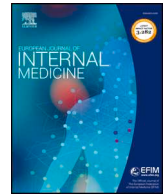




Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



## Editorial

## Chloroquine and COVID-19: A western medical and scientific drift?



Dear editor,

We read with interest the letter entitled “COVID-19 and hydroxychloroquine: is the wonder drug failing?” by U. Paliani and A. Cordona [1]. This work illustrates the need to be very careful in analyzing the literature at a time when scientific conflicts of this magnitude are taking place. Chloroquine and hydroxychloroquine have moved beyond their practical aspects as drugs or as potential toxic substances to become a clash on several fronts. The countries of the South use hydroxychloroquine and chloroquine on a massive scale, just as they used them before for malaria, or still use them now for systemic lupus erythematosus and rheumatic diseases. And, as more than 2 billion people at least have used this treatment, they have the greatest difficulty in believing that this product has become, by 2020, an extremely toxic product.

Coincidentally or as a consequence, the countries with the highest mortality from COVID-19 are also the countries that have demonized chloroquine the most, i.e. Western Europe and part of the United States. There is therefore a geographical pro- or anti-chloroquine correlation, on the one hand North-South, on the other hand West-East, which is beyond scientific data. A total of 4.6 billions of people live in countries where chloroquine or hydroxychloroquine are recommended for COVID-19. When there is such a tension in the analysis of the data, one has to be careful, and for example, some of the references [2] given in this article have now been retracted by the journal [3], then by 3 of the 4 authors [4] because the data presented were either manipulated or entirely invented. On the other hand, we have recently completed a meta-analysis that includes all comparative studies evaluating chloroquine derivatives [9]. On this occasion, we discovered that even in the British Medical Journal [6] the editorial office had asked to remove from the original paper [7] all tests that showed the efficacy of hydroxychloroquine (open review available at: <https://www.bmj.com/content/369/bmj.m1849/peer-review>), and in another article [8], it was found that there was a significant positive difference for the hydroxychloroquine-azithromycin combination, which the authors did not perform (ICU and/or death, 0/15 in treated patients versus 16/63 for standard care, bilateral Mid-P exact test  $p = 0.021$ ) and which the journal did not request [11].

It is therefore important in a situation such as this to allow time to do its work, knowing that hydroxychloroquine should be used under medical supervision after assessment of indications, contraindications and under reasonable dosages, duration of treatment with safety precautions. For example, in the recently published Recovery trial, the diagnosis is not made directly by the finding of COVID-19, such as PCR testing, but by the physician's conviction. The dosage is one that is known to be toxic (2.4 g of hydroxychloroquine on day 1, i.e. 4 times the dosage recommended in rheumatology therapy). Conversely, in

France, in the Discovery trial, the dosage of hydroxychloroquine is 400 mg/day, i.e. below the dosage we used in the same indication [5].

Many recent publications are characterized by a great heterogeneity of therapeutic strategies and the very common lack of clear diagnostic criteria, as for example in the last study published in the New Engl J Med on prophylaxis [10], where only 20 COVID tests were performed for 821 patients. This shows a drift in the scientific publications which sometimes leads to the retraction of the work, or sometimes to its radical questioning in this period of extreme tension around chloroquine. In practice, it is necessary to avoid drawing conclusions too quickly without an exhaustive research of the work carried out before concluding.

## References

- [1] Paliani U, Cardona A. COVID-19 and hydroxychloroquine: is the wonder drug failing? *Europ J Intern Med* 2020. <https://doi.org/10.1016/j.ejim.2020.06.002>.
- [2] Mehra MR, Desai SS, Ruschitzka F, Patel AN. Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. *Lancet* 2020. [https://doi.org/10.1016/S0140-6736\(20\)31180-6](https://doi.org/10.1016/S0140-6736(20)31180-6). Published Online May 22.
- [3] The Lancet Editors. Expression of concern: hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. *Lancet* 2020. [https://doi.org/10.1016/S0140-6736\(20\)31290-3](https://doi.org/10.1016/S0140-6736(20)31290-3). Jun 3.
- [4] Mehra MR, Ruschitzka F, Patel AN. Retraction—Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. *Lancet* 2020. [https://doi.org/10.1016/S0140-6736\(20\)31324-6](https://doi.org/10.1016/S0140-6736(20)31324-6). Jun 5.
- [5] Million M, Lagier JC, Gautret P, Colson P, Fournier PE, Amrane S, et al. Early treatment of COVID-19 patients with hydroxychloroquine and azithromycin: a retrospective analysis of 1061 cases in Marseille, France. *Travel Med Infect Dis* 2020. <https://doi.org/10.1016/j.tmaid.2020.101738>. May 5:101738.
- [6] Tang W, Cao Z, Han M, Wang Z, Chen J, Sun W, Wu Y, Xiao W, Liu S, Chen E, Chen W, Wang X, Yang J, Lin J, Zhao Q, Yan Y, Xie Z, Li D, Yang Y, Liu L, Qu J, Ning G, Shi G, Xie Q. Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised controlled trial. *BMJ* 2020;369:m1849. <https://doi.org/10.1136/bmj.m1849>.
- [7] Tang W., Cao Z., Han M., Wang Z., Chen J., Sun W., Wu Y., Xiao W., Liu S., Chen E., Chen W., Wang X., Yang J., Lin J., Zhao Q., Yan Y., Xie Z., Li D., Yang Y., Liu L., Qu J., Ning G., Shi G., Xie Q. 2020. Hydroxychloroquine in patients with COVID-19: an open-label, randomized, controlled trial. medRxiv 2020.04.10.20060558; Version 1 (initial preprint) accessed on 2020, May, 27 at : <https://www.medrxiv.org/content/10.1101/2020.04.10.20060558v1?versioned=true>.
- [8] Mahevas M., Tran V.T., Roumier M., Chabrol A., Paule R., Guillaud C., Gallien S., Lepeule R., Tali Szwebel T.A., Lescure X., Schlemmer F., Matignon M., Khellaf M., Crickx E., Terrier B., Morbieu C., Legendre P., Dang J., Schoindre Y., Pawlotski J.M., Michel M., Perrodeau E., Carlier N., Roche N., De Lastours V., Mouthon L., Audureau E., Ravaud P., Godeau B., Costedoat N. No evidence of clinical efficacy of hydroxychloroquine in patients hospitalized for COVID-19 infection with oxygen requirement: results of a study using routinely collected data to emulate a target trial. 2020. medRxiv 2020.04.10.20060699; <https://doi.org/10.1101/2020.04.10.20060699>.
- [9] Million M, Gautret P, Colson P, Roussel Y, Dubourg G, Chabriere E, et al. Clinical Efficacy of Chloroquine derivatives in COVID-19 Infection: Comparative meta-analysis between the Big data and the real world New Microbes and New Infections. In press, journal pre-proof. Available online 6 June 2020, 100709. <https://doi.org/>

<https://doi.org/10.1016/j.ejim.2020.06.020>

Received 19 June 2020; Accepted 22 June 2020

Available online 23 June 2020

0953-6205/ © 2020 Published by Elsevier B.V. on behalf of European Federation of Internal Medicine.

- [10.1016/j.nmni.2020.100709](https://doi.org/10.1016/j.nmni.2020.100709).
- [10] Boulware DR, Pullen MF, Bangdiwala AS, Pastick KA, Lofgren SM, Okafor EC, Skipper CP, Nascene AA, Nicol MR, Abassi M, Engen NW, Cheng MP, LaBar D, Lother SA, MacKenzie LJ, Drobot G, Marten N, Zarychanski R, Kelly LE, Schwartz IS, McDonald EG, Rajasingham R, Lee TC, Hultsiek KH. A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for Covid-19. *N Engl J Med* 2020. <https://doi.org/10.1056/NEJMoa2016638>. Jun 3 Online ahead of print. PMID: 32492293.
- [11] Mahevas M, Tran VT, Roumier M, Chabrol A, Paule R, Guillaud C, et al. Clinical

efficacy of hydroxychloroquine in patients with covid-19 pneumonia who require oxygen: observational comparative study using routine care data. *BMJ* 2020:369. <https://doi.org/10.1136/bmj.m1844>.

Matthieu Million<sup>a,b</sup>, Yanis Rousset<sup>a,b</sup>, Didier Raoult<sup>a,b,\*</sup>  
<sup>a</sup> *IHU-Méditerranée Infection, Marseille, France*  
<sup>b</sup> *Aix Marseille Univ, IRD, AP-HM, MEPHI, Marseille, France*

---

\* Corresponding author.