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Erisa Alia, MD, Jane M. Grant-Kels, MD, FAAD

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Does Hydroxychloroquine Combat COVID-19?

A Timeline of Evidence

By

Erisa Alia, MD and Jane M. Grant-Kels, MD, FAAD*

University of CT Dermatology Department

*Corresponding author: Jane M. Grant-Kels,
UCONN Dermatology Dept, 21 South Rd, Farmington, CT 06032
grant@uchc.edu

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Chloroquine (CQ) and hydroxychloroquine (HCQ) garnered scientific attention in early February following publication of reports showing in vitro activity of CQ against Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) or COVID-19. [1] On February 17, 2020, the State Council of China held a news conference indicating that chloroquine (CQ), had demonstrated efficacy in treating COVID-19 associated pneumonia in multicenter, non-randomized, clinical trials. [2, 3] This prompted multiple clinical trials in China (9 as of April 3rd). [4] Gao et al treated >100 patients with CQ reporting control in inhibiting the exacerbation of pneumonia, improved lung imaging findings and shortened disease course but detailed data underlying the claims have not yet been published. [3]

Hydroxycholoroquine (HCQ), an analogue of CQ with fewer side effects, better safety profile and less drug interactions, showed in vitro antiviral activity against SARS-CoV in the previous SARS outbreak. [5] Yao et al, compared the in vitro anti-SARS-CoV-2 activity of both drugs finding HCQ superior to CQ, recommending HCQ sulfate 400 mg twice daily on day 1, followed by 200 mg twice daily for the next 4 days to treat COVID-19. [6] Similar in vitro results were reported by the Wuhan Institute of Virology. [7] As the epicenter of COVID-19 shifted from China to Europe, Colson et al recommended use of HCQ as a possible prophylaxis and curative treatment for COVID-19. [8, 9]

Gautret, et al, were the first to report promising in vivo data of HCQ in a non-randomized clinical trial. [10] They used 200 mg of HCQ three times a day for 10 days, plus azithromycin (AZM) if deemed necessary. A higher frequency of SARS-CoV-2 clearance was noticed after 6 days of treatment with HCQ alone or HCQ+AZM versus the untreated control group (70% vs 12.5%; P<0.001). AZM added to HCQ was significantly more efficient for virus elimination. These findings were rapidly disseminated by the lay press and social media, leading to endorsement of HCQ by many government and institutional leaders, including President Trump who referred to this as a “game changer”. The demand for HCQ increased exponentially leading to an overall shortage making prescription refills challenging. [11, 12]

On March 31st, medRxiv.org published data of the first completed randomized clinical trial in Wuhan investigating the efficacy of HCQ in patients with COVID-19. 62 patients were randomized equally into two groups. The treatment group received oral HCQ 400mg/d (200 mg/bid) from day 1 to 5. Their article, currently under revision, reported significant difference in time to clinical recovery (TTCR) and radiologic findings between the groups. [13] (Table 1)

To date, despite enough rationale to justify investigation into the efficacy and safety of HCQ in COVID-19 (Table 2) [14, 15], the evidence regarding its effect remains limited. HCQ has not yet received FDA approval for use against COVID-19 and further trials are needed to establish guidelines. If emerging data from ongoing trials establishes the efficacy of HCQ for prophylaxis and treatment of COVID-19, **triage will be important to ensure that existing supplies are used appropriately.**

Table 1 summarizes the findings on the first randomized trial using HCQ against COVID-19 [13]

Endpoints	Treatment arm	Control arm
Body temperature recovery time*	2.2 days	3.2 days
Cough remission*	2 days	3.1 days
Chest computed tomography results improvement*^	80.6%	54.8%

* results are statistically significant

^ comparing results on day 0 and day 6

Table 2 summarizes the antiviral mechanism of action of CQ and HCQ. [14, 15]

Mechanism	Effect
halt the glycosylation of ACE2R	reduce binding of spike protein of coronavirus to ACE2R on host cell
increase the endosomal and lysosomal ph	prevent fusion of the virus with host cells and subsequent replication
prevent antigen processing and MHC-II-mediated autoantigen presentation to T cells	reduce T cells activation, expression of CD154 and other cytokines (IL-1, IL-6 and TNF α)
disrupts the interaction of cytosolic viral DNA/RNA with TLRs and the nucleic acid sensor cGAS*	halts transcription of pro-inflammatory genes attenuating the possibility of cytokine storm (type I interferons, IL-1, TNF α)

*HCQ only

Abbreviations: ACE2R: Angiotensin converting enzyme 2 receptor; MHC: major histocompatibility complex; TLR: toll-like receptor; cGAS: cyclic GMP-AMP) synthase; IL: interleukin; TNF α: tumor necrosis factor alpha

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