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Hydroxychloroquine use in the COVID-19 patient

Posted April 23, 2020

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 coronavirus disease 2019 (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. Hydroxychloroquine (HCQ) use in patients with COVID-19 is being investigated examining prophylaxis, postexposure prophylaxis, and treatment regimens.

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-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 coronavirus disease 2019 (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 SARS-CoV-2 clearance in patients receiving HCQ compared with controls receiving standard supportive care. HCQ was dosed at 200 mg every 8 hours (600 mg daily total) for 10 days, and of the 20 patients in the treatment arm, 6 patients in a nonrandomized 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% (14/20) vs 12.5% (2/16) for the HCQ and control groups, respectively ($P = .001$). The addition of azithromycin to HCQ in 6 patients resulted in improved viral clearance (6/6, 100%) compared with HCQ monotherapy (8/14, 57%).[4] 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 nonsevere COVID-19 patients randomized patients 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. 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 and the standard-care group (86.7% vs 93.3%, respectively).[5]

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

doi:10.3949/ccjm.87a.ccc011

have accelerated alleviation of clinical symptoms, postulated by the authors through anti-inflammatory effects and recovery of lymphopenia. There were no safety concerns reported in this study with this high dose of HCQ.[6]

A retrospective analysis of 368 patients hospitalized with COVID-19 in all the Veterans Health Administration medical centers across the U.S. categorized patients based on treatment with HCQ, treatment with HCQ and azithromycin or those unexposed to HCQ, with primary outcome measures of death and need for mechanical ventilation. There was no evidence that use of HCQ either with or without azithromycin reduced the risk of mechanical ventilation. Interestingly, increased overall mortality was identified in patients treated with HCQ alone. Limitations include this being a non-randomized retrospective study in an all-male cohort comprised of men with a median age > 65.[7]

Another study used data collected from 4 French hospitals in patients with documented SARS-CoV-2 pneumonia requiring oxygen ≥ 2 L/min aimed at assessing the effectiveness of HCQ at 600 mg/day. The composite primary endpoint was transfer to intensive care unit (ICU) within 7 days and/or death from any cause. Of the 181 patients studied, 84 received HCQ within 48 hours of hospital admission and 97 did not. Results showed HCQ added to standard of care was not associated with a reduction of admissions to ICUs or death 7 days after admission, compared to standard of care alone.[8] Authors also note that the rate of acute respiratory distress syndrome (ARDS) did not decrease in the treatment arm.

DOSING DATA

A potential therapeutic dosing regimen of HCQ in COVID-19 is yet to be elucidated. 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 the most effective regimen in inhibiting SARS-CoV-2 in vitro while still considering the drug's safety profile.[9] 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

Although used in rheumatologic patients at the usual maximum dose of 400 mg daily (or about 5 mg/kg), HCQ is generally very well tolerated. Common adverse effects to be expected include:

- Gastrointestinal distress and diarrhea, as seen mostly with 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 hepatic transaminase levels can also be seen and, rarely, 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 deficiency[10]
- Risk of dose-related retinopathy is appreciable, although most worrisome with long duration of HCQ use, older age, and higher body mass index[11]; 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 put out by the American Heart Association (AHA), American College of Cardiology (ACC), and 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.[12] Their recommendations include:

- 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 (> 4mEq/L) and hypomagnesemia (> 2mg/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. 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 > 500 msec in 7 out of 28 of those in the high-dose arm, and 3 out of 28 in the low-dose arm. There were 16 deaths out of 41 in the high-dose group, and 6 out of 40 in the low-dose group, with at least 2 patients in the high-dose group identified with ventricular tachycardia before death.[13]

One large study used claims data and electronic medical records to address safety concerns in new users of HCQ, and those on HCQ with the subsequent addition of azithromycin. 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.[14]

FUTURE RESEARCH

There are no clear data indicating that HCQ has a favorable effect on outcomes in COVID-19. Research is abundant, and several randomized controlled trials using both chloroquine and HCQ are under way examining prophylaxis, postexposure prophylaxis, and treatment regimens. We look forward to results of the ORCHID study (Outcomes Related to COVID-19 Treated With Hydroxychloroquine Among Inpatients With Symptomatic Disease, NCT04332991), the ROCOVERY trial, a randomized trial of treatments to prevent death in patients hospitalized with COVID-19 (EU Clinical Trials Register: EudraCT 2020-001113-21), and the large multicenter randomized clinical trial DISCOVERY (NCT04315948), comparing remdesivir, lopinavir–ritonavir, interferon beta1-A, and chloroquine vs standard of care.

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: 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.

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