Hydroxychloroquine for COVID19: The curtains close on a comedy of errors

Ilan S Schwartz,[a]* David R Boulware,[b] and Todd C Lee[c]

[a]University of Alberta, Edmonton, Alberta, Canada
[b]Division of Infectious Diseases and International Medicine, Department of Medicine, University of Minnesota, Minneapolis, USA
[c]Division of Infectious Diseases, Department of Medicine, McGill University Health Centre, Montréal, Québec, Canada

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Early in the COVID-19 pandemic, there was a desperate need for a therapy against the scourge which was decimating health care systems worldwide. As systems became overwhelmed, it was clear that effective, safe, accessible early outpatient treatments to prevent deterioration were needed. Scientists turned first to therapies that had shown anecdotal promise or in vitro activity against SARS. In many respects, hydroxychloroquine, an off-patent antimalarial used for autoimmune diseases, with decades of safety data, and with data suggesting *in vitro* efficacy in SARS-Cov-1, was an ideal candidate therapy.[1] What happened next, however, was an unfortunate comedy of errors which squandered resources and opportunities to find effective therapies.

Hundreds of (mostly small) clinical trials were launched in the spring of 2020 to evaluate if hydroxychloroquine could prevent or treat COVID-19. According to publicly available data, 247 such trials were registered.[2] In this gold rush, some of these trials competed for the same patients including, unfortunately, trials that we collectively participated in. Regrettably, before the first randomized controlled trial was complete,[3] hydroxychloroquine became a cause célèbre. It was endorsed by an array of notable (and polarizing) individuals and supported by a variety of confounded observational studies. Many providers began prescribing the drug[4] and patients began to either request hydroxychloroquine or, alternatively, to fear it due to the ensuing public pushback against the public promotion of this unproven treatment and a high-profile article which was subsequently retracted.[5] Consequently, most outpatient trials failed to enroll to completion, and none were independently large enough to definitively refute a small benefit in this setting.

Against this backdrop, the publication in this issue of *The Lancet Regional Health — Americas* of a large, double-blind randomized controlled trial of hydroxychloroquine in 1372 participants with initially mild COVID-19 conducted by the COPE-COALITION V group is noteworthy and laudable.[6] Although this well-designed and conducted trial fell short of its recruitment goal of 1620 infected participants — stymied by the high rate of enrolled participants in whom the infection could not be confirmed by PCR or serology — it is the largest outpatient therapeutic trial of hydroxychloroquine published to date. Like dozens of smaller trials published before, it failed to demonstrate any benefit to hydroxychloroquine in preventing progression of COVID-19 among outpatients with initially mild COVID-19.

With dozens of trials now published, we can finally close the curtains on hydroxychloroquine for COVID-19. However, we would be remiss if we did not draw some lessons for future pandemics and for clinical science in general.

1. Do not put the cart before the horse

While slow and arduous, the graduated progression of a candidate therapy from *in vitro* effect, to animal models, to progressively larger clinical trials is critical to avoid the misguided prioritization of agents with few prospects for success but with risks of diverting scarce resources and exposing patients to potential harm. For example, enthusiasm for hydroxychloroquine accelerated after a study showed it could block SARS-Cov-2 infection in cells derived from monkey kidneys.[7] Hydroxychloroquine increases cellular pH, thus interfering with a pH-dependent protease that facilitates viral entry.[1] However, in airway epithelial cells (which, of course, are more physiologically relevant for a respiratory infection), SARS-Cov-2 entry is facilitated by a pH-independent protease, thus circumventing the effect of the drug.[8] Moreover, the results of experiments in multiple animal models later showed no benefit of hydroxychloroquine in preventing or treating COVID-19.[9] By then, however, dozens of trials were already underway. Sequentially obtaining and scrutinizing these data could have prevented duplicative, negative clinical trials and widespread off-label prescribing.

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*Corresponding author.
E-mail address: ilan@ualberta.ca (I.S. Schwartz).

2. Science should step above the politics

Despite the absence of clinical trial data, many notable individuals threw their support behind hydroxychloroquine as a candidate therapy for COVID-19 and a quagmire of politics falsely removed equipoise and led to a massive failure to prove or disprove drug utility when it mattered. This issuance of an FDA Emergency Use Authorization and tapping the United States national stockpile directly undermined ongoing randomized clinical trials in that country.

3. There is no "I" in team

Whereas large clinical trial platforms like RECOVERY and REMAP-CAP led to major advancements in inpatient care of COVID-19 patients from the outset,[10] early outpatient studies were hampered by the lack of large, coordinated efforts to minimize duplication and accelerate results. However, current evaluative processes for academic advancement that value cowboys over collaborators are seemingly at odds with the need for robust cooperation that can advance science and improve patient care.

Ultimately, hydroxychloroquine did not have clinical benefit for COVID-19. The efforts of the trialists and the goodwill of patients who volunteered for the studies should not be diminished, but lessons extricated from this fiasco must galvanize us to do better in the next pandemic.

Contributors

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