A Prospective Clinical Study of Hydroxychloroquine in the Prevention of SARS-COV-2 (COVID-19) Infection in Health Care Workers after High-Risk Exposures

Protocol Version 1.4 – 28-MAY-2020

Statistical Analysis Plan

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1. Introduction

New major epidemic foci of coronavirus disease 2019 (COVID-19), have been identified and are rapidly expanding in Europe, North America, Asia, and the Middle East, with the first confirmed cases being identified in African and Latin American countries.[1] By March 16, 2020, the number of cases of COVID-19 outside China had increased drastically and the number of affected countries, states, or territories reporting infections to WHO was 143.1 On the basis of"alarming levels of spread and severity, and by the alarming levels of inaction", on March 11, 2020, the Director-General of WHO characterized the COVID-19 situation as a pandemic.

To respond to COVID-19, many countries are using a combination of containment and mitigation activities with the intention of delaying major surges of patients and levelling the demand for hospital beds, while protecting the most vulnerable from infection, including elderly people and those with comorbidities.

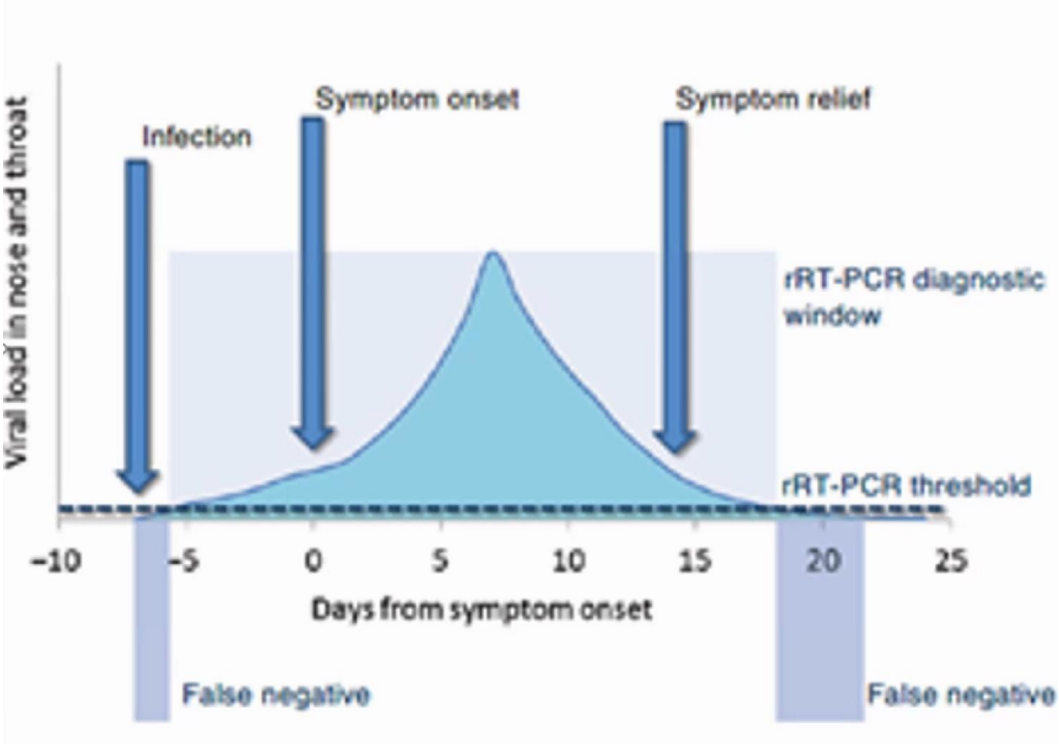
SARS-CoV-2, like other emerging high-threat pathogens, has infected health-care workers in China and several other countries. Epidemiological records in China suggest that up to 85% of human-to-human transmission has occurred in family clusters and that 2055 health-care workers have become infected, demonstrating that patient to healthcare worker is tractable.

From studies of viral shedding in patients with mild and more severe infections, shedding seems to be greatest during the early phase of disease. The role, if any, of asymptomatic carriers in transmitting infection is not yet completely understood. Pre-symptomatic infectiousness is a concern among healthcare workers and many countries are now using 1–2 days of symptom onset as the start day for contact identification.

Hydroxychloroquine and chloroquine are antimalarial agents that have been used for decades for both active treatment and prophylaxis. Several sources of data and rationale have been developed to support the notion that hydroxychloroquine may have activity against COVID-19.[2] [3] [4] [5] [6]

A prospective open-label trial from France evaluated the efficacy of hydroxychloroquine alone and in combination with azithromycin in symptomatic, hospitalized patients with positive COVID-19. The study composed of 36 patients, out of which 20 received 600 mg of hydroxychloroquine daily for 10 days. The remaining 16 patients who either refused the treatment or were not eligible to receive it because they were at other centers in France were considered as the control group. The primary endpoint was virological clearance of NP sampling at six days. Six patients who received hydroxychloroquine contributed incomplete NP sampling to the analysis because three worsened and were transferred to the intensive care unit, one patient died, one patient left the hospital, and one patient could not tolerate the study medication due to nausea. At day 6, 70% of hydroxychloroquine-treated patients were virologically cured comparing with 12.5% in the control group ($p= 0.001$). The investigators found the rate of recovery in patients taking hydroxychloroquine to be approximately 5 times more than that of patients in the control group.

Finally, research gaps about COVID-19 should be addressed in prospective, clinical trials as proposed in this study. The present study will leverage information concerning the infectious curve associated with COVID-19 exposure as illustrated in the figure.



2. Study design

This prospective open label trial will study the safety, tolerability, and efficacy of hydroxychloroquine in qualified health care workers. Qualified individuals will be administered hydroxychloroquine twice a day on day 1 (two 200 mg twice a day) and once a week (two 200 mg) afterwards for a total of 7 weeks. Dose de-escalation is permitted during the study if indicated clinically. All study individuals will follow the same visit and assessment schedule. Following study enrollment, participants will be scheduled to be assessed in person at Days 7, 14, 21, 28, 35, 42 and 49.

2.1. Sample size calculation

A total sample of 360 individuals (180 in each arm) would provide at least 80% power to detect a relative risk reduction of 40% in the rate of positive NP samples when the anticipated rate of positive conversion among those taking hydroxychloroquine is approximately 30%.

The power calculation, which was based on Pearson Chi Square test, assumes the following:

- One-sided Type I error rate of 0.05
- Anticipated positive NP samples rate of 30% in the clinical arm
- A 40% lower risk of a positive NP sample comparing the hydroxychloroquine group vs the controls
- Loss to follow-up rate of 15%

3. Aims and objectives

3.1. Objectives

For healthcare workers with

- One day or more of exposure to suspected and/or positive COVID-19 patients, including but not limited to those working in the Emergency Department or Intensive Care Unit.

OR

- Unprotected exposure to a known positive COVID-19 patient within 72 hours of screening.

3.2. Primary Objective

To assess the efficacy of hydroxychloroquine 400 mg twice a day (two 200 mg tablets twice a day) on day 1 followed by two 200 mg tablets once a week for a total of 7 weeks in the prevention of COVID-19 infection

3.3. Secondary Objective

To compare the rate of COVID-19 positive conversion among emergency department workers versus intensive care unit workers

4. Endpoints

4.1. Primary Efficacy Endpoint

Rate of COVID-19 positive conversion on weekly nasopharyngeal (NP) sampling

4.2. Secondary Efficacy Endpoints

Time-to-first clinical event consisting of a persistent change for any of the following:

- One positive NP sample
- Common clinical symptoms of COVID-19 infection including fever, cough, and shortness of breath
- Less common signs and symptoms of COVID-19 infection including headache, muscle pain, abdominal pain, sputum production, and sore throat

4.3. Exploratory Efficacy Endpoints

Time-to-first clinical worsening event consisting of any of the following:

- Hospitalization for COVID-19 infection
- Intensive care unit admission for COVID-19 infection
- All cause death

4.4. Safety Endpoints

Frequency, intensity, and relationship to study drug of adverse events and serious adverse events, change from baseline in body temperature.

5. Populations to be analyzed

5.1. Intention-to-treat (ITT)

- All subjects who received the study drug
- All subjects who participated in at least one post-baseline assessment

5.2. Per Protocol (PP)

All randomised study subjects completing the whole study period (complete cases)

6. Analyses

All statistical analyses and data summaries will be performed using SAS® (Version 9.1 or higher) or other validated software. The SAP will serve as the final arbiter of all statistical analyses. Data will be summarized overall using descriptive statistics. Continuous data will be summarized with number of subjects (n), mean, median, minimum, maximum, relevant quartiles, standard deviation, coefficient of variation, and geometric mean (where applicable). Categorical data will be summarized using frequency counts and percentages. Chi Square or Fisher exact test will be used for comparing binary outcomes between treatment and control groups. Continuous variables will be compared between the study groups by means of two sample T test or Wilcoxon-rank-sum test.

6.1. Primary Analysis of Efficacy

All subjects who received at least one dose of study medication, will be used as the primary population for assessment of efficacy. The proportion of people whose NP sample becomes positive at least once during the trial will be compared between the study groups using Chi square or Fisher exact test. Survival analysis will be utilized to estimate the potential effects of hydroxychloroquine on COVID-19 free survival times. We will apply generalized linear mixed models to compare the positive conversion rate of COVID-19 between the study arms while controlling for other confounding factors. AIC and BIC criteria will be used to choose an appropriate covariance structure between the measurements collected at consecutive visits. An interaction effect between time and study group will be added to the model to evaluate whether the relative risk of a positive conversion changes from visit to visit.

7. Missing data

If the proportions of missing data are above 5%, multiple imputation methods will be used to construct complete data sets under different missing patterns. Otherwise, linear mixed models will be used that allow for presence of missing values in the data.

8. References

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