What is Futility in Therapeutic Studies?

Matthieu Million[1,2], Didier Raoult[1,2]

[1]IHU Méditerranée Infection, Marseille, France

[2]Microbes Evolution Phylogeny and Infections (MEPHI), Institut de Recherche pour le Développement, Aix-Marseille Université, Marseille, France

[3]Assistance Publique-Hôpitaux de Marseille, Marseille, France

Word count : 237

Dear Editor,

We read with interest the randomised controlled trial (RCT) by Avezum *et al.* evaluating hydroxychloroquine (HCQ) for hospitalisation in COVID outpatients (1). Although the expected sample size was not reached, the study was stopped for futility. However, the trial showed that the risk of hospitalisation was decreased in patients treated with hydroxychloroquine (44/689 (6.4%) compared to those who were not (57/683 (8.3%), odds ratio 0.77, 95% confidence interval 0.52–1.12). The authors concluded that hydroxychloroquine was not effective, but the clinical relevance of the observed difference was not discussed. The sample size needed to show significance would be more than 5,500 patients. In contrast, a 23% decrease in the hospitalisation rate would have a major impact on the hospital overload which is associated with COVID and non-COVID excess mortality (2). Several other RCTs evaluating HCQ for COVID-19 mortality were also stopped for futility. In most cases, the prespecified sample size was not achieved, significance was not reached, and clinical relevance was not discussed. For instance, in the French HYCOVID (3) and DisCoVeRy (4) trials, HCQ was associated with a 46% and 18% reduction in risk of death compared with placebo, respectively. In relation to the >6 million deaths due to COVID worldwide since the beginning of the pandemic, such effect sizes are clinically relevant. In therapeutic studies, the clinical relevance or futility of the observed effect size should always be discussed before assessing significance (5).

Conflict of interest

DR is scientific board member of Eurofins company, founder and share holder of a microbial culture company (Culture Top), consultant for Hitachi High-Technologies Corporation, Tokyo, Japan from 2018 to 2020.

MM declared no conflict of interest.

References

1. Avezum Á, Oliveira GBF, Oliveira H, et al. Hydroxychloroquine versus placebo in the treatment of non-hospitalised patients with COVID-19 (COPE - Coalition V): A double-blind, multicentre, randomised, controlled trial. Lancet Reg Health Am. 2022;11:100243.
2. French G, Hulse M, Nguyen D, et al. Impact of Hospital Strain on Excess Deaths During the COVID-19 Pandemic - United States, July 2020-July 2021. MMWR Morb Mortal Wkly Rep. 2021;70(46):1613-1616.
3. Dubée V, Roy PM, Vielle B, et al. Hydroxychloroquine in mild-to-moderate coronavirus disease 2019: a placebo-controlled double blind trial. Clin Microbiol Infect. 2021;27(8):1124-1130.
4. Ader F, Peiffer-Smadja N, Poissy J, et al. An open-label randomized, controlled trial of the effect of lopinavir/ritonavir, lopinavir/ritonavir plus IFN-β-1a and hydroxychloroquine in hospitalized patients with COVID-19 – Final results from the DisCoVeRy trial. medRxiv 2022.02.16.22271064
5. Stang A, Poole C, Kuss O. The ongoing tyranny of statistical significance testing in biomedical research. Eur J Epidemiol. 2010;25(4):225-230.