Should Hydroxychloroquine (HCQ) or Chloroquine (CQ) be used in the treatment of COVID-19?

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This rapid review summarizes the available evidence on the efficacy and safety of hydroxychloroquine or chloroquine in treating patients with COVID-19. This may change as new evidence emerges.

KEY FINDINGS

There is insufficient evidence to support the routine use of CQ or HCQ for the treatment of COVID-19. Results from interim analyses of 2 large RCTs, the RECOVERY and the SOLIDARITY trials, reportedly showed no clinical benefit from HCQ for hospitalized patients with COVID-19.

- There are 3 randomized controlled trials that investigated the efficacy and safety of HCQ compared to standard therapy. Overall quality of evidence was very low.
- Meta-analyses from the "COVID-19 Living Data" project suggests that the use of HCQ may increase the incidence of adverse events at day 14 to day 28 (RR 2.49, 95% confidence interval: 1.04 to 5.98, moderate quality of evidence); the most common adverse event across the two trials is diarrhea (n=8).
- In a statement dated June 5, 2020, the investigators of the RECOVERY trial announced their decision to halt further enrollment to the HCQ arm of the trial because an interim analysis showed no clinical benefit from the use of HCQ in hospitalized patients with COVID.
- On June 15, 2020, the US FDA revoked the emergency use authorization for HCQ and CQ as treatment for COVID-19.
- On June 18, 2020, the WHO announced that recruitment to the HCQ arm of the Solidarity trial has been halted.

RESULTS

We found 3 randomized controlled trials and 5 cohort studies on the efficacy and safety of HCQ or CQ vs standard therapy. Study characteristics are summarized in **Appendix 1**. The study by Mehra et al. that was published in the Lancet on May 22, 2020 has since been retracted due to concerns regarding the veracity of the study data.(20)

In the course of scanning for literature relevant to this review, we came across the "COVID-19 Living Data" project. (21) The project aims to regularly (every 3 days) monitor, map, and summarize new evidence for treating and preventing COVID-19. The project website includes a summary of studies on the efficacy of hydroxychloroquine and/or chloroquine vs standard therapy. Subsequent to the manuscript retraction by the study's authors on June 4, 2020, the data from the Mehra et al study were deleted from the website.

Five of the studies identified in our search were included in the project's evidence summaries (RCTs: Chen J et al (22), Chen Z et al (23), Tang et al (16), quasi-experimental studies: Geleris et al (13), Mahevas et al (14)). Two studies identified in our search were excluded from the project's evidence summaries: Rosenberg et al (15), and Yu et al (24). These 2 studies were excluded as they were not considered "quasi-experimental studies" due to the lack of causal inference analysis (e.g. propensity score, inverse probability weighting).(25) Based on our own evaluation, these two studies had a high risk of bias.

Except for reservations in the assessment of quality of evidence (see footnote in Table 1), we agree with the approach taken by the "COVID-19 Living Data" project and, with due attribution, use the evidence summaries (forest plots, evidence profiles, and summary of findings) published on their website as of June 16, 2020 as a basis for the current update of our rapid review.

Randomized Controlled Trials (RCTs)

Overall quality of evidence from 3 RCTs was very low due to concerns regarding risk of bias, and imprecision (**Table 1**). Chen C et al (22) and Chen Z et al (23) recruited patients with mild to moderate disease. Tang et al (16) recruited patients with moderate disease.

Results were equivocal for the outcomes of viral negative conversion (Day(D)7), all-cause mortality (D7, D14 to D28), adverse events (D7), and serious adverse events (D7, D14 to D28). A meta-analysis (**Figure 1**) from two RCTs suggests that the use of HCQ may increase the incidence of adverse events at D14 to D28 (RR 2.49, 95% confidence interval: 1.04 to 5.98, low quality of evidence); the most common adverse event across the two trials is diarrhea (n=8).

Table 1. Summary of results from randomized controlled trials (from Evidence Profile on Hydrochloroquine vs Standard Care, "COVID-19 Living Data" project website)

Outcome	# of studies	n	Effect Estimate (95% CI)	Quality of Evidence
Viral negative conversion (D7)	1	30	RR 0.93 (0.73 to 1.18)	Very Low[a*]
All-cause mortality (D7)	1	150	No events	Very Low[a*]
All-cause mortality (D14 to D28)	2	180	No events	Very Low[a*]
Adverse Events (D7)	1	62	RR 5.00 (0.25 to 100.08)	Very Low[a]
Adverse Events (D14 to D28)	2	180	RR 2.49 (1.04 to 5.98)	Moderate[$]
Serious Adverse Events (D7)	1	62	No events	Very Low[a]
Serious Adverse Events (D14 to D28)	1	150	RR 5.70 (0.28 to 116.84)	Very Low[a]

CI: Confidence Interval, RR: Relative Risk

[a] Down-graded due to concerns with risk of bias (lowered quality of evidence by 1 level) and imprecision (very wide CI, lowered quality of evidence by 2 levels)

[b] Down-graded due to concerns with risk of bias

* The “COVID-19 Living Data” project rated down the quality of evidence of these outcomes due to indirectness. In our assessment, the studies that provided data for these outcomes were done in patient populations that were sufficiently aligned with our research question. We did NOT rate down for indirectness.

[$] The “COVID-19 Living Data” project rated down the quality of evidence for this outcome due to imprecision (small sample size). In our view, the estimate of effect is sufficiently precise and suggests definite harm (i.e. both the lower limit and the upper limit of the confidence interval had a RR >1). We assessed the quality of evidence for this outcome as moderate (rated down 1 level due to risk of bias).

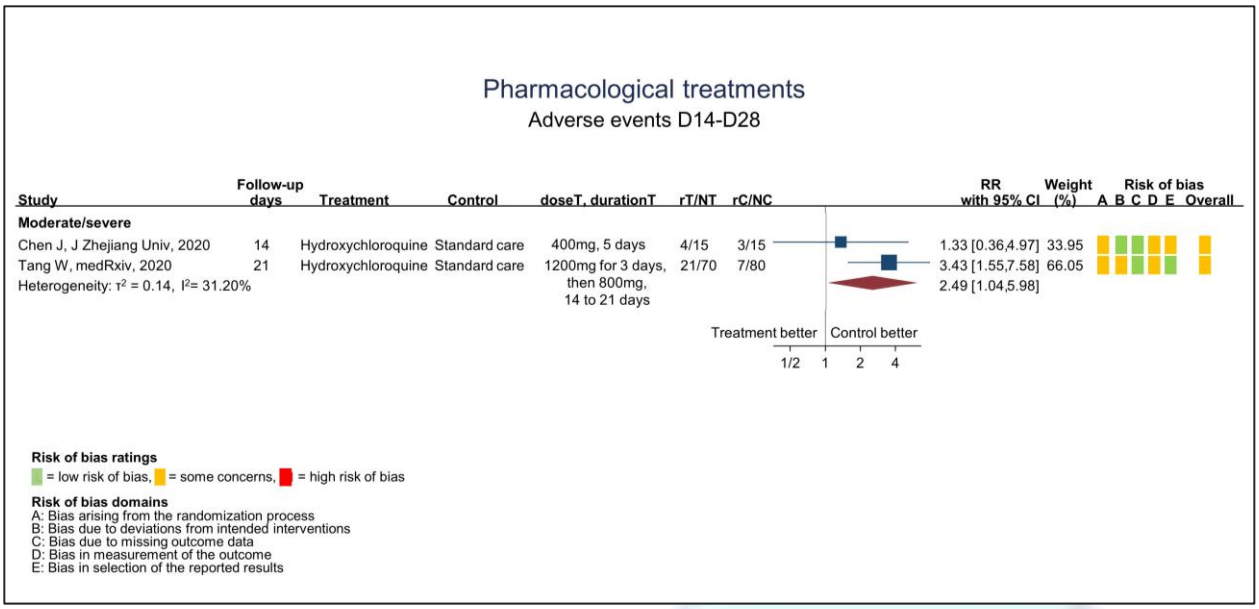

Figure 1. Forest plot for Hydrochloroquine vs Standard Care Adverse Events (D14 to D28), "COVID-19 Living Data" project website

Quasi-experimental studies

Two cohort studies were classified as quasi-RCTs by the "COVID-19 Living Data" project. These studies provide additional evidence on the efficacy and safety of HCQ or CQ vs standard care. We caution that although these studies used statistical means to correct for confounding (i.e. propensity score matching, inverse probability weighting), these methods can only correct for known and measured confounders.

Our own assessment showed that each of these studies had at least a moderate risk of bias. Well-designed observational studies start as low quality evidence in the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.(19) Based on a moderate risk of bias, the quality of evidence from these studies is further rated down to very low.

Geleris et al (13) and Mahevas et al (14) primarily included patients with moderate to severe COVID-19. Both studies showed equivocal results for the outcome of intubation or death. Mahevas et al showed equivocal results for the outcomes of death, and ARDS. (**Table 2**)

Table 2. Summary of results from quasi-RCTs

Study	n	Outcome Effect Estimate (95% CI)
Geleris et al	1376	Time to intubation or death • HR 1.04 (0.82 to 1.32)*

Mahevas et al	181	ICU + Death • RR 0.93 (0.48 to 1.81) Death • RR 0.61, (0.13 to 2.90) ARDS • RR 1.15, (0.66 to 2.01) ECG abnormalities (reported only for HCQ arm, n=84): • QTc >60ms: 7 • First degree AV block: 1

ARDS: Acute Respiratory Distress Syndrome, CI: Confidence Interval, CQ: Chloroquine, ECG: Electrocardiogram, HCQ: Hydroxychloroquine, HR: Hazards Ratio, ICU: Intensive Care Unit, RR: Relative Risk
*Primary adjusted analysis (Inverse probability weighting)

On June 5, 2020, the investigators of the RECOVERY trial, a randomized controlled trial investigating various treatments for COVID-19 including HCQ, released a statement about the interim results for the HCQ arm. Based on data from 4,674 patients hospitalized with COVID-19 (1,542 randomized to HCQ, 3,132 randomized to usual care alone), no significant clinical benefit was found for HCQ in terms of 28-day mortality (25.7% HCQ vs. 23.5% usual care, HR 1.11 [95% CI 0.98 to 1.26]), length of hospital stay, or other outcomes.(26) Full results have yet to be published.

On June 15, 2020, the US FDA revoked the emergency use authorization for Chloroquine and Hydroxychloroquine that it issued on March 28, 2020 in light of recent evidence from a large randomised trial that did not demonstrate benefit for mortality or other important clinical outcomes such as length of hospital stay or need for mechanical ventilation among patients hospitalized for COVID-19. (27) As a result, the US National Institutes of Health, in the June 16, 2020 update of its treatment guidelines for COVID-19, recommended against the use of HCQ or CQ for the treatment of COVID-19, except in a clinical trial. (28)

On June 17, 2020, the WHO Solidarity trial, which is investigating the relative effectiveness of 4 treatment options for COVID-19 (remdesivir, CQ or HCQ, Lopinavir/ritonavir, interferon beta-1a) on top of standard care vs. standard care alone, announced that it has stopped further recruitment to the HCQ arm.(29) This decision was based on a review of current evidence, the results of the RECOVERY trial, and results from the Solidarity trial.

CONCLUSION

There is insufficient evidence to support the routine use of HCQ or CQ for the treatment of COVID-19. Results from the interim analyses of 2 large RCTs, the RECOVERY and the SOLIDARITY trials, reportedly showed no clinical benefit from HCQ for hospitalized patients with COVID-19; the detailed results of these 2 studies are still not publicly available at the time of this review.

Conflicts of Interest: LPV is participating in the ACT-COVID trial, which will investigate various therapies for COVID-19. It originally included HCQ as one of the study treatments, but has since removed HCQ as a treatment after the release of the RECOVERY trial results. EU was previously employed with Abbvie. The company holds marketing authorization for Kaletra (Lopinovir/Ritonavir) which is currently being investigated as a treatment for COVID-19.

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Appendix 1. Study Characteristics

Author	Study Design	Population	Intervention	Comparator	Outcome	Estimate of Effect
Chen J	RCT n=30	Adult, clinically diagnosed COVID-19 patients (n=30) mild to moderate illness	HCQ 400 mg OD for 5 days	Standard care	Virologic clearance (pharyngeal swabs. Sputum or LRT secretions) on D7 Death within 2 weeks ADEs within 2 weeks	Computed RRs Negative conversion (D7): 0.93 No deaths Adverse events: 1.33
Chen Z	RCT n=62	Adults with RT-PCR confirmed COVI-19 and mild pneumonia by chest CT scan (n=62)	HCQ 4oo mg OD for 5 days	Standard care	Time to recovery (fever, cough, disease progression) Improvement in chest CT scan	Fever duration: Treatment: 2.2 (0.4) days vs. Control: 3.2 (1.3) days Cough remission time: Treatment<Control (no reported values) Disease progression: RR 0.21, (95% CI 0.03 to 1.7) Improvement in chest CT scan: RR 1.3, (95% CI 1.5 to 3.5) Adverse events for Treatment Arm: 2

Tang	RCT n=150	Adults with RT-PCR confirmed COVID-19 (n=150)	HCQ 600 mg BID + Mild/moderate disease: 400 mg BID x 2 weeks Severe disease: 400mg BID x 3 weeks	Standard care	Negative conversion at 28 days Adverse Events	Negative conversion: Hazard ratio 0.85, 95% confidence interval 0.58 to 1.23 No deaths, arrhythmias No explicit mention of need for MV or ICU admission
Geleris	Cohort n=1376	Adults with RT-PCR confirmed COVID-19 (n=1376) moderate to severer respiratory illness (O2Sat <94% on ambient air)	HCQ (600 mg BID D1, 400 mg OD D2 to D5) within 24 hours after admission (60% with Azithromycin) (n=811)	Standard care (22% with azithro) (n=565)	Time to intubation or death	Primary adjusted analysis (Inverse probability weighting): hazard ratio, 1.04; 95% CI, 0.82 to 1.32
Mahevas	Cohort n=181	Adults with RT-PCR confirmed COVID-19, required O2 (mask or nasal prongs at admission) (n=181) moderate to severe disease (O2 Sat 92% (89 to 94) on ambient air at admission)	HCQ 600 mg daily within 48 hours after admission (20% with azithro) (n=84)	Standard care (n=97)	Composite: ICU admission within 7 days and all-cause death Death within 7 days ARDS	ICU + Death: RR 0.93, 95% CI 0.48–1.81 Death: RR 0.61, 95% CI 0.13–2.90 ARDS: RR 1.15, 95% CI 0.66–2.01 ECG abnormalities (these outcomes reported only for HCQ arm, n=84): QTc >60ms: 7 First degree AV

						block: 1 patient in HCQ arm
Rosenberg	Cohort n=1438	RT-PCR confirmed COVID-19 (majority were adults) (n=1438) mild (>50%with O2 Sat >93%), moderate, severe disease	HCQ + azithro (n=735) HCQ alone (n=271) Azithro alone (n=211)	Neither (n=221)	In-hospital mortality Cardiac arrest Abnormal ECG findings	**HCQ vs Neither** In-hospital death (HR): 1.08 (0.63-1.85) Cardiac arrest (OR): 1.91 (0.96-3.81) Abnormal ECG findings (OR): 1.50 (0.88-2.58)
Yu	Cohort n=550	Critically-ill adult patients with confirmed SARS-CoV-2 infection by laboratory test/pathogenic test (n=550) critically ill requiring mechanical ventilation	HCQ 200 mg BID for 7 to 10 days (n=502)	No HCQ (n=48)	Death (60-day fatality) Inflammatory cytokine levels	Death (60-day fatality) HR: 0.36; 95% CI: 0.18–0.75; P=0.006)