

Review Article

Therapeutic status of hydroxychloroquine in COVID-19: A review

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Abstract

Hydroxychloroquine (HCQ), a 4-aminoquinoline, is used worldwide mainly for its role in management of malaria and rheumatoid arthritis. In the present pandemic of coronavirus disease (COVID)-2019, the drug is being repurposed, based on its in vitro evidence of efficacy against coronavirus. There has been a lot of information, for and against the drug, and this review is an effort to bring forth the evidence and current understanding regarding role of HCQ in COVID-19. Clinical studies, case reports, and in vitro studies have generated conflicting results. There are concerns for use of HCQ because of the variable results and the known adverse effects like QT prolongation and hypoglycemia. In the current scenario, recommendations from Indian Council of Medical Research for use of HCQ in the prophylaxis of COVID-19 are being followed.

Keywords: COVID-19, hydroxychloroquine, repurposing

Introduction

Since the beginning of COVID-19 pandemic and till the time of writing this review, hydroxychloroquine (HCQ) has generated various medical and political controversies. In a span of 4 months, benefits and harms of HCQ have been discussed at all levels, from the White House in Washington, to Kremlin in Moscow, to Parliament House in New Delhi. The National COVID-19 Task Force started by Indian Council for Medical Research, India, has issued many advisory recommendations for the chemoprophylactic use of HCQ among high risk population.^[1] In March, 2020, US FDA issued an Emergency Use Authorization (EUA), which allowed the use of chloroquine phosphate and HCQ in certain hospitalized patients with COVID-19 when a clinical trial was unavailable, or participation in a clinical trial not feasible. However, on 15th June, 2020, US FDA revoked its earlier order as the legal criteria for EUA were not met at this time.^[2]

The EUA status to HCQ by US FDA and registration of numerous clinical trials (n=114, as of June, 2020) for use of HCQ for treatment and prophylaxis of COVID-19 started because of lack of any approved drug for COVID-19 and availability of historical evidence of antiviral actions of HCQ. The repositioning of HCQ is also strengthened by the availability of ample scientific evidence of efficacy, and safety kinetics of HCQ. However, there are concerns about the cardiovascular adverse effects, self-administration and lack of screening of glucose-6-phosphate dehydrogenase (G-6PD) deficient individuals in the population before initiation of prophylactic administration.

Hydroxychloroquine

Chloroquine (CQ) and HCQ are aminoquinolones, which have been used for various diseases for the past many decades. HCQ contains one hydroxylated N-ethyl substituents of CQ.

HCQ has high apparent volume of distribution (525 ± 158 L/kg), and is slowly released from tissues. HCQ accumulates in RBCs. Plasma clearance is 11.9 ± 5.4 mL/min/kg. The initial half-life is short, however, the elimination half-life is of 1–2 months, leading to accumulation in tissues.^[3] HCQ has an oral bioavailability of $79 \pm 12\%$; and is $45 \pm 3\%$ bound in plasma.^[4] Following chronic oral administration of HCQ, three metabolites namely, desethylhydroxychloroquine (DHCQ), desethylchloroquine (DCQ), and bidesethylhydroxychloroquine (BDCQ) have been reported in plasma, with DHCQ being the major metabolite.

The proposed mechanism of action of both CQ and HCQ in rheumatic diseases includes suppression of T-lymphocyte responses to mitogens, inhibition of leukocyte chemotaxis, stabilization of lysosomal enzymes, inhibition of DNA and RNA synthesis and trapping of free radicals.^[3] As an anti-malarial agent, CQ is a blood schizonticide, and acts by concentrating in the parasite food vacuole, and preventing biocrystallization.^[3] As an immunosuppressant, HCQ is proposed to suppress intracellular antigen processing and loading of peptides onto MHC class II molecules.^[3] The role of HCQ in COVID-19 or other viral infections has been based on its anti-inflammatory and anti-viral actions demonstrated in earlier *in vitro* and *in vivo* studies.^[5]

Therapeutic Uses

HCQ has been used in the treatment of uncomplicated malaria (*P. falciparum*, *P. malariae*, *P. ovale*, *P. vivax*); prophylaxis of malaria in geographic areas where chloroquine resistance is not reported; treatment of chronic discoid lupus erythematosus and systemic lupus erythematosus in adults; treatment of acute and chronic rheumatoid arthritis in adults; juvenile idiopathic arthritis; porphyria cutanea tarda (off-label use); polymorphous light eruption; dermatomyositis; sarcoidosis; oral lichen planus; chronic erythema nodosum; actinic reticuloid, actinic lichen planus, Sjogren's syndrome; dyslipidemia; type-2 diabetes mellitus and the latest inclusion to the list is COVID-19.

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Therapeutic status in the management of COVID-19

A large number of clinical trials have been initiated in different parts of the world to study the efficacy and safety of use of HCQ in treatment and prevention of COVID-19 infection. The results of most of these studies are awaited.

Role of HCQ in the treatment of COVID-19

The evidence of the efficacy of HCQ in the treatment of COVID-19 consists of *in vitro* studies, case reports, observational studies, small sample size clinical studies and one large multi-national registry. The early *in vitro* evidence shows that CQ blocks COVID-19 infection at low micromolar concentration, with a half-maximal effective concentration (EC_{50}) of 1.13 μ M.^[6] Another *in vitro* study found that HCQ ($EC_{50} = 0.72 \mu$ M) was more potent than CQ ($EC_{50} = 5.47 \mu$ M).^[7] Later, the Chinese authorities briefed that CQ phosphate has shown marked efficacy and acceptable safety in treating COVID-19 associated pneumonia in multicentric clinical trials in China. Results from clinical trials involving 100 patients had shown superiority of CQ phosphate over control in inhibiting the exacerbation of pneumonia, improving lung imaging findings, promoting a virus negative conversion and shortening the disease course.^[6]

The initial pilot study for use of HCQ was conducted in China on 30 treatment naïve COVID-19 positive patients. Patients were given HCQ 400 mg/day for 5 days along with conventional treatment and the control arm had just the conventional treatment. After 7 days, 86.7% cases from HCQ group and 93.3% cases from control group ($P > 0.05$) had negative COVID-19 nucleic acid swabs. The median duration from hospitalization to virus nucleic acid negative conversion and the median time for normalization of body temperature was comparable in both the groups. Other parameters like radiological progression and incidence of adverse events were not statistically different in both the groups.^[8]

In an observational study conducted among consecutive patients in a New York City hospital, association between the use of HCQ and intubation or death was examined. The results showed that out of 1,376 patients, over a median follow-up of 22.5 days, 58.9% received HCQ (600 mg twice on day 1, then 400 mg daily for a median of 5 days); 45.8% of the patients were treated within 24 h after presentation to the emergency department, and 85.9% within 48 h. HCQ treated patients were more severely ill at baseline than those who did not receive HCQ. Primary end-point event (intubation or death in a time-to-event analysis) was seen in 25.1% patients. However, the investigators did not find any significant association between HCQ use and intubation or death (HR, 1.04, 95% CI, 0.82–1.32).^[9]

On the other hand, a multicentric clinical study, conducted in France, found significant decrease in the viral load with the use of HCQ or HCQ plus azithromycin as compared to conventional treatment. Patients (age >12 years) suffering from SARS CoV-2 infection in one of the centers were administered HCQ 200 mg three times daily for 10 days ($n = 26$) and patients in other centers were considered as controls ($n = 16$). Six patients of HCQ group also received azithromycin (500 mg on day 1 and then 250 mg/day for next 4 days). Significantly higher percentage of patients from HCQ+ Azithromycin or HCQ alone group were virologically cured ($P = 0.001$). Although the clinical study has limitations of a small sample size, and short duration of study, yet, the results are an important evidence for advocating the role of HCQ in the treatment of COVID-19.^[10]

However, the publication and then retraction of results of a multinational registry analysis of use of HCQ or CQ with or without a macrolide from across the globe led to further uncertainty.^[11,12] The article was retracted within days as an independent third party peer review proposed by the authors was not allowed by the company owning the data of the registry.^[12]

On the other hand, two international clinical trials, SOLIDARITY trial and RECOVERY (Randomized Evaluation of COVID-19 thERapY) trial stopped the HCQ arm to study the effectiveness of different interventions for treatment of COVID-19.^[13,14] The initial results of RECOVERY trial show the benefits of low-dose dexamethasone in reducing the 28-day mortality rate by 17% (0.83 [0.74–0.92]; $P = 0.0007$), with highest benefit among patients requiring ventilator support.^[14] These results have been further strengthened by the meta-analysis of four randomized controlled trials and cohort studies and case series. The results showed that the data was insufficient to prove the benefit of HCQ or CQ to treat COVID-19.^[15] A list of completed clinical trials evaluating the role of HCQ in treatment of COVID-19 is mentioned in Table 1.

Role of HCQ in the prophylaxis of COVID-19

Al-Kofahi *et al.* tried the population pharmacokinetic models to find the prophylactic dose of HCQ for pre-exposure and post-exposure cases. Extrapolating data from healthy volunteers and malaria patients, they suggested a loading dose of HCQ (800 mg), followed by 400 mg twice or thrice weekly for pre-exposure prophylaxis. Similarly, for post-exposure prophylaxis, 800 mg loading dose, followed in 6 h by 600 mg, then 600 mg daily for 4 more days. Both these dosage schedules helped in maintaining drug concentration higher than the trough levels.^[16]

Table 1: Clinical trials evaluating the role of HCQ in treatment of COVID-19

Study Title/Study Design	No. of Participants (n)	Interventions	Primary Outcomes
Efficacy and Safety Of HCQ For Treatment of COVID-19 Open label Randomized Parallel Assignment Interventional Study.	30	HCQ	The virological clearance rate of throat swabs, sputum, or lower respiratory tract secretions at day 3; day 5; and day 7. The mortality rate of subjects at weeks 2
A Comparative Study Of Ivermectin And HCQ On COVID-19 Patients in Bangladesh Patient Registry	116	HCQ Ivermectin	Number of participants with “treatment success” determined by a negative RT PCR for COVID19. Number of participants with “adverse effects” determined by the existence of the pharmacological side effects of the particular drug during treatment.
Favipiravir plus HCQ and Lopinavir/ Rotinavir plus HCQ in COVID-19 Non- Randomized Parallel Assignment Interventional Study	40	Favipiravir Lopinavir HCQ Rotinavir	Mortality [Time Frame: Up to 28 days] In-hospital mortality Length of hospitalization Laboratory Treatment Response (Blood cell count and CRP); return of CRP values to normal Dyspnea Oxygen saturation without supplemental oxygen. Measurement will be done after discontinuation of oxygen therapy for 5 min. Requirement of Oxygen therapy
Treatment of COVID-19 Cases and Chemoprophylaxis Of Contacts Of The Patients Open Label Randomized Parallel Assignment Interventional Study Phase-3	2300	HCQ	Study 1- Clinical and virological outcome in exposed contacts. Incidence of secondary PCR confirmed symptomatic Covid-19 episodes among contacts after high risk PCR + exposure Study 1- Transmission of SARS-CoV-2 in exposed contacts. Incidence of symptomatically compatible or a PCR-positive result regardless of symptoms Study 2- Virological outcome in index cases Reduction of viral RNA load in nasopharyngeal swabs at days 3, and 7 after treatment start. Study 2- Clinical outcome in index cases
Safety And Efficacy Of HCQ Associated With Azithromycin in SARS-CoV2 Virus (Coalition COVID-19 Brazil II) Open Label Randomized Parallel Assignment Interventional Study Phase-3	400	HCQ Azithromycin	Evaluation of the clinical status of patients on the 15 th day after randomization defined by the Ordinal Scale of 6 points (score ranges from 1 to 6, with 6 being the worst score)
Anti-Infective Agents Impact In COVID-19 Pneumonia (AZITHROVID) Cohort Retrospective Observational Study	132	Azithromycin HCQ	Favorable outcome. After being admitted, patient was monitored whether he does not required to be transferred in ICU or died because of a severe COVID-19 pneumonia within 7 days. The outcome was purely clinical. If patient was discharged at home after admission and/or was transferred into a rehabilitation center he was considered as a favorable outcome independently of any biological marker.
An Investigation Into Beneficial Effects of Interferon beta 1a , compared to Interferon beta 1b and the base Therapeutic Regimen In Moderate To Severe COVID-19 Open label Randomized Parallel Assignment Interventional Study Phase-2	60	HCQ Lopinavir/Ritonavir Interferon Beta 1a Interferon Beta 1b	Time to clinical improvement. Improvement of two points on a seven-category ordinal scale
Convalescent Plasma Therapy on Critically Ill COVID-19 Patients Open Label Randomized Parallel Assignment Interventional Study	49	HCQ Azithromycin	Death versus survival of treated patients. Evaluate the role of convalescent plasma in saving life of treated patients by measuring the final outcome whether treated patients survived or died
Efficacy and Safety of Favipiravir in management of COVID-19 Open Label Randomized Parallel Assignment Interventional Study Phase-3	100	Favipiravir HCQ	Viral clearance. Two successive negative COVID-19 PCR analysis tests 48-72 hours apart Clinical improvement. Normal body temperature for 48 hours

Amidst the controversy of the beneficial role of HCQ for prophylaxis of COVID-19, Dausa *et al.* have presented a case report of a patient of rheumatoid arthritis who developed COVID-19 although she had been taking HCQ 200 mg/day for the last 3 years.^[17] Shah *et al.* systematically

reviewed the role of CQ and HCQ in preventing the spread of COVID-19.^[18] The authors concluded from three *in vitro* studies and two clinical opinions that, although, the pre-clinical data is promising, yet, there is lack of significant clinical evidence.^[18] Additionally, results of a randomized

double-blind placebo controlled trial conducted to study the role of HCQ in post-exposure prophylaxis of COVID-19 do not show the benefit of HCQ. Adults who had household or occupational exposure to confirmed COVID-19 patients were enrolled within 4 days of the exposure. There was no significant difference in incidence of new illness compatible with COVID-19 with administration of HCQ (800 mg once, followed by 600 mg in 6–8 h, then 600 mg daily for 4 additional days) as compared to placebo. The adverse effects were more common with HCQ than placebo.^[19]

The latest case-control study using the ICMR data shows an association of risk ($P = 0.087$) of SARS-CoV-2 infection with lack of HCQ prophylaxis; and the number of maintenance doses taken following the loading dose showed a protective dose–response relation. Administration of four or more maintenance doses showed a significant declining trend.^[20] ICMR has recommended that asymptomatic healthcare workers (HCWs) involved in the care of suspected or confirmed cases of COVID-19; and asymptomatic household contacts of laboratory confirmed cases should take the prophylactic dose.^[1]

Discussion

On one hand, the evidence available till now is deficient in proving the benefits of use of HCQ for both treatment and prophylaxis; and on the other hand, there is a risk of adverse effects with these drugs. The EUA by US FDA is for treatment of COVID-19 and there is no mention of use of HCQ for prophylaxis purpose.^[2] Various issues have been raised from the above mentioned clinical studies, reports and analyses. The treatment dose for COVID-19 was decided from the *in vitro* studies with use of population pharmacokinetic models.^[7] The conflicting evidence is not showing any decrease or increase in risk of composite end point of intubation or death with use of HCQ among COVID-19 patients.^[9] The clinical trials were not randomized as one of those had severely ill patients in HCQ group and other had older patients in HCQ group.^[9,10] The results of the multinational registry were retracted before those could become a part of any treatment algorithm.^[11,12] Additionally, the dose of HCQ in the registry was higher than that advised by ICMR for prophylaxis among Indian population.^[1,11]

In this difficult situation, the role of HCQ in COVID-19 treatment or prophylaxis has to be decided specifically for Indian population. Rathi *et al.* are not in favor of blanket approval for use of HCQ for prophylaxis, as it can create an over-optimistic perception; it can also lead to widespread self-medication; it can increase the risk of serious adverse effects, some of which can be fatal, and it can also lead to decrease in the supply of HCQ for its anti-malarial use.^[21]

On the other hand, there are views that use of HCQ (in doses routinely used for malaria prophylaxis) may prevent infection or the development of severe symptomatic disease.^[22,23] Additionally, the concerns of G-6PD deficiency (ranging from 0% to 100%); and risk of ventricular arrhythmias can be taken care of by administration to the eligible individuals only.^[23] The ICMR advisory has enumerated the eligibility criteria, the exclusion criteria and key considerations for use of HCQ as prophylaxis for SARS CoV-2 infection. HCQ should always be given under strict medical supervision with an informed consent; it should be prescribed by a registered medical practitioner and the physicians should always be consulted for any adverse event or potential drug interaction. Adverse drug reactions should be reported to the Pharmacovigilance centers set up across the country under Pharmacovigilance Program of India.^[1]

Needless to say only time will verify or contradict these findings as more data is being generated.

Conclusion

Amidst the fast changing health guidelines and reporting of new evidence, therapeutic status of HCQ in treatment and prophylaxis of COVID-19 is not yet clear. In the Indian set-up, the ICMR guidelines can be helpful as we may be able to flatten the epidemiological incidence curve of COVID-19 in our country.

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Conflicts of interest

Dr. Sandeep Kaushal is PI in ICMR study entitled "ICMR - RUMC COVID-19 Cohort study for the assessment of Hydroxychloroquine Prophylaxis in Healthcare Workers".

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