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Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

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

Letter to the Editor

Doxycycline as an Alternative to Azithromycin in Elderly Patients



Dear Editor:

We read with great interest the article by Gautret et al. published in *International Journal of Antimicrobial Agents* entitled "Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open label non-randomized clinical trial" [1]. Administration of hydroxychloroquine resulted in virologic clearance of SARS-CoV-2 from respiratory secretions in 70% of patients by day 6. In those treated with the combination of hydroxychloroquine and azithromycin, virologic clearance was noted in 100% of patients by day 5. These findings suggest a promising role for this combination therapy in treating this novel coronavirus infection (COVID-19), with the potential to improve patient outcomes and reduce spread. This antimicrobial combination, however, raises concerns, given the increased risk of drug-drug interactions, especially cardiotoxicity with prolongation of QTc interval. This potential cardiotoxicity may limit its use in infected patients, with increased risk of morbidity and mortality in elderly people with underlying comorbidities, who are particularly susceptible to poor outcomes with SARS-CoV-2 infection. In addition to the elderly, another high-risk group, stem cell transplant recipients, may not be optimal candidates for this approach, given the impact of azithromycin, albeit long-term, on overall survival in this patient population [2].

We believe the results in this study are promising, but should be interpreted with caution, especially for patients at high risk of having major adverse events related to this antimicrobial regimen. In the study, the six patients who were treated with combination therapy were under 60 years of age, whereas the case-fatality rate is an estimated 8.0% in patients 70 to 79 years of age and reaches 14.8% in those over 80 years of age [3]. Therefore, potential therapy aimed at those over 70 years of age, with the highest mortality, will be a turning point in changing the outcomes of COVID-19 infection.

Given the potential risk of antimicrobial side effects, we suggest hydroxychloroquine combined with doxycycline, as an alternative to azithromycin, in patients at high-risk of developing drug-related adverse events. Doxycycline (and other tetracycline agents, such as minocycline), exhibit an immunomodulatory effect, antiviral activity *in vitro* against several RNA viruses, and also result in clinical improvement and reversal of cytokine storm in Dengue fever infection. The antiviral effect appears to be mediated by the effect of tetracyclines on the host Zinc-Finger Antiviral Protein (ZAP), which is important in host defense against RNA viruses. The host Zinc-Finger Antiviral Protein (ZAP) directly interacts with specific viral RNA sequences, repressing the translation of target

mRNA. Pre-clinical studies have shown that tetracyclines (doxycycline, minocycline, and other tetracycline or derivatives) can induce ZAP overexpression and thus confer an antiviral effect and suppression of different RNA viruses, previously noted with Ebola and Zika viruses [4,5]. Similar to COVID-19, several studies have pointed the central role that the cytokine cascade plays in the pathogenesis of dengue and hemorrhagic fever, leading to cytokine storms. Of note, doxycycline provides an anti-inflammatory effect by lowering pro-inflammatory cytokines, interleukin (IL)-6 and TNF-alpha, in patients with dengue hemorrhagic (DHF) effect. A clinical study examining the impact of doxycycline on patients with dengue virus infection showed an improvement of the patients in the study group with a rapid remission of DHF symptoms [6]. Thus, we propose consideration of doxycycline (or other tetracycline derivatives) as a second agent with hydroxychloroquine, particularly in elderly patients with multiple health conditions and those who are at risk of severe QTc prolongation secondary to drug-drug interactions. Further studies on proposed combinations are needed, since combinations may both act synergistically as an antiviral therapy against SARS-CoV-2, but also prevent bacterial super-infections, such as *Staphylococcus aureus*, following viral pneumonia.

The findings by Gautret et al. are dramatic, with significant potential in treatment of individual patients, as well as reduction of transmission of COVID-19. These findings should, however, be viewed with caution, given that there were no patients over 60 years of age included in the combination arm (hydroxychloroquine and azithromycin). Thus, those patients with highest mortality, greatest number of comorbidities with higher likelihood of drug-drug interactions, and with highest risk of arrhythmia, were not included in the study. We are encouraged by these initial findings and look forward to further data to guide the treatment and clinical care for all age groups of patients infected with this novel coronavirus, particularly the high risk elderly.

Ethical Approval

Not required

Declaration of Competing Interest

None

Funding

No funding

References

- [1] Gautret P, Lagier JC, 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.

DOI of original article: [10.1016/j.ijantimicag.2020.105949](https://doi.org/10.1016/j.ijantimicag.2020.105949)

- [2] Bergeron A, Chevret S, Granata A, et al. Effect of azithromycin on airflow decline-free survival after allogeneic hematopoietic stem cell transplant: The ALLOZITHRO randomized clinical trial. *JAMA - J Am Med Assoc* 2017. doi:[10.1001/jama.2017.9938](https://doi.org/10.1001/jama.2017.9938).
- [3] Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China. *JAMA* 2020. doi:[10.1001/jama.2020.2648](https://doi.org/10.1001/jama.2020.2648).
- [4] Li MMH, Aguilar EG, Michailidis E, et al. Characterization of Novel Splice Variants of Zinc Finger Antiviral Protein (ZAP). *J Virol* 2019. doi:[10.1128/jvi.00715-19](https://doi.org/10.1128/jvi.00715-19).
- [5] Muller S, Moller P, Bick MJ, et al. Inhibition of Filovirus Replication by the Zinc Finger Antiviral Protein. *J Virol* 2007. doi:[10.1128/jvi.01601-06](https://doi.org/10.1128/jvi.01601-06).
- [6] Bhattacharjee B, Bhattacharya S, Sardar B, et al. Dengue and doxycycline-experience in a tertiary care hospital in eastern India in the year 2017 - An initial report. *J Pharmacol Ther Res* 2018. doi:[10.35841/pharmacology.2.2.14-17](https://doi.org/10.35841/pharmacology.2.2.14-17).

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