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Commentary

Does hydroxychloroquine reduce mortality for COVID-19?

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A paper published in this issue of the European Journal of Internal Medicine shows results from the COVID-19 RISK and Treatments (CORIST) Collaboration Study [1]. The authors analysed data from a large multicentric Italian retrospective observational study based on 3,451 COVID-19 patients - including 576 deaths - to test a recently debated hypothesis: whether hydroxychloroquine (HCQ) can reduce (or prevent) COVID-19 in-hospital mortality [1–3].

Chloroquine (CQ) and its analogue hydroxychloroquine (HCQ) are antimalarial drugs - prescribed for many years now - that have been widely used for the treatment of autoimmune diseases, including rheumatoid arthritis and systemic lupus erythematosus [2,4]. Since some studies suggested a benefit of HCQ in viral infections, and in the absence of any proven treatment strategies for COVID-19, the drug has been advocated and politicized as promising therapy [2,3]. However, given the disappointing findings of early observational studies with HCQ on mortality or morbidity, particularly in combination with azithromycin (AZM) [5], several regulatory agencies suspended the prescription of HCQ for COVID-19, including the US Food and Drug Administration (FDA) [3] and the Italian Medicines Agency (AIFA) [1]. The World Health Organization too decided to discontinue HCQ treatment for COVID-19 patients in its Solidarity trial [6].

The CORIST study showed lower death rates among 2,634 patients who received HCQ (8.9 per 1,000 person-days) compared to 817 who did not (15.7 per 1,000 person-days). Using propensity score methods to adjust for multiple covariates, the authors found a 30% lower risk of in-hospital mortality among patients receiving HCQ (hazard ratio, HR: 0.70; 95% confidence interval, CI: 0.59-0.84) [1].

The CORIST results, although in agreement with a few longitudinal studies, are not in line with some recent systematic reviews and meta-analyses summarizing the current evidence from observational studies and randomized controlled trials (RCT) [7–10]. Two reviews in particular [8–10] found more than 15 observational studies analysing the effectiveness of HCQ as a treatment for COVID-19 progression. The pooled odds ratio (OR) was 0.90 (95% CI: 0.65-1.26), the meta-analysis showing considerable heterogeneity, with the large majority of the studies having moderate to serious risk of bias [8].

Evidence from RCTs is even more limited. A meta-analysis of completed and ongoing RCTs, pooling findings from published (mostly preprints) or unpublished data, found a borderline significant excess risk of 8% for all-cause mortality for COVID-19 patients treated with HCQ (pooled OR: 1.08; 95% CI: 0.99-1.18) [7]. It is worth noting that in these meta-analyses the RECOVERY trial alone [11] - still posted as a preprint – accounted for more than 85% of the overall evidence from RCTs [7,8].

HCQ was also proposed as a possible preventive therapy. However, a large RCT based on 821 subjects at high risk of SARS-CoV-2 infection did not find any prophylactic effect for HCQ [12].

Summarizing, the available data do not currently support any effectiveness for HCQ as treatment or prophylaxis for COVID-19. However, the still limited number of well-powered and well-conducted observational studies, the heterogeneity of findings from observational studies, and the scant evidence from RCTs - practically based on a single trial [11] - suggest that today's data on the efficacy of HCQ in reducing mortality among COVID-19 hospitalized patients are not conclusive.

Given this paucity of evidence, the findings of the CORIST study are welcome and important. CORIST is globally one of the largest well-conducted multicentric retrospective studies analysing the issue in real-life conditions. Moreover, members of the CORIST Collaboration did their best to minimize bias through statistical analysis. Thus, efforts

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to manage missing data, the use of propensity score methodology to obtain comparable intervention and comparison groups, the further provision of estimates using multivariable models and the consistent results provided by strata of potential covariates indicate that all possible statistical attention aimed at minimizing any biases has been attempted.

The CORIST study therefore adds knowledge on the issue. However, the different distribution in HCQ treated and non-treated groups by sex, age, concomitant treatments and pre-existing comorbidities calls for caution about the reliability of the estimates. Unmeasured or residual confounding could not be ruled out in CORIST, as the authors themselves note, particularly in an intensive care setting [2], in emergency conditions and considering the variability in clinical management due to the lack of proven treatment strategies.

We still cannot properly answer our original research question, since evidence from well-conducted RCTs is still needed to provide confirmation. In the near future, once the findings from the numerous trials on this issue have been published (more than 200, according to ClinicalTrials.gov), we should have a clearer picture of the efficacy of HCQ. Until then, treatment decisions for this disease will remain based on clinical judgment [2], bearing mind that: i) several studies reported the potential cardiovascular toxicities in patients treated with HCQ, alone or in combination with AZM [2,13–15]; ii) corticosteroids, including dexamethasone, have been found to be effective in reducing mortality among critical COVID-19 patients [16,17]; and iii) the major drug regulatory agencies discourage the use of HCQ for COVID-19 [1,3,6].

Declaration of Competing Interest

Silvano Gallus and Alessandra Lugo are currently collaborating in various projects with some of the Investigators of the CORIST Study, including Licia Iacoviello, Maria Laura Bonaccio, Carlo Signorelli, Anna Odone and Laura Carrozzi. No other competing interests are declared.

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