ORCHID

Outcomes Related to COVID-19 treated with Hydroxychloroquine among In-patients with symptomatic Disease

The PETAL Investigators

Sean Collins, MD, MSc
Professor and Executive Vice Chair
Department of Emergency Medicine

On the Call
*Wes Self (ORCHID Chair), Todd Rice, Matt Semler, Jon Casey

MGH Coordinating Center: Taylor Thompson, David Schoenfeld
NHLBI: Lora Reineck, Neil Aggarwal
PETAL Steering Committee Chair: Roy Brower
Sam Brown – ORCHID Co-Chair
Why ORCHID?

• PETAL is a publicly funded network for the prevention and early treatment of ARDS

• Hydroxychloroquine (HCQ):
  • Biologically plausible agent for prevention & early treatment of COVID-ARDS
    • Active against SARS-CoV-2 at micromolar concentrations in vitro
  • Widespread clinical use and promotion
  • Lack of clinical trial data

• High quality data on the clinical effects of HCQ are urgently needed
• Any trial result is informative
  • Benefit
  • Null
  • Harm
Overview

• Why Hydroxychloroquine?
• Brief ORCHID Design
• Unique COVID Challenges and Opportunities
• Study Update
History of (hydroxy)chloroquine

• Chloroquine is a quinine derivative (similar to quinacrine) developed in the 1930s as an antimalarial
• Directly toxic to Plasmodium spp. via multiple mechanisms
• More generally, it increases pH in lysosomes
• In vitro, (hydroxy)chloroquine is toxic to parasites, some bacteria, and inhibits viral replication
• Hints of possible efficacy for *Coxiella burnetti*, HIV, cryptococcus
  • As antimicrobial, only ever approved for malaria prevention and treatment
• Also observed to inhibit IL-1, TNF, IL-6
  • Hence application of hydroxychloroquine in mild auto-immune syndromes
(Hydroxy)chloroquine as an anti-viral

• Extensive *in vitro* efficacy for many viruses

• Studied in HIV
  • Helpful in some studies, harmful in one

• Studied in hepatitis, influenza, Dengue, and Chikungunya
  • No efficacy, suggestion of harm in Chikungunya

• No high quality controlled trials in betacoronaviruses
Clinical data for SARS-CoV-2: Case Series

• Case series (N=20) of hospitalized (non-ICU) patients in France from an investigator who has long advocated HCQ for multiple conditions\(^1\)
  - Potentially biased results, no meaningful controls
  - Report of rapid viral clearance
  - The group who received clinical azithromycin may have cleared virus more quickly

• Small Chinese pilot RCT (N=30)\(^2\)
  - Hospitalized patients with COVID
  - HCQ 400/d x 5d
  - No difference in viral shedding
  - No difference in severity or mortality

• As-yet-unpublished collection of case series (N=120) of apparently mild/moderate hospitalized patients from China.
  - Reportedly rapid viral clearance (”4.4 d after starting CQ”)
  - Reportedly low rate of progression to severe COVID-19 (“none critical”)

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2- Jun - J of Zhej Univ 2020 March
Overview

• Why Hydroxychloroquine?
• **Brief ORCHID Design**
• Unique COVID Challenges and Opportunities
• Study Update
Design Summary

• Multicenter, blinded, placebo-controlled RCT

• Target population: Hospitalized adults with COVID

• Intervention: Hydroxychloroquine
  • 400 mg BID on day 1
  • 200 mg BID days 2-5

• Control: Matched placebo

• 1° outcome: WHO COVID scale at Day 15
Inclusion Criteria

1. Age ≥18 years
2. Hospitalized (or in ED with anticipated hospitalization)
3. ARI (any of: cough, fever, SOB, sore throat)

4. Laboratory-confirmed SARS-CoV-2 within past 10 days or SARS-CoV-2 test results pending plus high clinical suspicion of COVID by fulfilling all:
   - Cough
   - B pulmonary infiltrates or new SpO2 ≤94% on RA
   - No alternative explanation for acute symptoms
Inclusion Criteria

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   - Cough
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   - No alternative explanation for acute symptoms

1° population for analysis: enrolled & COVID (+)
   - Enrolled COVID (-) monitored closely; maintain <10%
Exclusion Criteria

• Prisoner
• Pregnancy/breast feeding
• **Unable to randomize within 10 d of ARI symptom onset**
• **Unable to randomize with 48 hr of hospital presentation**
• Seizure disorder
• Porphyria cutanea tarda
• QTc >500 ms on EKG within 72 hr prior to enrollment
• Long QT syndrome
• Allergy
• Need for concurrent medications: amiodarone, cimetidine, dofetilide, phenobarbital, phenytoin, sotalol
• ≥1 dose of hydroxychloroquine or chloroquine in prior 10 days
• Unable to take enteral medications
• Unable to be contacted at Day 15
• Previous enrollment in this trial
Randomization & Study Medication

• 1:1 randomization
  • Hydroxychloroquine
  • Placebo

• Blinded: patient, clinicians, investigators

• Study medication within 4 hours of randomization

• Study Medication BID x 5 days (10 doses)
  • Remaining doses taken at home if discharged prior to Day 5
Hydroxychloroquine Dose

• ORCHID Dose: 400 mg BID x 2 doses then 200 mg BID x 8 doses
  • FDA Supported

• Common malaria dosing
  • 1200 mg Day 1
  • 400 mg Day 2 and Day 3

• HCQ regimens used for COVID vary somewhat:
  • 400 mg QD x 5 days [Shanghai protocol]
  • 400 mg BID Day 1, then 200 mg BID Days 2-5 [MGH, Vanderbilt protocols]
  • 400 mg TID Days 1-3, then 200 mg BID Days 4-10 [ASCOT protocol]
Hydroxychloroquine – *in vitro*

Clinical Infectious Diseases (2020), Mar 9

<table>
<thead>
<tr>
<th>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)</th>
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<tr>
<td>Xueting Yao¹#, Fei Ye²#, Miao Zhang¹#, Cheng Cui¹#, Baoying Huang²#, Peihua Niu², Xu Liu¹, Li Zhao², Erdan Dong³, Chunli Song⁴, Siyan Zhan⁴, Roujian Lu², Haiyan Li¹,²*, Wenjie Tan¹#, Dongyang Liu¹,*</td>
</tr>
</tbody>
</table>

1 Drug Clinical Trial Center, Peking University Third Hospital, Beijing, 100191, China.

- Physiologically-based pharmacokinetic models
- In-vitro HCQ PK
- Supports
  - Day 1 400 mg BID “load”
  - Then 200 mg BID maintenance
  - 5-day treatment course
  - Maintains therapeutic lung concentrations for 10 days
Safety Monitoring

• EKG prior to enrollment (QTc must be <500 ms)
• EKG/rhythm strip 24-48 hrs after 1st dose (QTc must be <500 ms)

• Day 1 – 5 monitoring of concomitant medications
  • A. Study drug or concomitant med must be stopped (e.g. amiodarone)
  • B. Discussion with clinical team on risk/benefits (e.g. flecainide)
Primary Outcome

**WHO COVID Ordinal Scale at Day 15**

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<tr>
<th>Level</th>
<th>Description</th>
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<tbody>
<tr>
<td>1</td>
<td>Death</td>
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<tr>
<td>2</td>
<td>Hospitalized on IMV or ECMO</td>
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<tr>
<td>3</td>
<td>Hospitalized on NIV or HFNC</td>
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<td>4</td>
<td>Hospitalized on supplemental O2</td>
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<td>5</td>
<td>Hospitalized not on supplemental O2</td>
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<tr>
<td>6</td>
<td>Not hospitalized with limitation in activity</td>
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<tr>
<td>7</td>
<td>Not hospitalized without limitation in activity</td>
</tr>
</tbody>
</table>

- Patient important
- Collectable in pandemic
- Widely used for COVID trials
- Enhanced power compared with binary outcome
Secondary Outcomes

• Mortality
  • 15 day all-cause all-location
  • 28 day all-cause all-location

• COVID Outcomes Scale
  • Day 3, Day 8, Day 29

• Free-Days
  • Oxygen
  • Ventilator
  • Vasopressor
  • ICU
  • Hospital
Analysis

• Proportional odds model for COVID Outcome Scale

• Sample size 510 patients enrolled
  • Outcomes predicted based on VIOLET\textsuperscript{1} Day 15 outcomes
  • 90% power (alpha=0.05) to detect OR=1.82 from primary model

Illustrative Effect Sizes with OR=1.82

<table>
<thead>
<tr>
<th></th>
<th>Death</th>
<th>Death/IMV</th>
<th>Death/IMV/Hospitalization</th>
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<tbody>
<tr>
<td>HCQ</td>
<td>6.7%</td>
<td>10.3%</td>
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<tr>
<td>Placebo</td>
<td>11.5%</td>
<td>17.3%</td>
<td>39.3%</td>
</tr>
</tbody>
</table>

1- Ginde, et al NEJM 2019 Dec 26;381(26)
COVID Challenges/Opportunities

• Equipoise at sites – FDA EUA issued
• Consent and Data Collection- minimize staff exposure & paper consent cannot leave room
• Rapid progress through cIRB, FDA, PRC, DSMB, database build
March 28, 2020

Re: Request for Emergency Use Authorization For Use of Chloroquine Phosphate or Hydroxychloroquine Sulfate Supplied From the Strategic National Stockpile for Treatment of 2019 Coronavirus Disease

Based upon limited in-vitro and anecdotal clinical data in case series, chloroquine phosphate and hydroxychloroquine sulfate are currently recommended for treatment of hospitalized COVID-19 patients in several countries, and a number of national guidelines report incorporating recommendations regarding use of chloroquine phosphate or hydroxychloroquine sulfate in the setting of COVID-19. FDA encourages the conduct and participation in randomized controlled clinical trials that may produce evidence concerning the effectiveness of these products in treating COVID-19. FDA is issuing this EUA to facilitate the availability of chloroquine phosphate and hydroxychloroquine sulfate during the COVID-19 pandemic to treat patients for whom a clinical trial is not available, or participation is not feasible.
Vanderbilt COVID-19 Guidelines

Clinical Recommendations for Treatment of COVID-19 Adult Patients
Written by: Faculty in Infectious Diseases, Emergency Medicine, Pulmonary/Critical Care, Hospital/General Medicine, Cardiology, & Radiology
Approved by: ACPC
Date: March 27, 2020

For patients who do not/will not meet trial criteria, treating clinicians may choose to administer hydroxychloroquine as a medication for COVID-19 based on emerging early observations, but keeping in mind the known adverse events (QT prolongation, bone marrow suppression, neuropathy, and many drug-drug interactions). Some prior trials in HIV and Chikungunya infection have suggested that hydroxychloroquine may worsen outcomes in those infections by increasing viral load.
COVID Challenges/Opportunities

• Equipoise at sites – FDA EUA issued

• Consent and Data Collection- minimize staff exposure & paper consent

• Rapid progress through cIRB, FDA, PRC, DSMB, database build
Informed Consent

• Individual informed consent from patient or Legally Auth. Representative

• No-touch system
  • Paper approach
    • Paper consent form provided, consent discussion, sign paper
    • Photo of consent signature page uploaded to REDCAP
    • Paper remains with patient
  • Electronic approach
    • Electronic link used in room with participant/sent to LAR, consent discussion
    • Electronic signature in REDCap
E-Consent Process

• Bring paper consent form into room with patient to review (stays there)
• 2 study personnel (or 1 personnel and bedside nurse as witness) in PPE go into room
• iPad or bedside computer in room to sign e-consent
E Consent - Step 1

Remember to open the eConsent as a survey before handing to the participant.

PART 1 OF 2: MAIN CONSENT FOR ALL SITES

Institutional Review Board
Informed Consent Document for Research

Study Title: Outcomes Related to COVID-19 Treated with Hydroxychloroquine among In-patients with Symptomatic Disease
Revision Date: 3/30/2020

This informed consent applies to adults.

Name of Participant:
First Name: [Name]
Last Name: [Last Name]
Gender: [Gender]
Address: [Address]
Phone: [Phone Number]
Email: [Email Address]

You are being invited to take part in a research study. This study is a multi-site study, meaning it will take place at several different locations. Because this is a multi-site study, the consent form includes two parts. Part 1 of the consent form is the Master Consent Form and includes information that applies to all study sites. Part 2 of the Master Consent Form is the Study Site Information and includes information specific to the study site where you are being asked to enroll. Both parts are necessary to fulfill the legal consent requirements.

KEY INFORMATION:
The first section of this document contains some key points that the research team thought you would find important. This is described in more detail after this section. If you do not understand something, please ask someone.

Information about this study:
You are being asked to take part in this research study because you have signs and symptoms that may be caused by Coronavirus Disease 2019 (COVID-19). These include fever, cough, difficulty breathing, and fatigue. In this study, we are trying to understand whether a medication called Hydroxychloroquine improves recovery from COVID-19 in patients admitted to the hospital. Hydroxychloroquine is used to treat malaria and some joint (rheumatologic) diseases, but it is unknown if it helps patients with COVID-19. This study hydroxychloroquine is considered investigational which means it has not been approved for use with COVID-19 by the U.S. Food and Drug Administration (FDA). While you are in this study, you will receive a study medication for 1 day. This medication could be either hydroxychloroquine or placebo that means a pill with no medicine in it. The identity of this medication will be determined by a computer program.

1. Study Procedure 1: Consent for Study Participation
   - **Timing:** Today
   - **Explanation:** Consent includes reading through this form, asking questions, and receiving answers.
   - **Risks or Discomforts:** You may not understand all the information in this form. Please be sure to ask questions so you understand.
   - **What you will do:** After reading this form and asking questions, if you agree to be in this research study, you will sign this form.
   - **What we will do:** We will go through this form with you, answer any questions you have, and give you a copy of the consent form.

2. Study Procedure 2: Randomization
   - **Timing:** Today (following signing of the consent)
   - **Explanation:** If you agree to be in this study, you will be assigned to one of two groups: the Hydroxychloroquine group or the Placebo Group. You will be assigned randomly, like the flip of a coin. This is called randomization and is done by a computer program.
   - **Risks or Discomforts:** You will receive Hydroxychloroquine or Placebos. Both are explained below.
   - **What you will do:** Agreeing to be in this study includes knowing that you will be assigned to one group or the other. You will not be able to pick which group you are in. You will not be able to choose groups and will not know which group you are assigned to.
   - **What we will do:** We will get the medicines for you that you will take as part of the study for the next 5 days. Your doctors, nurses, and study personnel will not know if you are taking Hydroxychloroquine or Placebo. If it becomes necessary for your doctors to know if you are taking Hydroxychloroquine or Placebo, they can find out which one you are taking.

3. Study Procedure 3: Study Medication
   - **Timing:** Today and then 24-48 hours after starting study treatment.
   - **Explanation:** You will be given medications as part of the study for a day for the next 5 days (10 doses). These medications will be given as pills that can be swallowed or placed down feeding tubes. The study medication will either be Hydroxychloroquine (the medication we are studying to
E Consent  - Step 2

Remember to open the eConsent as a survey before handing to the participant

PART 2 OF 2: STUDY SITE INFORMATION

Consent Part 2

Institutional Review Board
Informed Consent Document for Research

Study Title: Outcomes Related to COVID-19 Treated with Hydroxychloroquine among In-patients with Symptomatic Disease
Site Name: Vanderbilt University Medical Center
Site Principal Investigator: Wesley Seif, MD
Site Study Coordinator: Adrienne Baughman
Site Study Coordinator Contact: 615-936-4253

This informed consent applies to adults

This part of the consent form includes information about the site that is asking you to participate in this study and is specific to participation at your site only. Before making your decision, both the site-specific information and the general study information should be reviewed with you. Your medical record will contain a note saying you are in a research study and may contain some research information about you. Anyone you authorize to receive your medical record will also get this information.

Site specific procedures and risks:

Payments for your time spent taking part in this study or expenses:
you will not be paid for participation in this study.

Costs to you if you take part in this study:
There is no cost to you for taking part in this study.

Payment in case you are injured because of this research study:
If it is determined by Vanderbilt and study doctor that an injury occurred as a direct result of the tests or treatments that are done for research, then you and/or your insurance will not have to pay for the cost of immediate medical care provided at Vanderbilt to treat the injury.

How long will your information be used or shared?
Your Authorization for the collection, use, and sharing of your information does not expire. Additionally, you agree that your information may be used for similar or related future research studies.

What if you change your mind?
You may change your mind and cancel this Authorization at any time. If you cancel, you must contact the Investigators in writing to let them know by using the contact information provided in this consent form. Your cancellation will not affect information already collected in the study, or information that has already been shared with others before you cancelled your authorization.

Send written notice of cancelling your authorization to be in this study to:
Wesley Seif
1313 21st Ave South
Oxford House 312
nashville, Tennessee 37232

If you decide not to take part in this research study or you withdraw from the study, it will not affect your treatment, payment or enrollment in any health plans or affect your ability to get benefits.

You will get a copy of this form after it is signed.

STATEMENT BY PERSON AGREEING TO BE IN THIS STUDY:
Please read this consent form and the research study has been explained to me verbally. All my questions have been answered, and I freely and voluntarily choose to take part in this study.

I am consenting for myself  I am acting as the legal representative and consenting on someone's behalf

Signature: [Add signature]
Date: [Add date]

Form Status
Complete?: [incomplete]

[Save & Exit] [Save & ...]
E Consent - Confirmation of Consent
Data Collection - Takeaways

- After consent, all data is remote
- No specimen collection (initially)
- Phone follow-up & chart review for primary outcome
## Data Collection Schedule

<table>
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<tr>
<th>Study Activity</th>
<th>Pre-Enrollment Day 1</th>
<th>Post-Enrollment Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
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<th>Day 5</th>
<th>Day 7</th>
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</table>

X = mandatory assessments for all participants
A = mandatory assessments for admitted participants
* participants discharge before Day 5 will have doses of study drug assessed on Day 7 telephone call
COVID Challenges/Opportunities

• Equipoise at sites – FDA EUA waiver issued
• No use of paper consent
• Rapid progress through PETAL, MGH CCC/DCC, NHLBI, cIRB, FDA, & DSMB
  • Synergy across many groups
Study Timeline

**March 18**
ORCHID PETAL Discussion

**March 20**
PETAL steering cmte vote to approve ORCHID trial moving forward

**March 23**
First draft of protocol complete
Study Timeline

**March 25**
ORCHID Discussed at NHLBI COVID roundtable

**March 28**
Protocol Review Committee approval (PETAL)

**March 29**
FDA notification of IND exemption
Study Timeline

- **March 30**: cIRB Approval
- **April 1**: DSMB Approval
- **April 2**: First Patient Randomized
Timeline Summary

• PETAL SC approval of ORCHID to first patient enrolled = 13 days

• PETAL, NHLBI, MGH CCC/DCC, VCC, Novartis, cIRB (consent process), PRC, DSMB, VUMC cardiology (Roden), Database build and testing (VUMC Biostats)

• Normal process 12 months or more
Study Update

• VUMC – 12 patients enrolled as of 4/9
• Study drug- shipping to other PETAL sites in the next few days
• Goal- open other sites next week
Thank You