Opinion for the British Medical Journal - The War Against Chloroquine

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Dear Editor,

We were very impressed by the two editorials in the British Medical Journal that begin to reveal the magnitude of the crisis associated with the COVID epidemic, the overshadowing of scientific approaches, and the revelation of behaviours and conflicts of interest that, to our knowledge, have never reached this level [Abassi, Godlee]. From this perspective, our recent personal experience seems to us to be of significant relevance.

Following the first elements communicated by Chinese investigators reporting that chloroquine and remdesivir were effective in vitro against SARS-CoV-2 [Wang], our Chinese colleagues concluded that they would use hydroxychloroquine, well known to be non-toxic and administered per os [Multicenter] instead of remdesivir, which can only be administered by intravenous infusion (thus adding complications of 5 to 10% related to the infusion itself,

which was an unavailable and extremely expensive product whose actual toxicity had never been properly evaluated); this was common sense. Then a communication followed from the Chinese authorities saying that in the first 100 patients, they noticed a difference with chloroquine in terms of symptoms, radiological findings and viral carriage [Gao]. With only these elements available, we immediately submitted an official research project to carry out an observational study comparing the duration of viral carriage on hydroxychloroquine compared to the historical series from China reporting that it was about 20 days [Zhou]. This study began, and some patients received azithromycin in addition to hydroxychloroquine, for which we had preliminary results in vitro demonstrating efficacy against SARS-CoV-2 (azithromycin is effective against more than one RNA virus) and which is recommended to avoid bacterial superinfection in pneumonia. At that time, we had two surprises: first, an unexpected control group – patients hospitalized in Nice who did not receive hydroxychloroquine and who served as controls, and second, we saw that the addition of azithromycin significantly shortened the viral shedding period, despite the low number of patients [Gautret]. The reactions to this very simple paper, whose data have been subsequently confirmed in a meta-analysis [Million-1], were spectacular and so disproportionate that it leads us to wonder about the meaning of such overreactions.

I (DR) was first harassed by the publisher (Elsevier) of the journal in which we had published this article (International Journal of Antimicrobial Agents) because one of the co-authors was our collaborator and editor of the journal. Of course the editor for our paper was not this individual, but one of the best-known infectious disease specialists in the world, and the reviewer one of the best-known specialists in the field of coronaviruses in the world. Subsequently, the publisher initially asked me (DR) to retract this article myself, which I refused to do. I (DR) sent a letter from my lawyer to the effect that I would sue the publisher if he retracted it without our agreement, because there was no fault or error in the article.

Second, the publisher asked if we had any conflicts of interest with Sanofi, because in France Sanofi distributes the generic hydroxychloroquine drug. This was ridiculous, because of course we have no links of interest with any pharmaceutical company, which would be contrary to our ethics. Third, suddenly a scientific integrity consultant (Elisabeth Bik) began a search for errors in each of the 3500 publications I (DR) have authored. To my knowledge she found five, which is much less than I (DR) imagined among the articles on gels and Western Blot that I (DR) have published over my 40-year career. Finally, the journal accepted ten letters protesting our article, and while most of them seemed completely fanciful, we answered each one politely.

I (DR) could have taken this relentlessness personally, but two things quickly came to light. On the one hand, what we called LancetGate [Raoult] occurred, a quite extraordinary situation where a group of five unknown people reported that they had had access to more than 80,000 patient records, and that hydroxychloroquine was the cause of nearly 10% of cardiac deaths [Mehra-1]. One notes that, in the entire literature before 2020, in spite of the fact that hydroxychloroquine may have been prescribed in almost two billion people, only one accident of *torsade de pointes* has been reported [Verecki]. This same team published a paper in the New England Journal of Medicine [Mehra-2] that also had to be retracted, like the Lancet's paper, but it was fascinating to see the extent to which blindness allowed papers to pass what any reasonable reviewer would have stopped, because of their absolute technical impossibility [Raoult].

The BMJ did not escape this lack of objectivity by publishing an article in which the authors deliberately omitted evaluating the efficacy in mortality and critical care for the hydroxychloroquine and azithromycin combination [Mahevas, https://www.mediterranee-infection.com/correction-scientifique/] and another article published in preprint where the authors were asked to change elements that were favourable to hydroxychloroquine [Tang,

https://www.mediterranee-infection.com/tang-et-al-bmj-donnees-favorables-a-lhydroxychloroquine-supprimees/]. At the same time, after raging criticism about our article containing measurable data, which was comparative and showed statistically significant differences, it was published in the Lancet Infectious Diseases and in the New England publications on remdesivir, which were more or less nothing but advertising, without any comparative studies [Grein, Beigel]. Then a study on plasmapheresis was published in Blood without the slightest attempt to include a comparative group, which to my knowledge has not been subjected to any criticism [Xia]. If chloroquine had become cursed, we recently had the opportunity to do a meta-analysis study of all the identifiable, comparative publications on hydroxychloroquine (there are more than 200 on the COVID-19 site) and showed that the results were clearly dependent on the existence of conflicts of interest that included Gilead, the pharmaceutical company that developed remdesivir [Million-2]. We were able to show in a study that in France there was an almost perfect inverse correlation between the level of funding received by Gilead over the last 6 years (declared on the government transparency website) and the official positions taken towards hydroxychloroquine [Roussel]. We have noticed several times, particularly for French authors [Lescure], the absence of declarations of conflicts of interest when studies on hydroxychloroquine or remdesivir were published. During all that time, the stock shares of Gilead have had their ups and downs, which have probably resulted in stock transactions in excess of 100 billion dollars. And finally, Gilead managed to sell a considerable amount of remdesivir to the European Union at the same time that everyone realized that the treatment had no significant value in the management of COVID-19. Even worse, while it was suspected that remdesivir had mutagenic effects on the Ebola virus and coronaviruses [Warren, Agostini], a recent study in the New England Journal of Medicine showed that remdesivir, prescribed for a chronic SARS-CoV-2 carrier, was not effective, as viraemia persisted (which is really a proof of ineffectiveness, as in all chronic

viral infections) and in addition favoured the appearance of resistant mutants [Choi]. Remdesivir therapy entailed a risk of generating mutants whose fate was unpredictable. In addition, the possible combination with hyperimmune plasma, by exerting selection pressure on the spike protein, target of the vaccine, could lead to more specific selection of mutations at this site and make the entire vaccine strategy completely useless. In practice, as pointed out in a BMJ editorial about Tamiflu [Godlee], the complete lack of scientific control observed in this situation, including by the world's most reputable journals, will leave lasting marks, evidencing an attack on hydroxychloroquine out of all proportion. Although hydroxychloroquine is used in countries with populations of billions, western opinion leaders have fought a fundamental battle for the benefit of an ineffective and dangerous product, remdesivir, which earned millions for some opinion leaders and shareholders, while continuing to try to neutralize all economic therapeutic options gained by recycling old drugs (ivermectin, cyclosporine, etc.) in favour of an extremely costly vaccine strategy whose results, given the precipitous pace we have adopted, could lead to another major strategic failure.

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