

Chloroquine and Hydroxychloroquine in SARS-Cov-2. Repurposing the old drugs against today's deadly disease

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Abstract

Introduction: Chloroquine (CQ) and Hydroxychloroquine (HCQ) has received huge momentum as possible treatment for COVID-19. In India the drug is approved for prophylaxis of asymptomatic health workers treating suspected or confirmed COVID-19 cases, and asymptomatic household contacts of confirmed patients. The U.S. Food and Drug Administration (FDA) has issued Emergency Use Authorization (EUA) of HCQ to treat COVID-19.

Materials and Methods: Here we present the database of trials with these compounds in COVID-19.

Discussion: Early 15 registered clinical trials of CQ and HCQ in COVID -19 positive patients in China, showed that the drugs were superior to the control treatment in inhibiting the exacerbation of pneumonia, improving lung imaging findings, promoting a virus-negative conversion, and shortening the disease course. Some studies had no positive results including a multinational registry analysis of HCQ with or without a macrolide for treatment of COVID-19 published online in Lancet on 22nd May 2020. The study showed that there was decreased in-hospital survival and an increased frequency of ventricular arrhythmias when HCQ was used for treatment of COVID-19. In the light of this publication the WHO temporarily paused the HCQ arm of its 'Solidarity' global clinical trial on 26th May 2020 and trials with HCQ /CQ for COVID were also suspended. The Lancet paper was in controversy until finally on June 4th 2020 the article was retracted by authors.

Conclusions: Until we get results of WHO fast track 'Solidarity' clinical trial and other randomized clinical trials repurposing these drugs remains questionable.

Keywords: CQ/COVID-19 pandemic, Corona 'Solidarity' trial, Severe acute respiratory syndrome.

Introduction

Novel coronavirus (2019-nCoV), formally known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the etiological agent of the Corona Virus Disease 2019 (COVID-19) which emerged in Wuhan, Hubei province, China in December 2019. SARS-nCoV- 2 is a new emerging single-stranded, positive sense enveloped RNA member of family coronaviridae, order Nidovirales. It is the seventh human coronavirus described to date as being responsible for respiratory infection. COVID-19 has spread rapidly, put a lot of lives at risk with cases now confirmed in several countries. As of June 5th, 2020, the virus has caused 227029 confirmed infections and 6363 deaths in India. On 11th March 2020, the World Health Organization (WHO) declared this disease as pandemic.¹ The universal virulent disease pressurized clinicians and the Food and Drug Administration (FDA)

to act speedily to make medications available to the COVID -19 patients. The broad-spectrum antiviral effects of the antimalarial drugs chloroquine phosphate (CQ) and hydroxychloroquine sulphate (HCQ) warranted particular attention for repurposing this drug in the therapy of the disease.² Thus the age old anti-malarial drugs CQ and HCQ have been making headlines as possible treatments for the new SARS-CoV-2 infection. HCQ is already marketed for other conditions, so physicians were allowed to prescribe it off-label (means a medication is being used in a manner not specified in the FDA's approved packaging label or insert) to patients with Covid-19 even before the Emergency Use Authorization (EUA) or Centers for Disease Control and Prevention (CDC) dose recommendations were issued. The availability of some observational data from current ongoing trials regarding the possibility that the anti-malarial drugs may have

activity against SARS-CoV-2, the US President Donald Trump declared these drugs as “game changer” in addressing the pandemic, he openly encouraged patients to take the drugs and suggested he might do so himself, despite having tested negative for the virus³ It is matter of concern when the Head of the State of USA creates exceedingly positive insight of the effectiveness of HCQ among the public which led to high demand, short supply of these drugs in pharmaceuticals of entire world. After Trump’s statement, on 28 March 2020, the FDA authorized the use of HCQ and CQ under an EUA. The treatment has not been approved by the FDA's clinical trials process and is authorized under the EUA only as an experimental treatment for emergency use in patients who are hospitalized but are not able to receive treatment in a clinical trial. The CDC stated, the use, dosing, or duration of HCQ for prophylaxis or treatment of SARS-CoV-2 infection are not yet established.⁴

In India, HCQ is prescribed as a chronic therapy for patients suffering from lupus and rheumatoid arthritis, an auto immune disease and is available for over the counter (OTC) sale. The publicity of HCQ related to COVID – 19 has led to widespread off-label prescribing by medical doctors and dentists, including for themselves and their families. Reports have emerged that several common people were rushing to chemist shops to self medicate. The off –label prescribing and OTC use for COVID-19 raised important safety concerns. On 27th March 2020, Ministry of Health through a special amendment has categorized HCQ drug as a schedule H1 drug- which means it cannot be sold over the counter. The move came as reports emerged of hoarding and shortage of this drug due to the national lockdown, however the hoarding and shortage took place after the Indian Council of Medical Research (ICMR) recommended the drug for front line workers and high risk people who were in contact with the Covid-19 patient. To regulate and restrict the sale and distribution of the drug HCQ during this pandemic the Ministry in exercise of the powers conferred by Section 26B of the Drugs and Cosmetics Act, 1940 (23 of 1940), the Central Government has directed that sale by retail of any preparation containing the drug HCQ shall be in accordance with the conditions for sale of drugs specified in Schedule H1 to the Drugs and Cosmetics Rules, 1945.

India is the world's largest manufacturer of HCQ. It recently banned exports saying the stocks were needed for Indians, but the government lifted the ban on 7th April 2020 and said it would supply the drug to nations badly affected by the corona virus and neighboring countries to help out during the pandemic. This happened after US President Donald Trump has hyped HCQ as a possible cure for Covid-19 and also requested India to help with the supply. On 25th April 2020, FDA issued fresh guidelines, cautioning people against OTC use of HCQ and CQ for Covid-19 outside of the hospital setting or a clinical trial due to the risk of heart rhythm problems. It also stated that risks may increase when the drugs are combined with the antibiotic.

Materials and Methods

We meticulously searched the Pub Med database in addition also pooled the currently on-going trials with both these compounds against the COVID-19 up till 5th June 2020 and picked up the articles (published or pre-proof /pre-print) and news letters published on chloroquine / hydroxychloroquine and COVID-19 to discuss the usage of these drugs in relation to treatment and chemoprophylaxis of COVID-19.

Discussion

Chloroquine and hydroxychloroquine

CQ was approved by the FDA in 1949 while HCQ was approved in 1955 for prevention and treatment of malaria. HCQ in addition is also approved for long-term use in rheumatoid arthritis and lupus. Side effects of CQ and HCQ are irreversible visual changes, long QT or QT prolongation, muscle weakness or nerve pain, hypoglycemia, worsening of psoriasis Addition of hydroxyl molecule makes HCQ less permeable to blood-retinal barrier and allows faster clearance from retinal pigment cell, thereby suggesting a lesser risk of retinal toxicity with HCQ, as compared to chloroquine.⁵

Antiviral properties of CQ and HCQ

The anti-viral properties of CQ have been notably reported for SARSCoV-1,⁶ HCoV-229E in epithelial lung cell cultures^{7,8} HCoV-O43.⁹ Multiple mechanisms of action have been identified for CQ that disrupt the early stage of corona virus replication. CQ affects

immune system activity by mediating an anti-inflammatory response, which might reduce damage due to the exaggerated inflammatory response¹⁰ In the early in vitro studies by Wang M and colleagues it was found that chloroquine blocked SARS-nCoV- 2 infection.¹¹ HCQ was found to be more potent than CQ in the in-vitro studies.¹² Christian A. Devaux and colleagues in their review had given detailed diagrammatic description of CQ action on the novel coronavirus. CQ limits the biosynthesis of sialic acids that may be required for cell surface binding. SARS-CoV upregulates the expression of angiotensin converting enzyme 2 (ACE2) in lung tissue, a process that could accelerate their replication and spread CQ interferes with ACE2 receptor glycosylation thus preventing SARS-CoV-2 binding to target cells. CQ attempts to acidify the lysosomes and inhibits cathepsins. In addition, it also inhibits MAP Kinases thus inhibiting virus replication and alters M protein maturation alter virion assembly and budding.¹³

Clinical Trials of CQ and HCQ in COVID -19 positive patients

Studies with positive results

On March 16th 2020, Jianjun Gao and colleagues broke news of positive results of the initial 15 clinical trials registered under Chinese Clinical Trial Register carried out in different centres in China to test the efficacy and safety of CQ and HCQ in the treatment of COVID-19 associated pneumonia. More than 100 patients have demonstrated that CQ is superior to the control treatment in inhibiting the exacerbation of pneumonia, improving lung imaging findings, promoting a virus-negative conversion, and shortening the disease course. Severe adverse reactions to CQ were not noted in the aforesaid patients.¹⁴ Hereafter the Expert consensus and the Chinese medical advisory board has suggested CQ to be included in the SARS-CoV-2 treatment guidelines, issued by the National Health Commission of the People's Republic of China.^{15,16}

In the most discussed French open label non-randomized clinical trial, conducted in early march, 42 confirmed COVID -19 patients were, a total of 26 patients received 600mg of HCQ each day and 16 were control patients. The primary endpoint was virus

clearance at day-6 post-inclusion. Secondary outcomes were virological clearance overtime during the study period, clinical follow- up for body temperature, respiratory rate, long stay at hospital, mortality and occurrence of side-effects. Among HCQ -treated patients six patients received azithromycin (AZ) (500mg on day1 followed by 250mg per day, the next four days) to prevent bacterial super-infection under daily electrocardiogram control. Six patients in treatment group were lost to follow up so results of only 36 could be presented. The authors concluded that 20 cases treated in this study showed a significant reduction of the viral carriage at day 6-post inclusion compared to controls. AZ added to HCQ group were more efficient for virus elimination. The authors of this article stated that clinical follow-up and occurrence of side-effects in treatment group will be described in a further paper at the end of the trial.¹⁷ This study received widespread attention and criticism from some scientists carrying out similar type of study at other centers.

On 10th April 2020, Zhaowei Chen and co-scientists published the results of their randomized clinical trial, which they carried out in 62 COVID positive patients, 31 patients in control group received standard treatment (oxygen therapy, antiviral agents, antibacterial agents, and immunoglobulin, with or without corticosteroids) and 31 patients in the HCQ treatment group received additional oral HCQ 400 mg/d (200 mg/bid) between days 1 and 5. The study reported that the use of HCQ could significantly shorten the time to clinical recovery (TTCR) and promote the absorption of pneumonia. with only 2 patients having mild adverse reactions in the HCQ treatment group.¹⁸

Studies with unfavorable results

Michelle Fay Cortez carried out clinical study in 30 COVID-19 patients, 15 patients received 400 mg of HCQ for 5 days while another 15 patients did not receive HCQ. At the end of the study, 13(87%) patients who received HCQ tested negative for COVID-19 compared to 14 (93%) patients who also tested negative but did not receive the medication.¹⁹

A trial of AZ in addition to HCQ in COVID -19 patients carried out in France by J M Molina and colleagues found dissimilar results as compared previous ones and the author has criticized that HCQ has been

given too much of a high priority before there is enough evidence to show it is indeed effective.²⁰ but the study was short and, like another study above, did not have a control group to compare patients to.

In another multicenter, open-label, randomized controlled trial in China out of 150 patients hospitalized with COVID-19, seventy-five patients were assigned to HCQ plus standard-of-care (SOC) and 75 were assigned to SOC alone (control group). In the treatment group a loading dose of 1200 mg HCQ daily for three days followed by a maintained dose of 800 mg daily for the remaining days. The total treatment duration was 2 or 3 weeks for mild/moderate or severe patients, respectively. The primary end point, which was 28-day negative conversion rate was not different between SOC plus HCQ and SOC group. Negative conversion rate at day 4, 7, 10, 14 or 21 was also similar between the two groups. No different 28-day symptoms alleviation rate was observed between the two groups. The authors concluded that addition of HCQ did not result in a higher negative conversion rate but more alleviation of clinical symptoms than SOC alone in patients hospitalized with COVID-19 without receiving antiviral treatment, possibly through anti-inflammatory effects. Adverse events were significantly increased in HCQ recipients but no apparently increase of serious adverse events.²¹

Another most discussed is the retrospective study of COVID-19 patients treated till 11th April 2020 by Joseph Magagnoli and colleagues at Veterans Health Administration medical centers in U.S. Data of 368 veterans was divided into three groups, group 1 who received HCQ (n=97), group 2 who received HCQ plus AZ (n=113), group 3 who received the SOC. The two primary outcomes were death and the need for mechanical ventilation. Death rates were highest in the group that received HCQ alone (28%), followed by the group that received HCQ and AZ (22%). The group that did not receive had the lowest death rate (11%). With these outcomes the authors stressed and recommended the importance of awaiting for results of ongoing prospective, randomized, controlled studies before widespread adoption of these drugs.²² The study was criticized by other medical scientists working in similar trials because the patients who had more severe symptoms, which might partially explain the higher

death rates, were more likely to get medications. Patients in this study were above 65 years and male, which makes it difficult to apply the results to everyone. Randomized studies with a diverse population are needed to better understand the role of HCQ in COVID-19.

To overcome the pressure on health care system the WHO has launched fast track “Solidarity” an international clinical trial to find an effective and rationale treatment for COVID-19. In this single randomized trial, the patients are being enrolled which will help facilitate the rapid worldwide comparison of unproven treatments. This will overcome the risk of multiple small trials not generating the strong evidence needed to determine the relative effectiveness of potential treatments. Based on evidence from laboratory, animal and clinical studies the treatment options for this trial are SOC, Remdesivir, Lopinavir/ Ritonavir, Lopinavir/ Ritonavir plus Interferon beta -1a, CQ/HCQ.²³

A paper of multinational registry analysis by Mandeep R Mehra and colleagues published in Lancet on 22nd May 2020 hit the medical world as its results indicate that decrease in-hospital survival and an increased frequency of ventricular arrhythmias when used for treatment of COVID-19.²⁴ In the light of this publication the WHO temporarily paused the HCQ arm of its ‘Solidarity’ global clinical trial on 26th May 2020.

The paper was retracted by the Lancet on 4th June 2020 after a guardian investigation found inconsistencies in the data. WHO and several countries suspended randomized controlled trials of HCQ in COVID that were set up to find an answer. These trials are restarted.

Clinical Trials of CQ and HCQ for prophylaxis of COVID-19 infection

Use in prophylaxis is derived from available evidence of benefit as treatment and supported by in-vitro studies, preclinical data. No peer reviewed publication that evaluates either drug for exposure prophylaxis of SARS-CoV-2 infection is available.

In the United States and Europe, a handful of clinical trials have begun to test ways to keep health care workers and other vulnerable people safe from COVID-19.^{24,25}

A double-blind, randomized, placebo-controlled trial (NCT04303507) by Mathieu Gendrot and co-scientists will be initiated in May 2020 in health care settings in healthcare workers, or other individuals at significant risk who can be followed reliably for 5 months loading dose of 10mg base/kg, followed by 155 mg daily (250mg chloroquine phosphate salt or 200mg HCQ will be given for 3 months. Subsequent outcomes will be recorded episodes of symptomatic respiratory illness, including symptomatic COVID-19, clinical outcomes, and asymptomatic infection with the virus causing COVID-19 will be recorded during the follow-up period. If they are diagnosed with COVID-19 during the period of prophylaxis, they will continue their prophylaxis.²⁶

In India, the Indian Council of Medical Research(ICMR), under the Ministry of Health and Family Welfare, Government of India has recommended chemoprophylaxis with HCQ (400 mg twice on day 1, then 400 mg once a week thereafter for asymptomatic health-care workers treating patients with suspected or confirmed COVID-19, and for asymptomatic household contacts of confirmed cases.

Conclusions

This review highlighted the role of the well established drugs CQ and HCQ, in treatment and prophylaxis of COVID-19 through evidence of registered clinical trials. Some trials show positive results while others did not. The FDA authorized the use of HCQ and CQ under an EUA. Since the mass media plays a significant role, the knowledge is easily accessible to common man who can run to the pharmacy shop for medicating self. The government became cautious and took all right steps to avoid direct access of these medications in hand. To overcome the pressure on health care system the WHO has lunched fast track "Solidarity" an international multi-centric clinical trial to find an effective and rationale treatment for COVID-19. Until we get reports of this trial and other randomized confirmed clinical placement of these drugs in therapy of COVID remains questionable.

Source of Funding

None.

Conflict of Interest

None.

References

1. WHO Director-General's opening remarks at the media briefing on COVID-19- 11 March 2020
<https://www.who.int/dg/speeches/detail/>
2. Rome BN, Avorn J. Drug Evaluation during the Covid-19 Pandemic. *Perspect N Eng J Med* 2020:NEJM.org.
3. Marchione M "Game changer"? Trump-touted malaria drugs spur hope, shortages.
<https://www.washingtontimes.com/news/2020/mar/23/chloroquine-and-hydroxychloroquine->
4. Information for Clinicians on Investigational Therapeutics for Patients with COVID-19 updated on www.cdc.gov/coronavirus/ 2019.13 April 2020.
5. Marmor MF, Kellner U, Lai TY, Melles RB, Mieler WF. Recommendations on screening for chloroquine and hydroxychloroquine retinopathy. *American academy of ophthalmology* 2016. Revision ARTICLE IN PRESS
6. Japan Plans Alveco Clinical Trial for Coronavirus Academia.March 24 2020
7. Ansede M. Doscientos enfermos probarán un fármaco que ha bloqueado el coronavirus en minirriñones humanos. *EL PAÍS* (in Spanish). Retrieved 3 April 2020.
8. Apeiron Biologics moves forward with APN01 for treatment of COVID-19". www.the.pharma.letter.com. Retrieved 3 April 2020.
9. Jump up to: Mélanie Meloche-Holubowski. Début d'une étude clinique pour tester un médicament contre les effets de la COVID-19. *Société Radio-Canada*. 22 March 2020
10. Savarino A, Boelaert JR, Cassone A, Majori G, Cauda R. Effects of chloroquine on viral infections: an old drug against today's diseases? *Lancet Infect Dis* 2003; 3: 722–27.
11. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res* 2020.30 (3): 269–71.
12. Yao X, Ye F, Zhang M, Cui C, Huang B, Niu. 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* 2020;9.
13. Devaux CA, Jean-Marc R, Colson P, Raoult D. New insights on the antiviral effects of chloroquine against coronavirus: what to expect for COVID-19? *International Journal of Antimicrobial Agent*. Article in press.accessed on 23rd April 2020.
14. 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.
15. Harrison C. Coronavirus puts drug repurposing on the fast track. *Nat Biotechnol* 2020.

16. Zhonghua Jie He He Hu Xi Za Zhi. Chloroquine in the treatment of novel coronavirus pneumonia Expert consensus on chloroquine phosphate for the treatment of novel coronavirus pneumonia [in Chinese]. 2020;43: 20th March 2020
17. Gautreta P, Raoult D, Jean-Christophe L, Parola P. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open label non-randomized clinical trial. *Int J Antimicrob Agent*. 20th March 2020.
18. Chen Z, Hu J, Zhang Z, Jiang S, Han S, Yan D et al, Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial medRxiv preprint. 10th April 2020
19. Cortez MF, Che C. Malaria Drug Chloroquine No Better Than Regular Coronavirus Care, Study Finds. Bloomberg (newsletter) 25th March 2020
20. Molina JM, Delaugerre C, Goff JL, Lima BM. No evidence of rapid antiviral clearance or clinical benefit with the combination of hydroxychloroquine and azithromycin in patients with severe COVID-19. *Médecine et Maladies Infectieuses*. 10.1016/j.medmal.2020.03.006.
21. Tang W, Cao Z, Han M, Wang Z. Hydroxychloroquine in patients with COVID-19: an open-label, randomized, controlled trial. medRxiv preprint. 14th April 2020.
22. Magagnoli J, Narendran S, Pereira F, Cummings T, Hardin JW, Sutton SS et al. Outcomes of hydroxychloroquine usage in United States veterans hospitalized with Covid-19. medRxiv preprint April 21, 2020
who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments
23. Mehra MR, Desai SS, Ruschitzka F, Patel AN. Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. www.thelancet.com. Published online on 22nd May 2020.
24. Retraction—Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. www.thelancet.com Published Online June 4, 2020
25. Principi N, Esposito S. Chloroquine or hydroxychloroquine for prophylaxis of COVID-19. *Lancet Infect Dis* 2020 Published Online April 17, 2020)
26. Chloroquine/ Hydroxychloroquine Prevention of Coronavirus Disease (COVID-19) in the Healthcare Setting (COPCOV)
<https://clinicaltrials.gov/ct2/show/NCT04303507>
27. Gendrot M, Javelle E, Daultel EL, Clerc A, Savinib H, Bruno Pradines Chloroquine as prophylactic agent against COVID-19? Journal Pre-proof: *Int J Antim Agent* 2020.

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