



Hydroxychloroquine and the allure and perils of abandoning evidence-based science and policy in times of crisis. (SARS-CoV-2, Covid-19 pandemic)

Taking Bearings

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In a disaster, the coronavirus pandemic providing a ready example, cries to abandon caution and gamble on solutions can lead to spectacular success and deadly failures.

President Trump continues to tout an antibiotic and anti-viral drug called hydroxychloroquine as a potential treatment for Covid-19. More than just promoting the treatment, Trump urges its use, including prophylactic use.

With regard to efficacy, Trump said, "It may work, it may not." Moreover, because the drug has proven relatively safe when used under other specific circumstances (e.g., treatment of malaria, lupus, rheumatoid arthritis, and other autoimmune diseases), Trump asserts, "What is there to lose?"

At a minimum, a loss of scientific rigor and the potential to repeat some of the same mistakes made the hasty FDA approval of azidothymidine, aka AZT or Retrovir, in 1987. Like hydroxychloroquine, AZT wasn't a new compound, it was created in the 60s as chemotherapy drug. AZT proved ineffective for that purpose but was dusted off and, in desperation to stem rising HIV/AIDS deaths, tried as an anti-viral. Encouraging success from flawed trials and political pressure pushed the FDA into a rapid approval. While AZT arguably offered some benefits, and became part of the cocktail of drugs developed in the 90s to control AIDS, patients also suffered debilitating side effects, problems related to over dosage, and drug resistance.

In the current battle against SARS-CoV-2 and Covid-19 pandemic, the FDA has granted an emergency use authorization for hydroxychloroquine, and clinical use of the drug has been tried in China, Italy, and other places where critically ill patients had no other options. There is a spectrum of anecdotal evidence, from highly encouraging to "of no use" to potentially dangerous.

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Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial.

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Abstract

BACKGROUND: Chloroquine and hydroxychloroquine have been found to be efficient on SARS-CoV-2, and reported to be efficient in Chinese COVID-19 patients. We evaluate the role of hydroxychloroquine on respiratory viral loads.

PATIENTS AND METHODS: French Confirmed COVID-19 patients were included in a single arm protocol from early March to March 16th, to receive 600mg of hydroxychloroquine daily and their viral load in nasopharyngeal swabs was tested daily in a hospital setting. Depending on their clinical presentation, azithromycin was added to the treatment. Untreated patients from another center and cases refusing the protocol were included as negative controls. Presence and absence of virus at Day6-post inclusion was considered the end point.

RESULTS: Six patients were asymptomatic, 22 had upper respiratory tract infection symptoms and eight had lower respiratory tract infection symptoms. Twenty cases were treated in this study and showed a significant reduction of the viral carriage at D6-post inclusion compared to controls, and much lower average carrying duration than reported of untreated patients in the literature. Azithromycin added to hydroxychloroquine was significantly more efficient for virus elimination.

CONCLUSION: Despite its small sample size our survey shows that hydroxychloroquine treatment is significantly associated with viral load reduction/disappearance in COVID-19 patients and its effect is reinforced by azithromycin.

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KEYWORDS: 2019-nCoV; COVID-19; SARS-CoV-2; azithromycin; clinical trial; hydroxychloroquine

I hope the president is right, but even if he is ultimately proven correct then it's not because of his scientific insight but rather prophetic fulfillment of the saying, "Even a blind squirrel occasionally finds a nut." He certainly isn't using science.

In support of using hydroxychloroquine, Trump cites a "French study" that he claims shows "spectacular" or "encouraging" results. Alas, the paper announcing the French group's findings, 'Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial' (published in the International Journal of Antimicrobial Agents (IJAA) (See Note #1) was subsequently denounced by the journal's publisher, the International Society of Antimicrobial Chemotherapy (ISAC), who said that the organization "shares the concerns regarding the above article published recently in the International Journal of Antimicrobial Agents (IJAA). The ISAC 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." (See Note #2)

The "French study," conducted at the Méditerranée Infection University Hospital Institute in Marseille, claimed to find "hydroxychloroquine proves effective in the fight against Covid-19." Hydroxychloroquine, the authors argue, "from in vitro tests (i.e., data collected from laboratory tests focused on viral properties and reactions of reaction and structure, as opposed to results obtained from human trials) "hydroxychloroquine inhibits the novel coronavirus from binding to cells and also inhibited replication (reproduction) of the virus itself. "

Given this evidence and the fact that the drug has a proven record of safe clinical use, why not give it shot? A 50-50 gamble with no downside might seem prudent, perhaps even desirable. Alas, downside does exist, especially for people with conditions where hydroxychloroquine is already contraindicated.

Trump is essentially saying, "Eschew those randomized trials, full speed ahead," and to the lay person, this also seems logical, perhaps even urgent.

The danger, however, lies not only in known side effects but also the French study details.

The French study cited above enrolled 36 patients with COVID-19. Twenty patients received hydroxychloroquine (with six also given azithromycin, an antibiotic that fights bacteria). Sixteen patients at neighboring facilities were enrolled as a control group that did not receive hydroxychloroquine. Neither group, the treated nor the untreated, were randomized. Moreover, they were treated very differently over the course of the study. At a minimum, this produces confounders (essentially other explanations for observed results).

In terms of experimental design, an "arm" of a randomized trial refers to a randomly selected group receiving treatment (e.g., a specific drug), a competitive treatment (often used when evaluating experimental drugs or treatments), a placebo, or no treatment at all. Outcomes for the arms are then compared.

In the French study, those given hydroxychloroquine showed significant reduction in viral load over a six-day test period, and those also given azithromycin showed faster and more complete reductions (and elimination) in viral loads. This not only contributed to their own recoveries but also made the patients less infectious to others.

Encouraging? Yes. Definitive? No.

In fact, if one were forced to draw a conclusion based only on the data from the French study, one could conclude hydroxychloroquine treatment was highly risky.

Especially in rare situations (e.g., a pandemic emergency, lack of alternative treatments for critically ill patients, etc.) where urgency may prevail, evaluations of treatment made prior to randomized trials—like the one undertaken in France—are often scrutinized for other telltale hints that a treatment may work (or that additional investigation is warranted).

Dramatically different outcomes from expected values (e.g. significantly more people living than would normally be expected to live, or significantly faster response rates to treatment), justifiably excite additional interest.

These dramatic differences did not manifest in the small non-randomized French study. Their only reported data involves the viral load over six days of treatment, but there was what epidemiologists term "differential loss to follow-up."

During the trials, according to the original paper, "six hydroxychloroquine-treated patients were lost in follow-up during the survey because of early cessation of treatment."

No patients were lost out of the control group.

Of the 20 who were treated with hydroxychloroquine, six of those patients were excluded from the study results because one died, three became so ill they

required ICU care, and two patients dropped out the treatment (one because of severe nausea).

None of the control patients was admitted to an ICU, died, or was otherwise lost from the trial due to nausea. (See Note #3).

While certainly not definitively related causally (i.e., as a definite result of their treatment), if one were to consider overall clinical outcomes instead of just the tested viral loads of the treated group receiving hydroxychloroquine, then one might conclude—especially in comparison to a control group where none of the patients died or became so sick that they required ICU treatment—that the treatment INCREASED adverse outcomes (e.g. death, ICU treatment, severe nausea).

That's a result that screams "caution" and "more studies are needed."

Some non-randomized trials are undertaken just to see if the outcomes warrant more extensive testing (this is often referred to as phase 1 or phase 2 testing), but the results of non-randomized trials are always tentative and no ethical researcher (or investor) would draw definitive conclusions about a treatment without more extensive randomized trials.

There is quite a bit of difference, however, in a 50-50 shot if there is no significant downside; it's something else—and something far from science—to downplay dangers and promote only the upside of a treatment beyond the emergency use — as decided by physicians integrating a range of variables — currently authorized by the FDA.

Notes:

This article was updated on 3 April 2020 to include the statement by the International Society of Antimicrobial Chemotherapy (ISAC) referenced above and cited below (see Note #3).

(1) International Journal of Antimicrobial Agents (IJAA). Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial' Available online at <https://www.sciencedirect.com/.../artic.../pii/S0924857920300996>

(2) International Society of Antimicrobial Chemotherapy (ISAC). Statement on IJAA paper: Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial (Gautret P et al. PMID 32205204) Available online at https://www.isac.world/news-and-publications/official-isac-statement?fbclid=IwAR3u4AZg3KaGfE1uy7ywPCcJMF8qFMMMIUzH58_NthDE_7w_8h_QnFfQUbo

(3) The three patients receiving hydroxychloroquine were lost to the study because they became critically ill and were transferred to an intensive care unit (on days two, three, and four of the trial). One patient receiving hydroxychloroquine died on day three (interestingly, this patient tested negative for the coronavirus the day prior to dying). One patient left hospital and abandoned the trial on day three after testing negative for the coronavirus for two consecutive days, and another patient receiving hydroxychloroquine stopped on the third day because of nausea.

K. Lee Lerner's portfolio covering science and global issues includes multiple RUSA Book and Media Awards, books named Outstanding Academic Titles, and two global circumnavigations. He serves as an advisor, editor, and contributor to respected international news and academic resources.

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