EDITORIAL

Misguided Use of Hydroxychloroquine for COVID-19
The Infusion of Politics Into Science

Michael S. Saag, MD

This issue of *JAMA* contains yet another study, and certainly among the best published to date, demonstrating the lack of efficacy of hydroxychloroquine as a treatment of coronavirus disease 2019 (COVID-19).[1] This study, from the National Heart, Lung, and Blood Institute PETAL Clinical Trials Network, focused on hospitalized patients with moderate to severe disease. In this well-conducted, appropriately powered clinical trial, the authors randomized 479 patients to receive hydroxychloroquine (400 mg twice daily for 2 doses, then 200 mg twice daily for 8 doses) (n = 242) or placebo (n = 237). The trial was stopped early at the fourth interim analysis for futility. For the primary outcome, clinical status at 14 days measured on a 7-category ordinal scale, there was no significant difference between the hydroxychloroquine and placebo groups (median [interquartile range {IQR}] score, 6 [4-7] vs 6 [4-7]; adjusted odds ratio, 1.02 [95% CI, 0.73-1.42]). None of the 12 secondary outcomes were significantly different between groups, including mortality at 28 days: 10.4% in the hydroxychloroquine group vs 10.6% in the placebo group (absolute difference, −0.2% [95% CI, −5.7% to 5.3%]; adjusted odds ratio, 1.07 [95% CI, 0.54 to 2.09]).[1] Thus, the results conclusively show no benefit of hydroxychloroquine over placebo.

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Several published rigorous studies have demonstrated similar findings. In the well-conducted clinical trials published to date, hydroxychloroquine has been evaluated in a wide variety of populations, ranging from patients with severe illness[2-4] to individuals at risk of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, in whom the drug was used as primary prophylaxis[5]; these studies failed to show any beneficial effect of the drug. This raises the question: How did medicine get to the point where so many studies were conducted assessing the possible benefit of hydroxychloroquine, that led to nearly identical findings, and have been published in major journals?

To answer the question, it is important to reflect on the COVID-19 pandemic as it unfolded in early 2020. The epidemic was beginning to inundate health care systems in many of the major cities of the world, including the US.

Early in the pandemic, many patients were severely ill, with fever, cough, and respiratory distress, and no specific treatment was available. Patients' fear of not knowing what was coming next was harrowing. The disease process was not clearly defined and clinicians had no way to predict what would happen to those patients in the coming weeks, had nothing to offer other than symptomatic and supportive care, and were being overwhelmed by increasing numbers of critically ill patients and high COVID-19–associated mortality rates. Both patients and clinicians were desperate.

Enter hydroxychloroquine. On March 16, 2020, a study on use of hydroxychloroquine in patients with SARS-CoV-2 was "published" (online via YouTube) by Gautret et al[6] (followed 4 days later as a preprint in the *International Journal of Antimicrobial Agents*) and purportedly demonstrated "a rapid and effective speeding up of their healing process, and a sharp decrease in the amount of time they remained contagious." This open-label, nonrandomized study included only 36 hospitalized patients with documented SARS-CoV-2 infection at admission, regardless of clinical status. Among 26 patients who received hydroxychloroquine, 6 were lost during follow-up because of early cessation of treatment, and of the remaining patients, at day 6 after treatment, 70% (14/20) were virologically "cured" compared with 12.5% (2/16) in the control group (P = .001).[6] All 6 patients who received the combination of hydroxychloroquine plus azithromycin (500 mg on day 1 followed by 250 mg per day for the next 4 days) were polymerase chain reaction negative for SARS-CoV-2 in the nasopharynx. The preliminary data from this small study was "heard round the world."

These findings suggestive of possible benefit, along with the desperation of clinicians who were providing care for patients with a potentially fatal disorder for which there was no treatment, undoubtedly contributed to increased use of hydroxychloroquine for patients with COVID-19, despite lack of rigorous evidence for efficacy.

However, the politicization of the treatment was a more important factor in promoting interest in use of this drug. On April 4, the US president, "speaking on gut instinct," promoted the drug as a potential treatment and authorized the US government to purchase and stockpile 29 million pills of hydroxychloroquine for use by patients with COVID-19.[7] Of note, no health official in the US government endorsed use of hydroxychloroquine owing to the absence of robust data and concern about adverse effects. Nonetheless, use of hydroxychloroquine increased substantially, and the US Food and Drug Administration had issued an Early Use Authorization for the use of hydroxychloroquine as treatment for COVID-19 on March 28, 2020,[7] which was later revoked on June 15, 2020, following further examination of preliminary data.[8]

These events sparked an avalanche of studies, many of which are now completed and are being reported in the scientific literature. These well-conducted trials, including the study reported in this issue of *JAMA*, demonstrate the lack of efficacy of hydroxychloroquine in patients with COVID-19. In a twist of irony, the US president did not receive

hydroxychloroquine, with or without azithromycin, when he contracted COVID-19 and was hospitalized at Walter Reed National Military Medical Center in early October.[9]

Several lessons are gleaned from the experience with hydroxychloroquine in the treatment of COVID-19. First, a single report based on a small, nonrandomized study must be considered preliminary and hypothesis generating, not clinically actionable. Likewise, anecdotal case reports and case series that include several cases likewise must be considered anecdotal and preliminary. Second, US health officials, such as members of the Coronavirus Task Force, leaders from the National Institutes of Health, and officers of physician organizations and societies, who resisted being forced to promote the politically motivated use of hydroxychloroquine were correct and should be recognized for their steadfast commitment to science. Third, patients who have a potentially life-threatening disease are desperate and will accept any treatment that appears to be effective, especially when such treatment is promoted by individuals who ordinarily should be trusted, such as the US president.

The clear, unambiguous, and compelling lesson from the hydroxychloroquine story for the medical community and the public is that science and politics do not mix. Science, by definition, requires diligence and an honest assessment of findings; politics not so much. The number of articles in the peer-reviewed literature over the last several months that have consistently and convincingly demonstrated the lack of efficacy of a highly hyped "cure" for COVID-19 represent the consequence of the irresponsible infusion of politics into the world of scientific evidence and discourse. For other potential therapies or interventions for COVID-19 (or any other diseases), this should not happen again.

ARTICLE INFORMATION

Author Affiliation: Department of Medicine, School of Medicine, University of Alabama at Birmingham.

Corresponding Author: Michael S. Saag, MD, Department of Medicine, School of Medicine, University of Alabama at Birmingham, 845 19th St S, BBRB 256, Birmingham, AL 35294-2170 (msaag@uabmc.edu).

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