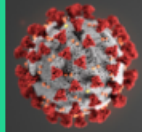


COVID-19 Science Update



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SPECIAL TOPIC: Hydroxychloroquine/Chloroquine and COVID-19

EXECUTIVE SUMMARY

U.S. and international efforts are underway to study the utility of hydroxychloroquine and chloroquine to prevent and treat COVID-19. Human data about these drugs' safety and effectiveness are limited at present to four small clinical studies of hydroxychloroquine as treatment. Two of the studies, one of which is pending peer review, demonstrated a possible benefit but both studies have methodologic limitations that in one case are substantial. The third study, which was randomized but limited in sample size, found no benefit. The fourth study, a small clinical case series, observed no clinical improvement and limited viral clearance among hydroxychloroquine-treated COVID-19 patients. Large randomized trials are needed to determine the efficacy and safety of these drugs for COVID-19.

BACKGROUND

Chloroquine (CQ) and hydroxychloroquine (HCQ) are used to treat malaria; HCQ is also used to treat rheumatoid arthritis and systemic lupus erythematosus. Both drugs have side effects and can cause a fatal heart rhythm disturbance ([QT prolongation](#) leading to [torsades de pointes](#)), especially when combined with other drugs that also prolong the cardiac QT interval (e.g., azithromycin).

[Multiple clinical trials](#) are planned, or ongoing, to investigate the potential efficacy and safety of CQ and HCQ as treatment for COVID-19. On March 29, 2020, the FDA issued an [Emergency Use Authorization \(EUA\)](#) for CQ and HCQ as treatment for COVID-19 in hospitalized adolescents and adults for whom a clinical trial is not available or participation is not feasible. Additionally, New York plans to distribute these drugs to severely ill patients through hospital networks, and some physicians have been prescribing HCQ for off-label treatment and prophylaxis. To date, CDC is aware of one [death](#) related to self-administration of non-pharmaceutical CQ.

In this issue, we summarize the existing human clinical data on HCQ to treat COVID-19. To date, no study has assessed CQ to treat persons with COVID-19 or the use of either CQ or HCQ to prevent infection with SARS-CoV-2, the virus that causes the illness COVID-19.

PEER-REVIEWED

[Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial](#). Gautret *et al.* IJAA 2020 (Mar 20, 2020)

Key findings:

- 70% of patients treated with HCQ (n=20) exhibited viral clearance of SARS-CoV-2 RNA in nasopharyngeal swabs within six days compared with 12.5% of control patients (n=16, p=0.001) (Figure).
- Six patients treated with HCQ also received azithromycin to prevent bacterial super-infection; all demonstrated virologic clearance within six days.

Methods: Non-randomized open-label trial from France that compared hospitalized patients treated with HCQ 200 mg three times daily (600 mg) for 10 days (n=20, of whom 6 also received azithromycin) with a hospitalized convenience sample (n=16). **Limitations:** Small sample size, control group included patients who declined HCQ treatment or were treated at other hospitals without a standard management protocol across sites; of 26 patients initially enrolled in the HCQ arm, 6 were excluded in the analysis due to death (n=1), ICU admission (n=3), and voluntary withdrawal (n=2); unclear whether the two arms were enrolled at the same points in their disease course; no data on clinical outcome or toxicity presented. These limitations are further discussed by [Kim et al.](#) and [Dahly, Gates, and Morris.](#)

Implications: The findings reported from this small, non-randomized trial found a possible benefit of HCQ for COVID-19 treatment, but the study has substantial limitations and must be interpreted with substantial caution.

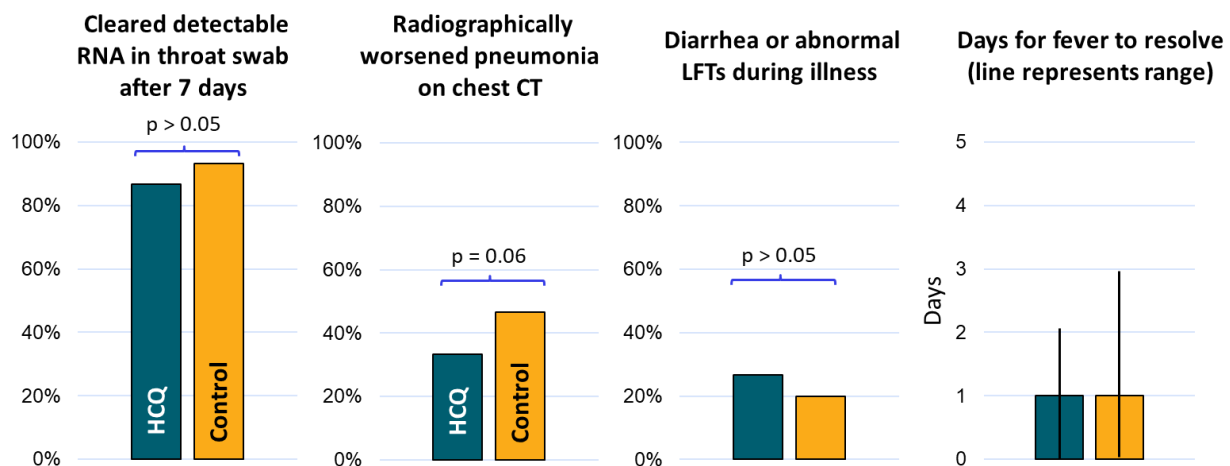
A pilot study of hydroxychloroquine in treatment of patients with common coronavirus disease-19 (COVID-19). Chen J *et al.* J Zhejiang Univ [Chinese][abstract in English] (Mar, 2020)

Key findings:

- Patients treated with HCQ (n=15) compared with control patients (n=15) demonstrated no significant difference in viral clearance by throat swab after 7 days (87% vs. 93%, $p > 0.05$).
- No differences were observed in median duration of hospitalization, time to defervescence, or adverse events (i.e., transient diarrhea or abnormal liver function tests).

Methods: Randomized open-label trial of HCQ 400 mg daily for five days plus conventional therapy vs. conventional therapy (control arm) among 30 treatment-naïve hospitalized patients with COVID-19 in Shanghai. Response assessed using throat swabs tested for SARS-CoV-2 RNA. **Limitations:** Small sample size; conventional therapy undefined.

Implications: The findings reported from this small randomized trial found that HCQ was not effective for COVID-19 treatment.



Note: adapted from Chen J *et al.* CT = computed tomography. HCQ = hydroxychloroquine. LFTs = liver function tests

[No evidence of rapid antiviral clearance or clinical benefits with the combination of hydroxychloroquine and azithromycin in patients with severe COVID-19 infection.](#) Molina *et al.* *Médecine et Maladies Infectieuses* (Mar 30, 2020)

Key findings:

- Among 11 patients treated with HCQ and azithromycin, 1 died, 2 were transferred to the ICU, and 1 was discontinued from the study due to dangerous cardiac QT prolongation.
- Among 10 surviving patients, 8 had detectable virus at least five days after starting treatment.

Methods: Clinical case series of 11 hospitalized patients with severe COVID-19, many with medical comorbidities: obesity (n=2), solid cancer (n=3), hematological cancer (n=2), HIV (n=1). All were administered HCQ (600 mg/day for 10 days) and azithromycin (500 mg on day 1 and 250 mg daily during days 2–5). Ten had fever and received supplemental O₂. **Limitations:** Small sample size; not randomized; no comparison group; no blinding; no description of baseline illness severity; limited data on clinical outcomes.

Implications: In this small, clinical case series of 11 patients treated with HCQ and azithromycin, a substantial fraction experienced severe outcomes from COVID-19; few of the surviving patients cleared the virus after five days of treatment.

PREPRINTS (NOT PEER-REVIEWED)

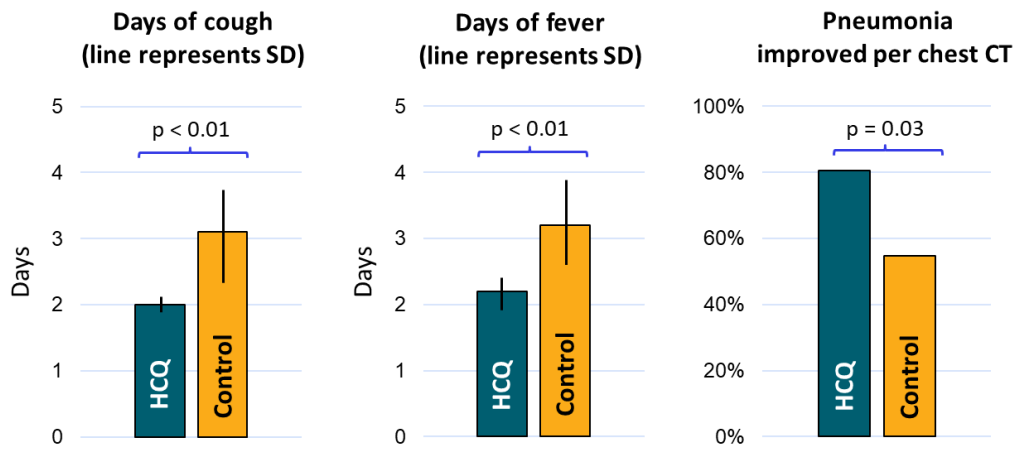
[Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial.](#) Chen Z *et al.* *medRxiv* (Mar 30, 2020).

Key findings:

- Patients treated with HCQ (n=31) compared with control patients (n=31) experienced a shorter duration of fever (2.2 vs. 3.2 days, $p < 0.01$) and cough (2.0 vs. 3.1 days, $p < 0.01$), and demonstrated greater radiographic improvement in pneumonia by chest CT (81% vs. 55%, $p = 0.03$)(Figure).
- No persons treated with HCQ progressed to severe illness (severe illness not defined) whereas 13% of control patients progressed. Among HCQ-treated patients, 6% experienced an adverse event (rash and headache) compared with none of the control patients.

Methods: Randomized trial of HCQ (200 mg twice daily for 5 days) plus standard therapy (supplemental O₂, antiviral agents, antibacterial agents, and immunoglobulin ± steroids) vs. standard therapy alone (control arm) among adults hospitalized with mild (SaO₂ >93%) COVID-19-associated pneumonia in Wuhan. Multiple reasonable exclusion criteria applied. **Limitations:** Small sample size; no viral burden data included; no description of randomization/enrollment; baseline severity of radiographic changes not described; inclusion of electrocardiogram (ECG) data would increase quality of the safety evidence.

Implications: The findings reported from this small unblinded randomized trial found that HCQ use was associated with improved clinical status. Data regarding SARS-CoV-2 burden were not reported.



Note: adapted from Chen Z *et al.* CT = computer tomography. HCQ = hydroxychloroquine. SD = standard deviation.

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