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Letter to the Editor

## Letter to the editor about "Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial"

*Dear Editor,*

While the whole globe is awaiting a successful treatment for COVID-19, Gautret et al. published the first open-label non-randomized clinical trial on the use of hydroxychloroquine for the treatment of COVID-19 [1].

In this study, a group of COVID-19 patients were treated with a daily dose of 600 mg of hydroxychloroquine (some of them concomitantly received azithromycin 500 mg on day 1 followed by 250 mg per day for four days) and were compared to a control group of patients, which included patients from other centers. The authors concluded that viral clearance at day 6 was significantly higher among hydroxychloroquine-treated patients, particularly those who received it in combination with azithromycin. The authors recommended treatment with hydroxychloroquine and azithromycin to cure patients with COVID-19.

In addition to the study limitations; including small sample size, lack of randomization and lack of blinding, which are expected in this unusual situation of study design during a pandemic; the study has other major flaws that render its conclusion questionable.

Among 42 eligible patients (intention-to-treat population), the authors reported viral clearance in 36 patients only. Six patients who were lost to follow-up in the treatment group were excluded from the analysis, four of whom had clinical deterioration (3 intensive care admissions and 1 death). On the other hand, five patients for whom polymerase chain reaction (PCR) was not done on day 6 were included in the control group and were counted as positive based on the preceding result (supplementary appendix of the article [1]). Excluding patients with worse outcomes from the treatment group and assuming treatment failure in some patients in the control group might have led to bias in the reported results.

Second, the authors planned to compare the clinical outcome as a secondary objective but it was not reported. Based on the information above, the analysis of clinical deterioration (either admission to the intensive care unit or death) among the intention-to-treat population (n=42), would result in 4/26 (15.3%) in the treatment group versus 0/16 (0%) in the control group. This reflects a trend towards worse clinical outcomes among COVID-9 patients treated with hydroxychloroquine.

Third, only eight patients (22.2%) of the reported study population had lower respiratory tract infections while the remaining patients either had an upper respiratory tract disease or were asymptomatic. This limits the generalizability of this study to severe cases for whom treatment is usually needed due to the risk of clinical deterioration.

Finally, the control group had patients from different centers which might have different levels of health care and different patient characteristics.

All of these reasons, along with the potential of this combination to prolong the QTc interval and predispose patients to ventricular arrhythmias, raise a concern about its role in the treatment of COVID-19 [2,3].

In conclusion, we recommend that the results of this study are considered only hypothesis-generating and not to be implemented in clinical practice, given the possible worsening of clinical outcomes, until more robust evidence is available.

### Declaration of Competing Interest

None.

### Funding

None.

### Ethical Approval

Not required.

### Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2020.106171.

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[1] Gautret P, Lagier J-C, Parola P, Hoang VT, Meddeb L, Mailhe M, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents 2020;56(1):105949.
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