SARS-CoV-2 and Role of Hydroxychloroquine

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Introduction/Intent of Document (Updated 3.28.20):

Purpose of Document: The authors created this document to share currently available information about HCQ and its potential role for SARS-CoV-2.

Summary of findings: At this time, there are no FDA-approved drugs for the treatment of patients with COVID-19. There are no currently available data from randomized clinical trials to inform clinical guidance on the use, dosing, or duration of hydroxychloroquine for prophylaxis or treatment of SARS-CoV-2 infection. The CDC's website states that hydroxychloroquine is currently under investigation in clinical trials for pre-exposure or post-exposure prophylaxis, and for the treatment of patients with mild, moderate, and severe COVID-19.

Authors' Opinion: There is limited data to support the use of hydroxychloroquine for the treatment of patients with SARS-CoV-2. There is no meaningful data to support the use of hydroxychloroquine for preexposure-prophylaxis; in addition to the absence of data for this purpose, dosing for this use is anecdotal at this time. The authors are aware of and support the AMA, APhA, ASHP Joint Statement About COVID-19 Medications released on 3.25.20 (available at https://www.ashp.org/News/2020/03/25/AMA-APhA-ASHP-Issue-Joint-Statement-About-COVID-19-Medications). The authors encourage providers to review this statement, as well as to encourage patients who meet qualifications to enroll in available clinical trials, so that we ultimately have robust data that we can use. There are several clinical trials available at www.clinicaltrials.gov, including one study currently enrolling patients through the University of Minnesota on post-exposure prophylaxis/pre-emptive therapy, available at: https://clinicaltrials.gov/ct2/show/NCT04308668. The authors are aware that new information is being released on a daily basis, and we will continue to research these issues and provide additional data as more becomes available.

Hydroxychloroquine

Indications

Hydroxychloroquine was FDA approved in 1955 for the treatment and prophylaxis of chloroquine-sensitive malaria and has since been FDA-approved for treatment of rheumatologic disorders such as systemic lupus erythematosus and rheumatoid arthritis.[1,2] Although not FDA approved, hydroxychloroquine has been used to treat myalgia and arthralgias associated with Sjögren's syndrome, cutaneous manifestations of dermatomyositis, lupus nephritis, chronic Q-fever, antiphospholipid antibody syndrome, sarcoid arthropathy, cutaneous sarcoidosis, and to suppress polymorphous light eruption.[3-6]

Mechanism of Action/Pharmacology *- see separate document for additional information on background on SARS-CoV-2 viral replication and proposed mechanisms of hydroxychloroquine*

Hydroxychloroquine possesses immunomodulator activity that includes a variety of proposed mechanisms such as: interference with lysosomal acidification; inhibition of proteolysis, chemotaxis, and phagocytosis; decreasing macrophage-mediated cytokine production; inhibition of phospholipase A2; binding and stabilizing DNA; inhibition of T- and B-cell calcium signaling; and inhibition of matrix metalloproteinases.[7]

In addition to immunomodulating activity, hydroxychloroquine possesses anti-infective activity against several RNA viruses. As an anti-infective agent, hydroxychloroquine, a weak base, concentrates within acidic organelles such as endosomes and lysosomes thereby alkalinizing the cell and disrupting normal activities.[8] Interestingly, chloroquine promotes zinc uptake by cells acting as a zinc ionophore, which further impairs viral replication.[9,10] Zinc and pyrithione, a zinc-ionophore, halted replication of SARS-coronavirus (SARS-CoV) in *vitro* as further discussed in the section on Clinical Trials.[10]

Pharmacokinetics

After oral administration of a single 200-mg dose in patients with rheumatoid arthritis, a mean oral bioavailability of 74% was reported;[2,4] however, oral bioavailability ranges from 30% to 100% in patients with rheumatoid arthritis, which indicates variability dependent upon extent of disease activity.[2,3,5] The drug displays linear kinetics with peak plasma concentrations occurring within 3 to 4 hours after oral administration.[2,5]

Hydroxychloroquine distributes extensively throughout tissues and has a very large volume of distribution (5,522 L in the blood and 44,257 L in the plasma).[2,4,6] High concentrations exist in the bone marrow, liver, kidneys, lungs, adrenal gland, pituitary gland, and especially melanin containing tissues such as the skin and eyes.[5,7,11] Approximately 30% to 40%% of hydroxychloroquine binds to proteins in the plasma, with 40% to serum albumin and 34% to alpha-1-acid glycoprotein.[12]

Hydroxychloroquine undergoes liver metabolism through dealkylation by cytochrome P4503A4 to active metabolites bidesethylchloroquine, desethylhydroxychloroquine, and desethylchloroquine.[2,6,11] The elimination half-life of 40 to 50 days reflects the extensive distribution into tissues rather than decreased excretion.[2] Approximately 16% to 30% of the dose is eliminated renally independent of creatinine clearance.[2]

Drug-drug Interactions

Drug interactions maybe classified as pharmacodynamic or pharmacokinetic in nature. Pharmacodynamic interactions result from the pharmacologic activity of hydroxychloroquine being additive or antagonistic to the pharmacology of other drugs, while pharmacokinetic interactions impact absorption, distribution, metabolism, or excretion of another drug. Pharmacodynamic drug interactions include drugs that decrease serum glucose, e.g., antidiabetic agents, drugs that prolong the QT interval (e.g., phenothiazines), and drugs that when used in combination with hydroxychloroquine result in additive toxicity (Table 1).[2-5]

Table 1. Select drug-drug interactions[2-5]

Drugs	Summary Description
Pharmacodynamic interactions	
Decrease blood glucose	androgens, antidiabetic agents, citalopram, escitalopram, maitake, monoamine oxidase inhibitors, pegvisomant, fluoroquinolones, salicylates
Prolong QT interval	amiodarone, chlorpromazine, ciprofloxacin, citalopram, disopyramide, dofetilide, dronedarone, escitalopram, haloperidol, ibutilide, ivosidenib, lenvatinib, mefloquine, methadone, procainamide, quinidine, quinine, sotalol, vandetanib, ziprasidone
Retinal toxicity	tamoxifen
Hemolytic reactions	dapsone
Decrease seizure threshold	antiepileptics, mefloquine
Additive toxicity, avoid use	artemether, lumefantrine, mefloquine
Pharmacokinetic interactions	
Phenothiazines	may increase the serum concentration of phenothiazines
Beta-Blockers	may decrease metabolism of metoprolol, propranolol; does not affect metabolism of atenolol, carteolol (ophthalmic), levobunolol, metipranolol, nadolol, sotalol
Cardiac Glycosides	may increase the serum concentration of digoxin
Cyclosporine	may increase the serum concentration of cyclosporine

The following drugs interact with chloroquine and should be used cautiously in patients receiving hydroxychloroquine.[2]

- Antacids and kaolin: Antacids reduce absorption of chloroquine; separate administration by at least 4 hours.
- Cimetidine: Cimetidine inhibits the metabolism of chloroquine resulting in an increased plasma level; avoid use.
- Ampicillin: In a study of healthy volunteers, chloroquine significantly reduced the bioavailability of ampicillin.

Contraindications

Hydroxychloroquine is contraindicated in patients with known hypersensitivity to 4-aminoquinoline compounds, i.e., drugs with an amino group at the 4-position of the quinoline, which include chloroquine and hydroxychloroquine.[2,6]

Warning/Precautions

Hydroxychloroquine should be used with caution in patients with macular disease, porphyria, or psoriasis and those who are receiving drugs that prolong the QT interval or decrease serum glucose.[2–5] In general, patients with gastrointestinal, neurological, or blood disorders, hepatic or renal impairment, and those with a sensitivity to quinine should be monitored closely for adverse events.[2–5]

Adverse Drug Effects

Hydroxychloroquine has several severe side effects necessitating vigilance on the part of the health care prescriber (Table 2). Common adverse events include:

Table 2. Adverse Effects[2–5,7]

Cardiovascular	Cardiomyopathy, prolonged QT interval, torsades de pointes, ventricular arrhythmia; all reported post-marketing
Dermatologic	Alopecia, angioedema, bleaching of hair, exacerbation of psoriasis, photosensitivity pigmentation changes (skin and mucosal; black-blue color), pruritus, rash, Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria
Endocrine	Exacerbation of porphyria, hypoglycemia, weight loss
Gastrointestinal	Abdominal cramping, anorexia, diarrhea, nausea, vomiting
Hepatic	Abnormal liver function tests, acute hepatic failure
Hematologic	Agranulocytosis, anemia, aplastic anemia, bone marrow failure, hemolysis (in patients with glucose-6-phosphate deficiency), leukopenia, thrombocytopenia
Immunologic	Drug reaction with eosinophilia and systemic symptoms
Nervous System	Ataxia, dizziness, emotional changes, fatigue, headache, irritability, lassitude, nervousness, nightmares, psychosis, seizure, sensorineural hearing loss, suicidal tendencies, vertigo
Neuromuscular and skeletal	Myopathy, palsy, or neuromyopathy leading to progressive weakness and atrophy of proximal muscle groups (may be associated with mild sensory changes, loss of deep tendon reflexes, and abnormal nerve conduction)
Ocular[a]	Corneal changes (corneal edema, corneal opacity, corneal sensitivity, corneal deposits, visual disturbance, blurred vision, photophobia), retinopathy (early changes reversible, may progress despite discontinuation if advanced)
Otic	Deafness, tinnitus
Respiratory	Bronchospasm, respiratory failure (myopathy-related)

[a]risk factors for retinal damage include daily doses >6.5 mg/kg (5 mg/kg base), duration of use >5 years, renal impairment, and concomitant use of tamoxifen or concurrent macular disease

Special Populations

Pediatrics

Hydroxychloroquine is FDA-approved for treatment and prophylaxis of malaria in children; the drug has not been studied in children with chronic disease, i.e., systemic lupus erythematosus and juvenile idiopathic arthritis.[2]

Pregnancy/Lactation

Women who used hydroxychloroquine during pregnancy had normal births; risks versus benefit should be considered.[2,3] The drug is excreted in breast milk and caution should be used when prescribing to a nursing mother as the infant may be particularly sensitive to the adverse effects.[2,3]

Geriatrics

As geriatric patients have decreased renal function, caution should be used when prescribing for patients older than 65 years.[2] Routine monitoring of renal function is warranted.

Administration

The oral tablet (200 mg of hydroxychloroquine sulfate, which is equivalent to 155 mg base) should be administered with food or milk to avoid any gastrointestinal discomfort.[2] Do not crush or divide film-coated tablets.

Hydroxychloroquine Clinical Trials

Completed In Vivo Trials

Gautret P, Lagier JC, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *International Journal of Antimicrobial Agents*. In Press March 17, 2020. doi:10.1016/j.ijantimicag.2020.105949

Gautret and colleagues conducted an open-label non-randomized clinical trial (that has not yet been published) in which they assessed the effect of hydroxychloroquine on SARS-CoV-2 infected patients as compared to a control group.[13] Depending on clinical presentation, patients were allowed to receive azithromycin (500 mg day 1, followed by 250 mg on days 2 through 5) to prevent bacterial superinfection based on clinical judgment of investigators. Patients in the treatment group received oral hydroxychloroquine sulfate 200 mg three times daily for ten days. Patients older than 12 years of age with PCR-documented SARS-CoV-2 carriage in a nasopharyngeal sample upon admission independent of clinical status were included. Patients were excluded if they had a known allergy to hydroxychloroquine or chloroquine, had a condition such as retinopathy, G6PD deficiency, QT prolongation (which have been associated with the study drug), or were pregnant or breastfeeding. The primary endpoint was virological clearance (presence or absence of SARS-CoV-2) at day 6 after study inclusion. A total of 26 patients received hydroxychloroquine and 16 served as controls; however, 6 patients in the chloroquine group were lost to follow-up due to early cessation of treatment. Therefore, results are for 36 patients (20 who received hydroxychloroquine and 16 who served as controls) who had at least six days of follow-up. Baseline characteristics were similar for the two groups with respect to gender, clinical status, and duration of symptoms prior to study inclusion. However, patients treated with hydroxychloroquine were older than controls (51.2 years vs. 37.3 years). Six patients in the hydroxychloroquine-treated group received azithromycin as compared to no patients in the control group. The primary outcome of virological cure at day 6 after study inclusion was achieved in 70% (14/20) of hydroxychloroquine-treated patients as compared to 12.5% (2/16) of controls ($p = 0.001$). The proportion of patients with negative PCR from nasopharyngeal samples also significantly differed between the two groups at days 3-,4-, and 5 after study inclusion. The proportion of patients with virological cure at day 3 was 10/20 (50%) in the hydroxychloroquine group, as compared to 1/16 (6.3%) of control patients ($p = 0.005$). At day 4, the rates of virological cure were 12/20 (60%) for patients in the hydroxychloroquine group as compared to 4/16 (25%) of those in the control group ($p = 0.04$). The rates of cure at day 5, were 13/20 (65%) in the hydroxychloroquine group as compared to 3/16 (18.8%) of controls ($p = 0.006$). When comparing those who received hydroxychloroquine and those who received hydroxychloroquine in combination with azithromycin, 100% of those treated with the combination achieved virological cure at 6 days post-inclusion, as compared to 57.1% of patients treated with hydroxychloroquine monotherapy and 12.5% in the control group ($p < 0.001$). One patient who received hydroxychloroquine and was PCR-positive at day 6 post study inclusion achieved virological cure at day 9 post-infection after receipt of azithromycin. The authors concluded that "Despite its small sample size our survey shows that hydroxychloroquine treatment is significantly associated with viral load reduction/ disappearance in COVID-19 patients and

its effect is reinforced by azithromycin." Limitations include that this study has not undergone peer review, small sample size, study design was non-randomized and unblinded, and limited long-term outcome follow-up. Additional data with larger, controlled trials is needed to confirm these findings. Furthermore, data to determine to assess the utility of hydroxychloroquine (and combination with azithromycin) as chemoprophylaxis, especially for healthcare workers (since virological clearance occurred at day 3 post-study inclusion and mean duration of viral shedding has been shown to be 20 days) and cause of failure for hydroxychloroquine would also be beneficial.

Gao J, Tian Z, Yang X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. Biosci Trends. 2020;14(1):72–73.

In preliminary reports from Chinese authorities, approximately 100 patients with COVID-19 being treated with chloroquine experienced a more rapid decline in fever, more rapid improvement via lung CT images, inhibiting the exacerbation of pneumonia, and required shorter time to recover compared to controls.[14] Chloroquine-treated patients did not show increase in severe adverse effects, but an in-depth survey of all adverse effects was not completed. Full data from these studies have not been released.

Completed In Vitro Studies

Yao X, Ye F, Zhang M, 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) [published online ahead of print, 2020 Mar 9]. *Clin Infect Dis*. 2020;ciaa237.

Yao and colleagues conducted an *in vitro* experiment to evaluate the antiviral and prophylactic activity of hydroxychloroquine and chloroquine and to build a physiologically-based pharmacokinetic (PBPK) model to predict lung tissue drug concentrations using different dosing regimens.[15] The *in vitro* study showed that chloroquine and hydroxychloroquine had good antiviral activity, with a 50% maximal effective concentration (EC_{50}) of 0.72 μM at 48 hours for hydroxychloroquine and EC_{50} of 5.47 μM at 48 hours for chloroquine. Both agents displayed concentration-dependent inhibition of viral replication, and based on the EC_{50} values, hydroxychloroquine was more potent than chloroquine at inhibiting SARS-CoV-2 *in vitro*. When each agent was added prophylactically, prior to viral challenge, hydroxychloroquine displayed a superior in vitro antiviral effect, with the EC_{50} = 5.85 μM at 48 hours for hydroxychloroquine and EC_{50} = 18.01 μM at 48 hours for chloroquine. At 24 hours, the EC_{50} of chloroquine was > 100 μM, and the highest concentration of chloroquine used in the study did not result in an inhibition rate more than 50%. Based on PBPK models, the study determined that a loading dose of hydroxychloroquine 400 mg orally twice daily, followed by a maintenance dose of 200 mg orally given twice daily for 4 days should be used to treat SARS-CoV-2 infection.

Liu J, Cao R, Xu M, et al. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. Cell Discov. 2020;6:16. Published 2020 Mar 18.

Liu and colleagues reported similar findings in a recently published letter to the editor in which they found that hydroxychloroquine and chloroquine both had in vitro activity against SARS-CoV-2.[16] At four different multiplicities of infection, the EC_{50} for chloroquine was 2.71, 3.81, 7.14, and 7.36 μM, and the EC_{50} for hydroxychloroquine was 4.51, 4.06, 17.31, and 12.96 μM. The authors stated that based on their data (which showed a significant difference in EC_{50} at certain multiplicities of infection), it

suggests that the anti-SARS-CoV-2 activity of hydroxychloroquine may be less potent as compared to chloroquine (at least at certain MOIs). The authors concluded that hydroxychloroquine can efficiently inhibit SARS-CoV-2 in vitro and that although it has potential to combat COVID-19 because of this activity and its anti-inflammatory properties, clinical trials are needed for confirmation.

Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res. 2020;30(3):269–271.

In this study by Wang and colleagues, the antiviral efficiency of seven different drugs (including chloroquine) were tested against a clinical isolate of SARS-CoV-2.[17] Chloroquine demonstrated inhibitory effects at both entry and post-entry stages of SARS-CoV-2. The EC_{50} and EC_{90} in the infected cells were 1.13 μM and 6.90 μM, respectively. The EC_{90} concentration can be clinically achievable with 500 mg administration (demonstrated in rheumatoid arthritis patients previously). The only other drug tested in the study that demonstrated effective inhibition was remdesivir.

Opinion Article on Dosing of Chloroquine for Prophylaxis

Chang, R.; Sun, W. Repositioning Chloroquine as Ideal Antiviral Prophylactic against COVID-19 - Time is Now. Preprints *2020, 2020030279 (doi: 10.20944/preprints202003.0279.v1).*

Chang and Sun discuss chloroquine for antiviral prophylaxis against COVID-19 in an article that has not yet been peer reviewed or published in a journal.[18] Based upon a review of the mechanism of action, laboratory efficacy, and pharmacokinetics of chloroquine for its established uses, the authors determined a dosing regimen for chloroquine prophylaxis specific to COVID. The authors recommend pre-exposure prophylaxis with chloroquine for those in areas of outbreak/endemic areas with a high risk of exposure at a dosing regimen of 500 mg daily for 30 days, followed by 250 mg daily until there is no longer a threat of infection. For post-exposure prophylaxis in asymptomatic individuals, the authors recommend chloroquine 8 mg/kg/day for 3 days, ideally taken within hours after known viral exposure. The authors also recommend additional research on this agent for prevention and to study their recommended regimens in parallel with their use in order to help contain the current pandemic. Since chloroquine 250 mg is equivalent to hydroxychloroquine 200 mg, the equivalent dose of hydroxychloroquine that would be recommended by these authors for pre-exposure prophylaxis is 400 mg hydroxychloroquine for 30 days, followed by 200 mg daily.

Ongoing Clinical Trials

There are currently several studies being conducted around the world. Three select studies (found on clinicaltrials.gov) are summarized below.[19-21]

1. Post-exposure Prophylaxis for SARS-Coronavirus-2. ClinicalTrials.gov. Identifier NCT04308668. Available at: https://clinicaltrials.gov/ct2/show/NCT04308668. Accessed March 20, 2020.[19]

- Design: a randomized clinical trial with an estimated 1500 participants is underway through the University of Minnesota (start date March 17, 2020)
- Study objective: to test if post-exposure prophylaxis with hydroxychloroquine can prevent progression development of symptomatic COVID-19 after known exposure to SARS-CoV-2
- Intervention (2 arms): treatment with hydroxychloroquine and placebo
    - The hydroxychloroquine dose is 800 mg orally once, followed in 6 to 8 hours by 600 mg, then 600 mg once daily for 6 consecutive days
    - A 200 mg tablet will be used and is based on a derivation of the dose used in malaria
- Outcome Measures
    - Primary outcome: incidence of COVID-19 disease and COVID-19 disease severity using an ordinal scale (both measured 14 days post enrollment)
    - Secondary outcome measures [and time frame]
        - Incidence of hospitalization [14 days]
        - Incidence of death [90 days]
        - Confirmed SARS-CoV-2 detection [14 days]
        - Symptoms compatible with COVID-19 [90 days]
        - Medicine discontinuation or study withdrawal [14 days]
- Study subjects
    - Inclusion criteria includes those age 18 years or older and exposure to COVID-19 case within 3 days as either a healthcare worker or household contact
    - Exclusion criteria includes symptomatic COVID-19 disease, current symptoms of fever, cough, or shortness of breath, retinal eye disease or contraindications to hydroxychloroquine, known G6PD deficiency, known chronic kidney disease, weight <40kg, and current use of certain antiarrhythmic drugs
- Results: pending (estimated completion in May 2021)

2. Treatment of Mild Cases and Chemoprophylaxis of Contacts as Prevention of the COVID-19 Epidemic (HCQ4COV19). ClinicalTrials.gov. Identifier NCT04304053. Available at: https://www.clinicaltrials.gov/ct2/show/NCT04304053. Accessed March 20, 2020.[20]

- Design: a randomized open-label clinical trial with an estimated 3040 participants (not yet recruiting)
- Study objective: to evaluate the efficacy of the 'test and treat' strategy of infected patients and prophylactic chloroquine treatment to all contact

- Arms and Interventions:
    - Active comparator: no intervention other than isolation of patient and contact tracing per national guidelines
    - Intervention (with isolation and tracing):
        - Cases (positive test): antiviral treatment with hydroxychloroquine and darunavir/cobicistat
        - Contacts (of cases): prophylaxis with hydroxychloroquine
        - Dosing:
            - hydroxychloroquine 800 mg on day 1, and 400 mg on days 2, 3, 4
            - darunavir 800 mg / cobicistat 150 mg once daily for 7 days
- Outcome Measures
    - Primary outcome: effectiveness of chemoprophylaxis assessed by incidence of secondary COVID-19 cases [time frame: up to 14 days after start of treatment]
    - Secondary outcome measures [and time frame]
        - The virological clearance rate of throat swabs, sputum, or lower respiratory tract secretions at days 3 [3 days after start of treatment]
        - The mortality rate of subjects at weeks 2 [up to 14 days after start of treatment]
        - Proportion of participants that drop out of study [up to 14 days after start of treatment]
        - Proportion of participants that show non-compliance with study drug [up to 14 days after start of treatment]
- Study subjects
    - Inclusion criteria includes those age 18 years or older and meet requirements of the COVID-19 diagnosis (acute respiratory infection or acute cough alone and positive PCR)
    - Exclusion criteria includes serious respiratory medical condition, critically ill patients, history of cardiac arrhythmia or QT prolongation, pregnancy, retinal disease or hearing loss, severe neurological and mental illness.
- Results: pending (estimated completion in July, 2020)

3. Chloroquine Prevention of Coronavirus Disease (COVID-19) in the Healthcare Setting (COPCOV). ClinicalTrials.gov. Identifier NCT04303507. Available at: https://clinicaltrials.gov/ct2/show/NCT04303507. Accessed March 22, 2020.[21]

- Design: a randomized, double-blind, placebo-controlled clinical trial with a parallel assessment of an estimated 10,000 participants (start date March 17, 2020)
- Study objective: to compare the number of symptomatic COVID-19 infections in healthcare workers or those at significant risk for infection in those who receive chloroquine as compared to placebo
- Intervention: treatment with chloroquine vs. placebo
    - Chloroquine dose: loading dose of 10mg base/kg, followed by 150 mg daily (250 mg chloroquine phosphate salt) for 3 months or until diagnosis of COVID-19

- Outcome Measures
    - Primary outcome: number of symptomatic COVID-19 infections in subjects randomized to chloroquine or placebo
    - Secondary outcome measures [and time frame]
        - Symptom severity [100 days]
        - Duration of COVID-19 [100 days]
        - Number of asymptomatic cases of COVID-19 [100 days]
        - Number of symptomatic acute respiratory illnesses [100 days]
        - Genetic loci and levels of biochemical components (correlated with frequency, acute respiratory illness, and disease severity) [100 days]
- Study subjects
    - Inclusion criteria includes those age 16 years or older not previously diagnosed with COVID-19 who work in a healthcare facility or high-risk environment or an inpatient or relative of a high-risk exposure group
    - Exclusion criteria includes contraindications to hydroxychloroquine (hypersensitivity, epilepsy, retinal disease), concomitant medication with significant interaction, inability to be followed up for the trial period (plan to follow for 5 months)
- Results: pending

Role of Zinc

Background

Zinc is essential in both cell-mediated and humoral immunity, with zinc deficiency resulting in dysfunction of both of these processes and increased susceptibility to infection. Supplementation of zinc has been shown to reduce the incidence of infection and cellular damage from increased oxidative stress.[22]

Increasing the intracellular concentration of zinc with zinc ionophores (such as pyrithione) has been shown to impair the replication of several RNA viruses, including polio and influenza, as well as the replication of SARS-CoV, as discussed in the study by te Velthuis and colleagues.[10]

In Vitro Studies

Xue and colleagues investigated the interaction of zinc ions with chloroquine in a human ovarian cancer cell line (A2780), and found that free zinc ions were more concentrated in lysosomes after addition of chloroquine.[9] They also found that the addition of copper or iron ions did not affect chloroquine-induced zinc uptake. They concluded that chloroquine is a zinc ionophore, and hypothesized that this may contribute to its anticancer activity.

te Velthuis and colleagues showed that zinc inhibited RNA-dependent RNA polymerase, a core enzyme for viral replication and transcription, in SARS-CoV *in vitro*.[10] They also demonstrated that the combination of low concentrations of 2 mM zinc and 2mM pyrithione (a zinc ionophore) inhibited the replication of SARS-coronavirus (SARS-CoV) in cell culture.

Han and colleagues demonstrated that zinc and zinc conjugates inhibited the activity of SARS-CoV papain-like protease 2 (PLP2), an enzyme that is essential for pathogenesis and virulence of the virus.[23] Zinc ion displayed potent activity and inhibited the enzyme activity with an IC_{50} = 1.3 *i*M, while the zinc

conjugates *N*-ethyl-*N*-phenyldithiocarbamic acid Zn (IC_{50} = 3.3 *i*M) and hydroxypridine-2-thione Zn (IC_{50} = 3.7 *i*M) were also effective in inhibiting SARS-CoV PLP2. Other divalent metals, including Mg, Mn, Ca, Ni, and Co, had no effects on the activity of SARS-CoV PLP2 at 10 *i*M while Cu ion at 10 *i*M weakly inhibited the activity of the PLP2 to 70%.

Guideline Recommendations

As of March 22, 2020, there are no FDA-approved drugs specifically for the treatment of patients with COVID-19. The CDC's website states that hydroxychloroquine is currently under investigation in clinical trials for pre-exposure or post-exposure prophylaxis, and for the treatment of patients with mild, moderate, and severe COVID-19. The CDC acknowledges that some clinicians have used hydroxychloroquine for the treatment of COVID-19, but that there is no data from randomized clinical trials to inform guidance on the use, dosing, or duration for prophylaxis or treatment of SARS-CoV-2. There are different dosing regimens of hydroxychloroquine that have been used by U.S. physicians, including: 400 mg BID on day one, then 400 mg daily for 5 days; 400 mg BID on day one, then 200 mg BID for 4 days; and 600 mg BID on day one, then 400 mg daily on days 2 through 5.[24]

Specific guidelines on the use of hydroxychloroquine in the treatment of COVID-19 by other organizations state that there is limited scientific information regarding efficacy. Researchers from China recommend that hydroxychloroquine be added to guidelines for the treatment of pneumonia caused by COVID-19 issued by the National Health Commission of the People's Republic of China based on preliminary results of its use in patients infected with the virus.[14] Several organizations have published recommendations regarding the use of hydroxychloroquine for treatment of COVID-19. Authors of the surviving sepsis campaign state that "There is insufficient evidence to issue a recommendation on the use of chloroquine or hydroxychloroquine in critically ill adults with COVID-19."[25] Preliminary guidelines published from Belgium recommend antiviral therapy as an adjunct to treatment of COVID-19 for hospitalized patients.[26] The National Institute for the Infectious Diseases from Italy recommends antiviral therapy including hydroxychloroquine for stable and unstable patients who present with respiratory and/or systemic symptoms.[27] Ireland also published recommendations on the use of antivirals for the treatment of COVID-19.[28]

Several individual hospital systems in the United States have developed guidelines for the use of antiviral therapy to treat COVID-19 infections. Two examples are Brigham and Women's Hospital (which is affiliated with Harvard Medical School) released COVID-19 Critical Care Clinical Guidelines as a work in progress, that will be updated on a daily basis (https://www.covidprotocols.org/), and the University of Michigan, which has released inpatient guidelines (http://www.med.umich.edu/asp/pdf/adult_guidelines/COVID-19-treatment.pdf).[29,30]

Resources

Information on COVID-19 is rapidly changing. Several resources are available (including those listed in the table below), which should be consulted on a regular basis for the most updated information.

CDC	https://www.cdc.gov/coronavirus/2019-ncov/index.html https://www.cdc.gov/coronavirus/2019-ncov/hcp/therapeutic-options.html
IDSA (Infectious Diseases Society of America)	https://www.idsociety.org/public-health/COVID-19-Resource-Center/
Clinical Trials	www.clinicaltrials.gov

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