Nullane salus extra ecclesiam

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Abstract

Randomized clinical trials are not relevant for infectious disease outbreaks due to a new pathogen, for which public health decisions have to be made urgently. An approach based on group comparisons, *in silico*, may provide valuable results in a reasonably short period of time for a negligible amount of money.

Keywords: Chloroquine derivatives, clinical trials, COVID-19, *in silico* comparison, SARS-CoV-2
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To the Editor,

In a randomized controlled trial (RCT), participants are assigned to receive either the treatment under investigation or, as a control, a placebo or the current standard treatment. The randomization process ensures that the various groups are, as far as possible, identical in demographics, socio-economic status and other conditions, which minimizes the potential for bias and the influence of confounding factors. The usually high number of required participants depends on the magnitude of the expected effect, implying a long duration of inclusion period. RCTs are considered the reference standard of clinical research for testing new drugs for chronic disease [1]. Among their limitations, RCTs are long-lasting and expensive, and usually directed towards high-risk groups to increase the likelihood of capturing enough end points [1]. RCTs are typically interventions aimed at assessing the effectiveness of a new preventive or curative treatment, as opposed to observational studies conducted in patients under standard care treatments. Interestingly, based on careful review of meta-analyses of RCTs and cohort or case–control studies assessing the same intervention, the 'average results' from the latter did not systematically overestimate the magnitude of the associations between exposure and outcome compared with RCTs [2].

In addition, RCTs are not relevant for urgent health matters such as infectious disease outbreaks due to a new or re-emerging pathogen, for which public health decisions have to be made urgently [1]. In such situations, decisions have to be taken on the basis of limited and often imperfect available data. In the current context of the coronavirus disease 2019 (COVID-19) pandemic, measures that have good rationale, but for which few data are available (e.g. travel restrictions, lockdowns and compassionate use of drugs) should also be considered as options and should be assessed and amended in a continuous manner [3]. Such an approach—almost empirical but pragmatic—is likely to be considered highly blasphemous by those believing that there is no salvation outside the RCT church, whatever the context. Expressing a view against the main stream, i.e. against the dogma of RCT supremacy, is at high risk of virulent reactions from some colleagues with a conservative view. Nevertheless, and fully aware of the heretic component of our position, we would like to suggest an alternative to RCT with the aim of challenging the efficacy of chloroquine derivatives and of their combination with azithromycin, which are currently used against severe acute respiratory syndrome coronavirus 2 infections by a majority of physicians, based on the results of preliminary studies [4,5]. Observational uncontrolled cohort studies conducted in individuals with COVID-19 under such treatments have been published [6–8], and RCT results have also been released [4,5,9,10]. We propose assembling that which is scattered. By bringing together the sparse published data on the subject, it may become possible to carefully compare a selection of outcomes in patients treated with chloroquine derivatives with the outcomes of matched patients receiving another treatment or standard care. Such an approach based on group comparisons, *in silico*, may provide valuable results in a reasonably short period of time for a negligible amount of money. Our group conducted such an analysis using aggregated data from published studies matched with our own observational data showing that individuals treated with a combination of hydroxychloroquine and azithromycin were three times less likely to die than matched patients treated with either lopinavir-ritonavir or standard care. Compared with patients included in

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a remdesivir study, we also showed a significant difference in the clinical outcome (proportion of cured individuals with negative viral load) in favour of hydroxychloroquine and azithromycin [11]. Full access to original data sets of COVID-19 studies should be warranted to public view, allowing comparison of raw data rather than aggregated data and avoiding the retraction of doubtful studies whose authors declined to share raw data for an external audit [12].

Declaration of competing interest

There is no conflict of interest.

References

[1] Frieden TR. Evidence for health decision making – beyond randomized, controlled trials. N Engl J Med 2017;377:465–75.
[2] Concato J, Shah N, Horwitz RI. Randomized, controlled trials, observational studies, and the hierarchy of research designs. N Engl J Med 2000;342:1887–92.
[3] Zhang W, Qian BY. Making decisions to mitigate COVID-19 with limited knowledge. Lancet Infect Dis 2020 Apr 7 [Epub ahead of print].
[4] Gautret P, Lagier JC, Parola P, Hoang VT, Meddeb L, Mailhe M, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents 2020 Mar 20:105949 [Epub ahead of print].
[5] Chen Z, Hu J, Zhang Z, Jiang S, Han S, Yan D, et al. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. MedRxiv 2020. https://doi.org/10.1101/2020.03.22.20040758.
[6] Gautret P, Lagier JC, Parola P, Hoang VT, Medded L, Sevestre J, et al. Clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin in 80 COVID-19 patients with at least a six-day follow up: a pilot observational study. Travel Med Infect Dis 2020 Apr 11:101663 [Epub ahead of print].
[7] 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 May 5:101738 [Epub ahead of print].
[8] 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 May 14;369:m1844.
[9] Chen J, Liu D, Liu L, Liu P, Xu Q, Xia L, et al. A pilot study of hydroxychloroquine in treatment of patients with common coronavirus disease-19 (COVID-19). J Zhejiang Univ (Med Sci 2020;49. https://doi.org/10.3785/j.issn.1008-9292.2020.03.03.
[10] Tang W, Cao Z, Han M, Wang Z, Chen J, Sun W, et al. Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised controlled trial. BMJ 2020 May 14;369:m1849.
[11] Giraud-Gatineau A, Lagier JC, Obadia Y, Chadet H, Raoult D. Adjusting series of patients for trial comparisons for COVID-19 treatments. 2020. Available at: https://www.mediterranee-infection.com/adjusting-series-of-patients-for-trial-comparisons-for-covid-19-treatments/.
[12] Ledford H, Van Noorden R. High-profile coronavirus retractions raise concerns about data oversight. Nature 2020 Jun 5. https://doi.org/10.1038/d41586-020-01695-w.