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Hydroxichloroquine for COVID-19 infection: Do we have a final word after one year?

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ABSTRACT

The results presently available from randomised clinical trials and their meta-analysis indicate that Hydroxychloroquine is not associated in COVID-19 patients with either decreased mortality or clinical worsening. Thus, the use of Hydroxychloroquine in COVID-19 patients cannot at present be encouraged. However, the hypothesis that Hydroxychloroquine might have a beneficial role in subgroups of patients at low risk and/or when used at low dosage (≤ 400 mg/day) deserves to be tested in large, well designed randomised clinical trials.

1. Introduction

Hydroxychloroquine (HCQ) is an anti-malaria drug in use for the treatment of rheumatologic diseases and human immunodeficiency virus infections but also used against SARS-CoV-1 and Ebola [1]. In the first phase of the SARS-CoV-2 pandemic, it was practiced as a potential therapy against COVID-19 in view of its capability to inhibit viral entry and spread in several *in vitro* and *in vivo* models [2]. In the absence of convincing alternative therapies and results from randomised clinical trials (RCTs), HCQ use rapidly spread worldwide, and several observational studies tested its efficacy [3]; among them, one of the earliest and most sized observational studies was presented by the COVID-19 RISK and Treatments (CORIST) Collaboration, and *e*-published in August 2020 in the European Journal of Internal Medicine [4]. The authors reported 30% lower risk of death in hospitalised COVID-19 patients who had received HCQ (HR=0.70; 95%CI: 0.59 to 0.84), in comparison with patients who did not.

Ever since, various other observational studies have been published, with contrasting results that have been meta-analysed. In one of the most complete meta-analyses, the use of HCQ against COVID-19 was associated with 20% lower mortality risk (pooled risk ratio: 0.80, 95% CI: 0.69 to 0.93, high heterogeneity, low level of certainty of evidence) pooling a total of 25 cohort studies ($N = 41{,}339$ patients) [3].

In the meantime, findings from larger and larger RCTs [5,6] and meta-analyses [3,7]became available. In contrast with the majority of observational findings, in RCTs the use of HCQ was not associated with beneficial effects: pooled risk ratio 1.08, 95%CI: 0.97 to 1.20, low heterogeneity, high level of certainty of evidence, pooling 11 RCTs, $N =$ 8709 patients [3]. Moreover, HCQ was not associated with an increased risk of serious adverse effects (pooled risk ratio: 1.12, 95%CI: 0.88 to 1.44) [3].

Furthermore, HCQ was not effective as a prophylaxis agent against SARS-CoV-2 infection, as it did not reduce clinical worsening, severe adverse events or all-cause mortality [8,9].

However, our findings from 27 cohort studies, including those of the CORIST collaboration, remain intriguing: indeed, 8 studies reported a statistically significant association of HCQ use with lower mortality (relative risk ratio in the range 0.07–0.70), 8 studies found that HCQ use was associated with a non-statistically significant reduced relative risk of mortality (range 0.62–0.99) and 11 cohorts reported a positive, non-statistically significant association with death (range 1.04–1.67). No study found a positive, statistically significant association of HCQ with increased mortality [3]. These results prompted us to further investigate the reason(s) of the apparent discrepancy between findings from observational and interventional studies.

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2. Disentangling the role of hydroxychloroquine

Using the same CORIST dataset, including more than 4000 COVID-19 hospitalised patients, we tried to disentangle the possible association of HCQ with mortality through an unsupervised machine learning analysis [10,11]. Using hierarchical clustering, we could identify two clusters of COVID-19 patients based on their socio-demographic and clinical characteristics: one, including younger patients with lower circulating inflammation levels and better renal function, and the other composed of generally older and more co-morbid subjects, more prevalently men and smokers. Interestingly, HCQ appeared to be associated with reduced mortality only in the low (hazard ratio 0.46, 95%CI: 0.39 to 0.54) but not in the high-risk cluster (hazard ratio 0.89, 95%CI: 0.65 to 1.22; P for difference $P < 0.001$), suggesting a selective beneficial effect of HCQ in low risk COVID-19 patients [11] This was in line with the findings of the IDENTIFY study, a multicentre US clinical trial [12]; in that study, HCQ treatment was associated with higher survival in the treated harm, especially in those patients that were predicted to benefit most, based on a supervised machine learning algorithm applied to their characteristics. Among these, creatinine level – a marker of renal function – was one of the most important features in predicting the response to HCQ, in line with the CORIST study [4,10]. Together, these two independent lines of evidence suggest that patient subtyping and classification may represent a key to clearly define the actual efficacy of HQC treatment.

Another point of discussion is the notable discrepancy in HCQ dosage reported so far in observational vs RCT studies: the reduced mortality associated with HCQ use was actually confined in cohort studies that used a daily dose $\leq$ 400 mg (overall relative risk 0.69; 95%CI: 0.57 to 0.85), whereas it was null in studies in which a dose $>$ 400 mg/day was used (overall relative risk 1.05; 95%CI: 0.73 to 1.53; $P = 0.050$ for difference) [3]. Notably, 5 over 11 RCTs used high doses of HCQ, including the large SOLIDARITY [5] and RECOVERY [6] studies, which both used 800 mg/day. The HCQ use was associated with an average 15% lower mortality in the 6 RCTs which used $\leq$ 400 mg/day of HCQ, but a 10% higher mortality in the 5 RCTs which used higher doses[3]. Though not statistically significant, this discrepant effect of lower and higher doses of HCQ warrants further consideration.

3. Provisional conclusions

Evidence from RCTs is of fundamental importance for the assessment of clinical guidance; but a lesson from the HCQ use in COVID-19 patients is that findings from observational studies performed in real life conditions should be taken into consideration as they may help disentangling complex clinical and pharmacological scenarios.

The results presently available from RCTs and their meta-analysis indicate that HCQ is not associated in COVID-19 patients with either decreased mortality or clinical worsening. Thus, the use of HCQ in COVID-19 patients cannot at present be encouraged. However, the hypothesis that HCQ might have a beneficial role in subgroups of patients at low risk and/or when used at low dosage ($\leq$ 400 mg/day) deserves to be tested in large, well designed randomised clinical trials. More in general, a personalised medicine approach needs to be adopted in future RCTs.

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