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Letter to the Editor

Reply to 'Low-dose hydroxychloroquine therapy and lower mortality in hospitalized patients with COVID-19: association does not mean causality'

Editor: Dr Jim Gray

We wish to thank De Schryver et al. [1] for their comments on our observational study about the use of hydroxychloroquine (HCQ) during the first wave of the coronavirus disease 2019 (COVID-19) pandemic in Belgium [2]. Our study remains the largest observational study performed to date on 'off-lab' use of HCQ, and is one of the few studies to compare HCQ use alone in a group of patients not exposed to any other anti-COVID-19 drugs.

The following points were raised regarding our study: (i) the impact of long-term data from patients still hospitalized at the time of analysis; (ii) potential indication bias and impact of a 'do-not-escalate' order; (iii) discrepancies with other observational studies and randomized controlled trials, such as RECOVERY and SOLIDARITY; and (iv) the exceptionality of our findings [2].

Firstly, in our initial study, we did not solely analyse patients with completed discharge data. The supplementary material reports results from an analysis of all patients with admission data, accounting for the missing discharge information by either (i) censoring the follow-up time at final follow-up, i.e. May 24 (assuming that patients without discharge data had not been discharged at that time); or (ii) treating them as missing at random (see online supplementary data of original article [2]). Findings were qualitatively similar in each case.

Secondly, another team of researchers from Sciensano recently carried out a retrospective case–control study on the outcomes of patients admitted to an intensive care unit (ICU) within the frame of the same COVID-19 hospital surveillance data [3], registered up to 9 August 2020 (n=1747). In a multi-variate mixed effects analysis including demographic, clinical and biological factors, HCQ therapy was associated with lower in-hospital mortality (odds ratio 0.64, 95% confidence interval 0.45–0.92). A subanalysis of patients who received invasive mechanical ventilation alone (n=999) found that HCQ therapy was still independently associated with decreased mortality [4] finding shows that the association between HCQ and mortality remains sizeable in a subcohort without any formal 'do-not-escalate' orders.

Thirdly, the authors referred to the randomized controlled trials RECOVERY and SOLIDARITY, which found no benefit of HCQ compared with standard care [5,6]. It is important to note that both trials, assuming potential antiviral activity of HCQ, administered a higher dosage of HCQ than was given in our cohort, and often at a rather late stage of the disease. The antiviral effect of HCQ could not be demonstrated in animals or humans, closing this hypothesis definitively [7–9].

Fourthly, regarding the 'exceptionality' of our findings, it is of value to highlight that several other observational studies using low-dose HCQ in hospitalized patients have also found an association with lower mortality [10–12] or ICU transfer when administered early during hospitalization [13]. However, it was acknowledged clearly and repeatedly in our article that the observations do not confirm a beneficial causal effect of low-dose HCQ. We highlighted the limitations of a retrospective observational study performed using national surveillance data [3], which was not designed primarily as an efficacy study and therefore did not register other potential confounders (such as frailty or comedications contra-indicating the use of HCQ).

We therefore fully agree with the title of De Schryver et al. [1] letter. Our conclusion was, in fact, that these observations should trigger new research questions on the long-known anti-inflammatory and antithrombotic properties of HCQ. Indeed, we want to stress that there is biological plausibility underlining a potential benefit of HCQ in COVID-19. HCQ activity shares similarities with the mechanisms of action of dexamethasone, which is the only intervention proven to be beneficial in severe cases of COVID-19 [14]. These mechanisms include inhibition of chemokines and pro-inflammatory cytokines associated with poor prognosis (interleukin-6, tumour necrosis factor-α) [15–17]. Moreover, there is now increasing evidence that severe COVID-19 is associated with immune and coagulation abnormalities observed in auto-immune diseases, such as systemic lupus erythematous [18–20]. Antiphospholipid auto-antibodies are found in a high proportion of patients with severe COVID-19, and have been associated with platelet hyperactivity, more severe disease and acute kidney injury [20,21]. Antiphospholipid auto-antibodies isolated from patients with COVID-19 have been shown to cause neutrophil extracellular traps released by neutrophils in vitro, and induce thrombosis in murine models [21]. Animal, in-vitro and human clinical studies have largely demonstrated the benefit of HCQ in the prevention of thrombotic complications related to antiphospholipid syndrome [22–24]. This subgroup of patients with immune abnormalities who could benefit from HCQ therapy may be under-represented in small randomized controlled trials that have not shown a benefit of low-dose HCQ [25].

In conclusion, our observational study provides results which fit the criteria for a coherent association according to Rosenbaum – temporal sequence, consistency of association (ICU vs non-ICU), coherence with existing knowledge (anti-inflammatory and antithrombotic properties) – and are analogous with other reports (observational studies using low-dose HCQ). It does not claim causality, but we encourage investigation of the effect of low-dose HCQ on inflammatory and coagulation parameters in COVID-19 to gain additional insight into its complex pathogenic pathways.

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