Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Travel Medicine and Infectious Disease 35 (2020) 101764

Contents lists available at ScienceDirect

Travel Medicine and Infectious Disease

journal homepage: www.elsevier.com/locate/tmaid

Editorial

Hydroxychloroquine-azithromycin for COVID-19 – Warranted or dangerous?

In light of the COVID-19 pandemic, the world is changing rapidly in unprecedented ways. Travel has been largely suspended. Global health concerns are locally relevant everywhere on the planet. And, the scientific community responsible for the care of travelers and infected individuals is rising to the opportunity with research and clinical guidance of relevance to both individualized medicine and public health.

What treatment should be advised for COVID-19? No specific antivirals are currently available for SARS-CoV-2. Antibody-based treatments are being evaluated. However, hydroxychloroquine-related compounds were reported to be active in vitro against SARS coronavirus from 2002 to 2003 [1] and later against MERS coronavirus [2]. In this issue of *Travel Medicine and Infectious Disease*, Million and colleagues report on the seeming effectiveness and good tolerability of hydroxychloroquine in combination with azithromycin in treating COVID-19 [3].

Separate from the treatment outcomes data reported by Million, the very existence of this paper provides encouragement in two ways. First, the paper demonstrates teamwork. Thirty-seven co-authors combined their efforts to document care and outcomes of 1061 patients. A Nigerian Igbo proverb states that “it takes a village to raise a child.” Similarly, a large team is required to mount such a huge clinical and research response to try to save patients from COVID-19. In addition, the TMAID publishing team worked rapidly. This paper includes data from April 2020, was reviewed by six different peer-reviewers, was extensively revised, and was accepted and published in May 2020. The speed and effectiveness of a rigorous review and publication process attest to the value of teamwork.

Second, this paper exemplifies the value of the scientific process. Fully separate from any celebrity opinions or political viewpoints, the authors proposed and studied a hypothesis in a rigorous observational study, presented their data carefully, responded effectively to the peer-review process and now make their data available for public review and interpretation.

So, how can we interpret the data of the study by Million et al. [3]?

With hydroxychloroquine-azithromycin treatment, mortality was effectively limited to “only” 0.9% among SARS-CoV-2-infected adults. Even though this was a hospital-based study (though not limited to hospitalized patients), the mortality wasn't much higher than the 0.6% death rate of all those infected worldwide, and it is much lower than the 26.3% inpatient case fatality rate in a large British study [4].

The seeming safety and effectiveness of hydroxychloroquine-azithromycin is in contradiction to data in a study published just a week earlier that showed dangerously increased death rates in hydroxychloroquine, chloroquine, and macrolide-treated patients [5]. That multi-nation registry of 96,032 hospitalized SARS-CoV-2 patients in 671 centers on six continents included 14,888 who were treated with chloroquine or hydroxychloroquine, with or without a macrolide [5]. Confounding factors were considered, and patients receiving remdesivir were excluded from the study. Mortality rates were 9.3% in the control (non-hydroxychloroquine/chloroquine) group, 18% in those who received hydroxychloroquine, 23.8% in those who received hydroxychloroquine and a macrolide, 16.4% in those who received chloroquine, and 22.2% in those who received chloroquine with a macrolide [5].

Specific features of Million's study impact interpretation of the findings. First, study subjects were included based on positive viral testing, regardless of the presence or absence of symptoms. Thus, some of these patients would probably not have become seriously ill whether or not they ever were diagnosed or treated. By contrast, the British study with a 23% case fatality rate(4) and the afore-mentioned,multinational registry study [5] only included those who were sick enough to be hospitalized. Second, a total of 350 potential study subjects were excluded from Million's study, some because of cardiac findings on screening and some because of use of other medications that might add increased cardiac risk. This was appropriate for the research methods and for patient safety, but this might have removed patients from consideration who would have had unfavorable outcomes (and, thus, increased the mortality rates toward levels comparable to other studies). Third, there was no control group in Million's study in France. It is possible that other helpful yet undocumented features of care in France, unrelated to medications, contributed to the seemingly favorable outcomes.

Widespread use of incompletely tested medications could potentially have dangerous side effects, and Million's group wisely did not include patients with identified risk for arrhythmia in their study. They screened patients carefully and all had a preliminary ECG. Among included patients, though, they found no obvious sign of medication toxicity. This too, is an important finding. In contrast, the multi-national study from Mehra et al. reported that new ventricular arrhythmias were approximately four times as common in those treated with hydroxychloroquine or chloroquine than in controls [5]. In that study, approximately 3.5% of control and treated patients had pre-existing arrhythmia on entry into the study (5**).** This discrepancy in screening may, to some extent, explain the different outcomes.

The Mehra study has now been retracted from the Lancet after serious concerns were raised about the validity of the data in this analysis. Several flaws in the data collection and analysis of the Mehra et al multi-nation registry study (5) set off alarm bells worldwide and resulted in retractions in the prestigious Lancet and NEJM journals. Hydroxycloroquine use in the USA was approved by FDA in 1955 [6]. Hydroxychloroquine and chloroquine are both included in the World Health Organization (WHO) Model List of Essential Medicines [7]. The arrhythmogenic side effects of hydroxychloroquine are well known, and Million's team limited its use in accordance with this knowledge.

https://doi.org/10.1016/j.tmaid.2020.101764
Received 29 May 2020; Accepted 29 May 2020
Available online 30 May 2020

While some readers will be encouraged enough by the results of Million's study to "just do something" in giving hydroxychloroquine-azithromycin combined treatment to COVID-19 patients, others will opt to await more "proof" of safety and efficacy from randomized blinded controlled clinical trials. Indeed, such a trial was started.

The World Health Organization Solidarity Trial [8] is assessing the antiviral remdesivir, the HIV drug combination lopinavir/ritonavir, the multiple sclerosis treatment interferon beta-1a, and the antimalarial drugs chloroquine and hydroxychloroquine. The study has already enrolled approximately 3500 patients in 17 countries, and recruitment continues in over 400 hospitals in a total of 35 countries [8]. However, WHO temporarily "paused" enrolment in the hydroxychloroquine arm of the study, not because of dangerous preliminary findings but, rather, because of data from the new multi-national study [5]. Since the retraction of the Mehra et al [5] study and after internal analyses, WHO has now restarted the hydroxychloroquine arm in the Solidarity trial.

With an observational study, Million and colleagues validate the legitimacy of considering hydroxychloroquine-azithromycin in treating hospitalized patients with COVID-19. However, data from other studies demand caution, especially if considering giving this treatment to individuals who might have an underlying arrhythmia. With time, we should soon know whether hydroxychloroquine-azithromycin use for COVID-19 is warranted or dangerous.

References

[1] Vincent MJ, Bergeron E, Benjannet S, et al. Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. Virol J 2005;2:69. https://doi.org/10.1186/1743-422X-2-69.

[2] Dyall J, Coleman CM, Hart BJ, Venkataraman T, Holbrook MR, Kindrachuk J, et al. Repurposing of clinically developed drugs for treatment of Middle East respiratory syndrome coronavirus infection. Antimicrob Agents Chemother 2014;58(8):4885–93. https://doi.org/10.1128/AAC.03036-14.

[3] Million Matthieu, Lagier Jean-Christophe, Gautret Philippe, Colson Philippe, Fournier, et al. Early treatment of COVID-19 patients with hydroxychloroquine and azithromycin: a retrospective analysis of 1061 cases in Marseille, France. Trav Med Infect Dis 2020. in press.

[4] Docherty AB, Harrison EM, Green CA, Hardwick HE, Pius R, Norman L, Holden KA, Read JM, Dondelinger F, Carson G, Merson L, Lee J, Plotkin D, Sigfrid L, Halpin S, Jackson C, Gamble C, Horby PW, Nguyen-Van-Tam JS, Ho A, Russell CD, Dunning J, Openshaw PJ, Baillie JK, Semple MG. ISARIC4C investigators. Features of 20 133 UK patients in hospital with **covid**-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. BMJ 2020 May 22;369:m1985. https://doi.org/10.1136/bmj.m1985.

[5] Mehra MR, Desai SS, Ruschitzka F, Patel AN. Hydroxychloroquine or chloroquine with or without a macrolide for treatment of **COVID**-19: a multinational registry analysis. Lancet 2020 May 22;S0140–6736(20). https://doi.org/10.1016/S0140-6736(20)31180-6. 31180-6.

[6] The American Society of Health-System Pharmacists . Hydroxychloroquine sulfate monograph for professionals. drugs.com/ppa/hydroxychloroquine.html#moreResources.

[7] World Health Organization. World Health Organization model list of essential medicines: 21st list 2019. World Health Organization; 2019https://apps.who.int/iris/handle/10665/325771. License: CC BY-NC-SA 3.0 IGO.

[8] https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19—25-may-2020.

Corneliu P. Popescu
Carol Davila University of Medicine and Pharmacy, Bucharest, Romania
Dr. Victor Babes Clinical Hospital of Infectious and Tropical Diseases, Bucharest, Romania

Philip R. Fischer*
Department of Pediatric and Adolescent Medicine, Mayo Clinic, 200 First Street, Rochester, MN, 55905, USA
E-mail address: fischer.phil@mayo.edu.

* Corresponding author.