Hydroxychloroquine and Azithromycin as a Treatment of COVID-19: Results of an Open-Label Non-Randomized Clinical Trial: Response to criticisms

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We thank the authors for comments provided for our article (1-3), but we would like to clarify key points for the story of this manuscript (4) that are critical in the context of COVID-19 outbreak and for the perspective of this work. When COVID-19 starts around the world the Editor-In-Chief of the Journal International Journal of Antimicrobial Agents (JM. Rolain) asked colleagues (D. Raoult, PR. Hsueh, and S. Stefani) to launch a special issue in the journal to create a real-time rapid debate around this emerging disease with special regards to therapeutic options (5). Our preliminary paper (4) in this way was relatively trivial i.e reported, in an emergency situation, a comparative analysis between a small group treated with hydroxychloroquine and another small group not treated with hydroxychloroquine showing a significant decrease of viral shedding after 6 days of therapy.

Surprisingly, despite the very small size of the group, the addition of azithromycin made a difference on the endpoint we chose, which is the disappearance of the viral load in the pharynx that is the only data that can be analyzed on a small group (6). Indeed, neither mortality, nor the passage in intensive care unit, nor the duration of the treatment can be evaluated on such a small group (6). This preliminary information was essential in our opinion especially as it confirmed the preliminary *in vitro* and *in vivo* results against SARS-CoV-2 announced by the Chinese (7-9), also confirming previous *in vitro* reports on the anti-SARS-CoV-1 coronavirus activity dating back to 2004 (10-13). This preliminary report paved the way for work testing its reproducibility.

On the therapeutic level, the hydroxychloroquine + azithromycin combination was found to be the most effective (4) consistent with *in vitro* synergistic antiviral activity reported in our laboratory (14,15). Azithromycin had already, contrary to what one of the authors says, been tested effectively on Zika (16, 17), so we knew that it had an antiviral action. With regard to our seminal paper on *in vivo* anti-SARS-CoV-2 activity of hydroxychloroquine (4), we were subjected to unprecedented violence. I (DR) was asked to

confess that I had a relationship and a conflict of interest with Sanofi, which is laughable when you use generics and you have had no relationship with the pharmaceutical industry at all at IHU (our center) for 5 years. The second thing is that I (DR) was harassed to give all the evidence to show that this was done after the agreement of our government, the evaluation by the Committee for the Protection of Individuals, and that it was done in all regularity (validated by ANSM, the French FDA, available online in the EU Clinial Trial Register Page, EudraCT number: 2020-000890-25). Subsequently, we were threatened for retractation of this article, with no justification other than the opinion of people who were fiercely hostile to the use of hydroxychloroquine. It should be noted that this paper is now by far the most cited paper in the literature on the treatment of COVID-19, exceeding 2,500 citations in Google Scholar.

As a result of this paper, half of the world's population lives in countries where hydroxychloroquine with or without azithromycin is largely prescribed against COVID-19, this currently concerns more than 4.5 billion people (18). On the other hand, methodological problems and problems of scientific misconduct with non-declaration of conflict of interest have multiplied for therapeutics in the best journals which ended up with the retraction of a paper (19).

Over the past few decades, randomized controlled trials (RCTs) have been considered the ultimate in defining the best treatment for a disease, especially in large international multi-center studies largely funded by pharmaceutical companies. This is not true because there are no significant differences in effect estimates between observational studies and RCTs, regardless of the specific design of the observational studies, heterogeneity or inclusion of studies of pharmacological interventions as demonstrated by a Cochrane review that analyzed 1583 meta-analyses covering 228 different medical conditions (20). RCTs introduce several biases (21), including that the physicians and patients included in these trials are not the same

as those included in observational studies (selection bias). Furthermore, the fact that RCTs on the same disease produce heterogeneous results with different directions of the effect shows that these approaches are not accurate (22) and does not prevent the effect of confounding factors. This inaccuracy has also been illustrated by the fact that the range for point estimate was wider for randomized, controlled trials than for observational studies in a meta-analysis of 99 reports on 5 different medical conditions from 5 major medical journals (Annals of internal medicine, BMJ, JAMA, the Lancet, and the New England Journal of Medicine) (23).

The limited role of RCTs in clinical practice is also confirmed by the fact that the majority (>80%) of infectious disease recommendations are not based on any placebo-controlled RCT. For example, the recommendations in the Infectious Diseases Society of America (IDSA) clinical practice guidelines are primarily based on evidence from non-randomized studies or expert opinion. Evidence based on at least one RCT makes up only 16% of the recommendations (24). This is also the case, for example, for quinine for malaria, penicillin, treatment of syphilis, treatment of typhoid, Q fever, Whipple's disease, and most vaccines, including rabies vaccine.

Beyond RCTs, big data studies were presented as a new reference. Here, we report an update of a meta-analysis (25) that highlights the Simpson's paradox (26): Big data studies, which "pool" raw data from very different groups, produce very heterogeneous and inconsistent results, whereas clinical studies, conducted by physicians who see patients, have consistent results. Overall, all of this suggests that well-conducted observational studies conducted by physicians who see patients and who know the disease are the best approach to control confounding factors and to define optimal patient management, particularly in an acute fatal pandemic disease such as COVID19 (21,23).

Finally, we have recently carried out a meta-analysis of all the work done on hydroxychloroquine (25) that is upgraded in this response. Here, we specifically focused on

mortality and viral shedding persistence, including two new randomized controlled trial reporting a favorable effect on viral shedding (27,28) (Figure 1). Importantly, while the conflict has been particularly violent in France and the United States, 5 studies from both these countries have shown that hydroxychloroquine reduces rate of hospitalization, length of hospitalization, mortality, and viral shedding in 4,642 (29), 3,737 (30), 2,820 (31), 2,541 (32) and 518 (33) patients. The methods are detailed in the supplementary data.

This new meta-analysis (Figure 1) included, for the mortality outcome, 48,655 patients (including 29,153 treated by a chloroquine derivative) from 31 studies in 11 countries (Andorra (34), Belgium (35), Brazil (36), China (37), Egypt (38), France (29,30,39-43), Italy (44-47), Iran (48), Saudi Arabia (49), Spain (50-52), USA (31-33,53-57), and two multinational teams (58,59). Studies assessing the death outcome but excluded from the present analysis and reasons for exclusion are detailed in Supplementary Table 1. Data extracted from the included studies for the mortality outcome are reported in Supplementary Table 2. A two-fold decrease of the risk of death was confirmed in clinical studies (number of comparisons (n) = 23, odds ratio 0.56, 95% confidence interval (95%CI) 0.48 – 0.65, p = 7.47×10^{-13}) and among big data studies (n = 14, OR = 0.89, 95%CI 0.81 – 0.98, p = 0.022 – Figure 1A). Heterogeneity was significant between clinical and big data studies (Q-value 39.8, p = 2.8×10^{-10}). Effect size was consistent among clinical studies (I^2 = 29%, p = 0.09) but not among big data studies (I^2 = 78%, p = 7.1×10^{-8}). Indeed, for instance, a big data study (31) recently reported a very significant two-fold decrease in mortality in 2,820 patients from the 8 hospitals of the Mount Sinai Health System (New York, USA). This result contrasts with other big data studies (29,53,57). Despite substantial heterogeneity, a significant summary effect was observed when including all comparisons from all included studies (n = 37, OR 0.78, 95%CI 0.72 - 0.85, p = 1.1×10^{-8}). Exclusion of the study from our center (30) did not modify neither the overall effect (n = 36, OR = 0.76, 95%CI 0.69 – 0.84, p = 6.0×10^{-8}) nor the

two-fold decrease in the risk of death among 18 clinical studies from other centers (n = 22, OR 0.55, 95%CI 0.46 - 0.65, $p = 2.0x10^{-11}$).

Looking at persistent viral shedding, a total of 5,204 patients (3,765 treated by a chloroquine derivative) from 12 studies from only 6 countries were included (5 from China (27,60-63), 2 from France (30,42), 1 from Pakistan (28), 1 from Saudi Arabia (64), 2 from South Korea (65,66) and 1 from Taiwan (67). Studies assessing the viral shedding outcome but excluded from the present analysis and reasons for exclusion are detailed in Supplementary Table 3. Data extracted from the included studies for the viral shedding outcome are reported in Supplementary Table 4. Overall, a substantial heterogeneity was found among all study ($I^2 = 78\%$), and this heterogeneity remained unchanged after excluding the only one found as a big data study associated with unfavorable outcome (66). Meta-analysis of clinical studies evidenced a significant two-fold decrease of the risk of viral persistence (13 comparisons, OR 0.50, 95%CI 0.32 – 0.79, p = 0.003, Figure 1B). Exclusion of our study (30) did not change the effect size (n = 12, OR = 0.48, 95% CI 0.26 – 0.87). Strikingly, none of the studies from USA assessed the virus persistence (68).

This new meta-analysis shows that, apart from the unverifiable work that did not assess virological outcome and carried out by people who had conflicts of interest with the pharmaceutical industry (69), the body of publications shows that hydroxychloroquine therapy is significantly and reproducibly correlated with a two-fold decrease in both mortality and viral shedding.

In practice, our seminal work (4) has benefited from a massive diffusion despite a profusion of papers that have not been verified but accepted each time they had a negative position towards hydroxychloroquine (6,68). However, the facts being stubborn, the accumulation of publications showing that hydroxychloroquine is effective following our paper leaves no doubt that this preliminary study did indeed paved the way for a therapeutic

strategy that is now being generalized throughout the world, and whose favorable results have been replicated several times. In addition, a group of American and Italian experts recently recommended the use of hydroxychloroquine and azithromycin in COVID-19 outpatients at the early stage of the infection (70).

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Declaration of competing interest

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Authors' contributions statement:

Writing – original draft: MM, PG & DR

Writing – review & editing: JCL, PC, PP, JMR & DR

Conceptualization: DR

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Figure 1. Meta-analysis on chloroquine derivatives against COVID-19

A. Mortality, B. 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). Randomized controlled trials are labeled "RCT" (highlighted in yellow) and studies whose authors reported conflicts of interests are written in red. *In this study, 226 patients were included but only 40 matched patients were included in the multivariate statistical analysis.