Hydroxychloroquine for COVID-19: What is Our Current State of Knowledge?

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ABSTRACT

Chloroquine and Hydroxychloroquine are drugs which have been widely used in malaria and rheumatoid arthritis respectively for over 50 years. There was anecdotal evidence of their efficacy in the earlier SARS outbreak in 2003. This prompted physicians from across the world to use them in the present SARS-CoV-2 pandemic that is currently sweeping the globe, with 5 million people already infected to date. These drugs are already in widespread use for the treatment of COVID-19 in India, mainly because they are cheap and easily available, and because of the absence of any readily available alternative therapy. This timely review discusses the pre-clinical evidence, and data from the eight available clinical trials. We emphasise that careful monitoring for cardiac toxicity is required when these drugs are used. Finally, we conclude that current data does not allow us to recommend for or against the use of these drugs. Results of two large RCTs, one from the NIH and the other from WHO (Solidarity) are eagerly awaited before the role of these drugs in COVID-19 can be definitively established.

"Hydroxychloroquine and Azithromycin taken together have a real chance to be one of the biggest game changers in the history of medicine"

Donald Trump. *President, USA*

"The evidence is anecdotal. The president is talking about hope".

Anthony Fauci, *Director, NIH.*

Chloroquine (CQ) is a widely used anti-malarial drug with immunomodulatory effects. Hydroxychloroquine (HCQ) is a more soluble and less toxic metabolite of chloroquine with fewer concerns about drug-drug interactions.[1,2] The molecular mechanism of action of chloroquine and hydroxychloroquine has not been fully elucidated. As both drugs are affordable and widely available, there has been a growing interest in the use of these agents as potential treatments for Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) till novel, specific treatments become available.

LEVELS OF EVIDENCE

1. ANECDOTAL: Doctors in Wuhan general Hospital made the intriguing observation that patients with SLE on HCQ did not seem to develop Covid-19. None of Wuhan hospital's dermatology department's 80 lupus patients were infected. They hypothesized that this may have been due to the long-term use of HCQ.[3]
2. IN VITRO STUDIES: The cellular evidence of CQ and HCQ is based on the observation that they elevate the pH at the surface of the cell membrane and thus, inhibit the fusion of the virus to the cell membrane. They also inhibit nucleic acid replication, glycosylation of viral proteins, virus assembly, new virus particle transport, and virus release thus achieving their antiviral effects.[4] CQ inhibits SARS-CoV entry by changing the glycosylation of ACE2 receptor and spike protein.[5] The in vitro study conducted after the SARS pandemic, caused by a very similar coronavirus (SARS-COV-1) in 2005,[6] demonstrated chloroquine to be effective in preventing the spread of SARS-CoV-1 in cell culture. Favourable inhibition of virus spread was observed when the cells were either treated with chloroquine prior to or after SARS-CoV-1 infection. Yao et al[1] conducted a similar in vitro study for SARS-CoV-2. Using PBPK (physiologically based pharmacokinetic) modelling and simulation techniques the optimal dosing regimen for hydroxychloroquine was evaluated in *in silico* models. HCQ exhibited a higher in vitro antiviral effect compared to chloroquine when the drug was added prior to the viral challenge. They also established the optimal dose of HCQ [400mg BD on D1 followed by 200mg BD D2-5] and demonstrated it reached a good concentration in lung tissue. They concluded based on their in-vitro model that HCQ was able to achieve treatment efficacy with a good safety profile. Wang et al[7] reported in vitro antiviral activity of CQ, with an EC50 (50% maximal effective concentration) of 1.13μM and an MOI (multiplicity of infection) of 0.05, and with high selectivity for SARS-CoV-2 rather than host cells.

   CQ and HCQ also have a host of pleiotropic effects including anti-platelet activity,[8] prevention of deep venous thrombosis[9] and a mouse model of antiphospholipid syndrome demonstrating partial prevention of endothelial dysfunction by HCQ.[10] These might prove significant with the emergence of case reports demonstrating coagulopathy and antiphospholipid antibodies in patients with COVID-19.
3. IN VIVO CLINICAL TRIALS: The first clinical evidence for the use of HCQ in the treatment of SARS-CoV-2 was reported in a news briefing by the Chinese Government. 62 COVID-19 positive patients with CT evidence of pneumonia hospitalised in Renmin hospital, Wuhan were included in this trial.[3] The patients had mild to moderate illness and were admitted in the ward (none in the ICU), needing around 3 L / min nasal oxygen. It was a parallel group trial in which 31 of the 62 patients were computer randomised to receive HCQ 200 mg bid for 5 days. Other standard treatment was unchanged in the 2 groups. The treatment group showed an overall faster clinical recovery as well as faster improvement in pneumonia on CT imaging (80% VS 54%). Crucially, none of the patients in the treatment group progressed to severe disease as opposed to 4 in the non HCQ group.

The second clinical study was a controversial study published by Gautret and colleagues from Marseilles, France.[2] In 80 hospitalized patients receiving a combination of hydroxychloroquine (200 mg of oral hydroxychloroquine sulphate, three times per day for ten days) and azithromycin (500mg on D1 followed by 250mg per day for the next four days), a clinical improvement was noticed in all but two elderly patients. A rapid fall of nasopharyngeal viral load tested by qPCR was noted, with 83% negative on Day 7 and 93% on Day 8. Virus cultures from patients' respiratory samples were negative in 97.5% patients by Day 5 allowing a rapid discharge of these patients from contagious wards after a mean stay of 5 days. This study was critiqued by scientists around the world. Hulme and colleagues applied a Bayesian reanalysis of the paper[11] and raised major concerns about the small size, the absence of a control limb, the fact that the physicians were not blinded, the obvious selection bias, and the inconsistently done PCR tests. Most glaringly, there had been 6 drop outs in the HCQ group (patients who had either died, needed ICU transfer, dropped out or had drug intolerance). These 6 results were surprisingly not included in the final analysis meaning Raoul "cured" only 100% of those patients who didn't get sicker, die or leave the study! To our minds this was a deeply flawed study and the journal in which it was published took the highly unusual step of saying "it did not meet the society's expected standards"[12].

Another multicentre, open-label, randomized, controlled trial conducted in China assessed the efficacy and safety of HCQ in adult patients with COVID-19.[13] The patients were assigned in a 1:1 ratio to receive either standard of care (SOC) or SOC plus HCQ [loading dose of 1200 mg daily for three days followed by a maintenance dose of 800 mg daily for the remaining days (total treatment duration: 2 weeks or 3 weeks for mild/ moderate or severe patients, respectively)].The negative conversion rate of SARS-CoV-2 among patients in the SOC plus HCQ group (85.4%) was similar to that of the SOC group 81.3% within 28 day. The negative conversion time did not differ between SOC plus HCQ and SOC group (median, 8 days vs. 7 days; P=0.341) .Compared to SOC alone, the addition of HCQ on SOC led to more rapid normalization of elevated baseline CRP(P=0.045) and recovery of baseline lymphocytopenia (P=0.547).

A more recent retrospective analysis of patients hospitalized with Covid-19 in the Veterans Health Administration medical centres across the United States analysed the associations between hydroxychloroquine and azithromycin (AZ) use and clinical outcomes[14]. The patients were categorized into three different groups based on the treatment received- HCQ (n=97), HCQ +AZ (n=113), or no HCQ (n=158). Compared to the no HCQ group (11.4%), there was a higher risk of death from any cause in the HCQ group (27.8%) (adjusted HR, 2.61; P=0.03) but not in the HCQ+AZ group (adjusted HR, 1.14; P=0.72). There was no significant difference in the risk of ventilation in either the HCQ group (adjusted HR, 1.43; P=0.48) or the HCQ+AZ group (adjusted HR, 0.43; P=0.09), compared to the no HCQ group.

These studies have highlighted the need for more robust clinical evidence before HCQ can be recommend in the treatment of SARS-CoV2 especially keeping in mind the potential side effects and drug interactions which it may lead to.

The recently published NIH guidelines for treatment of COVID-19[15] recommends against the use of hydroxychloroquine plus azithromycin outside of clinical trials because of the toxicity risk. It also mentions "insufficient clinical data to recommend either for or against using CQ or HCQ and if used, clinicians should monitor the patient for adverse effects especially prolonged QTc interval."

A recently published study from New York examined the association between HCQ use and intubation or death in 1376 patients hospitalized at a large medical centre.[16] They concluded that HCQ use was not associated with either a greatly lowered or increased risk of intubation or death stressing the need for further randomised controlled trials of HCQ in COVID-19 patients. The largest observational study, just published in JAMA[17] also showed that in 1438 patients hospitalized in 25 hospitals in New York, the use of HCQ and/or azithromycin had no impact on in-hospital mortality.

SOLIDARITY TRIAL: "Solidarity" is an international clinical trial launched by the World Health Organization (WHO) to help find an effective treatment for COVID-19 which will compare four treatment options against standard of care and to assess their relative effectiveness against COVID-19. HCQ is one of the arms in this trial to be used in a loading dose of 800mg BD, 6 hours apart followed by a maintenance dose of 400mg BD for 20 doses. Enrolling patients in one single randomized trial will help facilitate the rapid worldwide comparison of unproven treatments. Indeed, this may prove the final answer on the efficacy if any of this drug.

Doses of HCQ to be used: There has been no uniformity in the dose of HCQ used with different dosing schedules in each trial. The doses that have been employed are summarised in Table 1.

Table 1: Doses of HCQ used across different studies to date

Study	HCQ dosing	Azithromycin dosing (if used)	Remarks
In vitro study [1]	Optimal dose recommended: 400 mg BD on Day 1 followed by 200 mg BD for next 4 days	–	Positive study
Initial Chinese study[3]	200 mg BD for 5days	–	Positive study
French study[2]	200 mg TDS for 10 days	500 mg OD on Day1 followed by 250 mg OD for next 4 days	Controversial study
MOHFW (Ministry of Health & Family Welfare)[18]	400mg BD on Day1 followed by 200mg BD for next 4 days	500mg OD for 5 days	Based on evidence available till 31st March , 2020
Chinese open labelled RCT[19]	*Loading dose*:1200mg OD for 3 days *Maintenance dose* : 800mg OD for 2/3weeks (mild-moderate/severe cases respectively)	–	Negative study
CloroCovid-19 trial (High vs low dose CQ)[20]	*High dose*:600 mg/day twice daily for 10 days *Low dose*: 450 mg twice daily on 1st day and then once daily for four days	–	Recommendations against the use of high doses of CQ for severe SARS-CoV-2 because of safety concerns
SOLIDARITY trial	*Loading dose*: 800 mg BD (6 hours apart) on day1 *Maintenance dose*: 400 mg BD for 20 doses	–	Currently ongoing

PROPHYLAXIS

Despite lack of data on prophylaxis, the Indian Council of Medical Research has already recommended HCQ as pre-exposure prophylaxis for frontline healthcare workers having "high-risk" contact with patients with suspected or confirmed COVID-19 (400 mg twice a day on Day 1, followed by 400 mg once weekly for next 7 weeks), and post-exposure prophylaxis for household and healthcare worker contacts of patients with confirmed COVID-19 (400 mg twice a day on Day1, followed by 400mg once weekly for next 3 weeks).[18] The evidence for this dosing schedule is not clear. Several trials exploring the use of CQ or HCQ for prophylaxis of COVID-19 in health care workers (HCWs) are underway, in particular a large trial in Oxford called COPCOV which is a randomised, placebo-controlled prophylaxis Study (COPCOV)[21] using considerably higher doses of HCQ (a loading dose of 10 mg base/ kg followed 250mg chloroquine phosphate salt or 200mg of or hydroxychloroquine sulphate) to be taken daily for 3 months. It plans to recruit 40,000 HCWs and no definite conclusions on the utility of HCQ or chloroquine as a prophylactic agent can be drawn till this data is available. In addition, at present, there is no evidence to recommend mass prophylaxis at the population level.

SIDE EFFECTS AND TOXICITY

The World Health Organization lists HCQ as an essential medicine.[22] Majority of patients require no special caution except for patients with G6PD deficiency, diabetics and where significant drug interactions are likely. Long-term HCQ use can have adverse effects like cardiac arrhythmias (e.g., QT prolongation)[23] and retinal damage.[24] HCQ prevents the development of congenital heart block due to a potential inhibitory effect of type I interferon production and thus is safe in pregnant females.[25,26] In the French study[2] referred to earlier, patients receiving a combination of HCQ and azithromycin had only minor and rare side effects. Diarrhoea was the most common side effect, being seen in 4 of the 80 patients followed by nausea or vomiting (2/80) and blurred vision in one patient. In the trial conducted by Wei Tang et al,[13] a significantly higher dose of HCQ (1200 mg as loading dose and 800 mg daily as the maintenance dose) was used. Adverse events were accordingly significantly higher, being reported in 21 patients (30%) in the HCQ group compared to just 7 patients (8.8%) reporting side effects in the SOC group (P=0.001). No patients reported serious adverse events in the SOC group whereas 2 patients reported serious adverse events due to disease progression and upper respiratory infection.

Toxicity seems to be dose related which was demonstrated in a randomized, phase IIb clinical trial conducted by Borba et al.[20] They evaluated the effect of high doses (600 mg/day twice daily for 10 days) vs low doses (450 mg twice daily on 1st day and then once daily for four days) of chloroquine diphosphate as adjunctive therapy for patients hospitalized with SARS-CoV-2 Infection .They observed that 7 out of 37 patients in the high dosage group had QTc interval greater than 500 milliseconds as opposed to 4 in 36 patients in low dosage group. Ventricular tachycardia was seen in two patients in the high dosage group. Rhabdomyolysis developed in one patient which led to chloroquine discontinuation. These preliminary findings suggest that higher dosage of chloroquine should not be recommended for the treatment of severe COVID-19, especially among patients also receiving azithromycin and oseltamivir, because of safety concerns regarding QTc interval prolongation and increased lethality.

Chorin et al[27] conducted a retrospective study in 84 COVID-19 patients treated with a combination of HCQ and azithromycin. Baseline ECG monitoring was done to rule out any QT prolongation. QTc prolonged maximally from baseline between days 3 and 4. 30% of patients showed an increase in QTc by greater than 40ms. In 11% of patients QTc increased to >500 ms, representing high risk group for arrhythmia [the QTc increased from a baseline average of 447 ± 30 ms to 527 ± 17 ms (P < 0.01)]. There were no torsades de pointes events recorded for any patients, including those with a severely prolonged QTc. QTc should be regularly followed in patients who are treated with HCQ/AZ, particularly in those with co-morbidities and in those who are treated with other QT-prolonging medications.[28] Roden et al.[29] proposed mechanisms to minimize arrhythmia risk due to HCQ and Azithromycin use. They advised that if the baseline QTc interval is >500 msec or with known congenital long QT syndrome the drugs should be withheld and cardiac rhythm should be monitored. They also advised correction of hypokalaemia and hypomagnesemia. Recently a systematic review of 30 studies (28 ongoing) was published by Pacheo et al.[30] This rapid systematic review identified two clinical studies (with available data), with limited methodological quality, that evaluated the effects of hydroxychloroquine for COVID-19. They concluded that the efficacy and safety of HCQ and CQ in patients with COVID-19 is still uncertain and its routine use for this situation should not be recommended until the results of ongoing studies provide a proper assessment of their effects.

MONITORING FOR TOXICITY

Mount Sinai Health System in their treatment guidelines for SARS-CoV-2 infection has recommended a baseline ECG before initiation of HCQ to rule out any QT prolongation and to check for any other drugs causing QT prolongation which might aggravate the risk.[31] Based on the QTc interval their suggestions are mentioned in the figure below.

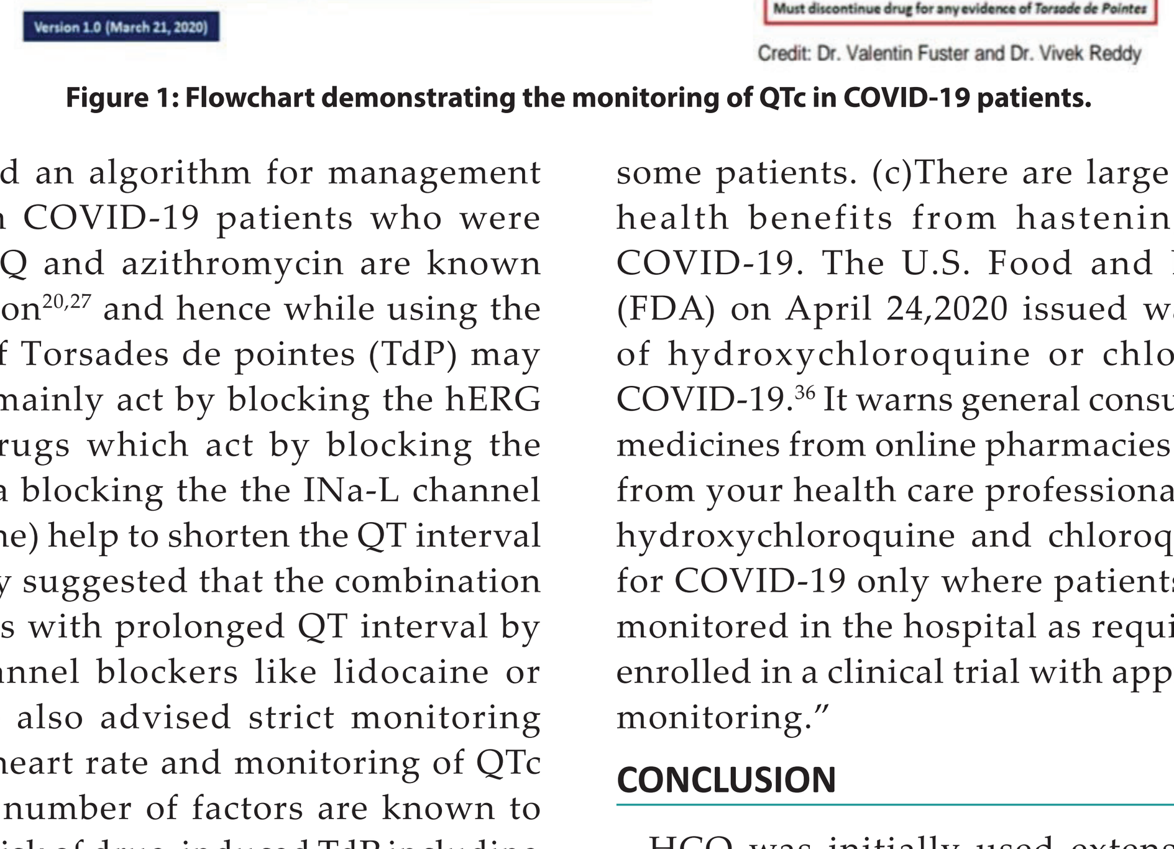

Figure 1: Flowchart demonstrating the monitoring of QTc in COVID-19 patients.

Mitra et al[32] proposed an algorithm for management of QT prolongation in COVID-19 patients who were hospitalized. Both HCQ and azithromycin are known to cause QT prolongation[20,27] and hence while using the combination the risk of Torsades de pointes (TdP) may increase. These drugs mainly act by blocking the hERG potassium channel. Drugs which act by blocking the late sodium current via blocking the the INa-L channel (lidocaine and mexiletine) help to shorten the QT interval and suppress TdP. They suggested that the combination can be given in patients with prolonged QT interval by using late sodium channel blockers like lidocaine or mexiletine. They have also advised strict monitoring of serum electrolytes, heart rate and monitoring of QTc interval using ECG. A number of factors are known to contribute to increased risk of drug-induced TdP including female sex, structural heart disease, congenital long-QT syndromes, electrolyte disturbances, hepatic/renal failure and concomitant QT prolonging medications.[33] The safety of QT prolonging medications may be maximized by close monitoring and optimization of these factors. A risk score has been derived and validated by Tisdale et al., for prediction of drug-associated QT prolongation among cardiac-care-unit-hospitalized patients. A Tisdale score of ≤ 6 predicts low risk, 7-10 medium risk, and ≥ 11 high risk of drug-associated QT prolongation.[34]

Concerns regarding mortality risk, and the intensity of QT and arrhythmia monitoring should be considered in the context of several important mitigating factors:[35] (a) The duration of use for these medications for COVID-19 infection is short (5 to 10 days for acute illness). (b) While QT-prolonging medication use has been associated with increased risk of death, this risk may be smaller than the potential benefit from treatment of COVID-19 for some patients. (c)There are large potential population-health benefits from hastening viral clearance of COVID-19. The U.S. Food and Drug Administration (FDA) on April 24,2020 issued warnings about the use of hydroxychloroquine or chloroquine for treating COVID-19.[36] It warns general consumers to "not buy these medicines from online pharmacies without a prescription from your health care professional." It also stresses that hydroxychloroquine and chloroquine "should be used for COVID-19 only where patients can be appropriately monitored in the hospital as required by the EUA or are enrolled in a clinical trial with appropriate screening and monitoring."

CONCLUSION

HCQ was initially used extensively in most centres treating COVID-19 patients across the world. The rationale was that this was a cheap, widely available, relatively safe drug which could easily be administered orally. Whilst there is some in-vitro rationale for its use the data from the present clinical studies is not convincing enough for us to presently recommend this drug. Caution must be exercised when using it, with monitoring for potential cardiac toxicity. A Cochrane review of the available data is underway[37] and the results of the large multi-centre SOLIDARITY trial which will include the use of HCQ across 150 sites is keenly awaited. The data from these larger, better designed RCTs are needed before we can make definite recommendations on the use of HCQ in the management of patients with COVID-19 infection. As available drug options are very limited at present, the medical community eagerly waits to learn if the current buzz around chloroquine and hydroxychloroquine proves to be hope or hype.

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