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.

International Journal of Antimicrobial Agents 57 (2021) 106240

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

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

Letter to the Editor

Effect of hydroxychloroquine and azithromycin on SARS-CoV-2 clearance in COVID-19 patients, a meta-analysis. ☆

Dear Editor,

We thank the authors of the commentary [1] on our article [2]. We are familiar with the study that these authors have published [3]. These authors conducted one of the first randomized trials on 30 patients, with 15 treated and 15 untreated patients, without finding any benefit in the hydroxychloroquine (HCQ) group. As the authors themselves noted, co-medications with inhaled interferon alpha or arbidol may have played a role in mitigating the effect of HCQ. Many recent publications support the efficacy of treatment with inhaled interferon alpha in COVID [4], so aerosols may have been effective and the gain in adding HCQ negligible. Indeed, this is supported by the very good response of the control group. Co-medications are widely used in Asian studies, notably in Chinese and Iranian ones, and are justified by the medical ethics to do the best possible for the patient, beyond strict methodological considerations. This attitude is diametrically opposed to most Western studies whose methodology is unethical, leaving patients with life-threatening viral disease untreated (placebo).

Moreover, the dosage and duration (patients in HCQ group were given HCQ 400 mg per day for 5 days [3]) were lower than in our protocol (600 mg per day for 10 days [2]), and this most likely explains a difference in the effect. The right dosage and duration of the right treatment to the right patient at the right time is the key to effective treatment. In spite of this, there are many studies in the literature, such as that of Chen J *et al.* [3], with underdosing or toxic dosage, of too short duration, in patients with contraindications or administered too late after the onset of an irreversible deleterious process.

Here, we report an updated meta-analysis of studies using HCQ and their efficacy on viral clearance (Figure 1) (supplementary file 1). This meta-analysis includes the study of the authors of the commentary [3] which showed no particular obvious bias, with the exception of co-medications. Overall, although significant heterogeneity was found (I^2 = 78%, p < .05), the effect on viral clearance was significant (Odds ratio (OR) 0.61, 95% confidence interval (CI) 0.40-0.93, p = 0.021). If we exclude the only study based on electronic medical files ("big data" study), the beneficial effect was even greater (OR 0.50, 95%CI 0.32-0.79, p = 0.0026). Finally, and as mentioned by the authors of this commentary, we had from the beginning insisted on the need to combine AZ with HCQ in COVID-19 patients [2].

Contrary to the authors of the commentary, we do not believe that randomized controlled trials (RCTs) are the right and definite answer. As shown by Concato *et al.* [5], RCTs more often show discordant and heterogeneous results than observational studies, and their summarized effects are not different from observational studies. Even though hydroxychloroquine is not the only effective molecule against SARS-COV-2 infection, many studies, including RCTs and observational studies, confirmed its beneficial effect on virological clearance, and this is illustrated and demonstrated in the meta-analysis presented herein (Figure 1).

☆ This article refers to 10.1016/j.ijantimicag.2020.105949 and 10.1016/j.ijantimicag.2020.106173.

DOIs of original articles: 10.1016/j.ijantimicag.2020.105949, 10.1016/j.ijantimicag.2020.106173

https://doi.org/10.1016/j.ijantimicag.2020.106240

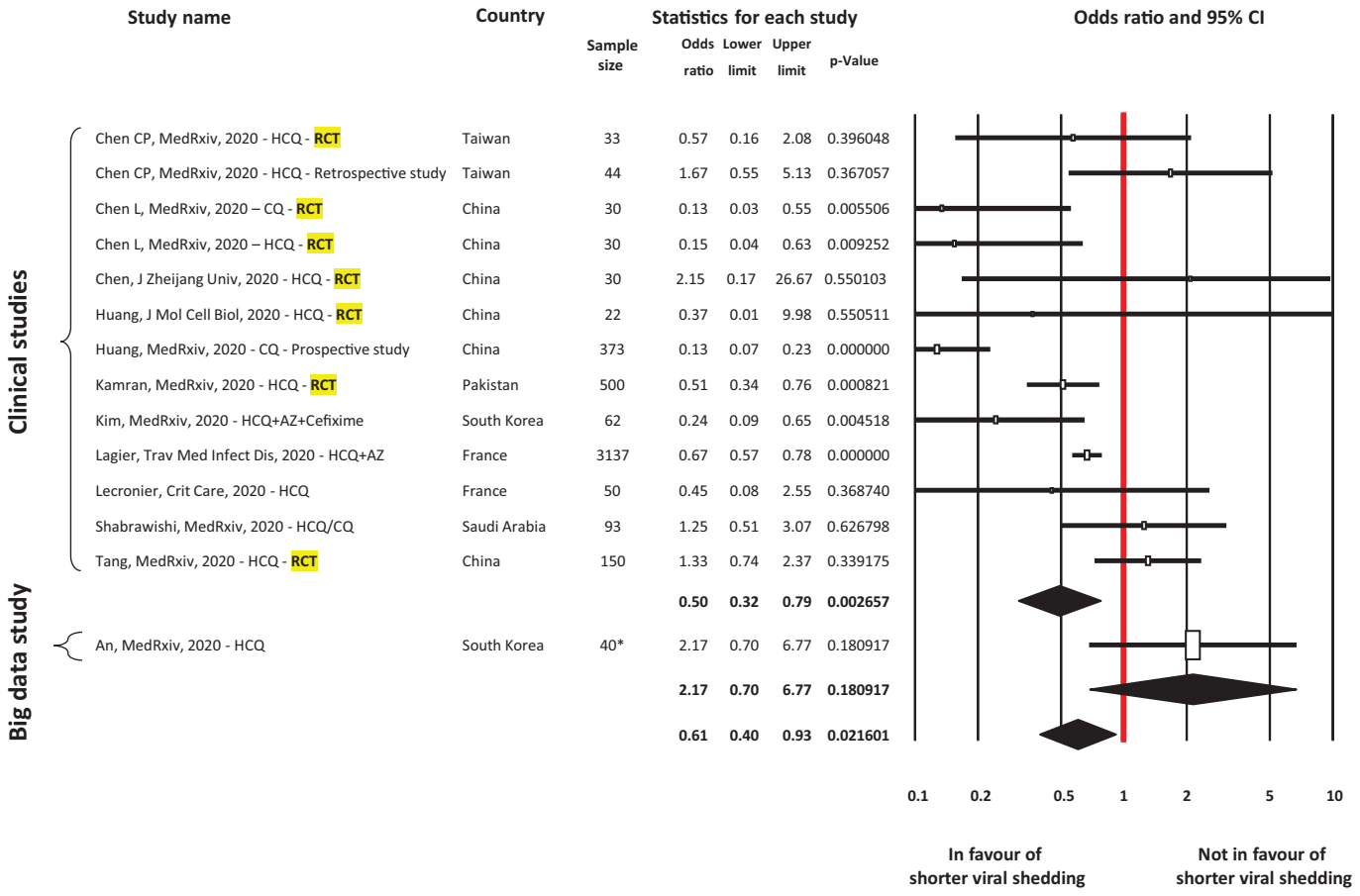

Figure 1. Meta-analysis on chloroquine derivatives against SARS-CoV-2 viral shedding
CI: confidence interval, HCQ: hydroxychloroquine, CQ: chloroquine, AZ: Azithromycin, RCT: randomized controlled trial. This meta-analysis was performed with a random-effects model using Comprehensive Meta-Analysis v3 (Biostat, Englewood, NJ, USA). Studies without PCR confirmation and/or not mentioning the proportion of positive samples were excluded. Randomized controlled trials are labeled "RCT" (highlighted in yellow). *In this study, 226 patients were included but only 40 matched patients were included in the multivariate statistical analysis.

Declaration of Competing Interest

The authors declare no competing interests.

Funding

No funding sources

Ethical approval

Not applicable

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2020.106240.

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Matthieu Million, Yanis Roussel
IHU-Méditerranée Infection, Marseille, France
Aix Marseille Univ, IRD, AP-HM, MEPHI, Marseille, France

Philippe Gautret
IHU-Méditerranée Infection, Marseille, France
Aix Marseille Univ, IRD, AP-HM, VITROME, Marseille, France

Didier Raoult*
IHU-Méditerranée Infection, Marseille, France
Aix Marseille Univ, IRD, AP-HM, MEPHI, Marseille, France

*Corresponding author.
E-mail address: Didier.raoult@gmail.com (D. Raoult)