeting if any the following occur: 1) Severe GI intolerance to chloroquine 2) Anaphylactic/high risk reaction to chloroquine 3) Symptomatic COVID-19 infection 4) QT prolongation and torsades de point that, in the opinion of the investigator, are clinically significant and indicate an unacceptable risk for the patient's participation in the study. 2) The occurrence of NCI-CTCAE Grade 3 or higher adverse events (including serious adverse events) that are related to study drug in 1 of the first 6 subjects, 2 of the first 23 or 3 of the first 45 or 5 subjects at any time. (It is estimated that the prevalence of Grade 3 or higher adverse events in the placebo group will be about 1 percent.), 3) At the request of the DSMB. The DSMB may only stop the trial for safety concerns. DSMB members: Dr. Teja Kapoor, Dr. Yevgenya Gartshteyn, Dr. Daniel DeMizio. The DSMB will meet monthly to evaluate any safety and unforeseen protocol issues.

ECG

Per the Food and Drug Administration Emergency Use Authorization guidelines with respect to chloroquine, a single 12-lead standard ECG will be obtained locally at Visit 1 and read by a qualified physician (the investigator or qualified designee) at the site to determine whether the patient meets entry criteria. However if the subject had received an ECG test within the past 12 months and no abnormalities were found, the ECG does not have to be obtained. An ECG test will be administered at the end of the study. Electrocardiograms may be obtained at additional times, when deemed clinically necessary. If the patient presents with unanticipated ECG findings, they will be referred to a cardiology specialist immediately. Patients with QTc between 460-500 msec will be reviewed with a Cardiologist before initiating treatment. Randomization: Randomization to the study drug versus the placebo will be performed in a 1:1 fashion. Simple randomization without blocking or stratification will be followed, with treatment allocation according to a pre-specified computer-generated randomization list provided to the research pharmacy. Blinding: Randomization will be accomplished by the Research Pharmacy, which will provide the study drug and the placebo in identical pill bottles. This will ensure double-blinding to both participants and the study team. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a patient's treatment assignment is warranted.

Patient safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the Research Pharmacy prior to unblinding a patient's treatment assignment unless this could delay emergency treatment of the patient. All calls resulting in an unblinding event are recorded and reported to the IRB. If an investigator, site personnel performing assessments, or patient is unblinded, the patient must be discontinued from the study unless there are ethical reasons to have the patient remain in the study.

Statistical analysis

Summary statistics for outcomes and predictor variables will be calculated, with comparisons made using Student's t-test and Wilcoxon rank-sum test for normally and non-normally distributed continuous variables, respectively. Counts and percentages will be calculated for categorical variables and compared using $\chi 2$ or Fisher's exact test as appropriate. COVID disease status will be ascertained based on medical records review for severe hospitalized patients, self-reported history of viral illness with serological confirmation of anti□COVID status, and anti-COVID antibody status. The association between CQ and disease will be explored. Efficacy analyses included all the patients who underwent randomization and who received at least one dose of CQ or placebo (modified intention-to-treat population). The primary end point, the percentage of patients with COVID infection at study end, will be compared in the CQ group and in the placebo group with the use of a stratified Cochran–Mantel–Haenszel test, with strata corresponding to the stratification factors (age and exposure levels). To isolate the association between CQ and possible confounders we will defined as those variables associated with both the outcome and the independent variable (CQ). Statistical calculations will be performed using STATA version 12. A two-tailed α of 0.05 was defined as the level of statistical significance for all tests.

Rationale:

We generally consider hydroxychloroquine and chloroquine as being effective in lupus, in part due to inhibition of type I interferon (considered our innate first line defense antiviral response), which has often raised concern about susceptibility to viral infection. However, data are accumulating at a very rapid rate that there may be a paradox. By raising endosomal pH (one of the mechanisms that leads to decreased TLR ligation and decreased IFN) COVID viral replication itself is decreased16 . Since acidification is crucial for endosome maturation and function, Liu and colleagues suggest that endosome maturation could be blocked at intermediate stages of endocytosis, which would then result in decreased transport of virions to the ultimate releasing site. A study by Goa et al. suggests that chloroquine has efficacy against the associated pneumonia in multicenter clinical trials conducted in China. Additionally, there have been two other small trials that raise more questions than provide definitive answers to the question of hydroxychloroquine efficacy in COVID-19. Specifically, the study by Gautret at al. was a single arm protocol in which 20 confirmed COVID-19 patients were given 600mg of hydroxychloroquine daily (and is some cases azithromycin) and their viral load in nasopharyngeal swabs was tested. Six patients were asymptomatic, 22 had upper respiratory tract infection symptoms and eight had lower respiratory tract infection symptoms. A significant reduction of viral carriage was reported. Of note, levels of HCQ were in accord or lower than those seen in our lupus patients prescribed 5mg/kg. The heterogeneity of the patients included, selection of the control population, high rate of lost to follow- 6 up and handling of missing

observations raise concerns about their conclusions. The other trial is a 30 patient, placebo-controlled study of hydroxychloroquine in patients with relatively mild COVID-19 infections, using 400 mg of HCQ daily, did not show any differences between drug and placebo groups in viral clearance, duration of hospitalization, and radiological progression of COVID-19 pneumonia. CQ and HCQ have been used interchangeably in the treatment and prophylaxis of malaria as well as the treatment of SLE. The current study proposes to evaluate the efficacy of CQ in preventing COVID-19 infections.