Commentary

Emergency Approval of Chloroquine and Hydroxychloroquine for Treatment of COVID-19

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Abstract

The world is suffering a respiratory pandemic disease caused by a novel coronavirus (2019-nCoV), commonly known as COVID-19 (coronavirus disease 2019). The Food and Drug Administration issued an emergency authorization for chloroquine and hydroxychloroquine as experimental treatments for COVID-19 leading to a shortage of both medications. A literature review conducted in April 2020 shows a lack of high-quality data available, resulting in ambiguous guideline recommendations. Decisions to use either drug should be made with careful consideration of risks versus benefits along with proper monitoring. Because of its higher potency and better safety profile, hydroxychloroquine may be the more reasonable treatment option if treatment is initiated.

Keywords

COVID-19, coronavirus, hydroxychloroquine, chloroquine, SARS-CoV-2, nCoV-2019

Introduction

The world is currently in the grip of a respiratory pandemic disease caused by a novel coronavirus (2019-nCoV) originating from the Wuhan province of China and commonly known as COVID-19 (coronavirus disease 2019).[1] The virus itself, 2019-nCoV, is thought to be related to Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and Middle East Respiratory Syndrome coronavirus (MERS-CoV). It has since been designated SARS-CoV-2. After being first detected in November 2019, by the end of April 2020, there were more than a million cases worldwide, with the United States having roughly one quarter of them.[2] Many people infected with this virus remain asymptomatic. However, the primary symptoms of COVID-19 include fever, cough, shortness of breath, fatigue, sputum production, and myalgias, which typically occur within 2 to 14 days after exposure.[1] The spread of disease appears to occur via respiratory droplets, which can transmit the disease directly through person-to-person contact or contact with contaminated surfaces. There are several ways of testing for this virus, with the preferred testing via real-time reverse transcriptase-polymerase chain reaction diagnostic panels. This method can provide results for patients suspected of the disease within 4 to 6 hours, but limited access and use of other testing methods has led to many reports of tests taking several days for results to be obtained.[1]

As of April 2020, there are no specific Food and Drug Administration (FDA)-approved medications for the treatment of COVID-19. Research for developing a vaccine for this disease is ongoing, but none are expected to be available for many months, if not years.[3] The FDA has also provided recommendations for studying convalescent plasma obtained from recovered COVID-19 patients as a potential treatment option because this has been effective in treating other viral outbreaks.[4] On March 29, 2020, the FDA issued an emergency authorization for both chloroquine and hydroxychloroquine as experimental treatments for COVID-19.[5] It is important to discern that this is not an FDA approval of these medications for the treatment of COVID-19. This emergency authorization theoretically applies only to governmental supplies of these drugs from the national stockpile, meaning that hospitals will need to request the medications through their states. Only hospitalized patients weighing ≥50 kg with confirmed cases of COVID-19 for whom a clinical trial is unavailable or infeasible are eligible to receive the drug from the federal stockpile per the directive.[6] Despite this, many prescribers are providing patients

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Table 1. Guidance Documents and Guideline Recommendations.

Organization	Recommendations
IDSA[8]	HCQ/CQ for COVID-19 hospitalized patients in the context of a clinical trial
	HCQ/CQ + AZT for COVID-19 hospitalized patients only in the context of a clinical trial
ATS[9]	No suggestion for or against HCQ/CQ in COVID-19 outpatient use
	No suggestion for or against HCQ/CQ in hospitalized COVID-19 patients without evidence of pneumonia
	Suggest HCQ/CQ on a case-by-case basis for hospitalized COVID-19 patients with evidence of pneumonia. Requirements for use include shared decision making, data collection, severe/worsening condition warranting investigational drug use and absence of drug shortage
SCCM[10]	Insufficient evidence to issue a recommendation for HCQ/CQ use in critically ill adults with COVID-19
Current Evidence	
Authors	Findings
Touret and de Lamballerie[15]	CQ inhibits the replication of SARS-CoV in Vero E6 cells
	CQ can be highly effective against HCoV-OC43 infection in newborn mice
Wang et al[16]	CQ effective in vitro against isolates of 2019-nCOV
Yao et al[17]	HCQ is more potent than CQ against SARS-CoV-2 in vitro
Gao et al[18]	CQ effective at improving pneumonia exacerbation, findings on lung imaging, promoting virus-negative conversion, and shortening COVID-19 without serious adverse reactions
Gautret et al[19]	HCQ treatment is significantly associated with viral load reduction/disappearance in COVID-19 patients, and its effect is reinforced by azithromycin
Lover[21]	Reanalysis of Gautret et al[19] data shows HCQ monotherapy had modest to no impact on clearance of viremia, but HCQ + AZT showed more significant results
Molina et al[22]	HCQ + AZT showed no evidence of rapid antiviral clearance or clinical benefit in severe COVID-19
Tang et al[23]	HCQ did not result in a higher negative conversion rate but more alleviation of clinical symptoms than SOC alone in patients hospitalized with COVID-19 without receiving antiviral treatment
Chen et al[24]	HCQ improved time to clinical recovery and proportion of patients with improved pneumonia

Abbreviations: ATS, American Thoracic Society; AZT, azithromycin; COVID-19, coronavirus disease 2019; CQ, chloroquine; HCQ, hydroxychloroquine; HCoV-OC43, human coronavirus subtype OC43; IDSA, Infectious Diseases Society of America; nCoV, novel coronavirus; SARS-CoV, Severe Acute Respiratory Syndrome Coronavirus; SCCM, Society of Critical Care Medicine; SOC, Standard of Care.

with prescriptions for chloroquine and hydroxychloroquine, so their use for treating COVID-19 has almost become common place.

The authorization of these agents for use in COVID-19 patients has been met with criticism because of the lack of published randomized controlled trials. Currently, there are 26 trials registered with ClinicalTrials.gov, with most not yet recruiting.[7] Outside of the United States, there are many trials being initiated or conducted, but published results are not yet available.[8] Multiple societies have released interim guidelines and guidance documents regarding COVID-19 treatment.[9-11] A summary of current guideline recommendations for use of these agents and supporting clinical evidence can be found in Table 1.

Pharmacology

Most commonly used as antimalarial or anti-inflammatory agents, the mechanism of action for both chloroquine and hydroxychloroquine against the novel coronavirus is not well understood. Proposed potential mechanisms include inhibition of viral enzymes that are responsible for processes such as viral DNA and RNA polymerase, viral protein glycosylation, virus assembly, new virus particle transport, and virus release.[12] These drugs may also exert efficacy via angiotensin-converting enzyme-2 cellular receptor inhibition, acidification at the surface of the cell membrane inhibiting fusion of the virus, and immunomodulation of cytokine release. Per the fact sheets provided with the emergency use authorization for patients meeting the aforementioned criteria, the recommended dosing for chloroquine is 1000 mg on day 1, followed by 500 mg daily via oral tablets for 4 to 7 days.[13] Hydroxychloroquine dosing is recommended as a total of 800 mg on day 1, followed by 400 mg daily for 4 to 7 days via oral tablets.[14] Multiple other regimens are being evaluated for both drugs.

Adverse effects such as QT interval prolongation, cardiomyopathy, retinopathy, and seizures are listed for both drugs.[13,14] Both concentrate in the liver and are substantially excreted by the kidneys. Monitoring is recommended with

a baseline echocardiogram as well as liver and renal function. Noteworthy drug interactions include increased hypoglycemic risk with antidiabetic medications or insulin, increased risk of ventricular arrhythmia with arrhythmogenic drugs, and impaired efficacy of antiepileptic drugs. Caution should be used in patients on concomitant drugs with known renotoxic or hepatotoxic effects.

Discussion

The evidence of use for hydroxychloroquine or chloroquine is insufficient at present to grant full FDA approval in the treatment of COVID-19 over normal supportive care. Intracellular studies by Touret and de Lamballerie,[15] Wang et al,[16] and Yao et al[17] showing in vitro efficacy against SARS-CoV-2 are promising and represent sufficient basis for human trials beginning. Although this call for human trials is being met, high-quality evidence cannot be reasonably expected for many months, if not years.[7,8]

Publications reporting results in human studies are subject to many flaws. Gao et al[18] did not publish any accompanying data to support their conclusion on chloroquine use, and therefore, this has not been subject to high-quality review. The homogeneity of the study sites used cannot be determined. Gautret et al[19] did not meet sufficient power, nor did they randomize their patients; thus, their results on hydroxychloroquine use may be biased. Their results have been called into question by the parent society publishing the article, stating that it did not meet standards for publication, based on unclear inclusion criteria and triage data.[20] Gautret et al also did not include 6 patients in their intention-to-treat analysis.[19] This study had 1 patient test negative on day 6, but positive on day 8. There is also concern about the severity of disease in the included patients because 85% did not even have a fever. Because of their small study population, the authors are unable to reliably estimate an effect size, so an independent secondary analysis using survival models was run on the available trial data.[21] The analysis showed that hydroxychloroquine monotherapy had modest to no impact on clearance of viremia on day 6 (CI = 0.797-34.143; $P = 0.085$) but that hydroxychloroquine combined with azithromycin showed more significant effects (CI = 1.954-1399.058; $P = 0.018$). These data should not be used as firm evidence either for or against hydroxychloroquine because the author notes that it is limited as a result of using only the available published data from Gautret et al and may, thus, be incorrect. However, it does suggest that hydroxychloroquine-azithromycin combination research should be included in developing studies, if not prioritized. One such small study (n = 11) that treated patients with hydroxychloroquine and azithromycin found no benefit in terms of antiviral activity or clinical benefit.[22] This small sample size and lack of published data also limit the generalizability of this article.

The 2 recent randomized controlled trials from Tang et al[23] and Chen et al[24] are both in preprint and have yet to be peer reviewed. Tang et al,[23] studying hydroxychloroquine, showed no benefit in terms of efficacy for negative conversion rate. However, they did show greater symptom alleviation (hazard ratio = 8.81; 95% CI = 1.09-71.3) and an increase in adverse effects compared with standard care (8.8% vs 30%). Chen et al[24] also reported improvements in symptom alleviation in addition to the hydroxychloroquine group having a higher proportion of patients with improved pneumonia.[24] The lack of peer review and differences in standard of care in these 2 trials significantly limit their utility. Both studies used only hydroxychloroquine in the treatment arm, unlike the Gautret et al[19] study, which used hydroxychloroquine plus azithromycin. They also raise concerns for hydroxychloroquine effectiveness despite the improvements in symptoms. It is expected that new evidence will continue to be published in the coming months.

The emergency authorization of hydroxychloroquine and chloroquine is intended to enable access for experimental treatment to federally secured stockpiles of these medications.[6] This is not an FDA recommendation or labeling of hydroxychloroquine or chloroquine for treatment of COVID-19. Impacts on the drug supply chain after this announcement, likely caused by the confusion between authorization and approval, were immediately evident. Five days after the announcement of the emergency authorization, the FDA announced a nationwide shortage of hydroxychloroquine and chloroquine.[25] Included in the authorization is a waiver for current good manufacturing practices applicable to the manufacture, packing, and holding of drug products.[6] Although this may speed up production of the medications to meet demand, there is the potential for inferior and potentially dangerous drug products to enter the market. This could in turn worsen the known adverse effects and cause significant patient harm.

Guideline recommendations for the use of hydroxychloroquine and chloroquine are ambiguous at the current time because of the aforementioned issues with studies and overall lack of evidence.[9,11] Citing either insufficient data to make recommendations, stating no suggestion, or only recommending use in the context of a clinical trial does not offer much guidance for practicing physicians. The FDA authorization adds to the ambiguity by making the drugs available for patients ineligible for or otherwise unable to be included in clinical trials, in conflict to Infectious Diseases Society of America recommendations for use only in the context of trials.[9] This essentially allows prescribers to order these medications for any patient based on their own judgment and contributes to the scarce drug supply and potential inappropriate use of the medications. A clarifying statement from the FDA may be helpful in dispelling the notion that these drugs are FDA approved for the treatment of COVID-19 and emphasize the appropriate patient

population to receive the medication. Ideally, the decision to use hydroxychloroquine or chloroquine should be made by an infectious disease physician when possible.

Dosing regimens for both hydroxychloroquine and chloroquine for COVID-19 need to be clarified because intracellular studies such as that of Yao et al[17] advocate for different dosages based on modeling data compared with dosing protocols from non-COVID-19 studies. Because of the lack of evidence in human trials as of yet, the dosing regimens provided in the emergency authorization fact sheets should be utilized despite their statement that the optimal dosage is not yet known.[13,14]

Caution with these drugs is warranted because of their list of serious adverse effects. Therefore appropriate monitoring is critical to reduce their incidence and frequency. In addition to renal and hepatic monitoring, the American College of Cardiology has released a position statement advocating for electrocardiographic/QT interval monitoring, correction of hypokalemia >4 mEq/L and hypomagnesemia >2 mg/dL, and avoiding other drugs that prolong QTc, such as azithromycin, when possible.[26] Patients on antiepileptics or who are diabetic should also be closely monitored, but the drugs are not contraindicated for use. Those with underlying conditions of heart disease, or renal or hepatic impairment may still receive the drug, but risks versus benefits should be extensively evaluated prior to doing so. The warnings for retinopathy are correlated with longer-term use and may not apply to short-term use for COVID-19 treatment.[13] There are already reports of induced toxicities from these medications, highlighting the dangers of adopting them into common practice so quickly.[27] The FDA authorization does lay out requirements for the health care system to whom the drugs are provided to track and report adverse effects, which will add to the clinical data behind future decisions for these drugs.[6]

Conclusion

Hydroxychloroquine and chloroquine have shown promising results in intracellular studies for use against SARS-COV-2.[10-12] However, high-quality human trials have yet to be completed. The emergency authorization from the FDA for their use does not indicate approval for their mass use in treating COVID-19, and current guidelines are ambiguous. Treatment should be carefully considered, with the risks and benefits evaluated and proper monitoring parameters utilized. Because of its higher potency and better safety profile, the emergency authorization fact sheet–provided regimen of hydroxychloroquine sulfate may be a more reasonable treatment option over chloroquine phosphate if any treatment is initiated.[11,14] Further evidence of these agents' use in the treatment of COVID-19 is warranted and currently underway, with results being eagerly awaited. With their already widespread use, retrospective studies will likely be seen even before the prospective clinical trials.

Declaration of Conflicting Interests

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