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.

Does hydroxychloroquine combat COVID-19? A timeline of evidence

To the Editor: Chloroquine (CQ) and hydroxychloroquine (HCQ) garnered scientific attention in early February after 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, nonrandomized, clinical trials.[2,3] This prompted multiple clinical trials in China (9 as of April 3, 2020).[4] Gao et al[3] 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.

Hydroxychloroquine (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[6] compared the in vitro anti–SARS-CoV-2 activity of both drugs, finding HCQ superior to CQ and 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. 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[8,9] recommended use of HCQ as a possible prophylaxis and curative treatment for COVID-19.

Gautret et al[10] were the first to report promising in vivo data of HCQ in a nonrandomized clinical trial. They used 200 mg of HCQ 3 times a day for 10 days, plus azithromycin if deemed necessary. A higher frequency of SARS-CoV-2 clearance was noticed after 6 days of treatment with HCQ alone or HCQ plus azithromycin vs the untreated control group (70% vs 12.5%; $P < .001$). Azithromycin 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 and making prescription refills challenging.[11,12]

On March 31, 2020, medRxiv.org published data of the first completed randomized clinical trial in Wuhan investigating the efficacy of HCQ in patients with COVID-19.[13] The trial randomized 62 patients equally into 2 groups. The treatment group received oral HCQ 400 mg/d (200 mg twice daily) from day 1 to 5. Their article, currently under revision, reported a significant difference in the time to clinical recovery and radiologic findings between the groups (Table I).[13]

To date, despite enough rationale to justify investigation into the efficacy and safety of HCQ in COVID-19 (Table II),[14,15] the evidence regarding its effect remains limited. HCQ has not yet received United States Food and Drug Administration 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.

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

From the Dermatology Department, University of Connecticut, Farmington, Connecticut.

Funding sources: None.

Conflicts of interest: None disclosed.

IRB approval status: Not applicable.

Reprints not available from the authors.

Correspondence to: Jane M. Grant-Kels, MD, UConn Dermatology Dept, 21 South Rd, Farmington, CT 06032

E-mail: grant@uchc.edu

Table I. Summary of the findings on the first randomized trial using hydroxychloroquine against COVID-19[13]

End points	Treatment arm	Control arm
Body temperature recovery time, d*	2.2	3.2
Cough remission, d*	2	3.1
Chest computed tomography results improvement, %*,†	80.6	54.8

*Results are statistically significant.
†Comparing results on day 0 and day 6.

Table II. Summary of the antiviral mechanism of action of chloroquine and hydroxychloroquine[14,15]

Mechanism	Effect
Halts the glycosylation of ACE2R	Reduces binding of spike protein of coronavirus to ACE2R on host cell
Increases the endosomal and lysosomal pH	Prevents fusion of the virus with host cells and subsequent replication
Prevents antigen processing and MHC-II–mediated autoantigen presentation to T cells	Reduces T-cell activation and 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 proinflammatory genes attenuating the possibility of cytokine storm (type I interferons, IL-1, TNF-α)

ACE2R, Angiotensin-converting enzyme 2 receptor; *cGAS*, cyclic guanosine monophosphate- adenosine monophosphate synthase; *IL*, interleukin; *MHC*, major histocompatibility complex; *TLR*, Toll-like receptor; *TNF*, tumor necrosis factor.
*Hydroxychloroquine only.

REFERENCES

1. Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res*. 2020;30(3):269-271.
2. Audio transcript of the news briefing held by the State Council of China on February 17, 2020 [in Chinese]. The National Health Commission of the People's Republic of China. Available at: http://www.nhc.gov.cn/xcs/yqfkdt/202002/f12a62d10c2a4 8c6895cedf2faea6e1f.shtml. Accessed February 18, 2020.
3. Gao J, Tian Z, Yang X. Breakthrough: chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. *Biosci Trends*. 2020;14(1):72-73.
4. Chinese Clinical Trial Registry (CHICTR). Available at: http://www.chictr.org.cn/searchprojen.aspx?title=hydroxychloroquine&officialname=&subjectid=&secondaryid=&applier=&studyleader=&ethicalcommitteesanction=&sponsor=&studyailment=&studyailmentcode=&studytype=0&studystage=0&studydesign=0&minstudyexecutetime=&maxstudyexecutetime=&recruitmentstatus=0&gender=0&agreetosign=&secsponsor=&regno=&regstatus=1008001&country=&province=&city=&institution=&institutionlevel=&measure=&intercode=&sourceofspends=&createyear=0&isuploadrf=&whetherpublic=&btngo=btn&verifycode=&page=1. Accessed April 3, 2020.
5. Biot C, Daher W, Chavain N, et al. Design and synthesis of hydroxyferroquine derivatives with antimalarial and antiviral activities. *J Med Chem*. 2006;49(9):2845-2849.
6. Yao X, Ye F, Zhang M, et al. In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). *Clin Infect Dis*. 2020. https://doi.org/10.1093/cid/ciaa237. [Epub ahead of print].
7. Liu J, Cao R, Xu M, et al. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. *Cell Discov*. 2020;6:16.
8. Colson P, Rolain JM, Raoult D. Chloroquine for the 2019 novel coronavirus SARS-CoV-2. *Int J Antimicrob Agents*. 2020;55(3):105923.
9. Colson P, Rolain JM, Lagier JC, Brouqui P, Raoult D. Chloroquine and hydroxychloroquine as available weapons to fight COVID-19. *Int J Antimicrob Agents*. 2020. https://doi.org/10.1016/j.ijantimicag.2020.105932. [Epub ahead of print].
10. Gautret P, Lagier JC, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int J Antimicrob Agents*. 2020. https://doi.org/10.1016/j.ijantimicag.2020.105949. [Epub ahead of print].
11. Mahase E. Covid-19: six million doses of hydroxychloroquine donated to US despite lack of evidence. *BMJ*. 2020;368:m1166.
12. Kim AHJ, Sparks JA, Liew JW, et al. A rush to judgment? Rapid reporting and dissemination of results and its consequences regarding the use of hydroxychloroquine for COVID-19. *Ann Intern Med*. 2020. https://doi.org/10.7326/M20-1223. [Epub ahead of print].
13. Chen Z, Hu J, Zhang Z, et al. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. medRxiv Available at: https://doi.org/10.1101/2020.03.22.20040758. Accessed April 3, 2020.
14. Zhou D, Dai SM, Tong Q. COVID-19: a recommendation to examine the effect of hydroxychloroquine in preventing infection and progression. *J Antimicrob Chemother*. 2020. https://doi.org/10.1093/jac/dkaa114. [Epub ahead of print].
15. Devaux CA, Rolain JM, Colson P, Raoult D. New insights on the antiviral effects of chloroquine against coronavirus: what to expect for COVID-19? *Int J Antimicrob Agents*. 2020. https://doi.org/10.1016/j.ijantimicag.2020.105938. [Epub ahead of print].

https://doi.org/10.1016/j.jaad.2020.04.031