Science vs. Trump: The dangerous promotion of hydroxychloroquine in treating COVID-19

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13 April 2020

Since March 19, during nearly every White House press briefing on the coronavirus crisis, President Trump has been recklessly promoting the anti-malarial drugs chloroquine and hydroxychloroquine as essential pharmaceutical weapons in the fight against COVID-19, despite members of his own task force emphatically stating that the data is ambiguous at best and there is need for reliable scientific investigation.

On March 24, the American Society of Health-System Pharmacists reported a shortage of chloroquine tablets as hospitals and doctors have been making massive purchases of the medication, leaving patients with lupus and rheumatoid arthritis in a difficult strait as they are unable to fill their prescriptions.

Trump said at a recent briefing, "We bought a tremendous amount of hydroxychloroquine, which I think is, you know, it's a great malaria drug … and there are signs that it works on [coronavirus], some very strong signs … we have some very good results and some very good tests. You've seen the same test that I have. In France, they had a very good test. But we don't have time to go and say, gee, let's take a couple of years and test it out."

Numerous health authorities have raised concerns about the nature of drug oversight at the Food and Drug Administration (FDA). On March 28, the FDA issued an emergency use authorization (EUA) to allow hospital administrations and physicians to use hydroxychloroquine and chloroquine for COVID-19 patients, without any clear evidence that the drugs can impact the course of the disease. Former FDA commissioner Scott Gottlieb noted that the EUA has jeopardized necessary research to determine the real value of these drugs in the fight against the coronavirus.

Jeffrey Flier, a former dean of Harvard Medical School, told Reuters, "The president is short-circuiting the process with his gut feelings. We are in an emergency and we need to rely on our government to ensure that all these potential therapies are tested in the most effective and objective way."

Paul Garner, coordinating editor of the Cochrane Infectious Diseases Group, cautioned against administering these medications outside of a controlled trial, stating, "They could do harm and result in more people becoming infected, as they see the disease as less of a threat and ignore actions that could prevent its spread." He told the *British Medical Journal*, "There is absolutely no evidence that chloroquine is effective in people infected with coronavirus."

How the CQ and HCQ work

Hydroxychloroquine (HCQ) and chloroquine (CQ) are antimalarial drugs and anti-inflammatory agents for the treatment of rheumatoid arthritis and lupus erythematosus, in use for more than 70 years. The interest in using them for COVID-19 has risen because they have demonstrated *in-vitro* ("within the glass") antiviral activity against the SARS-CoV-2 virus. *In vitro* means that the studies on the interaction of the drugs with the virus were done in the laboratory outside of their "biological context" in human beings. Though these *in-vitro* results appear promising, they do not necessarily predict equivalent response in the person receiving these medications.

Such laboratory experiments help investigators perform more detailed experiments that provide information on how the virus can enter cells, replicate, and propagate. They also allow trialing certain therapeutic drugs like HCQ to understand the mechanisms that inhibit the activities of the virus. These preliminary studies have shown that CQ increases the pH of the affected cells, preventing the virus from fusing to the respiratory cell's outer membrane. It was also demonstrated that it interferes with the virus's ACE2 surface cell receptors, the spike proteins, preventing it from binding to the cell, an initial necessary step for infection.

Another mechanism touted by scientists is the drugs' ability to regulate the immune system, which potentially could enhance the therapeutic impact against the cytokine storm that is seen in patients severely affected by the COVID infection. Initial clinical studies on COVID-19 patients demonstrated they had high levels of inflammatory molecules and poorer prognosis.

CQ was discovered in 1934 by a Hungarian scientist named Hans Andersag. The wholesale cost in the developing world is around $0.04 US, though it costs $5.30 per dose in the US. Because of mass use in areas of the world where malaria is endemic, some forms of malaria have become resistant to it. CQ has several negative drug-drug interactions and must be monitored carefully, as overdoses can be fatal.

According to epidemiologist Dr. Nanshan Zhong, credited for discovering the SARS coronavirus in 2003, and responsible for managing the COVID-19 outbreak in China, CQ is not a highly effective cure, but its effects deserve attention.

The clinical experience with HCQ

HCQ, a less toxic derivative of CQ first synthesized in 1946, has also demonstrated similar *in-vitro* potency, this according to Dr. Manli Wang, in a letter to the editor of *Cell Discovery* journal. Yet, Dr. Wang's team concludes that confirmation of their findings requires clinical trials.

HCQ, also known as Plaquenil, was approved in the US in 1955, and is on the list of the World Health Organization's essential medicines. It is used to treat various autoimmune disorders and those malarial infections still sensitive to CQ. There are contraindications to the use of HCQ for people with certain heart conditions, diabetes or psoriasis. Overdose can cause seizures, stopping of breathing and ventricular fibrillation—nonfunctioning heart rhythm. HCQ should only be prescribed

by a physician familiar with the medication.

In-vivo ("within the living") studies test the effects of these drugs on the whole living organism. Animal studies and human clinical trials are major components of such studies. Verification of the efficacy of these drugs becomes critical as the delivery of the active ingredient of the drug at the site of treatment can be impacted by the patient's metabolism. The drug also may prove to be too toxic to the patient, despite any efficacy against COVID-19.

Physicians in Wuhan saw no benefits to HCQ. One physician stated that he treated 16 patients with severe syndromes. They did not see any benefit with HCQ and he discontinued use after one patient developed a serious abnormal heart rhythm and died. Similarly, an ICU physician in Wuhan had noted equivocal results in patients who received the medication. They admit that these were based on anecdotal assessments.

In the only randomized Chinese study, a pilot study in the use of HCQ in the treatment of patients with COVID-19, published on February 29 in the *Journal of Zhejiang University*, 30 patients with mild to moderate disease were prospectively enrolled after informed consent was obtained.

Randomized trials are necessary, as they aim to reduce certain sources of bias when testing the effectiveness of new treatments. The patients were randomized equally to a control group without the drug and a group that was administered 400 mg of HCQ every day for five days. After seven days, the RNA testing demonstrated that the virus was cleared in only two of 15 patients taking HCQ, while in the control group one patient cleared the virus. The median duration of hospitalization, time for fevers to break and recovery of lung findings were similar. The main weakness of the study was the small number of patients.

References in the press and by the Centers for Disease Control to CQ's possible efficacy cite a letter by Dr. Xu Yang in *BioScience Trends* released on February 18, 2020, stating that results in more than 100 patients have demonstrated CQ is superior to the control treatment in inhibiting the exacerbation of pneumonia, improved imaging, and promoting viral clearance and shortening the disease.

According to the author, this was an open-label, multi-center, non-randomized trial on the efficacy and safety of chloroquine without a control arm—essentially an observational trial. On February 15, 2020, government and regulatory authorities agreed to add CQ to their recommendations for the prevention and treatment of COVID-19. In an email, the author of the study only referred to the above advisory meeting but did not offer his data for review. Attempts to locate this published study did not provide any results in PubMed.

It is worth noting that at a World Health Organization press conference in February, in response to a reporter's question on CQ, Janet Diaz, head of clinical care for the WHO Emergencies Program, said, "For chloroquine, there is no proof that that is an effective treatment at this time. We recommend that therapeutics be tested under ethically approved clinical trials to show efficacy and safety."

The WHO has initiated an international study called SOLIDARITY Trial that intends to look at the efficacy of several therapeutic agents to include CQ/HCQ in a randomized fashion.

The work of Dr. Didier Raoult

A small French study by famed microbiologist and infectious disease specialist, Dr. Didier Raoult, published on March 20, is the one repeatedly touted by President Trump. Twenty-six patients were treated with 200 mg of HCQ three times a day, combined with the antibiotic Azithromycin, for a total of 10 days. Sixteen patients were in a control group who did not receive the treatment. However, six of the patients who received HCQ were removed from the study—one died, three were admitted to the ICU and two withdrew from the study. These were not included in the final results. According to Raoult, after six days of taking HCQ, 70 percent were negative for COVID-19, while in the control group 12.5 percent were negative.

Analysis of the study by a French journal, *Prescrire International*, found, "amongst the 18 patients for whom the date of onset of symptoms is known, the median time before non-detection of the virus was 7.5 days, with a wide confidence interval. In the absence of a control group selected according to a similar protocol and followed in the same conditions, it is not known whether this time is shorter than without HCQ or not."

In the journal *For Better Medicine*, Leonid Schneider wrote, "The study was not randomized, ethically approved only after it already began, and it was not really controlled: the 16 control patients were treated in different clinics."

Dr. Raoult followed this a week later with an as of yet unpublished observational study of 80 patients treated with HCQ and Azithromycin. Again, there was a rapid fall of viral load with 83 percent negative on day 7.

In a commentary in *Science Translational Medicine*, Derek Lowe, a chemist on the advisory board of *Chemical & Engineering News*, offers a searing critique. Some of the inconsistencies he noted were that only 15 percent of the patients had fevers; four were considered asymptomatic carriers, raising questions how they were enlisted in the study; 20 percent of the patients did not receive the CT scan as claimed by the author, and of those that did, only 54 percent had radiological findings of pneumonia.

The discharge criteria changed during the course of the observational study. There are no individual patient data nor are viral load counts resulted, and, glaringly, there is no control group to compare the outcomes against. Three of the patients were transferred to the ICU and one patient on the main floor passed away. Two patients in the ICU were returned back to the main floor, but the status of the remaining patient was not reported. This would place the fatality rate at 1.3 percent, consistent with rates in Germany and the US.

Lowe writes: "Without matched controls, and without being able to look at individual patient data, we just don't know how good this treatment was or frankly if it was any good at all. We may be seeing a notable effect size in what is still a small trial, or we may be seeing something that's not that remarkable or the result of a poorly controlled protocol. We don't know. I understand the need for speed, and I'm glad that the Marseilles group is conducting studies and releasing them as preprints. *But this work does not help us anywhere as much as it should* ."

A speculator, a lawyer, and Fox News

In the lead-up to the White House's declarations on CQ/HCQ, James Todaro, an ophthalmologist from Michigan turned cryptocurrency investor, tweeted on March 13 that there was growing evidence of chloroquine as a highly effective treatment for COVID-19. He, together with a New York City attorney by the name of Gregory Rigano, had authored a paper linked to Google Documents suggesting that early trials in China and France appeared to show significant benefits in treating COVID-19. Google has since removed the paper from its website, citing grave concerns on the ethical implications of the manuscript.

The night before President Trump touted the potential benefits of HCQ in his White House press briefing, Rigano, falsely billed as an adviser to Stanford Medicine, a branch of Stanford University, appeared on Tucker Carlson's prime-time Fox News Channel program, announcing that HCQ was a cure for the coronavirus and had the potential to prevent the disease.

He said, “the president has the authority to authorize the use of HCQ against the coronavirus immediately. He has cut more red tape at the FDA than any other president in history.” In a prepared statement, he claimed that Dr. Raoult’s study showed a 100 percent cure rate against the coronavirus.

Joan Donavan, director of the technology and Social Change Projects at Harvard’s Shorenstein Center, tweeted on the same day, “Two bitcoin entrepreneurs are pushing a self-published ‘study’ claiming a cure for the virus. They haven’t done any original research, but instead have strung together lengthy quotes from other scientists, who have done very limited research.”

Dr. Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases, when asked at the White House press conference whether CQ had proven its efficacy as a prophylaxis against COVID-19, said, “The answer is no, and the evidence you’re talking about is anecdotal evidence.”

Dr. Raoult’s study had gone to press on March 17 in the *International Journal of Antimicrobial Agents*. On April 3, the International Society of Antimicrobial Chemotherapy, the society that publishes the journal, issued a statement, “The Board believes the article does not meet the Society’s expected standard, especially relating to the lack of better explanations of the inclusion criteria and the triage of patients to ensure patient safety … Although ISAC recognizes it is important to help the scientific community by publishing new data fast, this cannot be at the cost of reducing scientific scrutiny and best practices.”

In interviews, Gregory Rigano stated he had been working with Dr. Raoult on a chloroquine-based treatment. Dr. Raoult has not given any statements to the press since these controversies surfaced. But it is worth noting his comments to the press in the last two months. In an interview on January 21, Dr. Raoult seemed to dismiss the COVID-19 crisis, telling *Les Crises*, “All this is crazy. That is, there is no longer clarity. Whenever there is a disease in the world we wonder if we are going to have it happen here in France. It just becomes totally delusional … I don’t know, people don’t have anything to do, so they go to China to find something to be afraid of … well, it’s just not serious.”

Then on February 24, an article in *TourMAG*, quoted him touting the Chinese data: “One thing is certain, if a patient goes to Marseille hospitals for a Chinese coronavirus infection, Dr. Raoult recommends treatment with chloroquine. Since China has many patients, they can conduct a treatment assessment. The Chinese are investing massively in the subject, and there, chloroquine is the standard treatment.”

Then Dr. Raoult is quoted, “You know, there are more deaths from scooter accidents in Italy than from the coronavirus. This psychosis and media runaway come from sensitivity of the human race to the risk of extinction. Anthropologically, there is always a reason why we will die, each generation having its fantasies around the disappearance of the human species.”

On April 6, *Newsweek* magazine’s health section noted that several hospitals in Sweden had stopped prescribing CQ to COVID-19 patients due to adverse side effects such as loss of peripheral vision, severe abdominal cramps and unusual headaches. Magnus Gisslen, a physician at Sahlgrenska University Hospital infection clinic, told the local media, “there were reports of suspected more serious side effects than we first thought. We cannot rule out serious side effects, especially from the heart, and it is a hard-dosed drug. In addition, we have no strong evidence that chloroquine has an effect on COVID-19.”

The next day, without explanation, on April 7, the Center for Disease Control and Prevention updated their therapeutic options guidance, stating, “There are no drugs or other therapeutics approved by the US Food and Drug Administration to prevent or treat COVID-19.” Prior to the update, the guidance stated, “Although optimal dosing and duration of hydroxychloroquine for treatment of COVID-19 are unknown, some US clinicians have reported anecdotally different hydroxychloroquine dosing.” Any mention of HCQ has now been removed, but Trump continues to promote it relentlessly.

It is quite frequent in modern pharmacology that new drugs seem promising when tested in cell lines, only to find that when introduced into human phase 1 trials, they have no efficacy, or even make the patient worse, damaging the heart, kidneys, liver, etc. The COVID-19 pandemic puts a premium on finding new drugs with a therapeutic benefit. But this must be demonstrated through rigorous scientific processes so that patients can be assured both that the drugs will work and that—to throw Trump’s phrase back against him—the “cure” isn’t worse than the disease.