

Emily Littlejohn, DO, MPHDepartment of Rheumatologic and Immunologic Disease,
Orthopaedic & Rheumatologic Institute, Cleveland Clinic

Hydroxychloroquine use in the COVID-19 patient

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■ ABSTRACT

Hydroxychloroquine (HCQ) has multiple potential antiviral mechanisms of action that differ according to the pathogen studied (eg, Chikungunya, Dengue virus, human immunodeficiency virus, poliovirus, Zika virus). Data on HCQ for treatment of COVID-19 are rapidly evolving. To date, there is no evidence from randomized controlled trials that HCQ, or any single therapy, improves outcomes in patients infected with COVID-19. There are also no clinical trial data supporting prophylactic HCQ therapy in COVID-19. Use of HCQ in patients with COVID-19 is being investigated for prophylaxis, postexposure prophylaxis, and treatment.

■ INTRODUCTION

Hydroxychloroquine (HCQ) has multiple potential antiviral mechanisms of action that differ according to the pathogen studied (eg, Chikungunya, Dengue virus, human immunodeficiency virus, poliovirus, Zika virus). The anti-severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) effects of HCQ in vitro were attributed to a deficit in glycosylation of the viral cell surface receptor, the angiotensin-converting enzyme 2 (ACE2)¹ interfering with pH-dependent endosome-mediated viral entry. HCQ also has immunomodulatory effects through attenuation of cytokine production and inhibition of autophagy and lysosome and endosome function in host cells.^{2,3}

■ CLINICAL DATA

Data on treatment of COVID-19 are rapidly evolving. To date, there is no evidence from randomized controlled trials that any single therapy improves outcomes in patients infected with COVID-19. There

are also no clinical trial data supporting prophylactic HCQ therapy in COVID-19.

A small open-label nonrandomized French study (N = 36) done at the Méditerranée Infection University Hospital Institute in Marseille, France, reported improved severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) clearance in patients receiving HCQ compared with controls receiving standard supportive care.⁴ HCQ was dosed at 200 mg every 8 hours (600 mg daily total) for 10 days. Of the 20 patients in the treatment arm, 6 patients in a non-randomized manner also received azithromycin 500 mg on day 1, followed by 250 mg daily for 4 days. Viral clearance as measured by nasopharyngeal swabs at day 6 was 70% (14 of 20) vs 12.5% (2 of 16) for the HCQ and control groups, respectively ($P = .001$). The addition of azithromycin to HCQ in 6 patients resulted in improved viral clearance (100%, 6 of 6) compared with HCQ monotherapy (57%, 8 of 14). This was a small, nonrandomized study with unclear patient characteristics and controls, and with the removal of 6 cases from the analyzed treatment arm due to need for escalation of care. There were also no repeat or follow-up nasopharyngeal swabs to ensure complete viral eradication.

A pilot randomized controlled trial conducted in China in 30 patients with nonsevere COVID-19 randomized them to HCQ 200 mg twice daily for 5 days plus standard of care (including unspecified antiviral and antibacterial agents, and immunoglobulin with or without corticosteroids) or standard care alone in a 1:1 fashion.⁵ The primary end point was negative conversion rate of COVID-19 nucleic acid in respiratory pharyngeal swab on day 7 after randomization. Results of this study showed no difference in outcomes; viral clearance was similar in the HCQ plus standard-of-care group (86.7%) and standard-care group (93.3%).

In a multicenter, parallel, open-label, randomized Chinese trial that included 150 adult patients with COVID-19, adding high-dose HCQ at 1,200 mg daily

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for 3 days, followed by 800 mg daily for the remaining 2 to 3 weeks, to the current standard of care showed no differences in negative conversion rate of SARS-CoV-2 at day 4, 7, 10, 14, 21, or 28.⁶ In the standard of care plus HCQ group, negative conversion rate was 85.4% and in the standard of care group it was 81.3%. Those receiving HCQ did have accelerated alleviation of clinical symptoms, postulated by the authors to occur through anti-inflammatory effects and recovery of lymphopenia. There were no safety concerns reported in this study with this high dose of HCQ although diarrhea was reported in about 10% of patients.

One study supporting the benefit of HCQ analyzed 550 critically ill patients with COVID-19 who required mechanical ventilation in Tongji Hospital, Wuhan, China.⁷ In this study, 48 patients were treated with oral HCQ (200 mg twice a day for 7–10 days) in addition to standard treatments with antiviral drugs and antibiotics. Mortality rates showed 9 of the 48 HCQ-treated patients died (18.8%) while 238 of 502 patients from the non-HCQ group died (47.4%, $P < .001$). The average hospital stay time was similar between groups, but the length of hospital stay before death was longer in the HCQ group—suggesting increased survival with HCQ.

Laboratory testing showed that HCQ therapy significantly reduced IL-6 levels in plasma, and when HCQ treatment stopped, IL-6 levels rose back to the control-group level. It is important to note both the retrospective nature of this study and the small treatment arm ($n = 48$).

Newer data from the US, however, has largely confirmed its lack of efficacy. In a retrospective multicenter cohort of 1,438 patients hospitalized in New York, NY, patients were categorized into 4 treatment groups based on having received at any time during hospitalization: HCQ with azithromycin, HCQ alone, azithromycin alone, and neither drug.⁸ After adjustment for demographics, specific hospital, pre-existing conditions, and illness severity, no significant differences in mortality were found between any treatment arm.

A multicenter study in Brazil assessed whether HCQ alone ($n = 221$) or with azithromycin ($n = 217$), would improve clinical status at 15 days as evaluated with the use of a seven-level ordinal scale.⁹ There were no significant between-group differences in the proportional odds of having a higher (worse) score on ordinal scale at day 15, showing no effect of treatment with HCQ alone or HCQ plus azithromycin as

compared with the control group ($n = 227$). Important weaknesses of this study include its non-blinded nature and treatment group protocol deviations. Also, patients were enrolled up to 14 days after the onset of symptoms, a later intervention than many other studies, thus the results may not be indicative of a drug effect alone.

The Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial is designed to evaluate treatments to prevent death in patients hospitalized with COVID-19 (<https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-001113-21/GB>). Over 11,000 patients from 175 National Health Service hospitals in the United Kingdom have been enrolled. Preliminary results of the data for patients randomized to HCQ ($n = 1542$) compared with usual care ($n = 3132$) found no significant difference in the primary endpoint of 28-day mortality (25.7% hydroxychloroquine vs 23.5% usual care; hazard ratio 1.11).¹⁰ There was also no evidence of beneficial effects on hospital stay duration or other outcomes.

The role of HCQ as prophylaxis for COVID-19 in individuals exposed to SARS-CoV-2, was evaluated in a randomized, double-blind, placebo-controlled trial in the United States and Canada.¹¹ This study enrolled 821 asymptomatic adults who had household or occupational exposure to someone with confirmed COVID-19. Participants received placebo or HCQ 800 mg once, followed by 600 mg in 6 to 8 hours, then 600 mg daily for 4 additional days. The incidence of new COVID-19 cases did not differ significantly between the 2 groups. An important limitation of this study was the definition for “prior symptomatic” participants. COVID-19 testing was not available and not performed on the majority of participants deemed “positive.” Although this design was selected to simulate real world exposures, the results do not address prevention of confirmed positive cases.

■ DOSING DATA

A potential therapeutic dosing regimen of HCQ in COVID-19 has yet to be determined. In a study by Yao et al, the pharmacologic activity of HCQ was tested using physiologically based pharmacokinetic models. A suggested loading dose of 400 mg twice daily of HCQ sulfate given orally, followed by a maintenance dose of 200 mg given twice daily for 4 days, was determined to be the most effective regimen in inhibiting SARS-CoV-2 in vitro while still considering the drug’s safety profile.¹² Given what is known from dosing in rheumatic disease, doses up to

400 mg at any one time are generally well tolerated, with increased gastrointestinal effects at higher doses (although note that the study above used doses as high as 1,200 mg daily). There has been no standardization of dosing across ongoing studies.

■ RELEVANT ISSUES TO KEEP IN MIND

In patients with rheumatic disorders, HCQ therapy at the usual maximum dose of 400 mg daily (or about 5 mg/kg) is generally very well tolerated. Common adverse effects to be expected include the following:

- Gastrointestinal distress and diarrhea, mostly observed in large doses (≥ 400 mg) given on an empty stomach
- Hypoglycemia is not uncommon, especially in patients with “brittle” diabetes, and has also been reported in patients with impaired fasting glucose; it is best to take the medication with food to mitigate these effects
- Elevated transaminase levels also can be seen and, rarely, clinically significant acute hepatic injury or myopathy
- Other blood tests to monitor include the complete blood cell count with differential, which may rarely show leukopenia, neutropenia, anemia, and thrombocytopenia. There are no data to support testing for glucose-6-phosphate dehydrogenase (G6PD) or for withholding HCQ in patients with G6PD deficiency¹³
- Risk of dose-related retinopathy is appreciable, although most worrisome with long duration of HCQ use, older age, and higher body mass index¹⁴; this is unlikely a major concern with short-term use for COVID-19
- Use of HCQ in pregnancy is safe, and continuation of therapy is encouraged in lupus patients
- HCQ can cause photosensitivity, skin rash, pruritus, and skin discoloration and has been known to exacerbate psoriasis; these effects can manifest at any point in therapy.

QTc monitoring is infrequently done when HCQ is used as monotherapy in the doses noted above. The risk of prolonged QTc is realized mostly when HCQ is combined with other QTc-prolonging drugs such as azithromycin. This was directly addressed in a report by the American Heart Association (AHA), the American College of Cardiology (ACC), and the Heart Rhythm Society (HRS), which warns of the risk of severe electrical irregularities in the heart such as arrhythmias, polymorphic ventricular tachycardia, long-QT syndrome, and increased risk of

sudden death.¹⁵ Their recommendations include the following:

- Electrocardiographic/QT interval monitoring
- Withhold HCQ and azithromycin in patients with baseline QT prolongation (eg, QTc ≥ 500 msec) or with known congenital long-QT syndrome
- Monitor cardiac rhythm and QT interval; withdrawal of HCQ and azithromycin if QTc exceeds a present threshold of 500 msec
- In patients critically ill with COVID-19 infection, frequent caregiver contact may need to be minimized, so optimal electrocardiographic interval and rhythm monitoring may not be possible
- Correction of hypokalemia (> 4 mEq/L) and hypomagnesemia (> 2 mg/dL)
- Avoid other QTc-prolonging agents whenever feasible.

The serious toxicity of this class of medication has been underscored in a Brazilian study (clinicaltrials.gov, NCT04323527) that was recently cut short due to deaths and cardiotoxicity found at 2 differing doses of chloroquine taken with ceftriaxone and azithromycin with or without oseltamivir.¹⁶ Those in the high-dose chloroquine arm received 600 mg twice daily for 10 days, while those in the low-dose arm were given chloroquine 450 mg twice daily followed by 450 mg for 5 days. QTc was greater than 500 msec in 7 of 28 participants in the high-dose arm and 3 of 28 in the low-dose arm. There were 16 deaths of 41 (39%) in the high-dose group and 6 of 40 (15%) in the low-dose group, with at least 2 patients in the high-dose group identified with ventricular tachycardia without torsades de pointes before death. The authors note that study randomization resulted in more older patients with heart disease in the high-dosage group and thus this group may have been more susceptible to cardiac complications.

One large study used claims data and electronic medical records to address safety concerns in new users of HCQ and in those on HCQ with the subsequent addition of azithromycin.¹⁷ Preliminary results indicate there were no adverse events associated with short-term (1-month) HCQ treatment. However, long-term treatment with HCQ, as used for rheumatoid arthritis, was associated with a 65% increase in cardiovascular mortality. Further, significant risks were identified for combination users of HCQ plus azithromycin. Even in the short-term as proposed for COVID-19 management, there was an observed

5% to 20% increased risk of angina or chest pain and heart failure, and a 2-fold risk of cardiovascular mortality in the first month of treatment.

As of June 2020, the ORCHID study (Outcomes Related to COVID-19 Treated With Hydroxychloroquine Among In-patients With Symptomatic Disease, NCT04332991) has been halted by the National Institutes of Health as the data and safety monitoring board deemed the study drug (HCQ) very unlikely to be beneficial to hospitalized patients with COVID-19 (<https://www.nih.gov/news-events/news-releases/nih-halts-clinical-trial-hydroxychloroquine>).

FUTURE RESEARCH

There are no clear data indicating that HCQ has a favorable effect on outcomes in patients with COVID-19. The above studies have corroborated the lack of efficacy in both treatment and postexposure prophylaxis.

We still look forward to the large multicenter randomized clinical trial DISCOVERY (NCT04315948) comparing remdesivir, lopinavir–ritonavir, interferon beta1-A, and chloroquine versus standard of care. In addition, the trials WHIP COVID19 (NCT04341441) and HCQ for primary prophylaxis against COVID19 in healthcare workers (NCT04336748), will help add to our knowledge on use of HCQ for prophylaxis.

We also anticipate informative data from the COVID-19 Global Rheumatology Registry, a registry of COVID-19 rheumatology patients, which will help us understand characteristics and outcomes in patients already taking disease-modifying and immunosuppressive medications.

Note: Hydroxychloroquine (Plaquenil) should not be prescribed outside of clinical trials as this could lead to a potential shortage of HCQ for patients who take this drug long-term for their medical conditions.¹⁸

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Correspondence: Emily Littlejohn, DO, MPH, Orthopaedic & Rheumatologic Institute, A50, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; LITTLE3@ccf.org