Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Clinical Microbiology and Infection 27 (2021) 3–5

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Commentary

Has the door closed on hydroxychloroquine for SARS-COV-2?

Mical Paul

Infectious Diseases Institute, Rambam Health Care Campus, The Ruth and Bruce Rappaport Faculty of Medicine, Technion – Israel Institute of Technology, Haifa, Israel

ARTICLE INFO

Article history:
Received 20 September 2020
Received in revised form
12 October 2020
Accepted 13 October 2020
Available online 20 October 2020

Editor: L. Leibovici

Shortly following the onset of the SARS-COV-2 pandemic, Raoult's group from Marseille published a study describing improved virological cure with hydroxychloroquine (HCQ), especially in combination with azithromycin [1]. Beyond being "non-randomized" this was a small, unadjusted comparison including 36 patients in total, reporting only on virological cure and excluding from the analysis the most severely ill patients. It was probably meant as an alert for a potentially useful treatment and reported as responsible sharing of the local experience given the urgent situation (as the authors noted "we believe that our results should be shared with the scientific community"). Yet this publication launched a heated debate of HCQ believers and non-believers, moving far beyond the realm of science, with politicians expressing views, countries stockpiling the drug and people taking it prophylactically [2,3]. This also led to a flurry of studies, resulting now in more than 25 systematic reviews and/or meta-analyses summarizing specifically the efficacy of HCQ for COVID-19 from these studies on PubMed and 12 unpublished on medRxiv. A systematic review of observational studies and randomized controlled (RCTs) published recently in *Clinical Microbiology and Infection* concluded no benefit for HCQ and increased mortality with HCQ and azithromycin [4]. Is this the last word on HCQ for corona?

Beneficial effects of HCQ are possible given the multiple antiviral and anti-inflammatory properties of the drug. It is active *in vitro* against SARS-COV-2 and has been identified independently in screening of chemical libraries and through mapping to SARS-COV-2 protein targets [5–7]. These data are probably sufficient to warrant clinical assessment. Many observational studies were published following the first from Marseille. All suffer from limitations inherent to observations, augmented by the stress of the pandemic. Possibly, the debate arising following the first study from Marseille resulted in publication of observational studies that would not have been published otherwise [8]. While many sources of bias exist in observational studies, two should be stressed: confounding and deviations from the intended interventions. Whether believing or not in HCQ's efficacy or whether comparing between different centres, the patients treated with HCQ will not be similar to those not given HCQ. Enough data on the patients and a large enough sample size is needed to allow for adjustment. Previously identified risk factors for death in COVID-19 include age, male sex, ethnicity in the UK, deprivation, most comorbidities, disease presentation and hospital-level data [9–11]. All these data must be collected, compared and adjusted for as relevant. Unlike in RCTs, treatment is not standardized in observational studies. As a minimum, observational studies should define the start time, dosing and minimal duration of HCQ that can reasonably affect the course of the disease and collect data on concomitant therapy, especially medications that might affect the outcome (e.g. steroids). None of the studies to date addressed confounding or treatment definitions appropriately. Their risk of bias using the ROBINS-I tool is being summarized in a living systematic review [12,13]. None of the studies achieved low risk of bias overall and many were classified at critical risk.

Three RCTs covering the spectrum of COVID-19 disease severity currently provide high-quality evidence. The RECOVERY trial is a platform trial carried out in many hospitals in the UK including 4716 patients [14]. Although both probable and confirmed COVID-19 patients were included, 90% had virological confirmation of SARS-COV-2. HCQ dosing was high compared with usual dosing. However, considering both beneficial and adverse effects, the rate ratio for all-cause mortality at 28 days was 1.09, 95% CI 0.97–1.23 (>1 in favour of standard therapy). The CI is sufficiently narrow to direct practice, precluding a benefit for HCQ with 97% certainty (within a 5% significance level). With an upper 95% confidence OR of 1.23, it does not preclude an adverse impact on mortality. Its methodology is the robust methodology of a pragmatic non-blinded RCT examining an objective outcome, thus generating high-certainty evidence by the GRADE classification. The trial included hospitalized patients at a median of 9 (5–14) days after

DOI of original article: https://doi.org/10.1016/j.cmi.2020.08.022.
E-mail address: paulm@technion.ac.il.

https://doi.org/10.1016/j.cmi.2020.10.011

symptom onset, 76.4% required oxygen or mechanical ventilation at randomization and the 28-day mortality was 25.7% (1211/4716). Thus, it concludes on the lack of HCQ beneficial effects in this patient population, probably at an advanced phase of the disease with respiratory insufficiency.

Cavalcanti *et al.* reported on 504 patients with confirmed COVID-19 in 55 centres in Brazil, with mild to moderate COVID-19, hospitalized but without respiratory failure [15]. Accordingly, the mortality in the trial was lower (18/504, 3.6%). In this population, the patient-relevant outcome is probably deterioration to severe disease and ultimately mortality, and indeed the trial used a 7-point ordinal scale ranging from full recovery to death at 15 days. The trial reported an OR of 0.99 (95% CI 0.57–1.73) and 1.21 (95% CI 0.69–2.11) for a worst outcome with HCQ and HCQ + azithromycin, respectively, both vs. standard care. The OR for death in-hospital was 1.05 (95% CI 0.39–2.85). Skipper *et al.* [16] addressed the patient population in the community at onset of the disease, within a few days after symptom onset. This was a pragmatic study using social media, e-mail and web surveys for patient recruitment, randomization and self-reported outcome data collection. Patients had either confirmed COVD-19 (145/423, 34.3%) or were symptomatic after exposure to a confirmed COVID-19 contact. The between-group difference in symptom improvement at 14 days for HCQ vs. placebo was −0.27 points (95% CI −0.61 to 0.07 points, difference <1 in favour of HCQ). The outcome was assessed using a 10-point visual analogue scale ranging from no symptoms to severe symptoms (including hospitalization or death). Only two patients died in the trial (OR 1.01, 95% CI 0.06–16.29).

These three trials [14–16] were well designed and each addressed a different patient population, the need for virological confirmation as relevant and clinically meaningful outcomes. In the presence of such high-level evidence and power to refute an advantage to HCQ with respect to mortality for severely ill patients, observational studies do not have much contribution to decision making. Other small RCTs recruited mostly patients at low risk of death [17–23]. Some were at risk of bias with unclear randomization and unbalanced treatment groups with respect to baseline characteristics or adherence to assigned treatment [12,13]. The trials reported primarily on virological or clinical cure, finding no advantage for HCQ but for two small trials of 62 patients that reported on shorter time to clinical cure [21], and 48 patients that reported on faster virological eradication with HCQ [20]. All but one [17] did not address mortality [19,20] or reported that all patients survived [18,21–23]. The significance of virological eradication is unclear. While the initial viral load might be associated with mortality [24], there is no information correlating the virological response with outcomes, unlike the case with HIV. Moreover, information on persistent positive PCR among patients recovering from COVID-19 clinically is accumulating [25].

Recent observational studies and many viewpoints address the cardiotoxicity of HCQ and azithromycin or their combination. Chloroquine has been used for malaria among many millions of people, and HCQ has long been used in high doses for long durations (years) to treat chronic Q fever, with not much interest in its adverse event profile. While patients with severe COVID-19 are at higher risk for cardiac events, analysis of drug-related cardiovascular mortality typically requires a very large sample size. In a carefully designed, propensity score-matched analysis using more than 150 covariates, 5 days of azithromycin was associated with 47 additional cardiovascular deaths per 1 million courses [26]. Current studies try to show increased cardiovascular mortality in cohorts of a maximum of few hundred patients analysing “any” administration of the drugs [27,28]. Retrospective studies are not the appropriate design for estimation of cardiac arrest, arrhythmias or cause of death; adverse effects are not well documented in patients'charts, especially among critically ill patients. The differences between patients given treatment for COVID-19 or not require the huge sample size for appropriate adjustment. Among 2156/4716 of the patients in RECOVERY, HCQ did not cause cardiac arrhythmias. The current data on cardiac complications of HCQ in COVID is weak. HCQ commonly causes nausea and vomiting, which is relevant for patients with mild COVID.

For now, we have no evidence of clinical benefit with HCQ in the treatment of COVID-19. The Infectious Diseases Society of America recommends strongly against treatment with HCQ with or without azithromycin [29]. A further study might address patients at the very early stage of COVID-19, as in Skipper *et al.* [16], but among more patients with virological confirmation. An RCT including patients in the early stage of the disease is probably ethical and will provide the definitive answer, although the pre-test likelihood of a positive result is low with the existing evidence.

I agree with Professor Raoult that the world reacted inappropriately to his group's claim on HCQ's efficacy based on clinical impression, which should have been only a call for further well-conducted studies [30]. Investigators and clinicians also took sides, and we learned about the importance of academic bias on the studies performed and their results. The current status is an all or none treatment approach, with variability even within countries. I believe that the evidence is sufficient to exclude a benefit for HCQ in all stages of COVID-19 and there is no place for treatment of COVID-19 with HCQ, with or without azithromycin.

Transparency declaration

None.

Funding source

None

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