Hydroxychloroquine and Azithromycin as a Treatment of COVID-19: Results of an Open-Label Non-Randomized Clinical Trial: Response to David Spencer (Elsevier)

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We thank the authors for the 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. Indeed, neither mortality, nor the passage in intensive care unit, nor the duration of the treatment can be evaluated on such a small group. 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 (6-8), also confirming previous in vitro reports on the anti-SARS-CoV-1 coronavirus activity dating back to 2004 (9-12). 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 (13). Azithromycin had already, contrary to what one of the authors says, been tested effectively on Zika (14,15), 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. At the same time, the authors who published on remdesivir, for those we know,
the French, did not declare any conflict of interest in the New England Journal of Medicine
(16). In fact, it was much more credible to look for conflicts of interest relating to Gilead than
to Sanofi (17). 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 Clinical Trial Register Page, EudraCT number:
2020-000890-25). Subsequently, we were threatened for retraction 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 1600 citations in Google Scholar.

As a result of this paper, half of the world's population now benefits from a
recommendation of hydroxychloroquine with or without azithromycin, 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 including remdesivir in the best journals, including those of Elsevier, which
ended up with the retraction of a paper that had probably been completely invented (19).

Finally, we have recently carried out a meta-analysis of all the work done on
hydroxychloroquine (20) that is upgraded in this response. Here, we specifically focused on
mortality and viral shedding persistence, including a new randomized controlled trial
reporting a favorable effect on mortality (21) (Figure 1). Importantly, while the conflict has
been particularly violent in France and the United States, 5 studies from both these countries
has just shown that hydroxychloroquine reduces rate of hospitalization, length of
hospitalization, mortality, and viral shedding in 4,642 (22), 3,737 (23), 2,820 (24), 2,541 (25) and 518 (26) patients.

This new meta-analysis (Figure 1) included 18,211 patients (10,409 treated by a chloroquine derivative) from 12 studies and assessed mortality in 4 countries (China (27), France (22, 23, 28-30), Spain (31), and USA (24-26, 32, 33)). A two-fold decrease of the risk of death was confirmed in clinical studies (number of comparisons (n) = 8, odds ratio 0.53, 95% confidence interval (95%CI) 0.40 – 0.71, p = .00003) but not among big data studies (n = 6, OR = 0.92, 95%CI 0.76 - 1.10, p = .36 – Figure 1A). Heterogeneity was significant between clinical and big data studies (Q-value 9.45, p = .002). Effect size was consistent among clinical studies (I² = 31%, p = .18) but not among big data studies (I² = 69%, p = .006).

Indeed, a new big data study (24) 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 contrasted with other big data studies (22, 32, 33). Despite substantial heterogeneity, a significant summary effect was observed when including all comparisons from all included studies (n = 14, OR 0.79, 95%CI 0.67 - 0.92, p = .003). Exclusion of the study from our center (23) did not modify the overall effect (n = 13, OR = 0.82, 95%CI 0.70 – 0.97, p = .023) nor the two-fold decrease in the risk of death among the 7 clinical studies from other centers (n = 7, OR 0.48, 95%CI 0.32-0.72, p = .0004).

Regarding persistent viral shedding, a total of 4,540 patients (3,544 treated by a chloroquine derivative) from 8 studies from only 4 countries were included (5 from China (21, 34-37)), 1 from France (23), 1 from Saudi Arabia (38) and 1 from South Korea (39)) with a significant two-fold decrease of the risk of viral persistence (11 comparisons, OR 0.47, 95%CI 0.28 – 0.79, p = .005, Figure 1B). Exclusion of our study (23) did not change the effect size (n = 10, OR = 0.45, 95%CI 0.23 – 0.88, p = .02). Strikingly, none of the big data studies and none of the studies from USA assessed the virus persistence.
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 Gilead (17), 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 (40). However, the facts being stubborn, the accumulation of publications showing that hydroxychloroquine is effective following our paper, or at the same time by Chinese authors, 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.


18. Roussel Y, Raoult D. Hydroxychloroquine recommendations toward the world: first evaluations. IHU preprints 2020. doi: 10.35088/wjzn-1x68


A. Mortality

<table>
<thead>
<tr>
<th>Country</th>
<th>Study name</th>
<th>Odds ratio</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>p-Value</th>
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<tr>
<td>USA</td>
<td>Arash, Int J Infect Dis, 2020</td>
<td>0.61</td>
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<td>China</td>
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B. Persistent viral shedding

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<th>Upper limit</th>
<th>p-Value</th>
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<td>0.000000</td>
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<td>Saudi Arabia</td>
<td>Shabrashwishi, MedRxiv, 2020 - HCQ/CQ</td>
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<td>0.35</td>
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</tbody>
</table>

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

CI: confidence interval, HCQ: hydroxychloroquine, CQ: Chloroquine, RCT: randomized controlled trial, (H)CQ: chloroquine derivatives (hydroxychloroquine (HCQ) or chloroquine (CQ)). This meta-analysis was performed with a random-effects model using Comprehensive Meta-Analysis v3 (Biostat, Englewood, NJ, USA).