

Monday, July 6, 2020

Stephen M. Hahn M.D.
Commissioner of Food and Drugs
U.S. Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993-0002

RE: Request for Emergency Use Authorization of Hydroxychloroquine for Ambulatory Prophylaxis and Treatment of COVID-19

Dr. Hahn:

We have reviewed the extensive evaluation and request for US FDA Emergency Use Authorization of Hydroxychloroquine for Ambulatory Prophylaxis and Treatment of COVID-19 authored by Drs O'Neill, McKinnon, Wang, and Zervos. We concur with the request that the agency move forward immediately and grant the EUA as submitted.

On May 14, 2020, after about 1 million cases and 90,000 deaths in the US had already occurred, the National Institutes of Health announced it was launching an outpatient trial of hydroxychloroquine (HCQ) and azithromycin in COVID-19 patients to be conducted at NIAID-funded AIDS Clinical Trials Group (ACTG) research centers.¹ A month later the agency announced it was closing the trial due to lack of enrollment with only 20 of 2000 patients enrolled.² This action was taken because NIAID, the study leadership and the independent data and safety monitoring board determined that the rate of patient enrollment had been inadequate for the trial to meet its objectives in a timely manner. No safety concerns were associated with the trial. This trial known as A5395 serves as the best current working example of the lack of feasibility of outpatient trials for COVID-19 as directed by the National Institutes of Health. It is also a strong signal that future ambulatory trial results are not imminent or likely to report soon enough to form ambulatory patient guidelines or to have a significant public health impact on clinical outcomes.³ Investigator and health system initiated/sponsored studies are now needed using telemedicine and other methods in order to test HCQ without the requirement for an investigational new drug application (NDA) with the agency.

Hydroxychloroquine (HCQ), chloroquine, and mefloquine are antimalarial drugs that impair endosomal transfer of virions within human cells. HCQ is also a zinc ionophore that conveys zinc intracellularly to block the SARS-CoV-2 RNA-dependent RNA polymerase which is the core enzyme of the virus replication.⁴ At the time of this writing, there are > 200 clinical trials registered on clinicaltrials.gov utilizing these agents in COVID-19. The currently completed retrospective studies and randomized trials have generally shown these findings: 1) when started late in the hospital course and

for short durations of time, antimalarials appear to be ineffective, 2) when started earlier in the hospital course, for progressively longer durations and in outpatients, antimalarials may reduce the progression of disease, prevent hospitalization, and are associated with reduced mortality.^{5 6 7 2 5} In a retrospective inpatient study of 2541 patients hospitalized with COVID-19, therapy associated with an adjusted reduction in mortality was HCQ alone, HR=0.34 (95% CI 0.25-0.46), $p < 0.001$, and HCQ+azithromycin, HR=0.29, 95% CI 0.22-0.40, $p < 0.001$. HCQ was approved by the U.S. Food and Drug Administration in 1955, has been used by hundreds of millions of people worldwide since then, is sold over the counter in many countries and has a well characterized safety profile.⁸ FDA cautions about HCQ should not be applied to outpatient treatment in response to the evolving observations on HCQ administration to COVID-19 patients.⁹ State medical boards should rescind restrictions on HCQ use for COVID-19 patients in states where they have been put in place. While asymptomatic QT prolongation is a well-recognized and infrequent (<1%) complication of HCQ it is possible that in the setting of acute illness symptomatic arrhythmias could develop. Despite heightened scrutiny, data safety and monitoring boards have not declared safety concerns in any clinical trial published to date. Physicians should be allowed to assess the benefits and risks of HCQ as with any other therapy administered to patients at risk for arrhythmia or on one or more chronic QT prolonging medications. Rare patients with a personal or family history of prolonged QT syndrome, those on additional QT prolonging, contraindicated drugs (e.g. dofetilide, sotalol), should be treated with caution and a plan to monitor the QTc in the ambulatory setting.

We are completing follow-up of a prospective, controlled trial of HCQ prophylaxis in our frontline healthcare workers at Baylor University Medical Center in Dallas, TX.¹⁰ Over the course of 7 weeks of treatment and 49 days of follow-up after the last dose, there was one serious adverse event (hospitalization unrelated to the study or study medication) and no mortality. Importantly this was a practical trial that relied upon medical history disclosed by the healthcare worker and no baseline electrocardiogram was required. There were no clinical arrhythmia events or episodes of QTc prolongation captured in adverse event reporting.

In our view, a prophylaxis dosing scheme of HCQ 400 mg po bid on the first day of prophylaxis followed by 200 mg po bid on day a week during continued exposure for those who are frontline workers in hospitals and nursing homes is both safe and prudent given the totality of information concerning HCQ and the risks for and consequences of COVID-19 infection. A typical HCQ COVID-19 treatment regimen is 200 mg bid for 5 days and extended to 30 days for continued symptoms. A second agent with potential off-target antiviral effect (zinc lozenges, zinc sulfate, azithromycin, or doxycycline) can be administered along with HCQ with clinical judgement weighing the benefits and theoretical risks for myocardial toxicity or electrophysiological abnormalities much like that of systemic lupus erythematosus where HCQ is baseline therapy and one or more of these agents are used in upper respiratory tract infections.

In summary we ask the agency to act quickly and decisively with declaration of an EAU for HCQ as submitted by Drs O'Neill, McKinnon, Wang, and Zervos aimed at ambulatory use in prophylaxis and treatment of COVID-19. This important action will

help clinicians enact therapy in the ambulatory phase with the intent of reducing COVID-19 hospitalization and death.

Sincerely yours,



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¹ <https://www.nih.gov/news-events/news-releases/nih-begins-clinical-trial-hydroxychloroquine-azithromycin-treat-covid-19> accessed July 3, 2020

² <https://www.niaid.nih.gov/news-events/bulletin-nih-clinical-trial-evaluating-hydroxychloroquine-and-azithromycin-covid-19> accessed July 3, 2020

³ <https://clinicaltrials.gov/ct2/who> table

⁴ Te Velhuis AJ, van den Worm SH, Sims AC, Baric RS, Snijder EJ, van Hemert MJ. Zn(2+) inhibits coronavirus and arterivirus RNA polymerase activity in vitro and zinc ionophores block the replication of these viruses in cell culture. *PLoS Pathog.* 2010;6(11):e1001176. Published 2010 Nov 4. doi:10.1371/journal.ppat.1001176

⁵ Rosenberg ES, Dufort EM, Udo T, Wilberschied LA, Kumar J, Tesoriero J, Weinberg P, Kirkwood J, Muse A, DeHovitz J, Blog DS, Hutton B, Holtgrave DR, Zucker HA. Association of Treatment With Hydroxychloroquine or Azithromycin With In-Hospital Mortality in Patients With COVID-19 in New York State. *JAMA.* 2020 May 11;323(24):2493–502. doi: 10.1001/jama.2020.8630. Epub ahead of print. PMID: 32392282; PMCID: PMC7215635.

⁶ Arshad S et al, Treatment with Hydroxychloroquine, Azithromycin, and Combination in Patients Hospitalized with COVID-19, Published: July 01, 2020 DOI: <https://doi.org/10.1016/j.ijid.2020.06.099>

⁷ Mikami T, Miyashita H, Yamada T, et al. Risk Factors for Mortality in Patients with COVID-19 in New York City [published online ahead of print, 2020 Jun 30]. *J Gen Intern Med.* 2020;1-10. doi:10.1007/s11606-020-05983-z

⁸ Schrezenmeier E, Dörner T. Mechanisms of action of hydroxychloroquine and chloroquine: implications for rheumatology. *Nat Rev Rheumatol.* 2020;16(3):155-166. doi:10.1038/s41584-020-0372-x

⁹ <https://www.fda.gov/drugs/drug-safety-and-availability/fda-cautions-against-use-hydroxychloroquine-or-chloroquine-covid-19-outside-hospital-setting-or>

¹⁰ <https://clinicaltrials.gov/ct2/show/NCT04333225?term=mccullough&draw=2&rank=10>