The Saga of Hydroxychloroquine and COVID-19: A Cautionary Tale

The COVID-19 pandemic has stressed every component of our health care and public health systems with tremendous pressure to identify effective therapies. The saga of hydroxychloroquine should serve as a cautionary tale about the evaluation and promulgation of treatments during urgent situations; COVID-19 is not the first such situation and, unfortunately, will not be the last. We should examine carefully not only what we know about hydroxychloroquine but also how we learned it, disseminated it, and put it into practice.

Early in the COVID-19 pandemic, hydroxychloroquine quickly came to be widely used on the basis of very thin evidence—a very small randomized trial (1) and a poorly done small observational study (2), both originally posted on a preprint server rather than published in the peer-reviewed literature. Professional societies, public health agencies, and many politicians with no expertise in science or medicine allowed, endorsed, or promoted the use of hydroxychloroquine. The hope was that, despite the very limited evidence, it was truly effective and the availability of promising treatment would reassure the public. The number of prescriptions for hydroxychloroquine in the United States skyrocketed.

In early May 2020, two large observational cohort studies that found no association between administration of hydroxychloroquine and the rate of death or respiratory failure in hospitalized patients with COVID-19 were published in prominent journals (3, 4). These studies supported recommendations from the National Institutes of Health that hydroxychloroquine be used only in the context of clinical trials and not in routine care.

To date, very few adequately powered, randomized controlled trials (RCT) of the effectiveness and safety of hydroxychloroquine in the management of COVID-19 have been published in the peer-reviewed literature. Press releases have reported negative results from 2 large RCTs sponsored by the National Institutes of Health and the U.K. National Health Service RECOVERY consortium (5, 6). The planned methods for these trials seem to be rigorous, but results have not yet appeared as preprints or in peer-reviewed journals. An RCT of hydroxychloroquine as postexposure prophylaxis failed to show any benefit in preventing progressing to disease (7), and a second RCT in patients with mild to moderate disease also failed to demonstrate faster conversion to negative viral status in hydroxychloroquine-treated patients (8).

In this context, the study by Skipper and colleagues (9) is a welcome addition. The investigators set for themselves a challenging task. They sought to evaluate the utility of hydroxychloroquine in patients with very mild illness. This created significant operational hurdles related to conducting a trial at a time when in-person visits were difficult if not impossible and testing shortages made confirmation of a COVID-19 diagnosis quite difficult in patients with very mild illness. The study has

clear limitations related to these issues. Although 82% of patients had laboratory-confirmed COVID-19 or documentation of close contact with a confirmed case, only 58% of study participants themselves received COVID-19 testing. The primary outcome, which was changed during the study with the permission of the data and safety monitoring board, relied on a novel and not previously validated tool for symptom assessment. However, the study did use a masked placebo, and follow-up was excellent. The investigators found no clinically or statistically significant difference in change in symptom severity over 14 days in persons who received hydroxychloroquine compared with those who did not. Medication side effects, although minor, were more common in the hydroxychloroquine-treated group. As expected in a relatively young population with mild illness and little comorbid illness, hospitalizations were uncommon overall and did not differ statistically between the 2 groups.

Taken together with the other published RCTs, the current study by Skipper and colleagues (9) provides strong evidence that hydroxychloroquine offers no benefit in patients with mild illness. If the peer-reviewed findings confirm the preliminary reports of no benefit in sicker patients in the National Institutes of Health and RECOVERY trials, the saga of hydroxychloroquine and COVID-19 will likely reach its sad end.

The apparent ineffectiveness of hydroxychloroquine as a treatment of COVID-19 should not come as a surprise. Of all novel drugs that enter clinical phases of testing, about 90% fail to demonstrate effectiveness and safety. More simply put, many good ideas in medicine do not work. There is no shame in acknowledging that. But there are deeper lessons to be learned from the hydroxychloroquine experience in the current pandemic.

London and Kimmelman (10) have convincingly argued that research standards should not be lowered during a pandemic. However, there are enormous challenges to conducting and reporting research in such times as these. Hospitals overwhelmed with the provision of clinical care have had little spare capacity for conducting rigorous research. Patients, physicians, and politicians have been desperate for effective therapies and too willing to rely on thin scientific evidence. Individual groups and hospitals have launched scores of trials that will never meet their enrollment targets because of lack of coordination and cooperation among competing investigators and health care systems. The emergence of preprint servers, such as medRxiv, has allowed widespread dissemination of work that has not undergone careful review. Prestigious journals have worked feverishly to rapidly review studies that could have immediate impact but have occasionally fallen victim to deceit, damaging public confidence in their status as arbiters and presenters of objective facts. The scientific community needs to do a good bit of stock-

taking and soul-searching about its performance in meeting the challenges of the pandemic and how it will meet these challenges in future pandemics that are certain to emerge.

Unfortunately, the COVID-19 pandemic is far from over, but the emergence of data from well-done RCTs is a welcome development. Results of carefully done research, such as Skipper and colleagues' RCT, set an example for how we should search for effective therapies. It is time to move on from hydroxychloroquine.

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