Reply to the Letter to Editor by Lacout and colleagues: Chloroquine and Hydroxychloroquine for the Treatment of COVID-19: a Systematic Review and Meta-analysis

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We thank Lacout and colleagues for their comments on our systematic review and meta-analysis.¹ The authors propose that early use (e.g., ≤ 3 days since symptom onset) of hydroxychloroquine (HCQ) may be associated with better outcomes in patients with COVID-19. However, the available evidence including 3 recent randomized controlled trials (RCTs) has failed to show benefit of HCQ even in patients with shorter symptom duration and milder illness at baseline and those who were not hospitalized, or when used for post-exposure prophylaxis.

Boulware et al.² administered HCQ or placebo to participants within 4 days of exposure. The incidence of symptomatic illness did not differ significantly between HCQ (49 of 414 [11.8%]) and placebo (58 of 407 [14.3%]; absolute difference -2.4 , 95% confidence interval, -7.0 to 2.2 ; $P=0.35$).

In another RCT,³ there was no significant difference in clinical status at 14 days between the HCQ and placebo in prespecified subgroups by baseline illness severity or duration of symptoms: aOR for recovery in patients with symptoms 0 to 3 days was 0.95 (95% CI 0.52 to 1.73) and for 4 to 6 days 1.11 (95% CI 0.63 to 1.94).

In yet another RCT,⁴ no benefit of HCQ was seen in mild to moderate COVID-19 patients. Of the 59 patients who were enrolled within 3 days of onset, the number of patients who were at home at day 14 was 6/16 (38%) in the HCQ-plus-azithromycin group, 10/19 (53%) in the HCQ-alone group, and 14/24 (58%) in the control group.

The preprint systematic review cited by the authors⁵ has pooled the results across different outcomes (death, hospitalization, and infection). Meta-analysis should only be considered when a group of studies is sufficiently homo-

geneous in terms of participants, interventions, and outcomes to provide a meaningful summary. Also, one of the included trials studied the effect of HCQ as pre-exposure prophylaxis, a clinically distinct use from what the other trials studied. For these reasons, this meta-analysis might have yielded an erroneous pooled estimate and confidence interval.

Regarding cardiotoxicity, both chloroquine and HCQ interfere with ventricular repolarization, leading to prolongation of the QTc interval and an increased risk of torsades de pointes. Studies involving volunteers found mean increases in QTc of 6.1 ms after a dose of 600 mg and 28 ms after 1200 mg.

Thus, the available literature does not favor HCQ in the treatment of COVID-19 even if used early and in milder cases.

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