The efficacy of Chloroquine derivatives in COVID-19: a meta-analysis based on the first available reports

Matthieu Million[a,b*], Philippe Gautret[a,c*], Didier Raoult[a,b]

[a]IHU-Méditerranée Infection, Marseille, France

[b]Aix Marseille Univ, IRD, AP-HM, MEPHI, Marseille, France

[c]Aix Marseille Univ, IRD, AP-HM, SSA, VITROME, Marseille, France

Running title: Efficacy of Chloroquine derivatives in COVID-19

Keywords: coronavirus, COVID-19, SARS-CoV-2, Hydroxychloroquine, Chloroquine, meta-analysis

Corresponding author: Didier Raoult, IHU - Méditerranée Infection, 19-21 boulevard Jean Moulin, 13005 Marseille, France. Tel.: +33 413 732 401, Fax: +33 413 732 402;

E-mail: didier.raoult@gmail.com

Text word count: 976

Running title: Chloroquine derivatives efficacy in COVID-19

Introduction

We are currently facing a pandemic involving a newly discovered coronavirus (SARS-CoV-2) which putting our societies to the test in many ways. Despite controversy, only two drugs, namely hydroxychloroquine (HCQ) and chloroquine (CQ), have been used by physicians on a large-scale basis as treatment for COVID-19 [1]. According to the Sermo Real Time Covid-19 Barometer (https://www.sermo.com/, consulted 20 April), for over 20,000 physicians across 30 countries, chloroquine derivatives are the first medication used to treat COVID-19 patients in ICUs (67%), the second medication in other hospital settings (66%), and the third in outpatient settings (40%). While many countries recommend it for treating COVID-19, certain Western countries do not (https://www.mediterranee-infection.com/coronavirus-pays-ou-lhydroxychloroquine-est-recommandee/). It is therefore urgent to evaluate the efficacy of these medications against clinical, biological, radiological and virological outcomes of the disease. A large number of randomised clinical trials (RCTs) aimed at challenging the antiviral action of the two drugs against a placebo or other potentially active drugs are ongoing. Some of these studies have been published in peer-reviewed journals or released as pre-prints on various websites [2-5]. In this paper, we present the conclusions of a preliminary meta-analysis addressing this issue.

Methods

We conducted a meta-analysis of comparative studies between two groups that were expected to be similar with respect to demographics, chronic conditions and clinical presentation at enrolment. One group was treated with HCQ or CQ and one group was not treated with these molecules. The keywords “hydroxychloroquine”, “chloroquine”, “coronavirus”, “COVID-19” and “SARS-Cov-2” were used in the PubMed, Google Scholar and Google search engines without any restrictions as to date or language. Preprints were also included. Non-comparative (single-arm) studies were excluded.

Articles published in peer-reviewed journals, pre-prints and articles available on the internet, even when not published on official websites, were included. The following outcomes were considered: death, transfer to intensive care unit (ICU), clinical and radiological worsening, length of stay in hospital, and persistence of viral shedding as assessed by PCR. A randomised model was used with Comprehensive Meta-Analysis v3 (Biostat, Englewood, NJ, USA). This software made it possible to include dichotomous outcomes (number of events out of the total) and quantitative outcomes (mean in each group, sample size, p-value). According to Borenstein *et al.* [6], if a treatment is truly ineffective, half the comparisons would be expected to lie on either side of the no-effect line. This can be formally tested by comparing the number of comparisons in one direction versus the null value of 50% (sign test). This sign test was performed using the binomial distance as reported by Borenstein [6]. A p-value < 0.05 was considered significant.

Results

Ten comparative studies were identified involving 1,642 patients (965 patients treated with a chloroquine derivative) from five countries (Brazil, China, France, Iran, and USA) (Table S1). The 10 studies included three published papers, five pre-prints published on MedRxiv, one submitted paper that was neither published nor a pre-print, and one unpublished paper that was not a pre-print, both of which were available on the internet (uniform resource locator (url) provided in the supplementary data). All but one paper (in Chinese) were written in English. The four studies from China and the one from Iran were conducted on patients treated with several antivirals (lopinavir/ritonavir, oseltamivir, ribavirine, umifenovir and nebulisation of interferon aerosol) in addition to chloroquine derivatives. Two studies were conducted in France, including one in Paris and our seminal study in Marseille and other locations in southern France. Four RCTs were included in this analysis [2-5].

When considering all ten included studies (Figure 1, Table S2), chloroquine derivatives were associated with a lower need for hospitalisation (n = 1, Odds ratio (OR) 0.35, p = .024), shorter

duration of cough (n = 1, OR 0.13, p = .001), shorter duration of fever (n = 1, OR 0.14, p = .001), decreased C-reactive protein level (n = 1, OR 0.55, p = .045), and increased hospital discharge (n = 1, OR 0.05, p =.050). CQ derivatives were associated with a beneficial effect (OR < 1) for 11 of the 12 outcomes analysed (Figure 1). Of the 25 comparisons made, 19 were favourable (Table S1). Accordingly, the two-sided sign-test p-value was 0.015. The fatality rate was analysed in two studies with an opposite direction of effect. The study reporting an increased fatality rate was suspected of scientific misconduct (patients were significantly more severe in the treated group [7]). No significant negative effect was observed.

Three studies were identified with potential scientific misconduct as patients in the untreated group were treated [7], patients were treated after ventilation [8], and patients were significantly more severe in the treated group at baseline [8,9]. After excluding these three studies which had a very high risk of bias, seven studies, including 18 comparisons were analysed (Figure 2, Table S3). The favourable effects on the need for hospitalisation, duration of cough, duration of fever, C-reactive protein levels, and hospital discharge rate, were unchanged. However, a significant beneficial effect was also observed for clinical cure (n = 2, OR 0.48, p = .022) and for the outcome “death or transfer to the intensive care unit” (n = 1, OR 0.04, p < .001). In this subgroup analysis, the direction of effect was favourable for all 11 outcomes analysed. Of the 18 comparisons made, 15 were favourable (Table S1). The two-sided sign-test p-value was 0.0075. All data extracted from the articles and entered in the software are provided in supplementary files (Tables S1 and S4 to S7).

Discussion

Chloroquine derivatives present a paradox. On one hand, the heterogeneity of patients and treatment make it difficult to obtain a clear picture while the epidemic is still ongoing. Under these conditions, a meta-analysis allowing for the combination of different studies makes it possible to identify a general trend. This makes it possible to reconcile the chloroquine derivative efficacy that many doctors have perceived with the results of the first published studies. This meta-analysis is

based on several studies, including four RCTs, and identifies a favourable trend toward the benefit of chloroquine derivatives in the treatment of COVID-19 patients, enabling us to make a grade I recommendation for its use against the disease.

Acknowledgements

We thank Christian Devaux for helpful interactions and Fanyu Huang for Chinese to English translation of the study by Chen J *et al.* [3]. This work has received financial support from the French Government through the Agence Nationale pour la Recherche (ANR), including the "Programme d'Investissement d'Avenir" under the reference Méditerranée Infection 10-IAHU-03 and from the Méditerranée Infection foundation.

Author contributions

MM, PG and DR wrote the MS. MM and PG performed the meta-analysis, DR supervised the study.

Competing interest declaration

No competing interest to declare.

References

1. Colson P, Rolain JM, Lagier JC, Brouqui P, Raoult D. 2020. Chloroquine and hydroxychloroquine as available weapons to fight COVID-19. Int J Antimicrob agents. In press. https://doi.org/10.1016/j.ijantimicag.2020.105932
2. Chen Z, Hu J, Zhang Z, Jiang S, Han S, Yan D, Zhuang R, Hu B, Zhang Z. 2020. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. medRxiv 2020.03.22.20040758; https://doi.org/10.1101/2020.03.22.20040758
3. Chen J, Liu D, Lui L, Liu P, Xu Q, Xia L, Ling Y, Huang D, Song S, Zhang D, Qian Z, Li T, Shen Y, Lu H. 2020. A pilot study of hydroxychloroquine in treatment of patients with common coronavirus disease-19 (COVID-19). J Zhejiang Univ (Med Sci) 49:0-0 . https://doi.org/10.3785/j.issn.1008-9292.2020.03.03
4. Huang M, Tang T, Pang P, Li M, Ma R, Lu J, Shu J, You Y, Chen B, Liang J, Hong Z, Chen H, Kong L, Qin D, Pei D, Xia J, Jiang S, Shan H. Treating COVID-19 with Chloroquine. 2020. J Mol Cell Biol. In press. https://doi.org/10.1093/jmcb/mjaa014.
5. 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; https://doi.org/10.1101/2020.04.10.20060558
6. Borenstein M, Hedges LV, Higgins JPT, Rothstein HR. Introduction to Meta-Analysis. 2009. John Wiley & Sons, Ltd. 2009. https://doi.org/10.1002/9780470743386.
7. Mahevas M, Tran VT, Roumier M, Chabrol A, Paule R, Guillaud C, Gallien S, Lepeule R, Tali Szwebel TA, Lescure X, Schlemmer F, Matignon M, Khellaf M, Crickx E, Terrier B, Morbieu C, Legendre P, Dang J, Schoindre Y, Pawlotski JM, 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

8. Magagnoli J, Narendran S, Pereira F, Cummings T, Hardin JW, Sutton SS, Ambati J. Outcomes of hydroxychloroquine usage in United States veterans hospitalized with Covid-19. medRxiv 2020.04.16.20065920; https://doi.org/10.1101/2020.04.16.20065920
9. Barbosa J, Kaitis D, Freedman R, Le K, Lin X. Clinical outcomes of hydroxychloroquine in hospitalized patients with COVID-19: a quasi-randomised comparative study. Submitted to New Eng J Med. https://www.dropbox.com/s/urzapkyij542qx5/NEJM_Clinical%20Outcomes%20of%20Hydroxychlorquine%20in%20Patients%20with%20COVID19.pdf.pdf.pdf.pdf.pdf.pdf.pdf.pdf?dl=0

Figure legends

Figure 1. Forest plot reporting all comparisons of the efficacy of chloroquine derivatives in humans infected with COVID-19

CI: Confidence interval, CT: computed tomography, ICU: Intensive care unit. Viral load persistence was assessed by polymerase chain reaction. Very high risk of bias: studies with possible scientific misconduct (treated group were more severe at baseline, treatment took place after ventilation, patients in the “untreated” group were treated).

Figure 2. Forest plot reporting comparisons of the efficacy of chloroquine derivatives in humans infected with COVID-19 after the exclusion of three studies with very high risk of bias

CI: Confidence interval, CT: computed tomography, ICU: Intensive care unit. Viral load persistence was assessed by polymerase chain reaction.