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Hydroxychloroquine Post Exposure Prophylaxis (PEP) for High-Risk Contacts of COVID□19 Patients: A NYC Community-Based Randomized Clinical Trial

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1. Study Purpose and Rationale

COVID-19 is a massive threat to public health worldwide. Current estimates suggest that the novel coronavirus (SARS-CoV-2) is both highly contagious (estimated reproductive rate, 2-3) and five to fifty-fold more lethal than seasonal influenza (estimated mortality rate, 0.5-5%). Interventions to decrease the incidence and severity of COVID-19 are emergently needed.

Hydroxychloroquine (brand name, Plaquenil), an inexpensive anti-malarial medication with immunomodulatory effects (1-4), is a promising therapy for COVID-19. Chloroquine, a related compound with a less favorable toxicity profile, has shown benefit in clinical studies conducted in approximately one-hundred SARS-CoV-2 infected patients (1, 2). In vitro, hydroxychloroquine has been recently shown to have greater efficacy against SARS-CoV-2 versus chloroquine (5). Although the molecular mechanisms of action are incompletely understood, previous studies suggest that hydroxychloroquine may inhibit coronaviruses by changing cell surface pH, inhibiting the fusion of the virus to the cell membrane, and by inhibiting nucleic acid replication, glycosylation of viral proteins, virus assembly, new virus particle transport, and virus release (6).

The safety profile of hydroxychloroquine has been well-established over decades of regular use by patients with autoimmune disease. Indeed, hydroxychloroqine is on the World Health Organization (WHO) list of essential medications, highlighting it as one of the safest and most effective medications on the market. The major toxicity with short term use is QT prolongation, which may increase risk of arrhythmia. Other known toxicities include retinopathy, which is mainly observed at high daily doses (>5mg/kg/day), and hematologic abnormalities (agranulocytosis, thrombocytopenia).

Post-exposure prophylaxis (PEP) is a strategy that has been proved to reduce transmission and improve outcomes for both seasonal influenza and HIV. Although two trials of hydroxychloroquine for COVID-19 PEP have been recently initiated (NCT04304053 and NCT04308668), additional studies are urgently needed, particularly in urban US communities where community spread of COVID-19 is currently accelerating.

We propose a phase 2/3, double-blinded, randomized clinical trial of hydroxychloroquine PEP among close contacts of COVID-19 patients in New York City (NYC). The trial will be initiated at NewYork-Presbyterian (NYP)/Columbia University Irving Medical Center (CUIMC)/Weill Cornell Medical Center (WCMC). It will recruit adults (≥18 years old) with moderate or high-risk COVID-19 exposure, including household contacts of index COVID-19 cases or Persons Under Investigation (PUI), as identified by NYP/CUIMC/WCMC providers via outpatient or inpatient clinical evaluation. Extra institution index cases will be considered with sufficient source verification (i.e. test report, provider's note). Within 72 hours of diagnosis of the index case, participants will be randomized (1:1) at the individual level to a 5-day course of hydroxychloroquine versus an identical course of placebo. The primary outcome will be development of symptomatic COVID-19, with laboratory confirmation of infection, within 14 days of enrollment. Secondary outcomes will include duration of COVID-19 symptoms; need for hospitalization or mechanical ventilation; and COVID-19 mortality. The target

enrollment is N=1600 adults (800/arm), which will have 80% power to detect a 30% improvement in the symptomatic secondary attack rate (from 10.5% to 7.3%). The anticipated trial duration is 12 months.

This pragmatic, community-based, randomized clinical trial will rapidly and efficiently test the hypothesis that hPEP will reduce the symptomatic secondary attack rate among close contacts of known or suspected COVID-19 patients. If the study hypothesis is confirmed, this work could substantially improve COVID-19 outcomes in both the NYC and the global community.

2. Study Design and Statistical Procedures

We propose a single-center, double-blinded, placebo-controlled, randomized, Phase 2-3 clinical trial to test if hydroxychloroquine post exposure prophylaxis (hPEP) reduces the symptomatic secondary attack rate of COVID-19 among close contacts of known or suspected COVID-19 patients identified at the largest academic medical center in NYC and surrounding metropolitan area.

Setting: The study will be conducted in NYC, where the COVID-19 epidemic is rapidly accelerating. In order to optimize efficiency, the study will be initiated at the NYP/CUIMC campus in Washington Heights, with plans to expand across other NYP campuses if/as conditions allow. As this is a community-based study, where interaction is facilitated remotely, we wish to include the tri-state area as our immediate scope due to the patient demographic majority residing in this area.

Population: Currently asymptomatic adults (≥18 years old) meeting the following inclusion and exclusion criteria:

a. Inclusion criteria:

a. Household contact of index case: currently residing in the same household as an index case:

i. Index case definition: individual evaluated at outpatient, emergency department (ED), or inpatient services who (1) tests positive for COVID□19, or (2) are defined as suspected cases, or persons under investigations (PUI), by the treating physician.

b. Willing to take study drug as directed for 5 days.

b. Exclusion criteria:

a. Age <18 years old
b. Suspected or confirmed current COVID-19, defined as: (1) temperature > 38 Celsius; (2) cough; (3) shortness of breath; (4) sore throat; or, if available (not required), (5) positive confirmatory testing for COVID-19
c. Suspected or confirmed convalescent COVID-19, defined as any of the above symptoms within the prior 4 weeks.
d. Inability to take medications orally
e. Inability to provide written consent or eConsent
f. Known sensitivity/allergy to hydroxychloroquine

g. Current use of hydroxychloroquine for another indication
h. Pregnancy
i. Prior diagnosis of retinopathy
j. Prior diagnosis of G6PD deficiency
k. Major comorbidities increasing risk of study drug:
    i. Hematologic malignancy
    ii. Advanced (stage 4-5) chronic kidney disease or dialysis therapy
    iii. Known history of ventricular arrhythmias
    iv. Current use of drugs that prolong the QT interval (Table 1)

Table 1. Drugs that prolong QT, and for which current use will be an exclusion criterion for participation
Antiarrhythmics, Antimicrobials, Antidepressants, Antipsychotics and Others, including:

Amiodarone Levofloxacin Amitryptiline Haloperidol Cisapride Sotalol Ciprofloxacin Desipramine Droperidol Sumpatriptan Quinidine Gatifloxacin Imipramine Quetiapine Zolmitriptan Procainamide Moxifloxacin Doxepin Thioridazine Arsenic Dofetilide Clarithromycin Fluoxetine Ziprasidone Dolasetron Ibutilide Erythromycin Sertraline Methadone Ketoconazole Venlafaxine Itrconazole

Recruitment: Information regarding the study will be shared with directors of the outpatient, ED, and inpatient services at NYP. Among services that agree to participate, information will be shared with providers via e-mail, telephone, and/or video-conference. Recruitment will be conducted in individuals' preferred languages, using a telephone interpreter if necessary. Written materials will be provided in both English and Spanish. Recruitment will be accomplished by active surveillance and provider referral. Some interested participants might be patients at NYP (i.e. existing MRNs), but testing of the index case accomplished outside of the institution. Some NYP/CUIMC/WCMC faculty, trainees, and staff may be eligible to participate; it will be explicit that participation will be completely voluntary and 100% non-coercive.
Provider referral:
1. Identification of index case: as noted above, consistent with current clinical care, the providers will be asked to define the index case as individuals who (1) test positive for COVID-19, or (2) are defined as suspected cases, or persons under investigation (PUI), by the treating physician.
2. Determination of household contacts: The provider will ask the index case if he/she lives alone or has any household contacts. If the index case is unable to be interviewed (e.g., mechanically ventilated), the provider will ask the surrogate, as identified by the treating physician.
3. Invitation to be contacted by the study: For index cases with at least one household contact, providers will ask any household contact(s) present with the index case, if they would be interested in participating in a research study. The index case and any household contact(s) present may be provided with a copy of a printed flyer that explains the study in lay terms, in English and in Spanish. This flyer will include contact information for the study.

Active surveillance: research personnel will contact designated clinical personnel in participating services at least twice daily to ask if there are any index cases whose household contacts might be suitable for recruitment into the study. Research personnel will then contact the eligible

households.

Contact by the study: Study-initiated telephone contact: if verbal consent is given to the treating provider, trained personnel will call the household to screen potential participants. Household initiated telephone contact: if any household contacts decide they are interested in participating subsequent to the index case diagnosis (e.g., after reviewing the flyer) and call the provided number, trained research personnel will proceed with screening by phone. Screening: A structured interview will be used to assess inclusion and exclusion criteria. Screening forms for those who are found to be ineligible (or for those who are pre-screened as eligible but do not, for any reason, sign written informed consent or informed remote eConsent) will be abstracted, reviewed by the PI, and then discarded in a secure fashion such that no PHI is retained.

Informed consent: Trained research personnel will obtain informed consent after confirming eligibility and prior to randomization. Written informed consent will be obtained with electronic tablets. Immediately following participant use/contact, and prior to re-use or re-contact by any other participant, the tablet will be subjected to a standard cleansing with a Chlorox disinfection wipe.If in person contact is not possible, remote eConsent will be obtained. In the case of eConsent, trained research personnel will first discuss the content of the informed consent form with the participant via telephone or, preferably, video conference. In this manner, the research personnel will be available to answer any questions. The participant will immediately thereafter be asked to perform eConsent. The platform for eConsent will be an integrated data management system that is easy to navigate, allowing the user to proceed forward or backward within the system and to stop and continue at a later time. This system will be secure with restricted access, and will ensure confidentiality of the Subject's identity, study participation and personal information. This system will comply with the Columbia University Information Security Charter and the other Information Security Policies referred to in such Charter to the extent applicable.

After eConsent is provided, it will be automatically transmitted to the study via the integrated data management system. Randomization: Randomization to the study drug versus the placebo will be performed in a 1:1 fashion, stratified by age (<55 years old, 55+ years old) and chromosomal sex (male, female).

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.

Dispensing of study drug and placebo: consenting participants must pick up the study drug from a designated hospital location within 72 hours of the diagnosis of the index case. Or, if the consenting participants are unable to travel to the hospital, the study drug will be delivered to the participant's home (e.g., by FedEx or courier).

Study drug: the intervention will be a 5-day course of hydroxychloroquine sulfate (brand name, Plaquenil). Each participant will receive 12 tablets of hydroxychloroquine sulfate 200mg. They will be instructed to take two tablets (400mg) twice daily on day 1; for days 2-5, they will be instructed to take one table (200mg) twice daily. The rationale for this dosing regimen is as follows. A loading dose is important to efficacy, but loading doses >800mg/24 hours are expected to have a disadvantageous risk/benefit profile. The dose on the subsequent 4 days

(400mg/day) is within the standard long-term daily dosing range for autoimmune diseases. For comparison, other current trials of hPEP propose the following regimens:

- NCT04304053: 800mg on day 1, and 400mg on days 2, 3, 4. We believe that an additional day of therapy will be associated with minimal excess risk and the median incubation of CoV-SARS-2 is 5 days, suggesting that 5 days of prophylaxis may be superior to 4 days.
- NCT04308668: 800 mg orally once, followed in 6 to 8 hours by 600 mg, then 600mg once a day for 6 consecutive days. We believe that the loading dose and the follow-up doses are excessively high. Together with an extended (7-day) course of treatment, we believe that this regimen carries higher risk of adverse effects without clear benefit and with lower likelihood of regimen adherence.

Participants randomized to the placebo will receive an identical container of 12 placebo pills, with the same instructions for administration.

Follow up

Participant self-monitoring: participants will be asked to check and record their temperatures at home in the morning and in the evening. They will be instructed to contact the study if they develop a temperature >38 C, and/or if they develop cough or shortness of breath.
Daily telephone or email follow-up: research personnel will contact participants by phone on a daily basis for 7 days post-randomization, and at 14 (+/- 3) and 30 days (+/- 3). They will conduct a structured interview to ascertain potential symptoms of COVID-19 (the primary outcome), adherence to and potential adverse effects of the study drug, and extent of ongoing exposure to the index case. Alternatively, if preferred by the participant, the participant will be able to submit answers to the daily symptomatic questionnaire via secure web-based questionnaire to support remote administration and immediate data capture. Participants with symptoms or signs of COVID-19 will be referred to the study physician, who will contact the participant and determine if he/she meets PUI criteria. The study physician will refer PUIs for confirmatory COVID-19 testing at NYP/CUIMC/WCMC.

Psychosocial Questionnaire at Day7: Resources for mental health and wellness are provided at the end of the psychosocial questionnaire for all participants, as well as instructions for seeking medical attention if participants experience significant distress or feel unsafe.

Participants who score in the severe or extremely severe range on the depression subscale, express passive or active suicidal ideation, or express thoughts of self-harm will be informed of mental health support hotlines, advised to seek care from a mental health professional, and encouraged to contact emergency services if they feel unsafe. For such participants who respond to the questionnaire online or by paper, an attempt will be made to contact them at the time the questionnaire is viewed to provide the information above.

Active surveillance of healthcare utilization: the research personnel will monitor study participants to determine if any participants present to the outpatient clinic or to the ED, and/or if they require hospitalization.

Extended follow-up of symptomatic participants: participants who develop COVID-19 symptoms will continue to be followed-up by daily telephone calls until 3 days following resolution of

symptoms in order to measure the duration of symptom (secondary endpoint).

Statistics

We plan a phase 2 study at NYP/CUIMC/WCMC, with the phase 2 as an internal pilot for a potential phase 3 study, which would be conducted across all NYP sites.

Population: Household contacts of COVID-19 cases with high-risk COVID-19 exposures

Endpoint: Symptomatic, lab-confirmed COVID-19 over two-week follow-up, defined by:

1. COVID-19 infection confirmed within 14 days of enrollment, following self-report of COVID-19 symptoms to the research study.
2. COVID-19 infection confirmed within 14 days of enrollment, with self-report of COVID-19 symptoms to a treating physician.

Control outcome: The CDC has estimated symptomatic secondary attack rate of 10.5% (95% CI = 2.9%–31.4%) among household members of COVID-19 patients over 14 days (7) (https://www.cdc.gov/mmwr/volumes/69/wr/mm6909e1.htm).

Effect size: a 30% risk reduction from a 10.5% to 7.4% symptomatic secondary attack rate

Design:
• Placebo-controlled 1:1 randomized at NYP/CUIMC/WCMC
• Phase 2/3 internal pilot, with interim monitoring for futility and safety during the pilot phase
• Pilot phase: one-sided test at 10% significance; data obtained in pilot phase will be used to size the phase 3 trial, and the pilot data will be used in the final analysis at the end of phase 3
• Sample size for pilot phase: n = 800 per arm, i.e., total N = 1600
Secondary endpoints:
• Determination of symptoms consistent with PUI without confirmatory COVID-19 testing (e.g., if lost to follow-up)
• Duration, in days, of COVID-19 symptoms (cough, shortness of breath, and/or fever)
• Hospitalization for COVID-19
• Mechanical ventilation for COVID-19
• Mortality attributed to COVID-19

Additional notes on statistical design and analysis

This is a single-center, double-blinded, placebo-controlled, randomized internal pilot trial of a larger phase 2-3 seamless clinical trial. The trial objective is to evaluate if hydroxychloroquine post exposure prophylaxis (hPEP) given over a 2-week period will reduce symptomatic secondary attack rate of COVID-19 in household contacts of known or suspected COVID-19 patients. The study endpoint is symptomatic, lab-confirmed COVID-19 during the 2-week study period. In this pilot trial, we plan to randomize a total N=1600 participants to the treatment (hPEP) and the placebo in a 1:1 ratio, stratified by chromosomal sex and age group (<55 yo vs 55+).

The primary analysis will be comparing the rates of symptomatic, lab-confirmed COVID-19 in all randomized participants using one-sided Fisher's exact test. Intent-to-treat analysis will be used. Secondary endpoints include duration of COVID-19 symptoms without confirmatory test, hospitalization for COVID-19, requiring mechanical ventilation, and mortality. Statistical analysis of the secondary endpoints will be intent-to-treat, using Mann-Whitney test for numerical outcomes and Fisher's test for categorical outcomes. Adverse events and serious adverse events will be compared using Fisher's exact test. Interim analysis will be performed to monitor for futility using a Bayesian criterion. Specifically, an early stopping consideration will be invoked if it is unlikely that poor outcome of hPEP is lower than that of placebo; i.e., its posterior probability is smaller than alpha. The value of alpha will be determined before the first interim analysis.

Go and no-go decision and power consideration

We will plan to move forward to the phase 3 trial if at the end of the pilot phase, the primary analysis has a one-sided p-value less than 0.10. Assuming the placebo rate of COVID-19 outcome is 10.5%, the proposed sample size in the internal pilot will result in an 80% probability of moving forward if the study drug reduces risk by 30% (i.e., from 10.5% to 7.3%).

In addition, the pilot data will be used to re-estimate the sample size in the phase 3 trial, and will be used in the final analysis using adjusted analysis using weighted statistics so as to preserve the overall type I error. Details of sample size re-estimation will be determined before the pilot trial data is unblinded.

3. Study Procedures
    a. Procedures
        i. Questionnaires: questionnaires will be performed by telephone by trained research assistants or via web-based questionnaire to support remote administration and immediate data capture.
            1. Screening questionnaire (first call): inclusion and exclusion criteria
            2. Medical history questionnaire (first call): additional questions regarding medications used, number of persons in household
            3. Follow-up questionnaires
                a. Symptoms (respiratory, non-respiratory)
                b. Trial medicine adherence
                c. Psychosocial Behavior (Day7 only)
        ii. Active surveillance for health care utilization and COVID-19 testing at NYP/CUIMC
            1. Participants will be referred for clinical COVID-19 testing if deemed PUI by the study investigator(s)
    b. Study Drugs
        i. Hydroxychloroquine dose pack: 5-day course of hydroxychloroquine sulfate (brand name, Plaquenil). Each participant will receive 12 tablets of hydroxychloroquine sulfate 200mg. They will be instructed to take two tablets (400mg) twice daily on day 1; for days 2-5, they will be instructed to take one table (200mg) twice daily.
        ii. Placebo daily: Participants randomized to the placebo will receive an identical container of 12 placebo pills, with the same instructions for

administration.

c. Confidentiality of Study Data: The consent form signed by the participant will provide written assurance that all individual data collected in the study will be kept confidential to the extent provided by the Privacy Act of 1974. Any personal identifiers will be maintained on limited-access, secure servers and never put on endpoint devices so that confidential data are not released. Participants will be informed that: (1) the only people who will know that they are research participants are members of the research team and, if appropriate, their physicians or health care providers; (2) no individual identifying information about them will be disclosed to others, except if required by law; and (3) when the results of the study are published or discussed in conferences, no information will be included that would reveal their identity. Coded research data will be stored on password-protected, secure servers hosted by the Division of General Medicine and certified by CUIMC IT the CUIMC Radiology PACS, and in locked filing cabinets in General Medicine, and potentially on endpoint devices that will, in all cases, be encrypted. Identifiable data will be stored in the General Medicine Server described above and in locked filing cabinets in separately partitioned drives/cabinets. The linking file will be similarly protected with limited access.

d. Potential Risks:

i. Retinopathy: Hydroxychloroquine treatment has been associated with development of retinopathy, particularly at doses >5mg/kg/day. We will exclude participants <40 kg for whom the study dose might exceed this threshold. We will also exclude persons with established retinopathy from the study.

ii. Hematologic abnormalities: we will exclude individuals with known G6PD deficiency or hematologic malignancy.

iii. Allergy: we will exclude participants with known sensitivity to hydroxychloroquine.

iv. Arrhythmia: we will exclude individuals with known arrhythmia or use of anti-arrhythmic medications.

e. Protections Against Risks:

i. In addition to strict exclusion criteria, we will monitor participants for signs/symptoms of potential adverse effects of the study drug by daily follow-up for 7 days. On Day 7, a specific interview concerning acute side-effects of the study medication will be conducted. If any adverse drug effects are suspected based upon symptomatic report, the study physician will determine whether the symptoms are attributable to the study drug. Beyond the two-week period of initial follow-up, we will encourage all participants to reach out to the study coordinator for palpitations, dyspnea on exertion, or visual disturbances occurring up to 30 days after completion of participation. Serious adverse events (SAEs) will be recorded for the full duration of subject participation, however only adverse events of special interest will be recorded upon the Day 7 acute side-effect interview.

ii. To mitigate risks of COVID-19 among participants, all participants will receive counseling and information regarding current CDC guidelines for exposed household contacts of COVID-19 patients (e.g., decontamination of surfaces, avoidance of unprotected contacts with the index case).

f. Potential Benefits: if the study drug is effective, those randomized to the study drug may benefit from improved COVID-19 outcomes. If benefit is demonstrated, participants randomized to the control arm will have the opportunity to obtain the study drug after study completion. The societal benefits are potentially large.
g. Alternatives: non-participation.Data Safety and Monitoring Plan: A local Data and Safety Monitoring Committee (DSMC) has been established, with Dr. Bathon (rheumatology) as Chairman of the committee. In addition, the committee will consist of two other members, a pharmacist (TBD) and a statistician (Dr. Ying Wei). The DSMC will meet to review all safety data from the patients after the first 100 randomized patients completing their 2-week follow-up, and every 400 randomized patients thereafter. The unblinded statistician will prepare the data for DSMC's review. Each meeting will consist of an open session that includes the study investigators, and a closed session with only the unblinded statistician and the DSMC members.

References

1. Keyaerts E, Vijgen L, Maes P, Neyts J, Van Ranst M. In vitro inhibition of severe acute respiratory syndrome coronavirus by chloroquine. Biochem Biophys Res Commun. 2004;323(1):264-8.
2. Ooi EE, Chew JS, Loh JP, Chua RC. In vitro inhibition of human influenza A virus replication by chloroquine. Virol J. 2006;3:39.
3. Romanelli F, Smith KM, Hoven AD. Chloroquine and hydroxychloroquine as inhibitors of human immunodeficiency virus (HIV-1) activity. Curr Pharm Des. 2004;10(21):2643-8.
4. Vincent MJ, Bergeron E, Benjannet S, Erickson BR, Rollin PE, Ksiazek TG, et al. Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. Virol J. 2005;2:69.
5. Yao X, Ye F, Zhang M, Cui C, Huang B, Niu P, et al. In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Clin Infect Dis. 2020.
6. Fox RI. Mechanism of action of hydroxychloroquine as an antirheumatic drug. Semin Arthritis Rheum. 1993;23(2 Suppl 1):82-91.
7. Rachel M. Burke, PhD1; Claire M. Midgley, PhD1; Alissa Dratch, MPH2; Marty Fenstersheib, MD; Thomas Haupt, MS4; Michelle Holshue, MPH5,6; Isaac Ghinai, MBBS6,7; M. Claire Jarashow, PhD8; Jennifer Lo, MD9; Tristan D. McPherson, MD6,10; Sara Rudman, MD; Sarah Scott, MD6,12; Aron J. Hall, DVM1; Alicia M. Fry, MD1; Melissa A. Rolfes, PhD1. Active Monitoring of Persons Exposed to Patients with Confirmed COVID-19 — United States, January–February 2020. Weekly / March 6, 2020 / 69(9);245–246.