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Use of hydroxychloroquine in combination with azithromycin for patients with COVID-19 is not supported by recent literature.

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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.

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Letter to the Editor

Use of hydroxychloroquine in combination with azithromycin for patients with COVID-19 is not supported by recent literature

We reviewed with interest the study by Dr. Gautret and colleagues [1], which compares treatments for COVID-19. The authors present a small, non-randomized pilot study of hydroxychloroquine (HCQ) plus azithromycin (AZM) vs. HCQ alone vs. no treatment controls in 6, 14, and 15 subjects, respectively. The authors conclude that viral clearance is improved in patients treated with HCQ compared to controls, and augmented by adding AZM.

This report has garnered significant attention as the President of the United States has made numerous public comments and tweets about the promise of HCQ, based in part on these data. The United States Food and Drug Administration has taken the unprecedented step of approving an emergency use authorization for a new indication for HCQ [2]. The study by Gautret does not meets the standard to guide medical practice.

The authors did not follow the standard of intention-to-treat, and excluded from analysis persons who died, were transferred to the ICU, or stopped treatment for side effects. This trial design will not account for harm events from the study interventions, which is of particular concern given the likely additive effects on QT interval prolongation with HCQ and AZM. The primary endpoint of viral clearance does not equate with clinical efficacy. More important than a surrogate endpoint are patient-centered outcomes, e.g. relief of symptoms, functional status or survival. Flawed reporting exists in mention of a "single arm" trial design, despite 3 study arms, and lack of description in selection criteria for six patients in the combination "arm". Inclusion of patients in the control arm who refused to participate in the protocol is ethically questionable, and would bias the results. Missing data is not sufficiently presented, nor how missing data may have been handled (imputation, carry forward, etc).

Evidence to support experimental or off-label treatments for COVID-19 has been lacking, including HCQ alone or in combination with AZM. Well designed *in vitro* studies [3,4], and preliminary clinical trials results [5] have supported physicians to use their best medical judgment when prescribing HCQ off-label in the face of high mortality rates from COVID-19 and a well-established safety profile. The report by Dr. Gautret et al. does not build on this prior evidence, and does not support the use of HCQ in combination with AZM. Physicians should enroll patients in properly designed randomized clinical trials to understand the effects of approved drugs alone or in combination, when used for a new indication.

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