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Title

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Permalink

<https://escholarship.org/uc/item/8vh6b3rn>

Journal

Annals of Internal Medicine, 172(11)

ISSN

1056-8751

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Publication Date

2020-06-02

DOI

10.7326/m20-1334

Peer reviewed

Use of Hydroxychloroquine and Chloroquine During the COVID-19 Pandemic: What Every Clinician Should Know

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In the desperate search to find effective treatments for coronavirus disease 2019 (COVID-19), 2 generic drugs, used largely by rheumatologists and dermatologists to treat immune-mediated diseases, have entered the spotlight. The antimalarials hydroxychloroquine (HCQ) and chloroquine (CQ) have demonstrated antiviral activity against severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) in vitro and in small, poorly controlled or uncontrolled clinical studies (1-3). Normally, such research would be deemed hypothesis-generating at best. A tweet by President Trump on 21 March 2020 claiming that the combination of HCQ and azithromycin “ha[s] a real chance to be one of the biggest game changers in the history of medicine” accelerated a worldwide run on the drugs, with pharmacies reporting shortages within 24 hours. Here, we try to provide guidance regarding clinical decision making both for patients with COVID-19 and those with immune-mediated conditions, such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA), and strategies to mitigate further harm to these patients.

Data to support the use of HCQ and CQ for COVID-19 are limited and inconclusive. The drugs have some in vitro activity against several viruses, including coronaviruses and influenza, but previous randomized trials in patients with influenza have been negative (4, 5). In COVID-19, one small nonrandomized study from France (3) (discussed elsewhere in *Annals of Internal Medicine* [6]) demonstrated benefit but had serious methodological flaws, and a follow-up study still lacked a control group. Yet, another very small, randomized study from China in patients with mild to moderate COVID-19 found no difference in recovery rates (7). Sadly, reports of adverse events have increased, with several countries reporting poisonings and at least 1 death reported in a patient who drank fish tank cleaner because of its CQ content. Antimalarial drugs can cause ventricular arrhythmias, QT prolongation, and other cardiac toxicity, which may pose particular risk to critically ill persons. Given these serious potential adverse effects, the hasty and inappropriate interpretation of the literature by public leaders has potential to do serious harm. At this time of crisis, it is our ethical obligation as physicians and researchers to organize and refer patients to expedited, well-performed randomized trials that can clarify if, when, and for whom antimalarial medications are helpful in COVID-19. As of this writing, 10 such trials are under way, and information should be forthcoming within weeks.

Whereas the evidence supporting the use of antimalarial medications for COVID-19 is equivocal, the evidence for the use of these drugs to treat immune-

mediated diseases is not. For example, HCQ is a cornerstone of therapy for SLE. Hydroxychloroquine can effectively treat disease manifestations, such as joint pain and rashes; reduce thrombotic events; and prolong survival. Of note, landmark clinical trials have demonstrated that the withdrawal of HCQ can lead to flares of disease, including life-threatening manifestations, such as lupus nephritis (8). The current shortages of HCQ have therefore alarmed rheumatologists and patients. Offices across the country report fielding calls from concerned patients who are having difficulty obtaining their medication.

Given the likelihood that shortages will continue in the near term, we propose that manufacturers, clinicians, pharmacies, health systems, and governmental health agencies continue to coordinate an aggressive response to ensure that antimalarial drug use is appropriately managed during the COVID-19 pandemic. First, it is important to prioritize available supply for clinical trials evaluating important questions, such as dosing, prophylaxis, and treatment in COVID-19. Second, treatment interruptions for those with SLE and other rheumatic diseases must be prevented, because lapses in therapy can result in disease flares and strain already stretched health care resources. Third, stakeholders should work together to see whether dispensation of remaining supply to patients with COVID-19 makes sense as evidence rapidly changes. Fourth, clear messages that reflect the proper interpretations of available data must be disseminated with high frequency to counteract misinformation, including misleading statements or articles with “clickbait” material.

Finally, safeguards should be put into place to discourage overutilization by health professionals who are depleting supply by prescribing antimalarials for preexposure prophylaxis. Hoarding by health professionals for themselves and their friends or family is already occurring, but state governments and pharmacy boards have started to institute strict utilization policies to prevent further HCQ overutilization. Meanwhile, multiple manufacturers have already made critical commitments to initiate or increase production of HCQ.

What advice should clinicians give to patients with SLE or RA who have difficulty securing HCQ? The pharmacokinetics of HCQ are an important consideration in answering this question. With long-term use of HCQ, peak plasma levels occur 3 to 4 hours after each dose, with a terminal half-life of 40 to 50 days (9). The long half-life means that brief gaps in therapy, on the order of 1 to 2 weeks, are less concerning. However, longer treatment lapses put patients at risk for disease exacerbations, given studies showing that lower plasma con-

centrations of HCQ correlate with more SLE disease activity (10). In addition, in a well-designed clinical trial, a higher incidence of SLE flares was seen as soon as 2 weeks after the drug was stopped (8).

Patients may also wonder whether rationing their supply by halving their current dose is a good approach. Studies show significant heterogeneity in plasma concentrations of HCQ, even when standard doses of approximately 5 mg/kg are used (9). Therefore, some patients may do better than others with this approach.

The looming public health crisis for people with rheumatic diseases who will be unable to obtain HCQ is the result of a perfect storm of fear and dissemination of overpromised data. However, there is still time to mitigate the damage. Physicians should educate themselves about the strength of available data regarding HCQ and CQ in treating COVID-19. They should avoid misuse of HCQ and CQ for the prophylaxis of COVID-19, because there are absolutely no data to support this. Public figures should refrain from promoting unproven therapies to the public, and instead provide clear messages around the uncertainties we face in testing and using experimental treatments during the current pandemic, including the risk for serious adverse events. Well-done, randomized clinical trials should be performed urgently to test potential therapies, including HCQ. In the meantime, physicians should remember that first, we must do no harm to the patients with rheumatic disease for whom high-quality evidence shows that HCQ improves health.

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Acknowledgment: The authors thank the members of the COVID-19 Global Rheumatology Steering Committee and Dr. Annie Luetkemeyer, Professor in the Division of HIV, Infectious Diseases, and Global Medicine at Zuckerberg San Francisco General Hospital, University of California, San Francisco, for their input on the manuscript.

Disclosures: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M20-1334.

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Ann Intern Med. doi:10.7326/M20-1334

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Final approval of the article: J. Yazdany, A.H.J. Kim.